PHARMACOGENETICS OF SELECT GENES IN THE OPIATE METABOLISM AND RESPONSE PATHWAYS

A DISSERTATION

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~ Frank

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LIST OF ABBREVIATIONS

ABCB1	ATP binding cassette subfamily B number 1
ACB	African Caribbeans in Barbados
ADME	Absorption, distribution, metabolism, excretion
ADME-R	Absorption, distribution, metabolism, excretion, and response
AFR	African
ALU	Arthrobacter luteus element
AMR	Admixed American
ANOVA	Analysis of variance
AS	Activity score
ASW	American of African Ancestry in Southwest United States
ATP	Adenosine triphosphate
bam	Batch alignment/map (file type)
BEB	Bengali from Bangladesh
BIC	Bayesian information criterion
BWA	Burrows-Wheeler Aligner
CADD	Combined Annotation Dependent Depletion
CCD	Charge-coupled device
CDX	Chinese Dai in Xishuangbanna, China
CEU	Utah Residents (CEPH) with Northern and Western Ancestry
CHB	Han Chinese in Beijing China
CHS	Southern Han Chinese
CLM	Colombians from Medellin, Colombia
CLP	Cleanup plate
CNV	Copy number variation
CoD	Cause of death
COMT	Catechol-O-methyltransferase
CYP2D6	Cytochrome p450, family 2, subfamily D, polypeptide 6
CYP2D7P	Cytochrome p450, family 2, subfamily D, polypeptide 7 pseudogene
CYP2D8P	Cytochrome p450, family 2, subfamily D, polypeptide 8 pseudogene
CYP450	Cytochrome p450 mono-oxygenase
DI	Degradation index
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dNTP	Deoxynucleotide triphosphate
EAS	East Asian
EM	Extensive metabolizer
ESN	Esan in Nigeria

LIST OF ABBREVIATIONS (continued)

EUR	European
EWAS	Exome-wide association study
FIN	Finnish in Finland
g-MP	Genotype-inferred metabolizer phenotype
GATK	Genome Analysis Toolkit
GCTA	Genome-wide Complex Trait Analysis
GBR	British in England and Scotland
GDA	Genetic Data Analysis
GenCall	Genotype call score
GIH	Gujarati Indian from Houston, Texas
GO	Gene ontology
GUSBP11	Putative inactive beta-glucuronidase protein 11
GWAS	Genome wide association study
GWD	Gambian in Western Divisions in Gambia
h^2	Heritability
HCN1	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel
HCYPAND	Human cytochrome p450 allele nomenclature database
H_e	Expected heterozygosity
Hg19	Human genome build 19
Hg38	Human genome build 38
H_o	Observed heterozygosity
HSF	Human Splicing Finder
HWE	Hardy-Weinberg equilibrium
HYP	Hybridization plate
IBD	Identity-by-descent
IBS	Iberian Population in Spain (Chapters 2-4); Identity-by-state (Chapter 7)
ICA1	Islet cell autoantigen 1
ICA69	Islet cell autoantigen 1
ICAp69	Islet cell autoantigen 1
ICD-10	International Classification of Diseases, Tenth Revision
IGV	Integrated Genomics Viewer
IM	Intermediate metabolizer
INDEL	Insertion/deletion
IPC C_t	Internal PCR cycle threshold
ITU	Indian Telugu from the United Kingdom
JPT	Japanese in Tokyo, Japan
KHDRBS3	KH domain-containing, RNA-binding, signal transduction-associated protein

KHV	Kinh in Ho Chi Minh City, Vietnam
LD	Linkage disequilibrium
LR	Linear regression classifier
LWK	Luhya in Webuye, Kenya
M6G	Morphine-6-glucuronide
M1	O-desmethyltramadol
MAF	Minor allele frequency
MDR1	Multidrug resistance protein 1
MDS	Multidimensional scaling
miRNA	Micro RNA
MoD	Manner or death
MOR	Mu opioid receptor 1
MP	Metabolizer phenotype
MPS	Massively parallel sequencing
MSL	Mende in Sierra Leone
MXL	Mexican Ancestry from Los Angeles, USA
1NN	1-nearest neighbor classifier
N	Nortramadol
NC	No genotype call
NM	Normal metabolizer
NM-F	Normal metabolizer, fast
NM-S	Normal metabolizer, slow
kNN	k-nearest neighbor classifier
OPR	Opioid receptor
OPRM1	Opioid receptor mu 1
p10 GC	Tenth percentile genotype call score
p50 GC	Fiftieth percentile genotype call score
PC1	Principal component 1
PC2	Principal component 2
PCA	Principal component analysis
PCR	Polymerase chain reaction
PEL	Peruvians from Lima, Peru
PGM	Personal Genome Machine
PharmGKB	Pharmacogenomics Knowledgebase
PharmVar	Pharmacogene Variation Consortium
PJL	Punjabi from Lahore, Pakistan
PM	Poor metabolizer

PolyPhen-2	Polymorphism Phenotyping v2
PopART	Population Analysis with Reticulate Trees
PROVEAN	PROtein Variant Effect ANalyzer
PTC	Phenylthiocarbamide
PUR	Puerto Ricans from Puerto Rico
RF	Random forest classifier
RFL4B	Ret Finger Protein-like 4B
RGL4	Ral Guanine Nucleotide Dissociation Stimulator Like 4
RMLR	Regularized multinomial logistic regression
RNA	Ribonucleic acid
RNF211	RING Finger Protein 211
SALP	KH domain-containing, RNA-binding, signal transduction-associated protein
SAMtools	Sequence Alignment/Map Tools
SAS	South Asian
SIFT	Sort Intolerant From Tolerant
SLM2	KH domain-containing, RNA-binding, signal transduction-associated protein
SMRT	Single molecular, real time sequencing
SNP	Single nucleotide polymorphism
SNV	Single nucleotide variant
STU	Sri Lankan Tamil from the United Kingdom
T	Tramadol
t-MP	Toxicologically-inferred metabolizer phenotype
TSCA	TruSeq Custom Amplicon
TSI	Toscani in Italia
T-STAR	KH domain-containing, RNA-binding, signal transduction-associated protein
UCSC	University of California Santa Cruz
UGT	Uridine diphosphate glucuronosyltransferase superfamily
UGT2B7	Uridine diphosphate glucuronosyltransferase, family 1, polypeptide B7
UM	Ultra-rapid metabolizer
UNTHSC	University of North Texas Health Science Center
vcf	Variant call format (file type)
WEKA	Waikato Enrvironment for Knowledge Analysis
WHO	World Health Organization
YRI	Yoruba in Ibadan, Nigeria

PART 1

INTRODUCTION

CHAPTER 1

An Introduction of Pharmacogenetics and the use of Massively Parallel Sequencing as a Diagnostic Tool for Personalized Medicine

Drug metabolism and response vary among individuals and the consequences of drug exposure can be helpful (i.e., the drug eliminates the physiological stimulus for which the drug was taken), harmful (i.e., the drug over- or under-corrects the physiological stimulus for which the drug was taken), or deleterious (i.e., the drug causes a series of physiological events resulting in harm or death). The realization that humans have individualized responses to exogenous compounds date back to Ancient Greece, Egypt, and Rome where black spots on fava beans were associated with death. Priests recommended that certain people abstain from ingesting products derived from the fava plant (Meletis 2011). "Favism" was later characterized as the hemolytic anemias resulting from glucose-6-phosphate dehydrogenase deficiencies common to Central Africa and southwest Asia (Luzzatto, *et al.* 2016). Taste blindness studies of the early 1930s were performed by Arthur L. Fox (Fox 1932 and Wooding 2006). He and his colleagues accidentally ingested phenylthiocarbamide (PTC) powder and while most of the lab reported a bitter taste in their mouths, Fox could taste nothing. He further investigated this anomaly by testing responses to PTC in a larger cohort and grouped individuals into two categories: tasters and nontasters. In the 1950s, the underlying genetic factors influencing response to normal drug dose were explored by an interdisciplinary group of scientists. Early work focused on developing accurate and precise methods for genotyping, measuring enzyme activity, drug concentrations, and metabolite concentrations, and identifying networks of drug response and metabolism proteins. In 1975, accidental ingestion of an experimental chemical once again revealed a hallmark observation. Smith and his colleagues consumed approximately 32 mg of debrisoquine, a sympathicolytic antihypertensive drug (Smith 1986). His colleagues experienced no negative response to the accident but Smith reported severe orthostatic hypotension with blood pressure dropping to

70/50 mmHg. His symptoms lasted almost two days and were later attributed to genetic predisposition to poor metabolism of debrisoquine. During this time, the Smith and Eichelbaum research groups independently identified and characterized the cytochrome p450 mono-oxygenase (CYP450) enzyme polymorphisms related to drug oxidation (Fox 1932; Eichelbaum, *et al.* 1979; Smith 1986; Meyer 2004). This discovery was significant due to the broad spectrum of foreign and endogenous compounds that rely on oxidation via CYP450 for action and metabolism.

Present day prescription medication use has revealed similar degrees of response variation, with certain individuals demonstrating over or under "sensitivity" to different compounds. In April, 2005, thirteen days after his birth, a male child was found dead with no anatomical anomalies (Koren, *et al.* 2006). The cause of death (CoD) was morphine poisoning. During investigation of a possible infanticide, elevated levels of morphine were detected in his mother's breast milk. Genetic testing revealed the mother to be a rapid metabolizer of codeine which was administered to her as an analgesic for postpartum pain. It was determined that her rapid metabolizer status produced elevated levels of morphine in her blood. She then transferred morphine to her child during breastfeeding, causing opioid toxicity and accidental neonatal death. Cases such as this one that helped clarify the manner of death (MoD) demonstrate the need of molecular autopsy, i.e., genetic analyses regarding drug response, sudden cardiac arrest, etc. to help clarify instances where CoD and/or MoD are undetermined by traditional autopsy.

In 2015, an idiosyncratic response to drugs led to a lawsuit against a large pharmaceutical company (Wu, White, Oh, and Burchard 2015). After visiting a cardiologist for a heartbeat abnormality, a Hawaiian resident of Polynesian descent was diagnosed with

significant blockage of his left anterior and circumflex arteries. His cardiologist prescribed 75 mg of clopidogrel per day for the next six months. Clopidogrel is a platelet aggregation inhibitor used to treat stroke and myocardial infarction (i.e., heart attack). Thirty days after the prescription was written, the patient experienced a severe heart attack. It was later discovered that the 75 mg dose was deemed appropriate for the ~95% of clinical trial participants of European ancestry but clopidogrel efficacy was never evaluated in Pacific Islander populations. This group of individuals has an exceedingly high frequency (80%) of the allele conferring poor clopidogrel metabolism. Consequently, 75 mg of clopidogrel provide no significant reduction of stroke or heart attack risk in native Hawaiian individuals. This case also highlights individual variation in drug response due in part to an individual's genetics.

Pharmacogenetics, known as the elucidation of genetic factors responsible for variable drug responses, is an emerging interdisciplinary field and is the focus of this dissertation. Variation to drug therapy can have three outcomes: (1) the patient receives the desired effect; (2) the drug has no effect on the patient; or (3) the drug causes adverse reactions in the patient, e.g., death. Response to drugs and notable cases such as those mentioned above have been at the forefront of healthcare for some time and, more recently, have become a major interest of the toxicology, psychiatry, neuroscience, and forensic science communities (Bock, *et al.* 1994; Broly and Meyer 1993; Garrod 1996; Leppert 2011; Lam, *et al.* 2014; Baber, *et al.* 2015).

A logical target for understanding the molecular basis of drug metabolism was the CYP450 gene family, initially described by Smith and Eichelbaum (Smith 1986; Eichelbaum, *et al.* 1979; Meyer 2004), which encodes proteins responsible for a large portion of hepatic phase I drug metabolism (Slaughter and Edwards 1995; Ingelman-Sundberg 2003; Lewis 2004; Ingelman-Sundberg, et al. 2007). Phase I metabolism of a drug occurs in the liver and involves

at least one chemical reaction to increase the hydrophillicity of a compound, typically by the addition of a hydroxyl group or removal of a methyl group. CYP450 is a super-family of hemoproteins with a maximum light absorption at 450 nm when reduced and complexed with carbon monoxide (Ortiz de Montellano 2005). The heme complex acts as a cofactor for Phase I metabolic reactions and typically resides adjacent to the enzyme active site deep within its three-dimensional structure (Figure 1). This super-family is partially responsible for varying degrees of drug response across ethnic populations with African groups showing the most diversity and widest range of affect (Polimanti, *et al.* 2012). There are more than 50 unique enzymes within the CYP450 super-family (Table 1), all of which are essential for reduction of foreign and endogenous compound bioavailability. Of particular interest is CYP450 family 2 subfamily D polypeptide 6 (CYP2D6), which is responsible for approximately 30% of phase I metabolism of endogenous and foreign compounds (Ingelman-Sundberg 2005; Leppert 2011; Hicks, *et al.* 2013; Crews, *et al.* 2014). The *CYP2D* locus contains three homologous genes: *CYP2D8* pseudogene (*CYP2D8P*), *CYP2D7P*, and *CYP2D6* located in a ~45 kb region of chromosome 22 (Figure 1; Eichelbaum, *et al.* 1987; Kimura, *et al.* 1989; Gough, *et al.* 1993). CYP2D6 is the only active protein produced from this locus. The enzyme accounts for a relatively small amount of hepatic CYPs but is responsible for phase I metabolism of about 25% of current market drugs, converting them from pro-drug to active metabolite (e.g., codeine to morphine), active drug to active metabolite (e.g., oxycodone to oxymorphone), or active drug to inactive metabolite (e.g., nortriptyline and amitriptyline tricyclic antidepressants to their inactive (Z)-10-hydroxylated metabolites) (Ingelman-Sundberg 2005; Ingelman-Sundberg, *et al.* 2007; Leppert 2011). Accidental overdose and idiosyncratic drug responses have been associated with variable MPs: poor (PM), intermediate (IM), extensive/normal

(EM/NM), and ultra-rapid (UM), typically described using a toxicologically determined ratio of pro-drug to active metabolite but are also predicted to some degree genetically based on *CYP2D6* polymorphisms (Zhou, *et al.* 2008; Hiratsuka 2012; Sistonen, *et al.* 2012; Weber, *et al.* 2012).

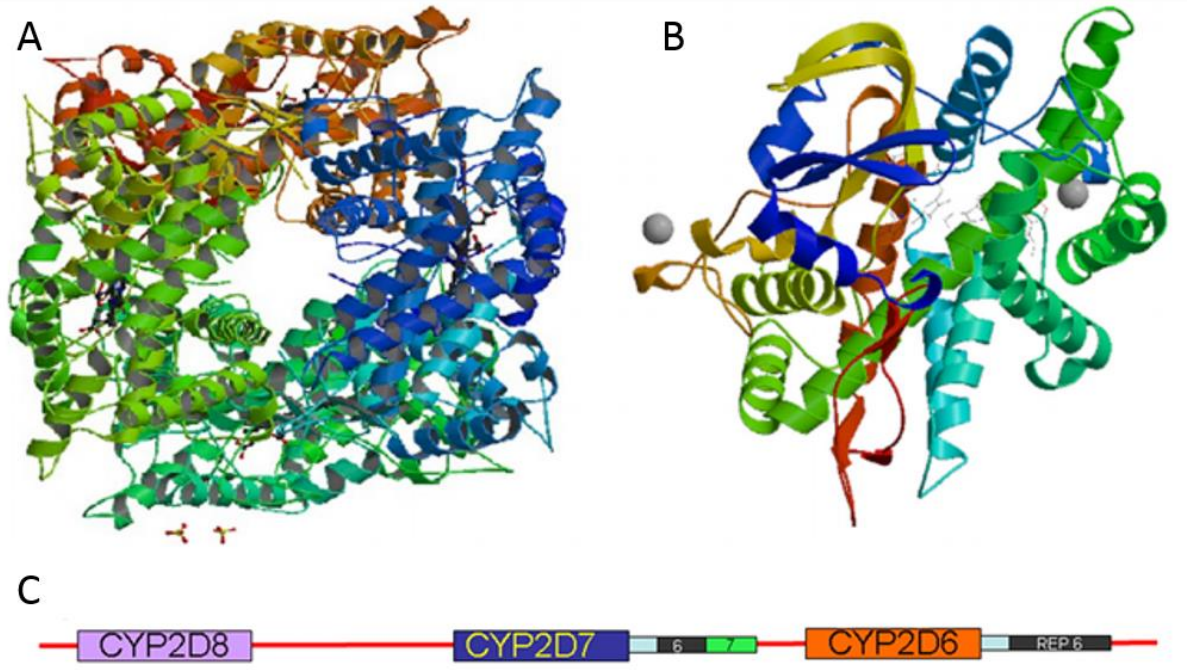

Figure 1. Computationally predicted three dimensional structure of CYP2D6 encoded by the wild-type * allele (*1, sub-image A) and a mutant, decreased function allele (*10, sub-image B). Sub-image C shows the *CYP2D* locus which contains the *CYP2D6* gene and two pseudogenes, *CYP2D7* and *CYP2D8*. Images modified from Black, *et al.* (2012) and He, *et al.* (2016).

Table 1. A list of 57 functional human cytochrome p450 genes; table modified from Zhou, *et al.* (2016).

Gene	Alias	Names	Chromosomal Location	Substrates/Function	Amino Acids	Exons
CYP1A1	*AHH; AHRR; CP11; CYP1; P1-450; P450-C; P450DX*	Cytochrome P450 1A1; CYP1A1; cytochrome P450-C; cytochrome P450-P1; cytochrome P450 form 6; xenobiotic monooxygenase; aryl hydrocarbon hydroxylase; flavoprotein-linked monooxygenase; dioxin-inducible cytochrome P1-450	15q24.1	Drugs, procarcinogens, steroids, and fatty acids	512	7
CYP1A2	*CP12; P3-450; P450(PA)*	Cytochrome P450 1A2; CYP1A2; P450 form 4; cytochrome P450 4; cytochrome P450; cytochrome P450-P3; dioxin-inducible P3-450; microsomal monooxygenase; xenobiotic monooxygenase; aryl hydrocarbon hydroxylase; flavoprotein-linked monooxygenase	15q24.1	Drugs, fatty acids, and steroids	516	7
CYP1B1	*CP1B; GLC3A; CYP1B1; P4501B1*	Cytochrome P450 1B1; microsomal monooxygenase; xenobiotic monooxygenase; aryl hydrocarbon hydroxylase; flavoprotein-linked monooxygenase	2p22.2	Drugs, procarcinogens, steroids, and fatty acids	543	3
CYP2A6	*CPA6; CYP2A; CYP2A3; P450PB; CYPIIA6; P450C2A*	Cytochrome P450 2A6; cytochrome P450(I); cytochrome P450 IIA3; coumarin 7-hydroxylase; xenobiotic monooxygenase; 1,4-cineole 2-exo-monooxygenase; flavoprotein-linked monooxygenase	19q13.2	Drugs and steroids	494	9
CYP2A7	*CPA7; CPAD; CYP2A; CYP11A7; P450-IIA4*	Cytochrome P450 2A7; cytochrome P450IIA4; cytochrome P450 IIA4	19q13.2	Xenobiotics, steroids, and fatty acids	494	9
CYP2A13	*CPAD; CYP2A; CYPIIA13*	Cytochrome P450 2A13	19q13.2	Drugs and other xenobiotics	494	9
CYP2B6	*CYP 2B; CYP 2B7; CYP 2B7P*	Cytochrome P450 2B6; cytochrome P450 IIB; 11,4-cineole 2-exo-monooxygenase	19q13.2	Drugs, steroids, and fatty acids	491	9
CYP2C8	*CYP 2C8*	Cytochrome P450 2C8; P450 form 1; cytochrome P450 IIC2; cytochrome P450 MP-12; cytochrome P450 MP-20; cytochrome P450 form 1; microsomal monooxygenase; xenobiotic monooxygenase; S-mephenytoin 4-hydroxylase; flavoprotein-linked monooxygenase	10q23.33	Drugs, steroids, and fatty acids	490	9
CYP2C9	*CPC9; CYP2C; CYP2C10; CYPIIC9; P450IIC9*	Cytochrome P450 2C9; cytochrome P-450MP; cytochrome P450 PB-1; microsomal monooxygenase; xenobiotic monooxygenase; flavoprotein-linked monooxygenase	10q24	Drugs, steroids, and fatty acids	490	9
CYP2C18	*CYP 2C; CYP 2C17; CYPI; P45011C17; P450-6B/29C*	Cytochrome P450 2C18; microsomal monooxygenase; unspecific monooxygenase; flavoprotein-linked monooxygenase; S-mephenytoin hydroxylase associated cytochrome P450	10q24	Drugs, steroids, and fatty acids	490	9

Table 1 (continued). A list of 57 functional human cytochrome p450 genes; table modified from Zhou, *et al.* (2016).

Gene	Alias	Names	Chromosomal Location	Substrates/Function	Amino Acids	Exons
CYP2C19	*CYP2C; CYPJ; P450C2C; CYPIIC17; CYPIIC19; P450IIC19*	Cytochrome P450 2C19; cytochrome p450-11A; cytochrome P450-254C; cytochrome P450 II C; microsomal monooxygenase; xenobiotic monooxygenase; mephenytoin 4'-hydroxylase; S-mephenytoin 4-hydroxylase	10q24.1-q24.3	Drugs	490	9
CYP2D6	*CYD6; CYP2D; CYP2D7AP; CYP2D7BP; CYP2D7P2; CYP2DL1; CYPIID6; P450C2D; P450DB1; CYP2D8P2; P450-DB1*	Cytochrome P450 2D6; cytochrome P45-DB1; microsomal monooxygenase; xenobiotic monooxygenase; debrisoquine 4-hydroxylase	22q13.1	Drugs	497	10
CYP2E1	*CYP2E; CYE1; P450-J; P4502C2E*	Cytochrome P450 2E1; cytochrome P450-J; microsomal monooxygenase; xenobiotic monooxygenase; 4-nitropheno 2-hydroxylase; flavoprotein-linked monooxygenase	10q26.3	Drugs, ethanol, and procarcinogens	493	9
CYP2F1	*CYP2F; C2F1*	Cytochrome P450 2F1; CYPIIF1; microsomal monooxygenase; xenobiotic monooxygenase; flavoprotein-linked monooxygenase	19q13.2	Drugs and coumarins	491	11
CYP2J2	*CP J2*	Cytochrome P450 2J2; CYPIIJ2; microsomal monooxygenase; arachidonic acid epoxygenase; flavoprotein-linked monooxygenase	1p31.3-p31.2	Fatty acids	502	9
CYP2R1	*CYP 2R1*	Vitamin D 25-hydroxylase; cytochrome P450 2R1	11p15.2	Vitamin D	501	8
CYP2S1	*CYP 2S1*	Cytochrome P450 2S1; CYPIIS1	19q13.1	Xenobiotics	504	9
CYP2U1	*SPG49; SPF56; P450TEC*	Cytochrome P450 2U1; spastic paraplegia 49	4q25	Amino acids, dehydroepiandrosterone, and long-chain fatty acids	544	5
CYP2W1	*CYP 2W1*	Cytochrome P450 2W1; CYPIIW1	7p22.3	Unknown	490	10
CYP3A4	*HLP; CP33; CP34; CYP3A; NF-25; CYP3A3; P340C3; CYPIIIA3; CYPIIIA4; P450PCN1*	Cytochrome P450 3A4; 1,8-cineole 2-exo-monooxygenase; steroid-inducible P450-III; albendazole monooxygenase; albendazole sulfoxidase; cytochrome P450 3A3; cytochrome P450 HLp; cytochrome P450 NF-25; cytochrome P450 subfamily IIIA (nifedipine oxidase) polypeptide 3; cytochrome P450 subfamily IIIA (nifedipine oxidase) polypeptide 4; cytochrome P450-PCN1; glucocorticoid-inducible P450; nifedipine oxidase; quinine 3-monooxygenase; taurochenodeoxycholate 6-α-hydroxylase	7q21.1	Drugs, steroids, and fatty acids	503	14

Table 1 (continued). A list of 57 functional human cytochrome p450 genes; table modified from Zhou, *et al.* (2016).

Gene	Alias	Names	Chromosomal Location	Substrates/Function	Amino Acids	Exons
CYP3A5	*CP 35; CYPIIIA5; P450PCN3; PCN3*	Cytochrome P450 3A5; cytochrome P450 HLp2; cytochrome P450-PCN3; microsomal monooxygenase; xenobiotic monooxygenase; aryl hydrocarbon hydroxylase; flavoprotein-linked monooxygenase	7q21.1	Drugs, steroids, and fatty acids	502	18
CYP3A7	*CP 37; CYPIIIA7; P450(HFL33); P450-HFLA; P-450111A7*	Cytochrome P450 3A7; cytochrome P450-HFLA; microsomal monooxygenase; xenobiotic monooxygenase; aryl hydrocarbon hydroxylase; flavoprotein-linked monooxygenase	7q21-q22.1	Drugs, steroids, and fatty acids	503	13
CYP3A43	*CYP 3A43*	Cytochrome P450 3A43	7q21.1	Low level testosterone 6β-hydroxylase activity	503	15
CYP4A11	*CP4Y; CYP4A2; CYP4AII*	Cytochrome P450 4A11; CYPIVA11P450-ω; 20-HETE synthase; alkane-1 monooxygenase; cytochrome P450HL-ω; cytochrome P-450; HK-ω fatty acid ω-hydroxylase; lauric acid ω -hydroxylase; 20-hydroxyeicosatetraenoic acid synthase	1p33	Medium-chain fatty acids such as laurate and myristate	519	12
CYP4A22		Cytochrome P450 4A22; CYPIVA22; cytochrome P450 4A22K; fatty acid ω-hydroxylase; lauric acid ω-hydroxylase	1p33	Unknown	519	12
CYP4B1	*CYPIVB1; P-450HP*	Cytochrome P450 4B1; cytochrome P450-HP; microsomal monooxygenase	1p33	Xenobiotics, steroids, and fatty acids	511	12
CYP4F2	*CP F2*	Leukotriene-B4 ω-hydroxylase 1; CYPIVF2; cytochrome P450 4F2; cytochrome P450-LTB-ω; leukotriene-B4 20-monooxygenase 1	p13.12	Eicosanoids	520	13
CYP4F3	*CP F3; CYP4F; LTB4H*	Leukotriene-B4 ω-hydroxylase 2; CYPIVF3; cytochrome P450 3F3; cytochrome P450-LTB-ω; leukotriene-B4 ω-hydroxylase; leukotriene-B4 20-monooxygenase 2	19p13.2	Eicosanoids via ω-hydroxylation	520	15
CYP4F8	*CYPIVF8; CPF8*	Cytochrome P450 4F8; microsomal monooxygenase; flavoprotein-linked monooxygenase	19p13.1	Eicosanoids, forming 19R-prostaglandins	520	13
CYP4F11	*CYPIVF11*	Cytochrome P450 4F11	19p13.1	Flavoprotein hydroxylation	524	13
CYP4F12	*CYPIVF12; F22329_1*	Cytochrome P450 4F12	19p13.1	Fatty acids	524	13
CYP4F22	*LI3; ARC15; INLNE*	Cytochrome P450 4F22	19p13.12	Fatty acids	524	14
CYP4V2	*CYP 4AH1; BCD*	Cytochrome P450 4V2	4q35.2	Fatty acids	531	14
CYP4X1	*CYPIVX1*	Cytochrome P450 4X1	1p33	Flavoprotein hydroxylation	525	11
CYP4Z1	*CYP 4A20*	Cytochrome P450 4Z1	1p33	Flavoprotein hydroxylation	509	12

Table 1 (continued). A list of 57 functional human cytochrome p450 genes; table modified from Zhou, *et al.* (2016).

Gene	Alias	Names	Chromosomal Location	Substrates/Function	Amino Acids	Exons
CYP5A1	*TXBAS1; TS; TXS; CYP5; TXAS; THAS; GHOSAL; BDPLT14*	Thromoxane A-synthase; TXA synthase; cytochrome P450 5A1	7q34-q35	Thromboxane synthesis	534	18
CYP7A1	*CP7A; CYP7; CYPVII*	Cholesterol 7α-monooxygenase; cytochrome P450 7A1; cholesterol 7α-hydroxylase	8q11-q12	Conversion of cholesterol to bile acids	504	6
CYP7B1	*CP7B; CBAS3; SPG5A*	25-Hydroxycholesterol 7α-hydroxylase; cytochrome P450 7B1; oxysterol 7α-hydroxylase	8q21.3	Conversion of cholesterol to bile acids	506	6
CYP8A1	*CYP 8; PGIS; PTGI; PTGIS*	Prostacyclin synthase; prostaglandin I2 synthase	20q13.13	Isomerization of PGH2 to prostacyclin	500	10
CYP8B1	*CYP 12; CP8B*	7α-Hydroxycholes-4-en-3-one 12α hydroxylase; CYPVIIIB1; cytochrome P450 8B1; sterol 12α-hydroxylase	3p22-p21.3	Steroids	501	1
CYP11A1	*CYP 11A; CYPXIA1; P450SCC*	Mitochondrial cholesterol side-chain cleavage enzyme; steroid 20-22-lyase; cytochrome P450 11A1	15q23-q24	Side-chain cleavage of cholesterol pregnenolone	521	12
CYP11B1	*CYP 11B; FHI; CPN1; P450SCC*	Mitochondrial cytochrome P450 11B1; CYPXIB1; cytochrome P450C11; steroid 11β-hydroxylase	8q21.3	Steroids	503	11
CYP11B2	*CYP 11BL; CYP 11B; CPN2; ALDOS; CYPXIB2; P450C18; P450aldo*	Mitochondrial cytochrome P450 11B2; cytochrome P450C18; aldosterone synthase; steroid 11β-monooxygenase; steroid 11β/18-hydroxylase; aldosterone-synthesizing enzyme	8q21-q22	Steroids, especially productions of aldosterone	503	9
CYP17A1	*CYP 17; CPT17; S17AH; P450C17*	Steroid 17α-hydroxylase/12,20 lyase; cytochrome P450C17; steroid 17α-monooxygenase; 17α-hydroprogesterone aldolase	10q24.3	Steroids, especially conversion of pregnenolone and progesterone	508	8
CYP19A1	*CYP 19; ARO; ARO1; CPV1; CYAR; CYPXIX; P-450AROM*	Aromatase; estrogen synthase; cytochrome P-450AROM; cytochrome P450 19A1; microsomal monooxygenase; flavoprotein-linked monooxygenase	15q21.1	Steroids, especially formation of aromatic C18 estrogens and C19 androgens	503	14
CYP20A1	*CYP-M*	Cytochrome P45020A1; cytochrome P450 monooxygenase	2q33.2	Unknown	462	14
CYP21A2	*CYP21; CYP21B; CAH1; CPS1; CA21H; P450c21B*	Steroid 21-hydroxylase; 21-Ohase; cytochrome P450XXI; cytochrome P450-C21B	6p21.3	21-Hydroxylation of steroids; required for adrenal synthesis of mineralocorticoids and glucocorticoids	495	11

Table 1 (continued). A list of 57 functional human cytochrome p450 genes; table modified from Zhou, *et al.* (2016).

Gene	Alias	Names	Chromosomal Location	Substrates/Function	Amino Acids	Exons
CYP24A1	*CP24; CYP24; HCAI; P450-CC24; cytochrome P450 family 24 subfamily A member 1; HCINF1*	Mitochondrial 25-hydroxyvitamin D3-24-hydroxylase	20q13.2	Vitamin D degradation	514	12
CYP26A1	*CP26; CYP26; P450RAI; P450RAI1; cytochrome P450 family 26 subfamily A member 1*	4-Hydroxylate; 18-hydroxylase	10q23.33	Retinoic acid hydroxylase	497	8
CYP26B1	*CYP26A2; P450RAI-2; P450RAI2; RHFCA; cytochrome P450 family 26 subfamily B member 1*	Broad acting hydroxylase; retinoic acid monooxygenase	2p13.2	Retinoic acid hydroxylase	512	8
CYP26C1	*FFDD4; cytochrome P450 family 26 subfamily C member 1*	Broad acting hydroxylase; retinoic acid monooxygenase	10q23.33	Retinoic acid hydroxylase	522	7
CYP27A1	*CP27; CTX; CYP27; cytochrome P450 family 27 subfamily A member 1*	Sterol 27-hydroxylase	2q35	Bile acid biosynthesis	531	11
CYP27B1	*CP2B; CYP1; CYP1alpha; CYP27B; P450c1; PDDR; VDD1; VDDR; VDDRI; VDR; cytochrome P450 family 27 subfamily B member 1*	25-Hydroxyvitamin D3 1α-hydroxylase; 1α-hydroxylase	12q14.1	Vitamin D3 1α hydroxylase; activates vitamin D3	508	9
CYP27C1	*cytochrome P450 family 27 subfamily C member 1*	Sterol monooxygenase	2q14.3	Unknown	372	9
CYP39A1	*cytochrome P450 family 39 subfamily A member 1*	Oxysterol 7-α-hydroxylase 2	6p12.3	7α-hydroxylation of 24-hydroxycholesterol	469	18
CYP46A1	*CP46; CYP46;cytochrome P450 family 46 subfamily A member 1*	Cholesterol 24-hydroxylase	12q32.2	Cholesterol 24-hydroxylase	500	15
CYP51A1	*CYP51; P45014DM*	Lanosterol 14α demethylase	7q21.2-q21.3	Cholesterol biosynthesis	503	12

These MPs have been used as an adjunct to guide prescription medication practices and have provided critical information in legal cases to describe CoD and/or MoD. Genetic predictions of MP are based on the presence of one or more causal *CYP2D6* polymorphisms (Gaedigk, *et al* 2008 and 2016). Reference to the haplotype of polymorphisms within *CYP2D6* is known as a star (*) allele (Figure 2). As of 2015, over 100 different * alleles and 18 full gene duplications have been characterized that impart metabolic phenotype differences (Marez, *et al.* 1997; Gaedigk, *et al.* 2008; Crews, *et al.* 2014; Gaedigk, *et al.* 2016). A number of * alleles have been characterized based on the presence of single SNPs or INDELs while others contain variation along the length of the gene. For example, *CYP2D6**7 contains 2935A>C (rs5030867; Figure 1) only while *CYP2D6**28 contains 19G>A (rs72549358), 1661G>C (rs1058164), 1704C>G (rs78482768), 2850C>T (rs16947), and 4180G>C (rs1135840). The causal aspect of carrying one or more SNPs or INDELs relative to the reference genomes is risk of altering the amino acid sequence (i.e., a non-synonymous mutation) or introducing a premature stop codon (i.e., a missense mutation) and thereby changing the protein and/or active site structure. *CYP2D6* * alleles have been used to characterize MP distribution in human populations using the activity score (AS) approach. AS is a qualitative measure of MP by which individual alleles of the *CYP2D6* genotype (or individual haplotypes of the *CYP2D6* * allele diplotype) are assigned a value from 0-1, based on experimentally observed enzyme activity, and summed (Table 2) (Gaedigk, *et al.* 2016). For example, a NM/EM individual carries the *CYP2D6* diplotype *1/*4; *1 is the fully functional wild-type allele and is assigned an AS of 1 while *4 is non-functional and is assigned an AS of 0. The sum of the AS for each * allele is the AS for this individual. Note that this example individual carries an allele conferring a fully

functional enzyme so he/she is considered an NM/EM even though *4 abolishes enzyme activity (Table 2).

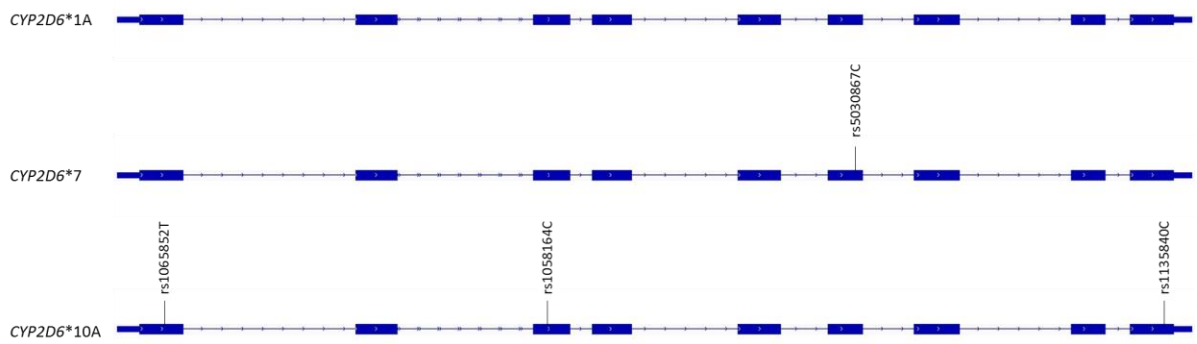

Figure 2. Example *CYP2D6* star (*) alleles. Blue rectangles and horizontal lines represent *CYP2D6* exons and introns, respectively; single nucleotide polymorphism (SNP) rs numbers are provided for select * allele defining loci; designated SNP alleles are in relative to the hg19 reference genome. *CYP2D6**1A is the wild type * allele; *CYP2D6**7 and *CYP2D6**10A demonstrate how individual SNPs, or a collection of SNPs along the length of the gene, confer different * alleles.

Table 2. Metabolizer phenotype (MP) defined by CYP2D6 activity score. Table modified from data presented by Crews, *et al.* 2014. Asterisks indicate *CYP2D6* star (*) alleles; up arrows (↑) indicate increased function alleles, down arrows (↓) indicate decreased function alleles, horizontal double sided arrows (↔) indicate normal function alleles, and horizontal bars (−) indicate null/no function alleles. Placement of gene duplications into a metabolizer phenotype category is based on the assumption of duplication producing one additional * allele (three total * alleles). This categorization may change if the duplication event results in more than three alleles for an individual.

MP	Percent of Patients	Activity Score	Definition	Example Genotype
UM	1-2	>2.0	↔/↑, ↑↑, ↑/↑xN, ↑/↑xN, ↑/↔xN, ↑/↓xN, ↔/↔xN, ↔/↑xN, −/↑xN, ↓/↔xN, ↓/↑xN	*2/*1xN, *1/*53
EM	77-92	1.0-2.0	↔/↔, ↓/↓, ↔/↓, ↑/↓, ↑/−, ↓/↓xN, ↔/−xN, −/↓xN, −/↔xN, ↑/−xN, ↔/↓xN	*1/*1, *1/*2, *1/*4, *2/*5
IM	2-11	0.5	↓/−, ↓/−xN	*4/*10A, *5/*41
PM	5-10	0	−/−, −/−xN	*4/*4, *7/*5, *5/*5

CYP2D6 * alleles encoding normally active protein confer the EM phenotype when present in homozygous normal/normal, heterozygous normal/decreased function, or heterozygous normal/null genotypes. *CYP2D6**1 and its derivatives (*1A, *1B, *1C, *1D, and

*1E) encode normal fully functional enzymes (Kimura, *et al.* 1989; Marez, *et al.* 1997; Sachse, *et al.* 1997). The *CYP2D6**1 has allele frequencies of 0.32, 0.50, 0.35, 0.49, 0.38, in the African, Admixed American, East Asian, South Asian, and European global populations, respectively. Also encoding a fully functional enzyme is *CYP2D6**2 which has at least twelve sub-types (*2A through *2H and *2J through *2M) all characterized by the presence of the 2850C>T (rs16947) and 4180G>C (rs1135840) SNPs which do not alter protein function relative to *CYP2D6**1. This allele is quite frequent in global populations and may be more common than the reference allele in some populations (Marez, *et al.* 1997; Gaedigk, *et al.* 2016). Other alleles resulting in normal enzyme function include *CYP2D6**27, *33, *35, *39, *45 (debated), and *48.

Null * alleles do not encode an active form of CYP2D6 and, when found as homozygous null/null or heterozygous null/decreased function genotypes, confer the PM phenotype in various ways. The mechanisms are: (1) Disruption of reading frame caused by INDELs and SNPs which generate premature stop codons or altered protein folding, such as 2549delA (rs35742686), which produces *CYP2D6**3 (Kagimoto, *et al.* 1990). *CYP2D6**3 encodes a truncated protein product and was first detected in Caucasian (frequency of 0.013) PMs but also has been observed in African Americans with an allele frequency of 0.0031 (Crews, *et al.* 2014); (2) Full-length non-functional * alleles due to SNPs and/or INDELs that are tolerated during splicing and protein folding. *CYP2D6**12, *14, and *18, for example, contain 124G>A (no rs number), 1758G>A (rs5030865), and 4125-4133dupGTGCCCACT (rs765776661), respectively, which do not disrupt formation of CYP2D6 but alter amino acid composition in such a way that renders the protein completely inactive (Marez, *et al.* 1996; Yokoi, *et al.* 1006; Wang, *et al.* 1999); (3) Deletion of *CYP2D6* as seen in *5 which has a 5-

7% allele frequency across most ethnic groups (Gaedigk, *et al.* 1991; Steen, *et al.* 1995); and (4) Formation of a hybrid gene with the highly homologous *CYP2D7P* as seen in *11 (Marez, *et al.* 1995; Skierka, *et al.* 2012).

A number of *CYP2D6* * alleles give rise to significantly decreased enzyme activity including, but not limited to, *CYP2D6**10, *14, *17, *41, and *51. The consequence of harboring these variant * alleles is typically enzyme instability, poor substrate recognition by the enzyme active site, and reduced affinity of the enzyme for a given substrate (Zhou 2009). The IM phenotype occurs when these alleles are found in heterozygous null/decreased function genotypes. Decreased function alleles are probably the most diverse in terms of population association. For example, *CYP2D6**10 (Figure 1) has a frequency near 0.43 in East Asian (Japanese and Korean) populations but only 0.050 in Caucasian and African American populations (Leathart, *et al.* 1998; Bradford 2002). Conversely, *17 is observed at frequencies of 0.090 (Ethiopian) and 0.34 (Zimbabwean) in African populations but is low or nearly absent in the American, East Asian, and European populations (average frequencies of 0.026, 0.00010, 0.0036, respectively [Bradford 2002]).

There are two forms of increased function *CYP2D6* * alleles come in two forms: (1) alleles which confer increased affinity of the enzyme for the substrate and (2) duplicated functional alleles. To date, *CYP2D6**53 is the only * allele encoding an enzyme that decreases required drug concentration for half-maximal enzyme saturation (K_m) by any notable quantity (73% decrease with bufuralol-10-hydroxylation) (Ebisawa, *et al.* 2005; Sakuyama, *et al.* 2005). This allele is rare with frequencies of 0.0050 in a Mexican population sampled by Contreras, *et al.* 2011 and 0.0017 in a Japanese population sampled by Ebisawa, *et al.* 2005. Gene duplications have been reported for *CYP2D6**1, *2, *4, *9, *10, *17, and *35, each of which

(except *9 and *17) have multiple subtypes. Approximately 5.21% of the total United States population exhibits duplications with three or more copies of *CYP2D6*, though the exact number and frequency of each is typically not reported. The UM phenotype may arise if the duplicated allele is fully functional and paired with a decreased (*10/*1x2; AS = 2.5), normally (*2/*1x2; AS = 3), or increased (*53/*1x2; AS = 3.5) function allele. Alternatively, a gene duplication may not confer the UM phenotype if the duplicated allele is functionally deficient and paired with a normally active (*1/*10x2; AS = 2) or another functionally deficient (*9/*10x2; AS = 1.5) allele. Gene duplications and the resulting MP are listed in Table 2 (Zhou 2009; Beoris, *et al.* 2016).

Recently Gaedigk, *et al.* (2016) used AS to characterize intra-MP variability in world populations in the absence of toxicological and/or pharmacological data (Figure 3). While previously described in select studies (Sistonen, *et al.* 2007; Gaedigk, *et al.* 2008; Chen, *et al.* 2015) as an additional observation, this study was the first to highlight variation within the four major MPs. Figure 3a divides the EM (or NM) population into five distinct sub-categories based on AS from 1 to 2 and the genotype responsible for conferring that AS.

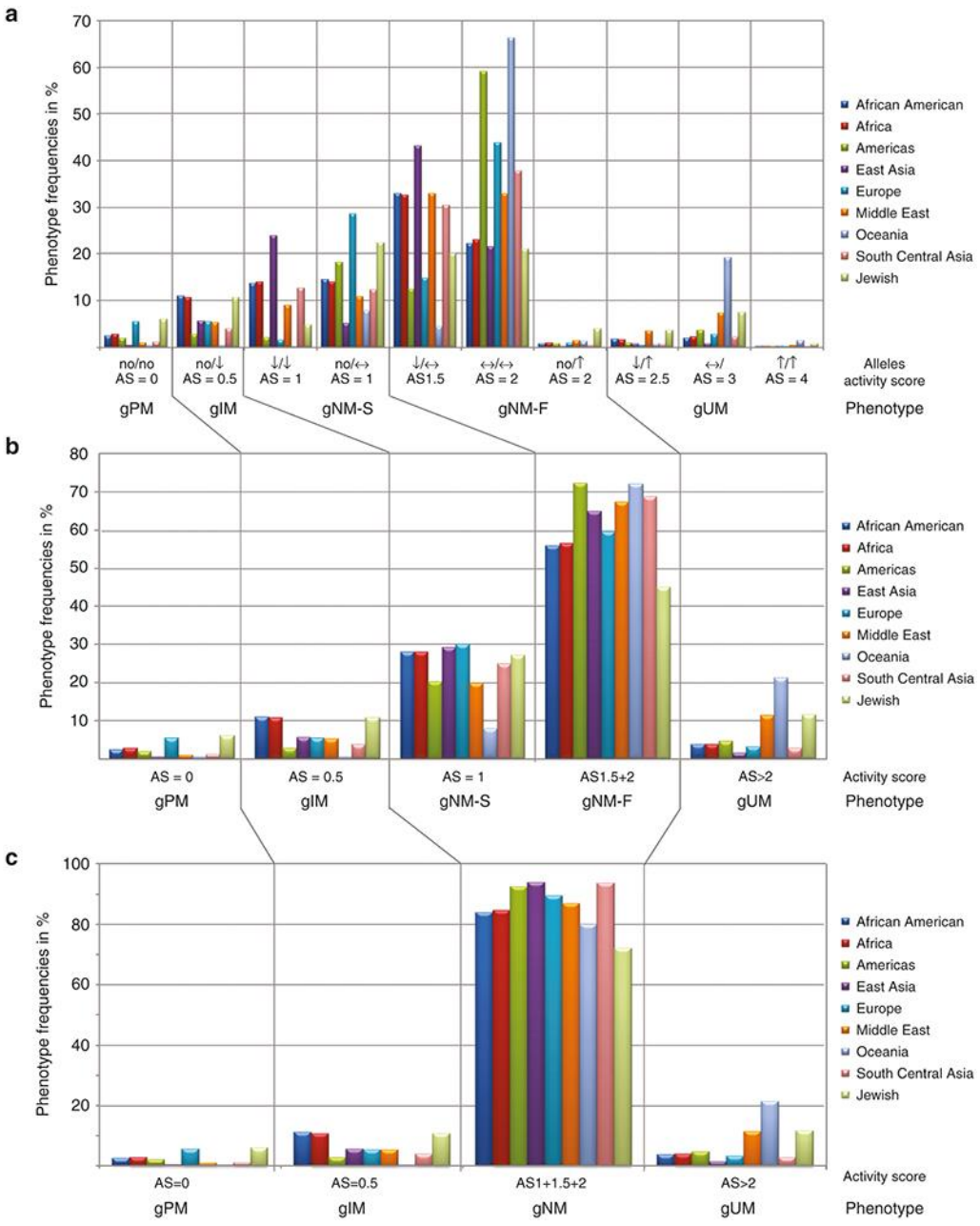

Figure 3. CYP2D6 phenotype prediction from genotype data (image borrowed from Gaedigk, *et al*. 2016. An activity score (AS) was assigned to each genotype (no, ↓, ↔, and ↑ indicate genotypes with no-, decreased-, normal-, and/or increased-function allele combinations, respectively). Panel A shows average frequencies for the different allele combinations and their respective phenotype classifications into poor (gPM), intermediate (gIM), normal-slow (gNM-S), normal-fast (gNM-F), and ultrarapid (gUM) metabolizer groups. The prefix "g" indicates that the phenotype is predicted from genotype. For panel B, genotypes giving rise to AS = 1 or AS = 2 were grouped as indicated. Panel C depicts the translation of genotype or AS into phenotype according to the classification used in Clinical Pharmacogenetics Implementation Consortium guidelines. Note that genotypes falling into the AS = 1 group are inconsistently classified as gIM or gNM throughout the literature.

While CYP2D6 plays a substantial role in opiate metabolism, SNPs in other genes can further define metabolizer status (Figure 4; Diatchenko, *et al.* 2005; Lam, *et al.* 2014; Bastami, *et al.* 2014; Baber, *et al.* 2015). The personalized medicine community has more recently been investigating genetic variability of trans-acting metabolic proteins, in particular those implicated in analgesic response, opiate metabolism, and addiction (Rakvåg, *et al.* 2005; Fujita, *et al.* 2010;Yuferov, *et al.* 2010; Crist and Berrettini 2013;Lam, et al. 2014; Baber, et al. 2015; Bastami, *et al.* 2014; Altar, *et al.* 2015). These additional genes of interest encode opioid receptor mu 1 (OPRM1; mu opioid receptor 1), uridine diphosphate glucuronosyltransferase family 1 polypeptide B7 (UGT2B7), adenosine triphosphate (ATP) binding cassette subfamily B number 1 (ABCB1; p-glycoprotein; multidrug resistance protein 1), and catechol-O-methyltransferase (COMT). OPRM1 serves as the primary action site for commonly used opioids and morphine, a common primary metabolite. UGT2B7 converts morphine to morphine-6-glucuronide (M6G); these two compounds are the primary cause of the analgesic effect of opiates. *ABCB1* encodes p-glycoprotein, a membrane-associated transporter responsible for the efflux of morphine from the brain, gastrointestinal tract, kidneys, and liver. Finally, COMT interacts with the opioid receptor mechanism and modulates pain response through catecholamine breakdown. Polymorphisms within these genes have been demonstrated to impact opiate metabolism by altering the performance of their protein products (Table 3) (Lam, *et al.* 2014; Baber, *et al.* 2015). Although considerably less variable than *CYP2D6* based on currently employed methodologies, SNPs within *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* provide additional genetic information on how various aspects of opiate metabolism occur within the body and the phenotypic variability in those processes.

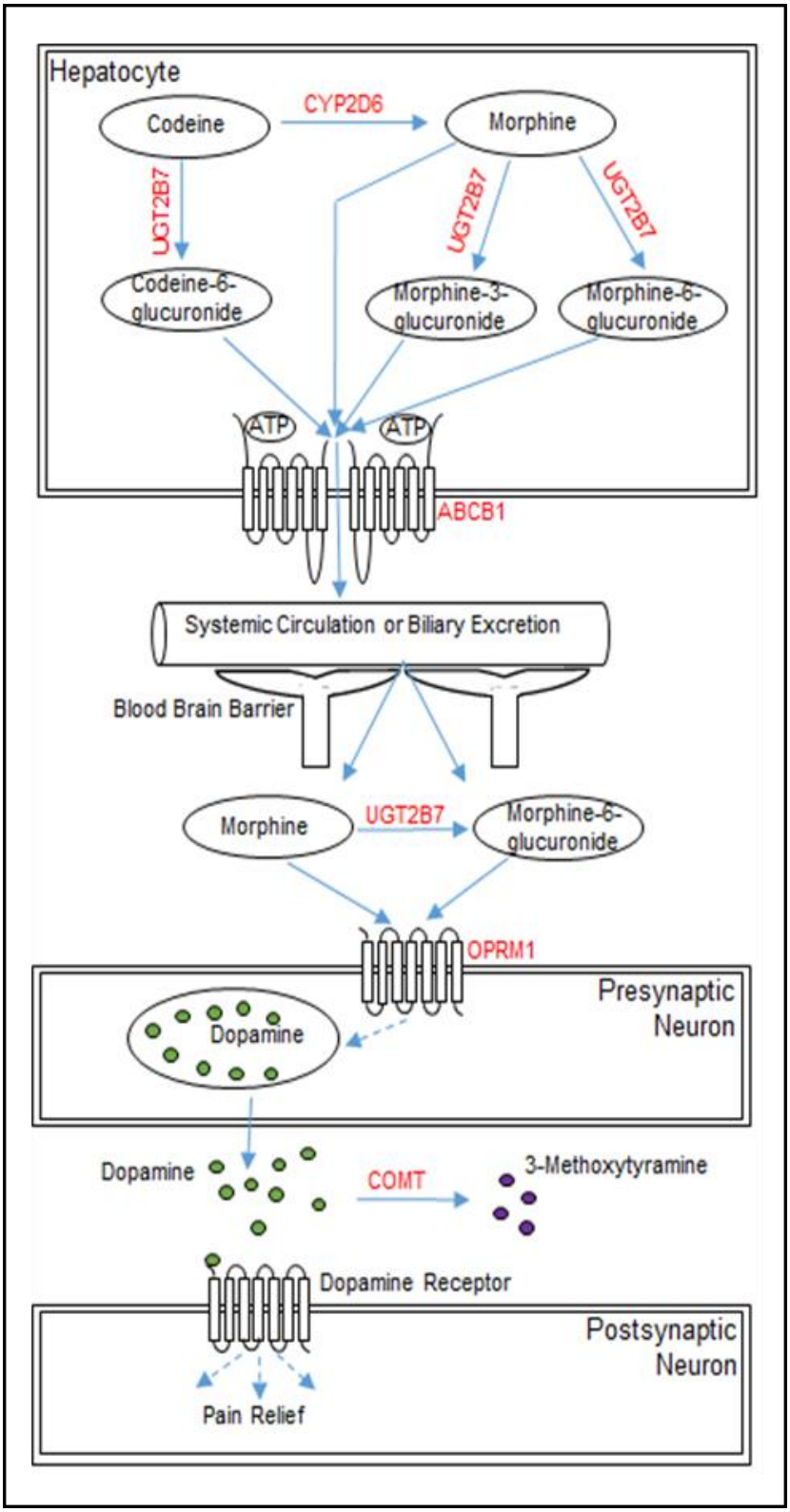

Figure 4. Participation of the selected proteins in analgesia production following opiate administration. Codeine is used as an example opiate; proteins of interest are in red text.

Table 3. Commonly typed causal single nucleotide polymorphisms (SNPs) in *CYP2D6*, *OPRM1*, *UGT2B7*, *ABCB1*, and *COMT* (Diatchenko, *et al.* 2005; Lam, *et al.* 2014). Many *COMT* SNPs are not independently associated with variable enzyme activity, but haplotypes of multiple SNPs in this gene have shown positive linear correlations with enzyme activity. The *CYP2D6* SNPs are a representative sampling of those responsible for conferring the four major metabolizer phenotypes; asterisks indicate *CYP2D6* star (*) alleles.

Gene	SNP rs Number	Enzyme Activity
CYP2D6	-	*1A, Wild type, considered fully functional
	rs16947, rs1135840	*2D, Normal function except when duplicated
	rs35742686, rs1135824	*3A, Nonfunctional, frameshift mutation
	rs3892097, rs28371733	*4, Nonfunctional, splicing defect
	-	*5, Nonfunctional, complete gene deletion
	rs5030655	*6, Nonfunctional, frameshift mutation
	rs5030656	*9, Partially functional
	rs1065852	*10, Partially functional
	rs28371706, rs16947	*17, Partially functional
OPRM1	rs1799971	Decreased
UGT2B7	rs7439366	Increased
	rs62298861	Increased
ABCB1	rs2229109	Unsure
	rs1128503	Decreased
	rs2032582	Decreased
	rs1045642	Decreased
COMT	rs4633	Not independently associated with activity
	rs4818	Not independently associated with activity
	rs4680	Decreased
	rs2239393	Not independently associated with activity
	rs165728	Not independently associated with activity
	rs165599	Not independently associated with activity

Phase II metabolism also occurs in the liver and is characterized by additional chemical reactions, such as glucuronidation, acetylation, and sulfation, that further increase the hydrophillicity of toxins and facilitate their distribution and/or excretion from the body in the urine or feces (e.g., hormones are readily glucuronidated to minimize the energy required to distribute them throughout the body). The UGT super-family is involved in phase II drug metabolizing glucuronidation reactions which increase the polarity of xenobiotics and

endogenous toxins by conjugating to them the glucuronic acid moiety of uridine diphosphate glucuronic acids. The resulting glucuronic acids are more easily excreted from the body due to increased solubility (Guillemette 2003). Studies of the UGT super-family reveal its involvement in approximately 35% of all drugs which undergo phase II metabolism (Evans and Relling 1999). *UGT2B7* is found on chromosome four, contains six exons, encodes one specific UGT enzyme found mostly in the brain, pancreas, lungs, gastro-intestinal tract, mammary glands, and liver, and is often recognized for its broad substrate specificity. The polymorphic nature of this enzyme was described initially by Ritter, *et al*. (1990), who performed the original protein purification and amino acid sequence prediction. Saeki, *et al.* (2004) identified twenty-one polymorphisms within the gene region of Japanese individuals, relative to the reported sequence by Ritter, *et al.* (1990), which led to characterization of four distinct *UGT2B7* * alleles (*1 through *4) and a number of distinct subtypes (*1a-*1k, *2a-2g, *3, and *4). Functional characterization of * alleles has shown that genotypes containing *2 produce glucuronic acid metabolites at higher concentrations than the *1 wild type, though most studies show that concentrations remain within safe therapeutic windows for a number of drugs (Saeki, *et al.* 2004; Chung, *et al.* 2008; Du, *et al.* 2016; Vandenbossche, *et al.* 2014). Conversely, Sawyer, *et al.* (2003) showed that *1/*2 heterozygotes displayed the highest glucuronidation activity in terms of morphine metabolism. *UGT2B7**3 and *4 are characterized by the A71S and D398N amino acid changes, respectively, and show reduced glucuronidation activity (Wang, *et al.* 2011; Yuan, *et al.* 2015).

ABCB1 encodes p-glycoprotein (also called multidrug resistant protein 1, MDR1), a transporter containing two homologous halves, each with six transmembrane domains (Figure 5) (Hodges, *et al.* 2011). The protein is an ATP-dependent translocator capable of performing

excretory and protective roles within the body by controlling drug efflux from certain tissues (e.g., limits access to the brain via the blood-brain barrier). *ABCB1* is found on chromosome seven and contains 29 exons, two of which are untranslated (Bodor, *et al.* 2005). Three important inter-ethnically variable polymorphisms have been identified within the gene, 1236T>C (rs1128503), 2677 T>G/A (rs2032582), and 3435T>C (rs1045642), but the literature remains inconclusive regarding phenotypic impact of one allele over another (Mathijssen, *et al.* 2003; Schwab, *et al.* 2003; Wang, *et al.* 2005; Leschziner, *et al.* 2007; Zhang, *et al.* 2008; Schaich, *et al.* 2009). Initially studied independently, these three SNPs exhibit high linkage disequilibrium (LD) and are inherited as a haplotype, frequently found in the CGC or TTT form in most populations (Hodges, *et al.* 2011). The four *ABCB1 ** alleles are defined relative to the CGC haplotype (*1); however, their use in the literature is inconsistent. For example, Kim, *et al.* (2001) define *ABCB1**2 as the TTT form while Kroetz, *et al*. (2003) defines the same * allele as the CGT form. Pharmacogenomics. Knowledge. Implementation. (PharmGKB) defines them as *ABCB1**1-CGC, *2-CGT, and *13-TTT (PharmGKB). Barratt, *et al*. (2012) demonstrated that individuals harboring the TTT haplotype required only 62% of the methadone required by individuals with other haplotypes.

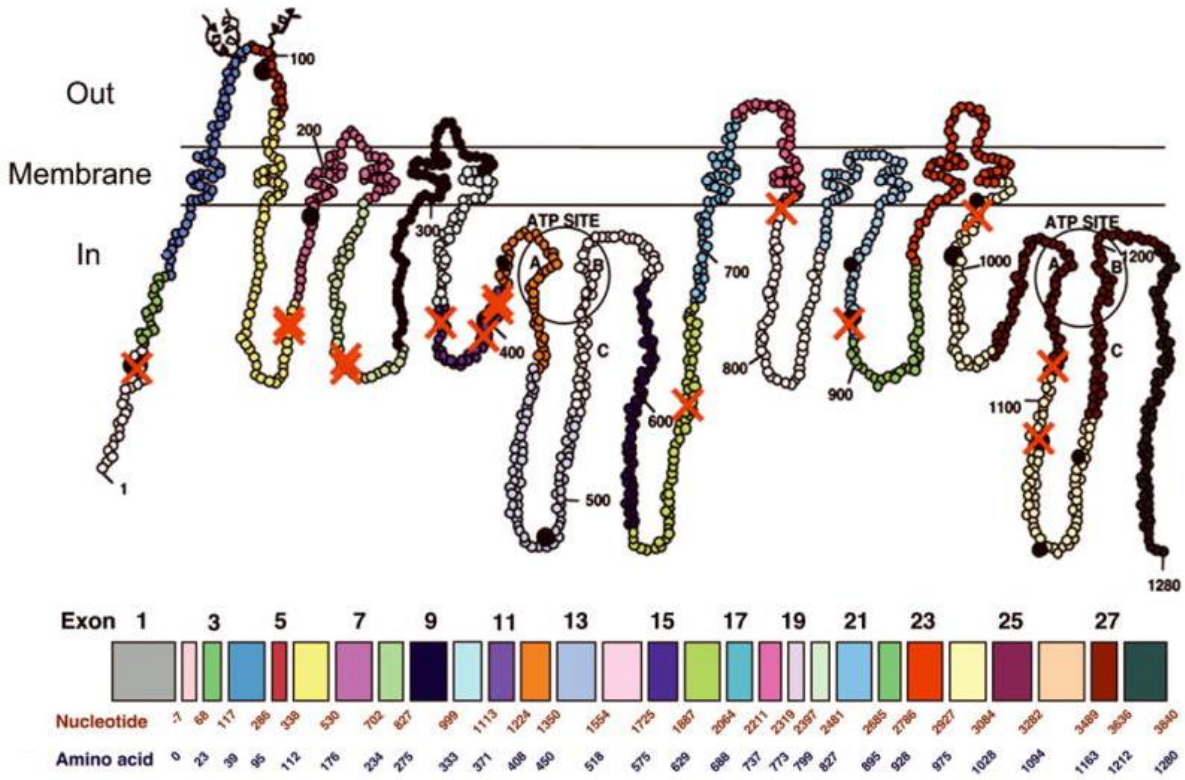

Figure 5. Two-dimensional structure of P-glycoprotein (P-gp) and corresponding representative SNP locations within the *ABCB1* exonic region of the American population. This figure illustrates the approximate locations of amino acid changes along the P-gp protein resulting from non-synonymous polymorphisms. A red "X" marks the approximate location of each polymorphism identified by Kimchi-Sarfaty, *et al.* (2007); black dots represent the approximate locations of common amino acid changes previously reported in P-gp; exons 1-28 are labeled by color and nucleotide length. Image borrowed from Kimchi-Sarfaty, *et al.* (2007).

Opioid receptors (OPRs) are part of the G-protein coupled receptor super-family which activate downstream signaling pathways through interaction with heterotrimeric G-proteins (Waldhoer, *et al.* 2004). OPRM1 consists of seven transmembrane domains (Figure 6), three intra- and extra-cellular domains, and an extracellular N-terminus encoded by a gene containing 15 total exons (Waldoeher, *et al.* 2004). Despite the total number of exons, each transcript from *OPRM1* contains only four exons. The receptor is responsible for binding natural or synthetic opioid agonists and propagating analgesia. *OPRM1* spans approximately

200kb of chromosome 6, which is highly homologous with other OPRs (Diatchenko, *et al.* 2011). *OPRM1* is quite polymorphic but is not defined using the * allele designation as is used for *CYP2D6*, *UGT2B7*, and *ABCB1*. Approximately 3,324 polymorphisms have been identified along the *OPRM1* gene region, most of which have frequencies below 1%. The most common SNP is A118G (rs1799971) which causes an aspartate to asparagine amino acid change at position 40 of the extracellular receptor region, resulting in poor receptor glycosylation and decreased opioid potency (Campa, *et al.* 2008; Ting and Schug 2016). This variant is found most frequently in Asian populations (nearly 0.50) and is substantially less common in Caucasians (frequency ranging from 0.08-0.17) (Janicki 2013). Studies of the phenotypic impact of low frequency polymorphisms (less than 0.05) are limited.

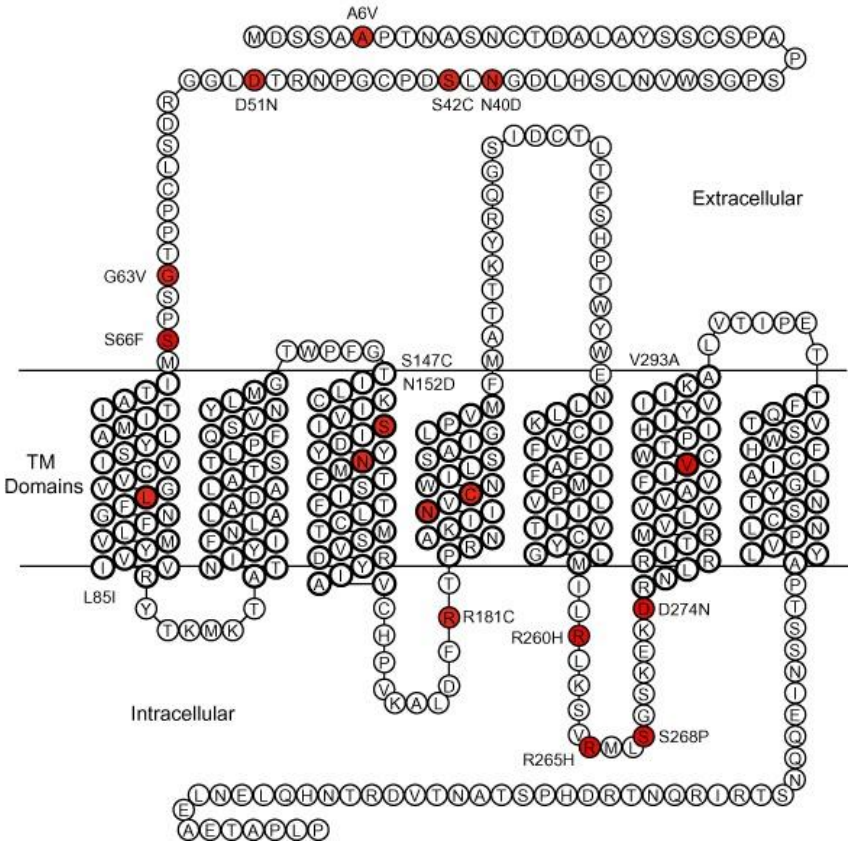

Figure 6. Naturally occurring, non-synonymous OPRM1 variants reported, and their position on the μ-opioid receptor protein. Residues where an amino acid exchange occurs are indicated in red. Image borrowed from Knapman and Connor (2014).

The *COMT* locus resides on chromosome 22 and contains eight exons which encode the COMT enzyme responsible for metabolizing and inactivating catecholamines such as dopamine, noradrenaline, and adrenaline and regulating their propagation through synapses of the brain (Janicki 2013). Due to its responsibility of moderating analgesia and feel-good sensations, this enzyme has been a primary target for investigating underlying genetic factors associated with pain management and psychiatry (Diatchenko, *et al.* 2005; Webster 2008; Schacht 2016). *COMT* is polymorphic, but like *OPRM1*, is not defined using the * allele designation even though the benefits of a more standardized allele nomenclature have been suggested and demonstrated in other pharmacogenes (Diatchenko*; et al.* 2005; Handoko, *et al.* 2005). The most widely studied polymorphism in the gene region is G472A (rs4680 or rs165688) which causes the non-synonymous valine to methionine amino acid substitution at position 158 and a 3- to 4-fold decrease in COMT activity (Zubieta, *et al.* 2003; Ross, *et al.* 2008). Homozygous AA individuals have been shown to have higher ratings of pain than individuals with the AG or GG genotypes (Lotta, *et al.* 1995; Zubieta, *et al.* 2003; Rakvåg, *et al.* 2005; Webster 2008). Exploration of non-exonic regions of the gene also has shown positive linear correlation with certain diseases (e.g., schizophrenia); however, the collective group of SNPs has not been associated with brain expression levels in a reproducible manner (Bray, *et al.* 2003; Chen, *et al.* 2004; Christoffersen, *et al.* 2016).

The polymorphic natures of CYP2D6, UGT2B7, ABCB1, OPRM1, and COMT are relatively well understood on the individual-gene level in various population groups (Cusato, *et al.* 2016; Gaedigk, *et al.* 2016; Sridharan, *et al.* 2016; Sutiman, *et al.* 2016; and Zahari, *et al.* 2016). However, the combined and pairwise predictive power within their gene regions has scarcely been described in healthy or affected populations. In a group of psychiatric patients,

Altar, *et al.* (2015) demonstrated that a combinatorial pharmacogenetics approach using allelic variations from four genes can guide antidepressant selection and predict antidepressant efficacy better than each individual gene alone. Therefore, it is reasonable to explore the relationship between other genes and develop combinatorial pharmacogenetic predictive models for drug efficacy and patient response. Bastami, *et al.* (2014), Lam, *et al.* (2014), and Baber, *et al.* (2015) studied *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* in various combinations in relation to codeine-based treatment and reported certain causal SNPs and their allele frequencies. While informative, these studies are based on cohorts selected for the presence of specific characteristics (e.g., abdominal hysterectomy (Bastami, *et al.* 2014), drug related deaths with codeine as a contributing factor (Lam, *et al.* 2014), and women who delivered a child via cesarean-section (Baber, *et al.* 2015)) with no mention of population-affinity information as a contributing factor to variable metabolic activity resulting from allele frequency differences between/among populations. As a result, false positive associations between genotype and resulting phenotype may arise. These studies provided summary statistics for select polymorphisms in each gene but lacked the association between/among genes required for a multigenic approach to personalized medicine. Ideally, study subjects would belong to a defined population and be positively selected for the desired phenotype. Due to the presence of relatively recent founder effects and resulting minimal degree of population substructure, populations such as Finns and Ashkenazi Jews may be enriched for rare mutations relative to the overall European population (Peltonen, *et al.* 1999; Kere 2001; Palo, *et al.* 2009; Lim, *et al.* 2014).

CYP2D6 is highly polymorphic and there is significant variation in allele frequencies within and among populations. While exhibiting less overall variation than *CYP2D6*, the

UGT2B7, *ABCB1*, *OPRM1*, and *COMT* pharmacogenes also are phenotypically relevant. Genetic variation at these loci may affect protein activity and/or structure but the extent of this variation cannot be captured fully by existing structured SNP panels. Genome-wide association studies (GWAS) and SNP arrays rely on targeted identification or typing of known causal SNPs that have been shown to affect metabolic activity or those that are candidate enzyme-altering sites. These assays lack the ability to comprehensively identify SNPs, and especially previously undescribed SNPs, within a gene (Koch 2004). Extensive variation combined with targeted approaches, that may not detect full variation, leads to less effective genotyping in the event that an individual(s) contains an allele characterized by absence of the gene (*CYP2D6**5) or a rare variant not previously reported. Additionally, GWAS and SNP arrays are limited by the potential need to resequence targets to confirm allele calls (Koch 2004). Massively parallel sequencing (MPS) offers a considerable advantage over the GWAS and SNP array approaches due to a lower biased and robust generation of large amounts of sequence data, with reliable read depth (i.e., the number of times a single region of DNA is sequenced) using minimal input amounts of DNA. GWAS using SNP array data suffer from genotype ascertainment bias due to the methods of SNP inclusion during assay development (Lachance and Tishkoff 2013). These loci tend to be selected from existing DNA sequence data and may represent loci with relatively high global minor allele frequencies (e.g., 0.01) to ensure representation of a majority of global genetic variation. However, by targeting only loci with high global frequency, the assay lacks the ability to directly genotype loci that may be enriched for in the rare ancestral or diseased population in question. Use of MPS in pharmacogenetic studies enables relatively reduced genotype ascertainment bias and analysis of many targeted genomic regions (full-gene, distant regulatory elements, multiple genes, etc.) simultaneously (Xin and Wang, 2003;

Saeki, *et al.* 2004; Wang, *et al.* 2014; Ge, *et al.* 2016; Modaresi-Nejad, *et al.* 2015; Wang, *et al.* 2015).

There are many MPS technologies and chemistries commercially available (Figure 7) but two of the most commonly employed MPS instruments rely on sequencing-by-synthesis of clonally amplified DNA using two distinct chemistries: reversible terminators and semiconductor pH detection (Lysholm, *et al.* 2011). The massively parallel nature of MPS is achieved by clonal amplification of relatively small target DNA fragments on either a flow cell or bead within a micelle. The target DNA hybridizes to an oligo-covered surface and serves as a template for thousands of PCRs. This process results in a "lawn" of small clusters (MiSeq chemistry) or micro-beads coated in identical/clonal DNA clusters. Sequencing with the Illumina MiSeq Desktop Sequencer utilizes fluorescently-labeled reversible terminator deoxynucleotide triphosphates (dNTPs) (Goodwin, *et al.* 2016); this chemistry is employed for data generation in this dissertation. The reversible terminator ensures that only one dNTP is added to the growing chain during every flow of pooled dNTPs across the flow cell. After fluorescent signal detection via charge-coupled device (CCD) cameras, the terminator is removed and the next flow is performed, adding one additional dNTP. The process is continued over several hundred cycles and many images of the fluorescently-labeled cloned fragments on a flow cell are collected over the run time. In contrast, the chemistry employed on the Ion Personal Genome Machine (PGM) and Ion S5 does not make use of optical signals, thereby overcoming any optic and fluorescent dye artifacts. The PGM and S5 sequence target DNA molecules and detect each dNTP incorporated into the growing chain using ion semiconductors (i.e., a miniature pH meter). The four dNTPs are flowed sequentially across the semiconductor chip and for each dNTP incorporated into the newly synthesized strand, a proton (H^+) is

released into solution (Lysholm, *et al.* 2011; Levy and Myers 2016). The change in pH that occurs following proton release is detected by a sensing layer of the semiconductor chip and is recorded in a flowgram. Terminator moieties are not used for this chemistry so multiple identical dNTPs (i.e., homopolymeric stretches of more than one cytosine) can be added during the same flow (Quail, *et al.* 2012; Levy and Myers 2016). For this chemistry, the magnitude of signal intensity (decrease in pH) is proportional to the number of dNTPs incorporated during a single flow.

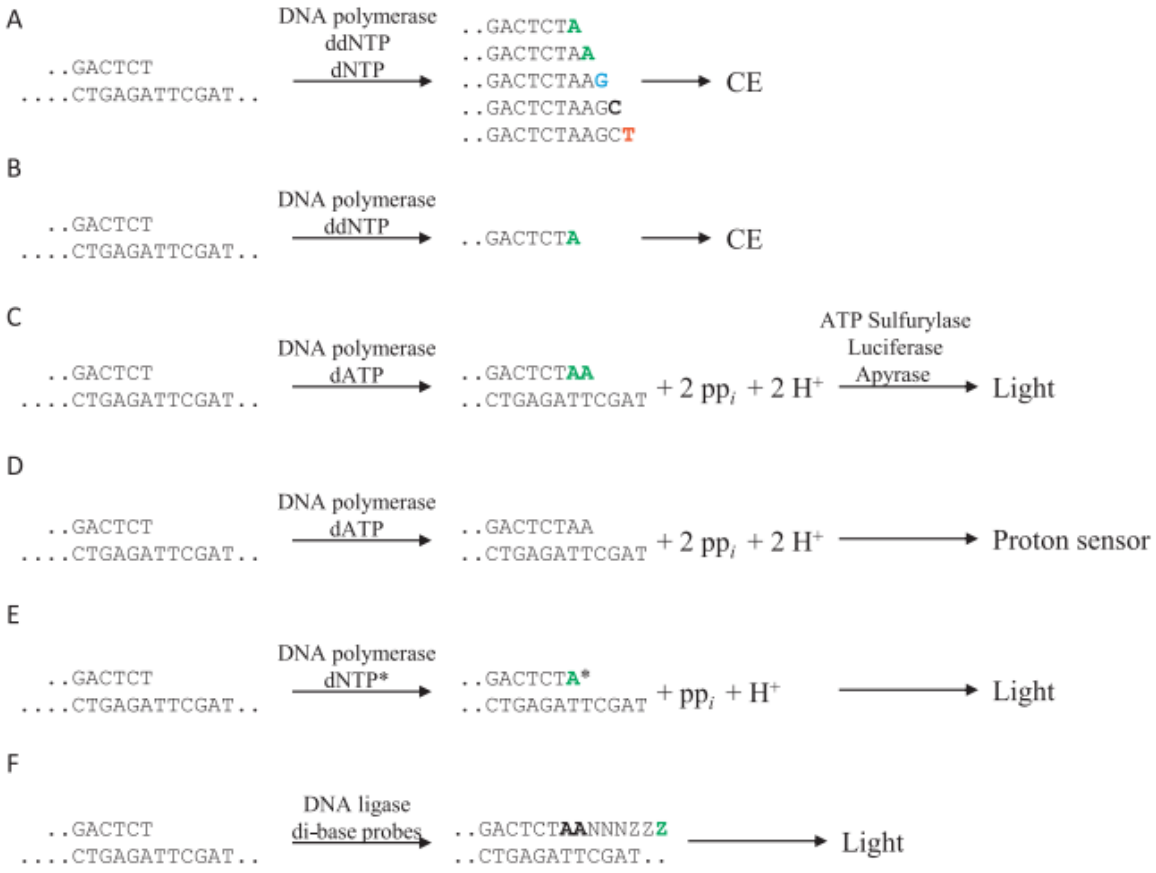

Figure 7. Sequencing methods. (A) Traditional DNA sequencing method used for decades. DNA is synthesized in the presence of fluorescently labeled ddNTPs. The differently sized fragments are separated by CE and the sequence of fluorescently labeled nucleotides is detected by a camera. (B) Single base extension. The SBE primers are extended with a fluorescently labeled ddNTP complimentary to the nucleotide in the SNP locus. The extended SBE primers are detected by CE. (C) Pyrosequencing (i.e., another method similar to the ion semiconductor chemistry). Nucleotides are added sequentially to the sequencing reaction. Incorporation of one or more nucleotide(s) to the growing strand release one or more pyrophosphate(s) that are used in secondary enzymatic reactions to generate light. The light emission is detected by a camera. (D) Semi-conductor sequencing. Nucleotides are added sequentially to the sequencing reaction. Incorporation of one or more nucleotide(s) to the growing strand release one or more hydrogen ion(s) that are detected by an ion sensor. (E) Sequencing by synthesis. DNA synthesis is performed with fluorescently labeled dNTPs with reversible 30 terminators (marked by an asterisk). Each addition of a nucleotide to the growing strand is detected by a camera. The terminator is chemically removed allowing for the next nucleotide to be incorporated. (F) Sequencing by ligation. The sequencing primer is hybridized to the target DNA and four sets of four fluorescently labeled di-base probes (all the 16 possible combinations) are added sequentially to the ligase reaction. Successful ligation of a probe to the sequencing primer is detected by a camera. The probes are cleaved (between the N and Z nucleotides) and another cycle of ligations can begin. Image borrowed from Børsting and Morling 2015.

Application of pharmacogenetic information relies on haplotype interrogation, as described for the *CYP2D6* * allele nomenclature. Making haplotype inferences requires computational and/or observational phase of genetic data (Figure 8). Phased genetic data not only identify the two alleles within a genotype but also contain information about the parental origin of alleles across multiple genotypes. In Figure 8, the order of alleles within the genotype in red are changed to generate phased data; the resulting haplotypes, AABABAA and ABBAABA, were inherited from the green and blue parents, respectively. Generating phased data can be achieved computationally (e.g., algorithmic interpretation of phase) and/or observationally (e.g., long-read DNA sequencing). Computational phasing algorithms utilize dense genotype coverage (i.e., genotyping many SNPs in a relatively small region or across the entire genome) and a reference genome (Browning and Browning 2011). The 1000 Genomes Project (Karolchik, *et al.* 2012; 1000 Genomes Project Consortium, *et al.* 2015) is typically used as a phase reference due to its modest representation of global allele frequency differences. This breadth of global population coverage allows for detection of a relative majority of variation in the human population and subsequently offers a reliable base on which to infer genotype phase. Short-read DNA sequencing is limited in terms of genomic region assembly especially for duplicated and/or repeat regions (Alkan, *et al.* 2011). Computational phase is limited by multiple factors including sample size, degree of sample relatedness, marker density, underlying population substructure, and associated allele frequency differences (Kong, *et al.* 2008; Marchini, *et al.* 2006). Observational phase via long-read DNA sequencing, for example, provides a considerable advantage over computational phase and short read DNA sequencing because alleles at adjacent SNPs can be sequenced in the same read. Figure 9 shows this concept with representative short and long reads, using the MiSeq

and MinION as example sequencing platforms, and the SNP loci potentially captured in each read. Using short reads (Figure 9B), relatively few loci with globally frequent alternate alleles (e.g., >0.01 in 1000 Genomes Project; Figure 9A-C loci with substantial abundance of red color) can be captured in the DNA sequence. Relative to MiSeq and S5 sequencing, the longer MinION reads capture variants farther than ~600 bases from one another, such as those in large pharmacogenes. Long-read sequencing platforms, such as the MinION (Oxford Nanopore Technologies) and Single Molecule, Real Time (SMRT) sequencing (Pacific Biosciences of California, Inc.), are theoretically capable of producing continuous DNA reads resulting in comprehensive phased haplotype data (Figure 9C) (Ammar, *et al.* 2015; Goodwin, *et al.* 2016; Ip, *et al.* 2015; Lindberg, *et al.* 2016). These phased haplotypes can then be used to easily infer * allele designation and resulting metabolizer phenotype. Unfortunately, these long/continuous-read platforms are largely still under development (SMRT and MinION) and have error rates and read quality that are inappropriate for clinical diagnostics using pharmacogene targets (MinION).

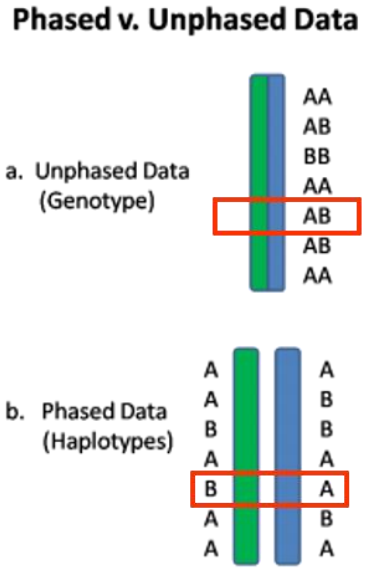

Figure 8. Examples of raw, unphased genotype data (a) and the same data after computational and/or observational phased genotype information.

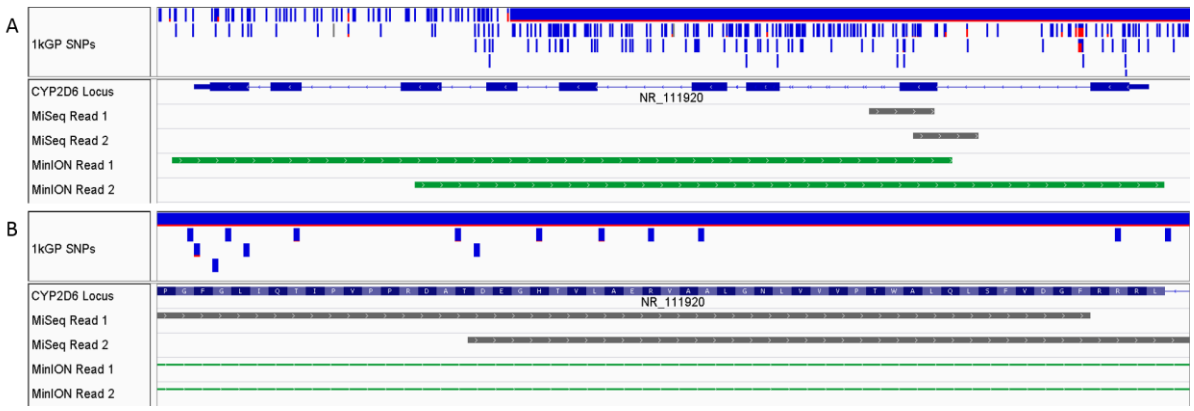

Figure 9. Integrative Genomics Viewer software screenshot of the *CYP2D6* locus (A) and a zoomed-in portion of exon 2 (B). The top track in each panel shows the observed 1000 Genomes Project (1kGP) SNPs, INDELs, and/or gene conversions with blue and red boxes indicating the relative frequency of the reference and alternate allele conditions in 2,504 1kGP individuals ($N_{alleles}$ = 5,008). The second track contains the CYP2D6 locus (A) or the amino acid string sequence (B). Tracks 3 and 4 contain horizontal gray bars representing short DNA reads using the MiSeq as a representative short-read chemistry; track 5 and 6 contain horizontal green bars representing long DNA reads using the MinION as a representative long-read chemistry.

In ante- and post-mortem patients, genetic characterization of the highly polymorphic *CYP2D6* locus has helped make inferences regarding appropriate dosage of prescription opioid-based medications and provided insight into CoD and/or MoD. However, *CYP2D6* alone is not a sole biomarker for prediction of metabolizer phenotype and findings from additional relevant loci can be especially meaningful for the healthcare, psychiatric, and forensic genetics communities. For example, individuals with normal CYP2D6 activity may experience adverse effects following drug administration due to over- or under-active trans-acting proteins. To date, however, there are no studies utilizing an extended opiate pathway to infer phenotypic effect with more comprehensive genetic profiles of patients. Additionally, need for haplotype phase is a large limitation to cost-effective clinical application of pharmacogenetic data. This dissertation aims to understand the relationship between genetic variation in genes encoding highly variable, metabolically-relevant proteins within the same metabolic pathway and evaluate the predictive capabilities of a pathway-driven

pharmacogenetic profile under the **global hypothesis that comprehensive (full-gene) and combinatorial (multi-gene) pharmacogenetic profiles of select genes in the opiate metabolism and response pathways can be used to better predict MP of an individual**. This global hypothesis was addressed using two Specific Aims: (1) define a comprehensive list of opiate metabolism and response gene polymorphisms in unexposed populations and (2) evaluate the predictive capability of polymorphisms on deceased tramadol-exposed Finns.

Specific Aim 1 has three sub-Aims: (a) assess the global genetic diversity of opiate metabolism and response genes in healthy cohorts, (b) perform full-gene haplotype analyses of *CYP2D6*, and (c) perform full-gene haplotype analyses of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*. Using publically available sequence data from the 1000 Genomes Project (N ~ 2,500) and variant effect prediction algorithms, thousands of polymorphisms in the five genes of interest were characterized. The phased nature of the 1000 Genomes Project genotypes was exploited to perform haplotype analyses for all five genes. These data identified key relationships between individual SNPs and/or haplotypes in major global population groups.

Specific Aim 2 was divided into two sub-Aims: (a) predict MP of deceased Finns using *CYP2D6* alone and (b) perform combinatorial modeling of MP in the same cohort of deceased Finns. Here, machine learning algorithms were used to predict MP of 208 deceased tramadol-exposed Finns. The resulting predictive model will be an invaluable contribution to the personalized medicine, pharmacogenetics, and molecular autopsy communities because it can accurately predict MP categorical variables and potentially guide clinical use and prescription of the synthetic opioid agonist tramadol better than current methods of 1) single gene genetic predictions of phenotypic response and/or 2) patient response monitoring and adjusting drug dosage accordingly.

References

Please refer to the reference list after Chapter 8 for all references cited within Chapters 1 and 8.

PART 2

ELUCIDATION OF THE GENETIC VARIATION OF OPIATE METABOLISM AND RESPONSE GENES IN WORLD POPULATIONS

CHAPTER 2

Global Genetic Variation of Select Opiate Metabolism Genes in Self-Reported Healthy Individuals

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Abstract

CYP2D6 is a pharmacogene encoding an enzyme impacting poor, intermediate, extensive, and ultrarapid phase I metabolism of many marketed drugs. The pharmacogenetics of opiate drug metabolism is particularly interesting due to the relatively high incidence of addiction and overdose. Recently, trans-acting opiate metabolism and analgesic response enzymes (UGT2B7, ABCB1, OPRM1, and COMT) have been incorporated into pharmacogenetic studies to generate more comprehensive metabolic profiles of patients. With use of massively parallel sequencing, it is possible to identify additional polymorphisms that fine tune, or redefine, previous pharmacogenetic findings, which typically rely on targeted approaches. The 1000 Genomes Project data were analyzed to describe population genetic variation and statistics for these five genes in self-reported healthy individuals in five global super- and 26 sub-populations. Findings on the variation of these genes in various populations expand baseline understanding of pharmacogenetically relevant polymorphisms for future studies of affected cohorts.

Introduction

The cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) is a clinically significant enzyme responsible for approximately 30% of phase I metabolism of approximately 25% of marketed drugs.[1,2] Of particular interest is the enzyme's role in the conversion of pain medications to active metabolites, namely morphine.[3-5] The highly polymorphic nature of *CYP2D6* results in various metabolizer phenotypes (MP; poor [PM], intermediate [IM], extensive [EM], and ultra-rapid [UM]),[6-8] typically inferred from the diplotype of *CYP2D6* star (*) alleles (a haplotype of one or more polymorphisms along the length of the gene),[9] that have been associated with lack of therapeutic response, idiosyncratic responses, or even death.[10-12]

Comprehensive pharmacogenetic studies have shown that single nucleotide polymorphisms (SNPs) in other opiate metabolism and pain relief pathway genes also confer variable degrees of enzyme activity.[13-17] These additional genes of interest include uridine diphosphate glucuronosyltransferase, family 1, polypeptide B7 (*UGT2B7*), adenosine triphosphate (ATP) binding cassette, subfamily B, number 1 (*ABCB1*), opioid receptor mu 1 (*OPRM1*), and catechol-O-methyltransferase (*COMT*). *UGT2B7* encodes an enzyme that converts morphine to morphine-6-glucuronide; these two compounds are the primary cause of the analgesic effect of opiates. *ABCB1* encodes p-glycoprotein (or multidrug resistance protein 1; MDR1), a membrane-associated transporter responsible for the efflux of morphine from various organs. *OPRM1* encodes the primary receptor for signal transduction of the analgesic response. Lastly, *COMT* encodes a protein that interacts with the opioid receptor mechanism to modulate pain response through catecholamine breakdown. Polymorphisms within these genes can impact opiate metabolism by altering the performance of their protein products,

leading to non-effective treatment or clinical complications following opiate medication administration.[14,15]

Previous pharmacogenetic studies have focused on identifying common causal polymorphisms using genome-wide association studies (GWAS) (targeted SNP arrays and targeted massively parallel sequencing (MPS)) to determine the MP of ante- and post-mortem patients.[17-19] While valuable, these methods fail to assess polymorphisms comprehensively in a target sequence on the individual and population levels. Additionally, they hinder discovery of novel polymorphisms that may provide greater insight into phenotypic variability and subsequent resequencing of target loci may be required for confirmation of allele calls.[20] MPS of the full gene region may reveal additional variants, with reliable depth of coverage, which refine the current working knowledge of *CYP2D6* * alleles, for example, those which introduce premature stop codons before the defining polymorphisms of a * allele.

Pharmacogenetic population studies often control for presence of disease phenotype while placing less emphasis on demography and population substructure as contributing factors to variable allele distribution which may confer different metabolic profiles in populations.[10,21,22] Consequently, false positive associations may arise regarding the relationship between genotype and MP.[23]

Herein, an *in silico* study of the complete gene sequences of *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, *COMT*, and their respective promoter regions was performed to identify novel SNPs, insertion/deletion (INDEL) polymorphisms, and copy number variants (CNVs), define baseline population genetic variation, and identify potential phenotypic variability in opiate metabolism and pain relief. A summary is provided of population statistics, variant effect predictions, and clustering of super- and sub-populations based on SNPs, INDELs, and

CNVs in five genes whose protein products are associated with opiate metabolism. Finally, the distribution of *CYP2D6* * alleles in five super-populations and 26 sub-populations is shown which provides additional information regarding variability within the population of EMs.[24] These findings serve as substantial population genetic data for healthy cohorts which may guide the pharmacogenetics community towards studies involving comprehensive genetic screening.

Materials and Methods

Gene and promoter regions were identified using GeneCards® Human Gene Database.[25] Genotype data were obtained from 2,504 unrelated healthy individuals whose sequence data were downloaded from Phase 3 of the 1000 Genomes Project using the University of California Santa Cruz (UCSC) Table Browser[26,27] and the appropriate hg19 reference genome coordinates for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, *COMT*, and their respective promoter regions. The 1000 Genomes Project reports data with sequence depth of coverage $\geq$ 4X.

Population genetic summary statistics and statistical tests were performed for five super-populations (African [AFR], Ad Mixed American [AMR], East Asian [EAS], European [EUR], and South Asian [SAS]) and 26 sub-population (Supplemental Table 1). Allele frequencies, observed and expected heterozygosity calculations, and tests for departures from Hardy-Weinberg equilibrium (HWE) and pairwise linkage disequilibrium (LD, assuming HWE) were performed using Genetic Data Analysis Software (GDA).[28] Allele frequency 95% confidence intervals were estimated using the normal approximation to the binomial method. Tests for HWE departures and pairwise LD were performed for super- and sub-populations

due to the potential for loci meeting HWE expectations or pairwise loci linkage equilibrium in sub-populations but deviating from these expectations when pooled into super-populations.[29] Due to the size of *ABCB1* and *OPRM1* and the number of polymorphisms within each gene, computation constraints with software memory were experienced while performing all tests for pairwise LD between these polymorphisms (~17 million and ~23 million pairwise comparisons for *ABCB1* and *OPRM1*, respectively). Consequently, tests for pairwise LD for *ABCB1* and *OPRM1* polymorphisms were performed between HWE-deviating loci and all other loci. Both tests are sensitive to low frequency alleles and focusing on this subset of loci for pairwise LD testing, under the assumption of HWE, could indicate if the polymorphisms are subject to some selective pressures and/or genotyping errors as a result of the relatively low coverage of 1000 Genomes Project data.[30] Here we use "linkage disequilibrium block" to describe a cluster of polymorphisms with significant deviations from pairwise LD with all other polymorphisms for a gene. Ensembl Variant Predictor (Release 84, March 2016)[31] and Sort Intolerant From Tolerant (SIFT)[32-36] were used to determine SIFT, Polymorphism Phenotyping v2 (PolyPhen-2),[37,38] and Protein Variant Effect Analyzer (PROVEAN)[39-41] variant effect predictions and scores for all identified polymorphisms. Intronic positions within 1 000 bases of an exon were further analyzed using Human Splicing Finder (HSF).[42] Multidimensional scaling (MDS) plots and principal component analysis (PCA) plots were generated in RStudio®.[43] *CYP2D6* * alleles were assigned according to the presence of causal polymorphisms associated with known phenotype[9] and were used to assign activity scores and MP to each individual.[44] Haplotypes producing no amino acid changes and lacking causal intronic polymorphisms were considered *1; haplotypes conferring the combination of R296C and S486T amino acid changes but lacking any other amino acid change and intronic causal

polymorphisms were considered *2. Individuals possessing *CYP2D6** alleles with undetermined effects on activity (*22, *28, and *43, for example), or haplotypes that could not be associated with a * allele, were removed from MP analyses.

Results

CYP2D6

Allele frequencies for 418 polymorphic loci (402 SNPs, 15 INDELs, and one CNV) in the *CYP2D6* region for five super-populations and 26 sub-populations are listed in Supplemental Table 2. The average observed heterozygosity for 26 sub-populations was 0.0341 ± 0.102 with a range of 0.0253 ± 0.0836 (CHS) to 0.0439 ± 0.114 (GWD) (Table 1 and Supplemental Table 3). When pooled, the average super-population observed heterozygosity was 0.0384 ± 0.0980 for AFR, 0.0337 ± 0.102 for AMR, 0.0281 ± 0.0918 for EAS, 0.0359 ± 0.107 for EUR, and 0.0339 ± 0.107 for SAS (Table 1 and Supplemental Table 3). After Bonferroni correction ($p < 0.000120$), one locus in GBR (rs35742686), one locus in EAS (rs374153932), and four loci in AFR (rs78854695, rs28371705, rs28371703, and rs376217512) significantly deviated from HWE, all of which are less than that due to chance alone (i.e., ~21) (Table 2 and Supplemental Table 4).

Table 1. Average super-population and sub-population observed (H_o) and expected (H_e) heterozygosities across 418 *CYP2D6*, 613 *UGT2B7*, 5,986 *ABCB1*, 6,831 *OPRM1*, and 1,007 *COMT* polymorphisms.

Gene	Super-Population	Average H_e	Average H_o	Sub-Population	Average H_e	Average H_o
CYP2D6	AFR	0.0429 ± 0.110	0.0384 ± 0.0980	YRI	0.0417 ± 0.110	0.0365 ± 0.0956
				LWK	0.0435 ± 0.110	0.0386 ± 0.0984
				GWD	0.0433 ± 0.111	0.0440 ± 0.114
				MSL	0.0420 ± 0.109	0.0370 ± 0.0949
				ESN	0.0424 ± 0.111	0.0404 ± 0.107
				ASW	0.0417 ± 0.108	0.0360 ± 0.0956
				ACB	0.0429 ± 0.112	0.0346 ± 0.0895
	AMR	0.0372 ± 0.114	0.0337 ± 0.102	MXL	0.0340 ± 0.105	0.0296 ± 0.0892
				PUR	0.0405 ± 0.120	0.0413 ± 0.127
				CLM	0.0386 ± 0.115	0.0317 ± 0.0922
				PEL	0.0324 ± 0.108	0.0296 ± 0.0983
	EAS	0.0308 ± 0.102	0.0281 ± 0.0918	CHB	0.0310 ± 0.101	0.0310 ± 0.100
				JPT	0.0329 ± 0.109	0.0298 ± 0.0995
				CHS	0.0296 ± 0.0980	0.0253 ± 0.0836
				CDX	0.0288 ± 0.0955	0.0260 ± 0.0843
				KHV	0.0275 ± 0.0910	0.0282 ± 0.0955
	EUR	0.0400 ± 0.121	0.0359 ± 0.107	CEU	0.0410 ± 0.122	0.0353 ± 0.104
				TSI	0.04070 ± 0.123	0.0373 ± 0.112
				FIN	0.0376 ± 0.1160	0.0357 ± 0.111
				GBR	0.0402 ± 0.121	0.0320 ± 0.0949
				IBS	0.0401 ± 0.121	0.0386 ± 0.117
	SAS	0.0374 ± 0.118	0.0339 ± 0.107	GIH	0.0381 ± 0.121	0.0362 ± 0.115
				PJL	0.0340 ± 0.111	0.0333 ± 0.108
				BEB	0.0371 ± 0.1130	0.0312 ± 0.0949
				STU	0.0374 ± 0.119	0.0309 ± 0.0975
				ITU	0.0381 ± 0.121	0.0374 ± 0.119
UGT2B7	AFR	0.0573 ± 0.117	0.0582 ± 0.121	YRI	0.0530 ± 0.109	0.0554 ± 0.115
				LWK	0.0610 ± 0.125	0.0668 ± 0.140
				GWD	0.0524 ± 0.110	0.0503 ± 0.109
				MSL	0.0495 ± 0.103	0.0492 ± 0.105
				ESN	0.0604 ± 0.124	0.0663 ± 0.140
				ASW	0.0605 ± 0.125	0.0681 ± 0.143
				ACB	0.0639 ± 0.134	0.0551 ± 0.115
	AMR	0.0675 ± 0.150	0.0613 ± 0.136	MXL	0.0621 ± 0.140	0.0694 ± 0.158
				PUR	0.0723 ± 0.161	0.0684 ± 0.151
				CLM	0.0741 ± 0.166	0.0653 ± 0.146
				PEL	0.0448 ± 0.105	0.0420 ± 0.104
	EAS	0.0611 ± 0.142	0.0644 ± 0.151	CHB	0.0646 ± 0.150	0.0847 ± 0.200
				JPT	0.0636 ± 0.145	0.0654 ± 0.149
				CHS	0.0605 ± 0.141	0.0698 ± 0.165
				CDX	0.0595 ± 0.139	0.0468 ± 0.111
				KHV	0.0570 ± 0.133	0.0529 ± 0.127
	EUR	0.0741 ± 0.168	0.0777 ± 0.177	CEU	0.0738 ± 0.169	0.0836 ± 0.193
				TSI	0.0745 ± 0.167	0.0834 ± 0.189
				FIN	0.0744 ± 0.168	0.0665 ± 0.150
				GBR	0.0726 ± 0.167	0.0725 ± 0.168
				IBS	0.0746 ± 0.168	0.0814 ± 0.184
	SAS	0.0720 ± 0.164	0.0740 ± 0.170	GIH	0.0727 ± 0.167	0.0744 ± 0.172
				PJL	0.0738 ± 0.165	0.0730 ± 0.165
				BEB	0.0701 ± 0.159	0.0731 ± 0.167
				STU	0.0719 ± 0.165	0.0780 ± 0.181
				ITU	0.0713 ± 0.164	0.0713 ± 0.166

AFR: African; AMR: Ad Mixed American; EAS: East Asian; EUR: European; SAS: South Asian; ACB: African Caribbean in Barbados; ASW: American of African Ancestry in Southwest USA; BEB: Bengali from Bangladesh; CDX: Chinese Dai in Xishuangbanna, China; CEU: Utah Residence with Northern and Western Ancestry; CHB: Han Chinese in Beijing; CHS: Southern Han Chinese; CLM: Colombians from Medellin, Colombia; ESN: Esan in Nigeria; FIN: Finnish in Finland; GBR: British in England and Scotland; GIH: Gujarati Indian from Houston, Texas; GWD: Gambian in Western Divisions in Gambia; IBS: Iberian Population in Spain; ITU: Indian Telugu from the United Kingdom; JPT: Japanese in Tokyo, Japan; KHV: Kinh in Ho Chi Minh City, Vietnam; LWK: Luhya in Webuye, Kenya; MSL: Mende in Sierra Leone; MXL: Mexican Ancestry from Los Angeles, USA; PEL: Peruvians from Lima, Peru; PJL: Punjabi from Lahore, Pakistan; PUR: Puerto Ricans from Puerto Rico; STU: Sri Lankan Tamil from the United Kingdom; TSI: Toscani in Italia; YRI: Yoruba in Ibadan, Nigeria

Table 1 (continued). Average super-population and sub-population observed (H_o) and expected (H_e) heterozygosities across 418 *CYP2D6*, 613 *UGT2B7*, 5,986 *ABCB1*, 6,831 *OPRM1*, and 1,007 *COMT* polymorphisms.

Gene	Super-Population	Average H_e	Average H_o	Sub-Population	Average H_e	Average H_o
ABCB1	AFR	0.0295 ± 0.0872	0.0294 ± 0.0873	YRI	0.0288 ± 0.0884	0.0287 ± 0.0885
				LWK	0.0309 ± 0.0909	0.0300 ± 0.0880
				GWD	0.0283 ± 0.0860	0.0296 ± 0.0914
				MSL	0.0303 ± 0.0875	0.0295 ± 0.0855
				ESN	0.0302 ± 0.0895	0.0300 ± 0.0903
				ASW	0.0279 ± 0.0847	0.0277 ± 0.0853
				ACB	0.0294 ± 0.0877	0.0297 ± 0.0893
	AMR	0.0209 ± 0.0771	0.0209 ± 0.0781	MXL	0.0202 ± 0.0783	0.0194 ± 0.0775
				PUR	0.0209 ± 0.0763	0.0219 ± 0.0812
				CLM	0.0215 ± 0.0779	0.0212 ± 0.0767
				PEL	0.0199 ± 0.0780	0.0205 ± 0.0821
	EAS	0.0186 ± 0.0758	0.0184 ± 0.0751	CHB	0.0177 ± 0.0733	0.0171 ± 0.0711
				JPT	0.0193 ± 0.0775	0.0196 ± 0.0795
				CHS	0.0192 ± 0.0779	0.0191 ± 0.0762
				CDX	0.0177 ± 0.0747	0.0182 ± 0.0789
				KHV	0.0188 ± 0.0769	0.0178 ± 0.0735
	EUR	0.0189 ± 0.0759	0.0192 ± 0.0780	CEU	0.0185 ± 0.0757	0.0193 ± 0.0807
				TSI	0.0195 ± 0.0771	0.0186 ± 0.0738
				FIN	0.0184 ± 0.0753	0.0188 ± 0.0785
				GBR	0.0182 ± 0.0762	0.0191 ± 0.0801
				IBS	0.0193 ± 0.0778	0.0201 ± 0.0817
	SAS	0.0174 ± 0.0688	0.0173 ± 0.0678	GIH	0.0175 ± 0.0706	0.0169 ± 0.0666
				PJL	0.0185 ± 0.0724	0.0185 ± 0.0723
				BEB	0.0170 ± 0.0677	0.0175 ± 0.0695
				STU	0.0165 ± 0.0658	0.0159 ± 0.0631
				ITU	0.0175 ± 0.0707	0.0174 ± 0.0713
OPRM1	AFR	0.0405 ± 0.101	0.0407 ± 0.102	YRI	0.0408 ± 0.104	0.0413 ± 0.106
				LWK	0.0412 ± 0.104	0.04100 ± 0.102
				GWD	0.0392 ± 0.101	0.0399 ± 0.105
				MSL	0.0380 ± 0.0968	0.0384 ± 0.0983
				ESN	0.0430 ± 0.108	0.0425 ± 0.107
				ASW	0.0390 ± 0.100	0.0414 ± 0.109
				ACB	0.0396 ± 0.100	0.0404 ± 0.103
	AMR	0.0299 ± 0.0949	0.0291 ± 0.0923	MXL	0.0302 ± 0.0982	0.0327 ± 0.108
				PUR	0.0313 ± 0.0953	0.0307 ± 0.0945
				CLM	0.0304 ± 0.0954	0.0309 ± 0.0983
				PEL	0.0244 ± 0.0852	0.0225 ± 0.0778
	EAS	0.0225 ± 0.0822	0.0228 ± 0.0835	CHB	0.0232 ± 0.083	0.0235 ± 0.0844
				JPT	0.0206 ± 0.0810	0.0210 ± 0.0824
				CHS	0.0235 ± 0.0834	0.0241 ± 0.0858
				CDX	0.0223 ± 0.0835	0.0228 ± 0.0873
				KHV	0.0226 ± 0.0829	0.0226 ± 0.0830
	EUR	0.0299 ± 0.0962	0.0302 ± 0.0980	CEU	0.0304 ± 0.0984	0.0302 ± 0.0987
				TSI	0.0290 ± 0.0939	0.0293 ± 0.0977
				FIN	0.0299 ± 0.0967	0.0315 ± 0.103
				GBR	0.0297 ± 0.0960	0.0292 ± 0.0957
				IBS	0.0304 ± 0.0981	0.0309 ± 0.0994
	SAS	0.0259 ± 0.0881	0.0258 ± 0.0888	GIH	0.0266 ± 0.0897	0.0265 ± 0.0901
				PJL	0.0256 ± 0.0880	0.0264 ± 0.0924
				BEB	0.0250 ± 0.0860	0.0245 ± 0.0851
				STU	0.0263 ± 0.0897	0.0267 ± 0.0916
				ITU	0.0254 ± 0.0887	0.0248 ± 0.0883

AFR: African; AMR: Ad Mixed American; EAS: East Asian; EUR: European; SAS: South Asian; ACB: African Caribbean in Barbados; ASW: American of African Ancestry in Southwest USA; BEB: Bengali from Bangladesh; CDX: Chinese Dai in Xishuangbanna, China; CEU: Utah Residence with Northern and Western Ancestry; CHB: Han Chinese in Beijing; CHS: Southern Han Chinese; CLM: Colombians from Medellin, Colombia; ESN: Esan in Nigeria; FIN: Finnish in Finland; GBR: British in England and Scotland; GIH: Gujarati Indian from Houston, Texas; GWD: Gambian in Western Divisions in Gambia; IBS: Iberian Population in Spain; ITU: Indian Telugu from the United Kingdom; JPT: Japanese in Tokyo, Japan; KHV: Kinh in Ho Chi Minh City, Vietnam; LWK: Luhya in Webuye, Kenya; MSL: Mende in Sierra Leone; MXL: Mexican Ancestry from Los Angeles, USA; PEL: Peruvians from Lima, Peru; PJL: Punjabi from Lahore, Pakistan; PUR: Puerto Ricans from Puerto Rico; STU: Sri Lankan Tamil from the United Kingdom; TSI: Toscani in Italia; YRI: Yoruba in Ibadan, Nigeria

Table 1 (continued). Average super-population and sub-population observed (H_o) and expected (H_e) heterozygosities across 418 *CYP2D6*, 613 *UGT2B7*, 5,986 *ABCB1*, 6,831 *OPRM1*, and 1,007 *COMT* polymorphisms.

Gene	Super-Population	Average H_e	Average H_o	Sub-Population	Average H_e	Average H_o
COMT	AFR	0.0489 ± 0.118	0.049 ± 0.118	YRI	0.0479 ± 0.118	0.0467 ± 0.114
				LWK	0.0493 ± 0.118	0.0479 ± 0.114
				GWD	0.0498 ± 0.121	0.0520 ± 0.128
				MSL	0.0484 ± 0.117	0.0473 ± 0.114
				ESN	0.0474 ± 0.117	0.0514 ± 0.131
				ASW	0.0503 ± 0.120	0.0498 ± 0.120
				ACB	0.0493 ± 0.120	0.0481 ± 0.117
	AMR	0.0453 ± 0.123	0.0442 ± 0.121	MXL	0.0442 ± 0.121	0.0462 ± 0.128
				PUR	0.0466 ± 0.125	0.0445 ± 0.120
				CLM	0.0461 ± 0.124	0.0472 ± 0.127
				PEL	0.0372 ± 0.111	0.0392 ± 0.123
	EAS	0.0429 ± 0.124	0.0425 ± 0.122	CHB	0.0442 ± 0.125	0.0423 ± 0.120
				JPT	0.0442 ± 0.124	0.0466 ± 0.131
				CHS	0.0411 ± 0.123	0.0420 ± 0.126
				CDX	0.0423 ± 0.123	0.0392 ± 0.115
				KHV	0.0424 ± 0.124	0.0418 ± 0.123
	EUR	0.0435 ± 0.122	0.0443 ± 0.125	CEU	0.0435 ± 0.123	0.0458 ± 0.130
				TSI	0.0441 ± 0.125	0.0467 ± 0.133
				FIN	0.0414 ± 0.115	0.0401 ± 0.112
				GBR	0.0437 ± 0.124	0.0436 ± 0.124
				IBS	0.0428 ± 0.122	0.0451 ± 0.129
	SAS	0.0456 ± 0.123	0.0437 ± 0.118	GIH	0.0463 ± 0.125	0.0460 ± 0.124
				PJL	0.0455 ± 0.124	0.0446 ± 0.123
				BEB	0.0448 ± 0.123	0.0404 ± 0.111
				STU	0.0459 ± 0.124	0.0417 ± 0.112
				ITU	0.0444 ± 0.121	0.0452 ± 0.126

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Table 2. Number of loci that deviated from Hardy-Weinberg Equilibrium (HWE) expectations and the number of pairwise loci comparisons that exhibited linkage disequilibrium (LD) for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* polymorphisms in five super-populations and 26 sub-populations. Bonferroni corrected HWE p-values were 0.000120, 8.16×10^{-5}, 8.35×10^{-6}, 7.32×10^{-6}, and 4.96×10^{-5} for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, respectively; Bonferroni corrected pairwise LD p-values were 5.34×10^{-7}, 2.67×10^{-7}, 5.50×10^{-8}, 2.24×10^{-8} and 9.87×10^{-8} for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, respectively.

Gene	Super-Population	Significant HWE Deviations	Significant LDs	Sub-Population	Significant HWE Deviations	Significant LDs
CYP2D6	AFR	4	3,693	YRI	0	516
				LWK	0	500
				GWD	0	449
				MSL	0	452
				ESN	0	422
				ASW	0	331
				ACB	0	634
	AMR	0	799	MXL	0	383
				PUR	0	560
				CLM	0	504
				PEL	0	380
	EAS	1	1,048	CHB	0	438
				JPT	0	385
				CHS	0	455
				CDX	0	425
				KHV	0	721
	EUR	0	1,031	CEU	0	595
				TSI	0	494
				FIN	0	387
				GBR	1	575
				IBS	0	402
	SAS	0	933	GIH	0	402
				PJL	0	443
				BEB	0	472
				STU	0	512
				ITU	0	393
UGT2B7	AFR	4	7,728	YRI	2	4,403
				LWK	0	3,643
				GWD	2	4,271
				MSL	1	4,053
				ESN	2	4,711
				ASW	0	2,671
				ACB	0	3,546
	AMR	3	7,282	MXL	0	2,917
				PUR	0	3,526
				CLM	0	3,731
				PEL	1	3,160
	EAS	2	5,308	CHB	36	24,147
				JPT	1	3,965
				CHS	2	4,500
				CDX	1	4,174
				KHV	1	4,313
	EUR	3	6,295	CEU	1	4,153
				TSI	0	3,793
				FIN	0	4,332
				GBR	0	3,743
				IBS	1	4,159
	SAS	3	6,574	GIH	0	3,405
				PJL	2	3,968
				BEB	1	3,542
				STU	1	3,962
				ITU	3	4,959

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Table 2 (continued). Number of loci that deviated from Hardy-Weinberg Equilibrium (HWE) expectations and the number of pairwise loci comparisons that exhibited linkage disequilibrium (LD) for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* polymorphisms in five super-populations and 26 sub-populations. Bonferroni corrected HWE p-values were 0.000120, 8.16×10^{-5}, 8.35×10^{-6}, 7.32×10^{-6}, and 4.96×10^{-5} for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, respectively; Bonferroni corrected pairwise LD p-values were 5.34×10^{-7}, 2.67×10^{-7}, 5.50×10^{-8}, 2.24×10^{-8} and 9.87×10^{-8} for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, respectively.

Gene	Super-Population	Significant HWE Deviations	Significant LDs	Sub-Population	Significant HWE Deviations	Significant LDs
ABCB1	AFR	9	72,978	YRI	0	11,405
				LWK	0	4,972
				GWD	1	12,227
				MSL	2	14,988
				ESN	1	12,071
				ASW	0	2,947
				ACB	1	13,847
	AMR	2	31,011	MXL	0	7,170
				PUR	1	9,362
				CLM	1	11,249
				PEL	0	5,597
	EAS	5	37,802	CHB	2	15,053
				JPT	0	5,892
				CHS	2	15,271
				CDX	0	6,908
				KHV	1	9,580
	EUR	2	26,637	CEU	2	10,442
				TSI	0	9,939
				FIN	0	3,123
				GBR	1	8,771
				IBS	1	9,135
	SAS	3	25,566	GIH	1	8,190
				PJL	1	9,611
				BEB	1	8,979
				STU	1	10,653
				ITU	1	9,323
OPRM1	AFR	12	172,560	YRI	2	36,581
				LWK	1	27,603
				GWD	4	47,005
				MSL	2	33,978
				ESN	0	24,996
				ASW	0	11,928
				ACB	1	18,034
	AMR	5	92,744	MXL	2	30,805
				PUR	1	31,564
				CLM	2	36,436
				PEL	0	60,103
	EAS	5	62,824	CHB	2	33,915
				JPT	4	38,296
				CHS	2	32,577
				CDX	2	23,930
				KHV	5	42,291
	EUR	6	76,181	CEU	3	36,491
				TSI	2	32,190
				FIN	1	33,169
				GBR	4	37,849
				IBS	1	22,631
	SAS	5	77,803	GIH	1	30,707
				PJL	4	41,472
				BEB	2	23,612
				STU	4	44,452
				ITU	3	33,269

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Table 2 (continued). Number of loci that deviated from Hardy-Weinberg Equilibrium (HWE) expectations and the number of pairwise loci comparisons that exhibited linkage disequilibrium (LD) for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* polymorphisms in five super-populations and 26 sub-populations. Bonferroni corrected HWE p-values were 0.000120, 8.16×10^{-5}, 8.35×10^{-6}, 7.32×10^{-6}, and 4.96×10^{-5} for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, respectively; Bonferroni corrected pairwise LD p-values were 5.34×10^{-7}, 2.67×10^{-7}, 5.50×10^{-8}, 2.24×10^{-8} and 9.87×10^{-8} for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, respectively.

Gene	Super-Population	Significant HWE Deviations	Significant LDs	Sub-Population	Significant HWE Deviations	Significant LDs
COMT	AFR	1	7,362	YRI	0	1,421
				LWK	0	1,428
				GWD	0	1,252
				MSL	0	1,003
				ESN	2	2,492
				ASW	0	772
				ACB	0	1,132
	AMR	2	7,004	MXL	0	1,196
				PUR	0	2,068
				CLM	2	1,669
				PEL	0	4,661
	EAS	2	6,712	CHB	0	2,396
				JPT	0	1,940
				CHS	0	1,777
				CDX	0	1,890
				KHV	1	3,079
	EUR	3	7,835	CEU	1	2,229
				TSI	0	1,685
				FIN	2	2,123
				GBR	0	2,162
				IBS	0	2,391
	SAS	2	7,502	GIH	0	2,202
				PJL	0	1,870
				BEB	0	3,969
				STU	3	5,326
				ITU	0	1,874

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After Bonferroni correction, sub-populations exhibited an average of 470 ± 90 significant pairwise LDs with a range of 331 (ASW) to 721 (KHV) significant pairwise LDs and 3,693 AFR, 799 AMR, 1,048 EAS, 1,031 EUR, and 933 SAS significant pairwise LDs were observed ($p < 5.74 \times 10^{-7}$), all of which are less than that due to chance alone (~4,358 pairwise comparisons) (Table 2 and Supplemental Figure 1). LD heat-maps of five super-

populations (Supplemental Figure 2) show a cluster of six to seven polymorphisms (rs29001678 [AMR, EUR, SAS only], rs1081000, rs28695233, rs75276289, rs76312385, rs74644586, and rs1080996), which appear to form an LD block. There were an average of 44 ± 14 significant pairwise LDs between these seven polymorphisms and others within the gene, with a range of 33 (AMR) to 71 (AFR) significant pairwise LDs. This group of polymorphisms is found within *CYP2D6* intron 1 (hg19 positions 42526524-42526573) and do not alter CYP2D6 function; however, rs1080995, rs74644586, and rs76312385 are part of the *CYP2D6**21A haplotype and may be observed in any *CYP2D6** allele with an intron 1 gene conversion with *CYP2D7* (*CYP2D6**11, *14B, *21B, *63, *73, *84, *88, *98, *102, *103, *104, and *105).[9]

MDS plots (Figure 1) were created using *CYP2D6* polymorphism pairwise genetic distances between super-populations and within super-populations (between sub-populations). There was substantial separation of the AFR and EAS populations from the cluster of AMR, EUR, and SAS populations while sub-population clustering is quite diverse within each super-population.

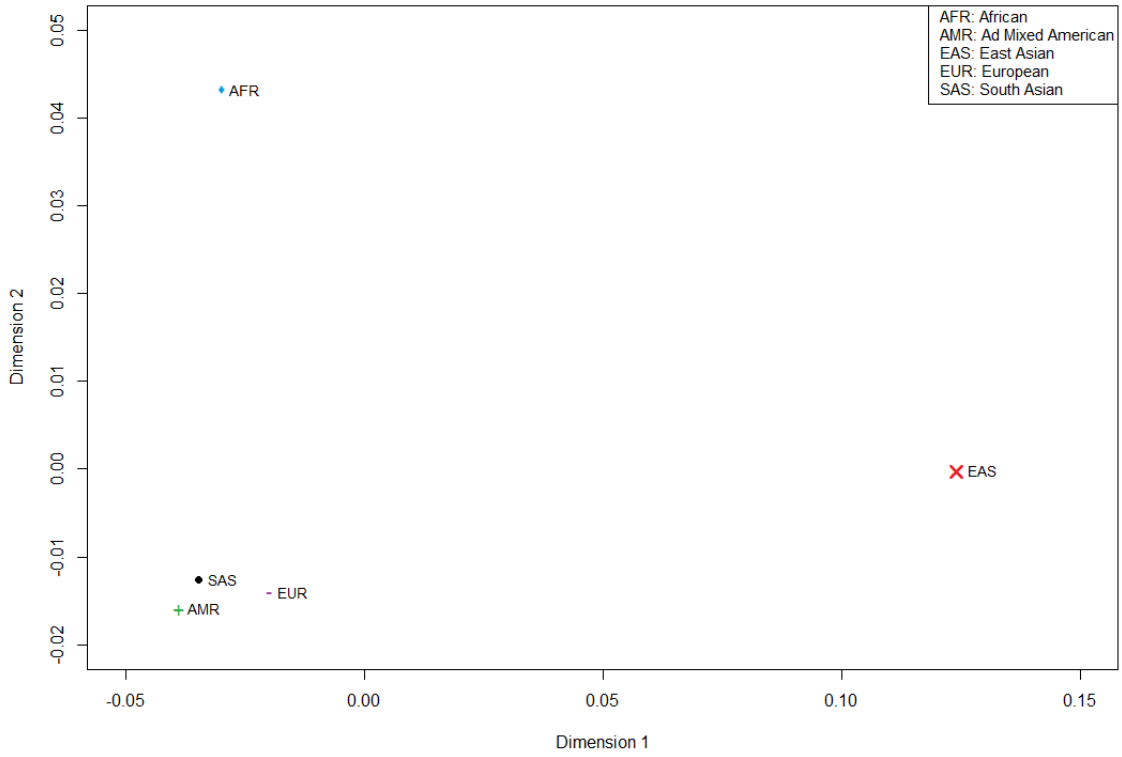


Figure 1. Multidimensional scaling plots of *CYP2D6* polymorphism pairwise genetic distances of five super-populations and 26 sub-populations based on 1000 Genome Project Phase 3 genotype data. African (AFR) populations are marked with a blue diamond, Ad Mixed American (AMR) populations are marked with a green plus sign, East Asian (EAS) populations are marked with a red "X", European (EUR) populations are marked with a purple minus sign, and South Asian (SAS) populations are marked with a solid black circle.

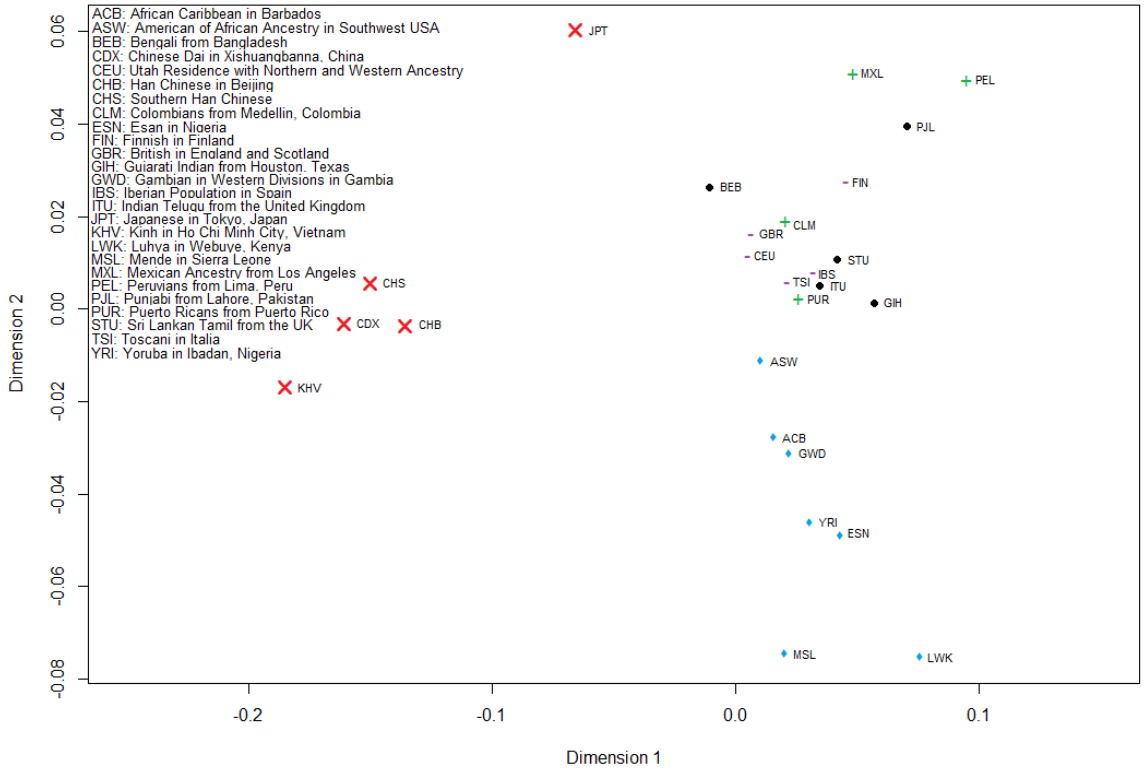


Figure 1 (continued). Multidimensional scaling plots of *CYP2D6* polymorphism pairwise genetic distances of five super-populations and 26 sub-populations based on 1000 Genome Project Phase 3 genotype data. African (AFR) populations are marked with a blue diamond, Ad Mixed American (AMR) populations are marked with a green plus sign, East Asian (EAS) populations are marked with a red "X", European (EUR) populations are marked with a purple minus sign, and South Asian (SAS) populations are marked with a solid black circle.

Variant effect prediction for 418 *CYP2D6* polymorphisms was performed using SIFT, PolyPhen-2, and PROVEAN (Table 3 and Supplemental Table 5).[32-41] Individual polymorphisms were assigned to one of five categories based on their SIFT, PolyPhen-2, and PROVEAN scores: tolerated with no discrepancies (predictions are concordant), discrepancies but most likely tolerated (predictions are discordant but favor tolerance), discrepancies but most likely damaging (predictions are discordant but favor intolerance), damaging with no discrepancies (predictions are concordant), and conflicting results (only two scores are reported and their predictions are discordant). Summaries of their frequencies and distribution

across each gene are shown in Table 3 and Figure 2a, respectively. Due to the potential for multiple alternate alleles at the 54 damaging, or most likely damaging, polymorphisms (locus rs1135830, for example, can produce a non-synonymous amino acid change or a premature stop codon), 47 single amino acid changes, four premature stop codons, two frame-shift mutations, one copy number variant, one in-frame insertion, and one in-frame deletion mutations would arise. 50% (80/160) of the intronic and/or splice-associated polymorphisms were scored by HSF (Figure 2a and Supplemental Table 5). Seven of these loci (rs5030656, rs192358451, rs377504871, rs78854695, rs267608282, rs28371702, and rs267608275) were predicted to alter, or most likely alter, splicing of the gene. The locus rs28371702 is considered part of the haplotype for 35 * alleles although it has not been reported as functionally relevant.[9] The remaining six polymorphisms have not been reported as part of a recognized * allele. Interestingly, the four intronic polymorphisms that are recognized by The Human Cytochrome p450 Allele Nomenclature Database[9] for causing splice-defects (883G>C [rs201377835], 1846G>A [rs3892097], 2950G>C [no rs number; invariable according to 1000 Genomes Project], and 2988G>A [rs28371725]) were either not scored by HSF or not considered variable sites in the 1000 Genomes Project and so genotypes were not exported from the UCSC Table Browser.

Table 3. Qualitative prediction of variant effect, average prediction scores, and distribution of qualitative overall polymorphism effect categories for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* and promoter regions. Note that not all polymorphisms were assigned a score by each variant effect algorithm so the total counts for each algorithm may not equal the total of the other algorithms and may be different than the total number of polymorphisms for each gene (N).

Algorithm	Effect Category	CYP2D6 (N=119)		UGT2B7 (N=55)		ABCB1 (N=94)		OPRM1 (N=75)		COMT (N=45)	
		Count	Average Score	Count	Average Score	Count	Average Score	Count	Average Score	Count	Average Score
SIFT	Damaging	3	0.00900 ± 0.00870	0	-	0	-	10	0.000400 ± 0.00130	4	0.0165 ± 0.0158
	Deleterious	47	0.0157 ± 0.0147	17	0.0124 ± 0.0182	30	0.0160 ± 0.0167	6	0.00670 ± 0.103	3	0.00330 ± 0.00580
	Tolerated	63	0.634 ± 0.3707	33	0.666 ± 0.397	38	0.286 ± 0.239	46	0.324 ± 0.384	38	0.616 ± 0.364
PolyPhen-2	Probably Damaging	16	0.978 ± 0.0241	5	0.963 ± 0.0322	5	0.9688 ± 0.0377	16	0.991 ± 0.0209	0	-
	Possibly Damaging	17	0.743 ± 0.147	7	0.726 ± 0.0986	16	0.692 ± 0.117	5	0.682 ± 0.196	4	0.718 ± 0.194
	Benign	43	0.116 ± 0.129	22	0.0493 ± 0.0833	47	0.0505 ± 0.0714	21	0.0636 ± 0.0917	11	0.0939 ± 0.133
PROVEAN	Deleterious	52	-4.89 ± 2.16	18	-5.05 ± 2.41	30	-4.90 ± 2.23	19	-4.54 ± 1.56	5	-5.20 ± 1.94
	Neutral	61	-0.422 ± 0.978	37	-0.204 ± 0.839	64	-0.708 ± 0.851	56	-0.0130 ± 0.518	40	-0.186 ± 0.531
Polymorphism Effect		**Count**	**Frequency (%)**	**Count**	**Frequency (%)**	**Count**	**Frequency (%)**	**Count**	**Frequency (%)**	**Count**	**Frequency (%)**
Damaging, no discrepancies		36	30.3	12	21.8	12	12.8	0	0	4	8.89
Discrepancies, most likely damaging		18	15.1	3	5.45	13	13.8	17	22.7	1	2.22
Discrepancies, most likely tolerated		10	8.4	5	9.09	19	20.2	13	17.3	1	2.22
Tolerated, no discrepancies		53	44.5	35	63.6	50	53.2	36	48	36	80
Conflicting results		2	1.68	0	0	0	0	9	12	3	6.67

SIFT, PolyPhen-2, and PROVEAN score cutoffs are 0.05, 0.5, and -2.5, respectively, for distinguishing between harmful and tolerated polymorphisms.[26-35]

SIFT "damaging" and "deleterious" predictions, and PolyPhen-2 "probably damaging" and "possibly damaging" predictions, are qualitative classifications indicating greater and lesser degrees of confidence, respectively, in the predicted damage caused by a polymorphism.[26-32]

Algorithm	Effect Category	CYP2D6 (N=80)		UGT2B7 (N=104)		ABCB1 (N=564)		OPRM1 (N=126)		COMT (N=84)	
		Count	Average Score	Count	Average Score	Count	Average Score	Count	Average Score	Count	Average Score
Human Splicing Finder	Alters	43	74.8 ± 6.15; 74.8 ± 6.16; -0.165 ± 6.13	62	74.2 ± 7.39; 74.4 ± 8.56; 1.50 ± 14.3	293	72.6 ± 9.14; 70.9 ± 9.08; 3.92 ± 26.6	64	70.7 ± 12.9; 70.3 ± 11.6; 6.16 ± 51.8	49	70.6 ± 14.0; 74.4 ± 9.51; 11.7 ± 36.3
	Creates	27	44.3 ± 10.4; 74.2 ± 6.88; 71.7 ± 79.8	22	47.7 ± 7.14; 73.3 ± 6.69; 55.6 ± 16.8	85	50.1 ± 15.5; 72.3 ± 7.80; 73.0 ± 118	40	52.3 ± 15.5; 70.8 ± 9.02; 49.9 ± 68.1	23	50.6 ± 12.1; 75.7 ± 7.89; 57.1 ± 42.3
	Breaks	29	73.5 ± 7.38; 43.8 ± 13.2; -26.8 ± 15.7	24	72.6 ± 9.44; 53.4 ± 13.1; -24.4 ± 27.1	151	72.3 ± 9.28; 51.8 ± 16.0; -25.7 ± 30.7	34	72.1 ± 10.1; 53.7 ± 16.8; -23.2 ± 32.4	16	74.9 ± 4.93; 48.6 ± 11.8; -34.8 ± 16.2
	Activates Cryptic Site	3	35.2 ± 18.5; 75.2 ± 7.88; 182 ± 164	2	46.7 ± 0.445; 74.6 ± 1.05; 59.8 ± 3.77	126	51.6 ± 18.4; 72.8 ± 8.14; 79.58 ± 145.7	3	45.7 ± 6.29; 69.4 ± 3.15; 54.2 ± 22.2	3	44.2 ± 2.53; 71.0 ± 2.53; 60.85 ± 3.46
Polymorphism Effect		**Count**	**Frequency (%)**	**Count**	**Frequency (%)**	**Count**	**Frequency (%)**	**Count**	**Frequency (%)**	**Count**	**Frequency (%)**
Most likely effects splicing		4	5	2	1.92	127	22.5	3	2.38	3	3.57
Potentially effects splicing		3	3.75	9	8.65	171	30.3	13	10.3	8	9.52
Probably no effect on splicing		73	91.25	93	89.4	266	47.2	110	87.3	73	86.9

Average HSF scores are reference (hg19) consensus score, mutant consensus score, and variation score.[42]

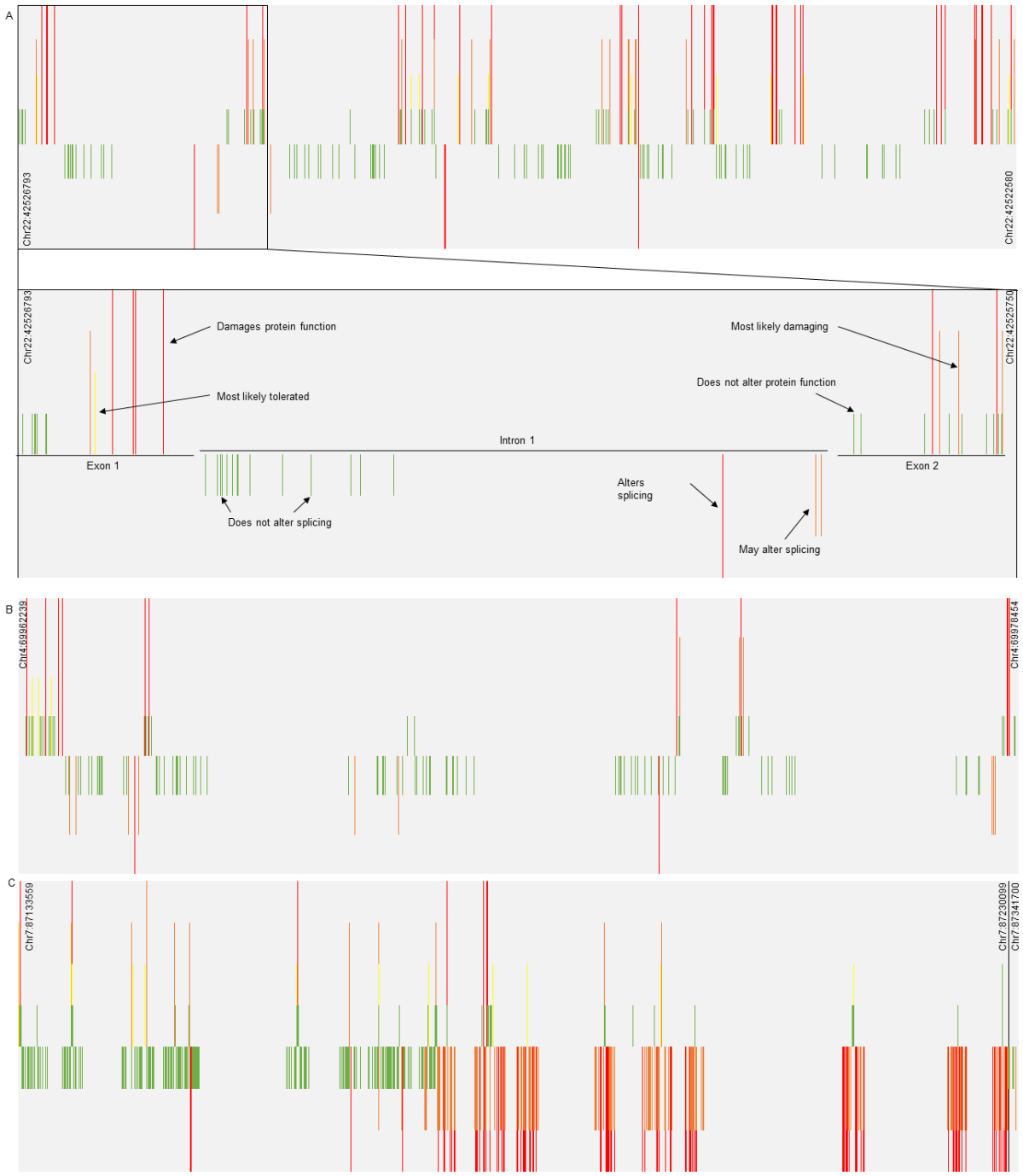


Figure 2. Qualitative summary of variant effect predictions. Each grey box represents a single gene: *CYP2D6* (a), *UGT2B7* (b), *ABCB1* (c), *OPRM1* (d), and *COMT* (e); the top vertical bars of each gene represent exonic polymorphisms scored by Sort Intolerant From Tolerant (SIFT), PolyPhen-2, and/or PROVEAN, the bottom bars represent intronic and splice-associated polymorphisms within 1,000 bases of an exon that were scored by Human Splicing Finder (HSF), and black lines spanning both sections represent large unscored intronic regions that were removed; *CYP2D6* (a) and *UGT2B7* (b) are to scale while *ABCB1* (c), *OPRM1* (d), and *COMT* (e) have large intronic sequences (vertical black lines) removed; hg19 reference genome coordinates are provided.

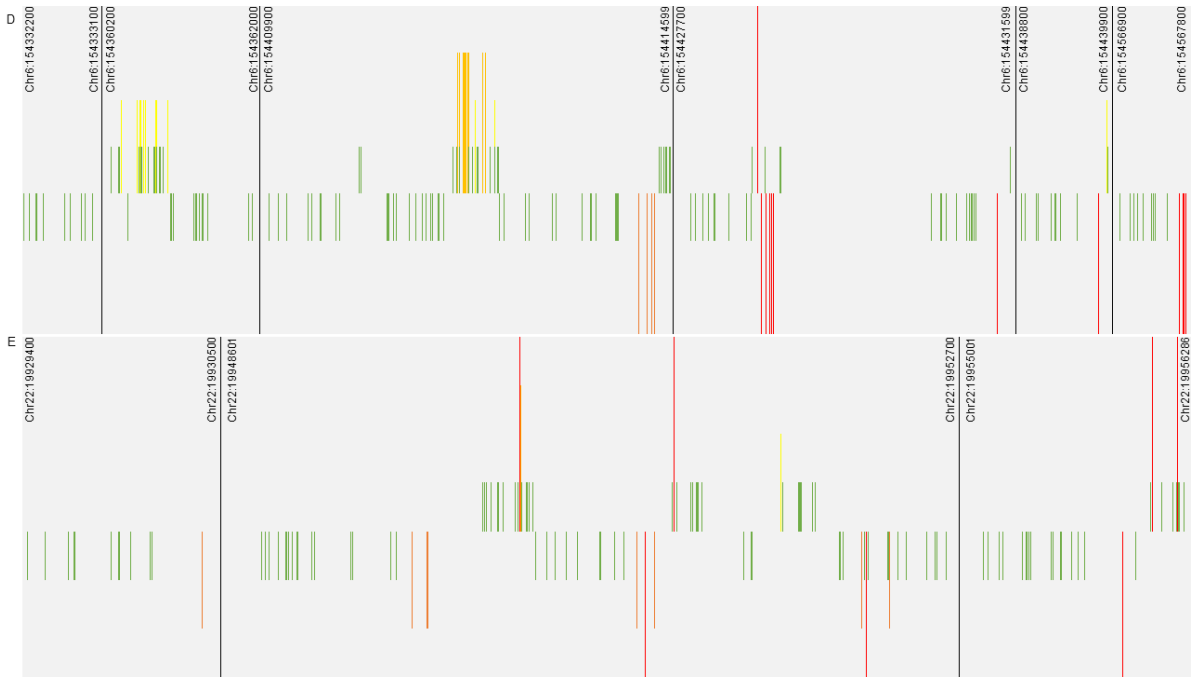


Figure 2 (continued). Qualitative summary of variant effect predictions. Each grey box represents a single gene: *CYP2D6* (a), *UGT2B7* (b), *ABCB1* (c), *OPRM1* (d), and *COMT* (e); the top vertical bars of each gene represent exonic polymorphisms scored by Sort Intolerant From Tolerant (SIFT), PolyPhen-2, and/or PROVEAN, the bottom bars represent intronic and splice-associated polymorphisms within 1,000 bases of an exon that were scored by Human Splicing Finder (HSF), and black lines spanning both sections represent large unscored intronic regions that were removed; *CYP2D6* (a) and *UGT2B7* (b) are to scale while *ABCB1* (c), *OPRM1* (d), and *COMT* (e) have large intronic sequences (vertical black lines) removed; hg19 reference genome coordinates are provided.

The Human CYP Allele Nomenclature Database[9] was used to assign * alleles to each sample. 210 unique haplotypes were observed in the 1000 Genomes Project Phase 3 dataset, representing 37 * alleles (Supplemental Table 6). The average super-population observed and expected heterozygosities were 0.72 ± 0.080 and 0.78 ± 0.091, respectively. Using * allele assignments, *CYP2D6* significantly deviated from HWE expectations after Bonferroni correction in the AFR, AMR, EAS, and SAS super-populations ($p < 0.0348$ for AFR and $p = 0.0420$, 0.0442, and 0.0348 in AMR, EAS, and SAS, respectively) and seven sub-populations ($p = 0.000200$, 0.0277, 0.00290, 0.00510, 0.0202, 0.157, and 0.423 in ASW, LWK, MSL, YRI, CLM, GBR, and STU, respectively). After Bonferroni correction ($p = 0.01$ and $p = 0.0019$ for

super- and sub-populations, respectively), the AFR super-population ($p < 0.01$) and ASW ($p = 0.000200$) significantly deviated from HWE expectations. Of the 210 observed haplotypes, only 14 (6.67%) are identical to those reported in the Human CYP Allele Nomenclature Table. Though not reported in the reference table, 84.8% of the remaining haplotypes could be associated with a * allele based on the presence of causal polymorphisms, however, 18 of them could not. These haplotypes represent 0.499% (25/5008) of the total 1000 Genomes Project haplotypes and contain combinations of functionally relevant amino acid changes (Supplemental Table 6).

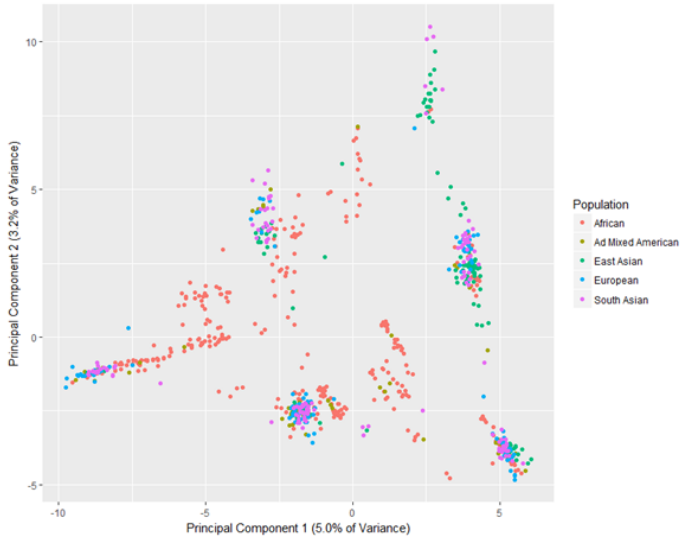
MP was assigned according to Gaedigk, *et al.* 2008[44] (Table 4). A chi-squared goodness-of-fit test indicated no significant differences between observed MP frequencies of 1000 Genomes Project super-population data and theoretical predictions ($p = 0.99$), previously reported values for general United States major population groups ($p = 0.54$),[45] and world populations (African, American, East Asian, European, and South Central Asian) ($p = 0.99$).[46]

Table 4. CYP2D6 metabolizer status counts and frequencies in five super-populations (bolded) and 26 sub-populations based on available 1000 Genomes Phase 3 causative SNP genotype data. The number of individuals in each population is indicated in parentheses; "Undetermined" metabolizer phenotype individuals contain at least one *CYP2D6** allele with unknown effect on enzyme activity.

Population	Poor		Intermediate		Extensive		Ultrarapid		Undetermined	
	Count	Frequency	Count	Frequency	Count	Frequency	Count	Frequency	Count	Frequency
AFR (661)	**9**	**0.0136**	**35**	**0.053**	**564**	**0.853**	**0**	**0**	**53**	**0.0802**
ACB (96)	2	0.0208	6	0.0625	82	0.8542	0	0	6	0.0625
GWD (113)	1	0.00885	2	0.0177	103	0.912	0	0	7	0.0619
ESN (99)	1	0.0101	11	0.111	79	0.798	0	0	8	0.0808
MSL (85)	3	0.0353	2	0.0235	70	0.824	0	0	10	0.118
YRI (108)	0	0	5	0.0463	97	0.898	0	0	6	0.0556
LWK (99)	0	0	4	0.0404	84	0.848	0	0	11	0.111
ASW (61)	2	0.0328	5	0.082	49	0.803	0	0	5	0.082
AMR (347)	**10**	**0.0288**	**10**	**0.0288**	**291**	**0.839**	**0**	**0**	**36**	**0.104**
PUR (104)	6	0.0577	5	0.0481	81	0.779	0	0	12	0.115
CLM (94)	4	0.0426	4	0.0426	74	0.787	0	0	12	0.128
PEL (85)	0	0	0	0	78	0.918	0	0	7	0.0824
MXL (64)	0	0	1	0.0156	58	0.906	0	0	5	0.0781
EAS (504)	**0**	**0**	**13**	**0.0258**	**488**	**0.968**	**0**	**0**	**3**	**0.00595**
CHS (105)	0	0	3	0.0286	100	0.952	0	0	2	0.019
CDX (93)	0	0	3	0.0323	89	0.957	0	0	1	0.0108
KHV (99)	0	0	5	0.0505	94	0.949	0	0	0	0
CHB (103)	0	0	2	0.0194	101	0.981	0	0	0	0
JPT (104)	0	0	0	0	104	1	0	0	0	0
EUR (503)	**29**	**0.0577**	**32**	**0.0636**	**433**	**0.861**	**0**	**0**	**9**	**0.0179**
CEU (99)	5	0.0505	9	0.0909	81	0.818	0	0	1	0.0101
GBR (91)	11	0.121	11	0.121	68	0.747	0	0	1	0.011
IBS (107)	3	0.028	2	0.0187	98	0.916	0	0	4	0.0374
TSI (107)	5	0.0467	7	0.0654	93	0.869	0	0	2	0.0187
FIN (99)	5	0.0505	3	0.0303	90	0.909	0	0	1	0.0101
SAS (489)	**10**	**0.0204**	**24**	**0.0491**	**441**	**0.902**	**2**	**0.00409**	**12**	**0.0245**
PJL (96)	1	0.0104	7	0.0729	87	0.906	0	0	1	0.0104
BEB (86)	2	0.0233	5	0.0581	76	0.884	0	0	3	0.0349
STU (102)	3	0.0294	4	0.0392	90	0.882	1	0.0098	4	0.0392
ITU (102)	3	0.0294	5	0.049	90	0.882	1	0.0098	3	0.0294
GIH (103)	1	0.00971	3	0.0291	98	0.951	0	0	1	0.00971

AFR: African; AMR: Ad Mixed American; EAS: East Asian; EUR: European; SAS: South Asian; ACB: African Caribbean in Barbados; ASW: American of African Ancestry in Southwest USA; BEB: Bengali from Bangladesh; CDX: Chinese Dai in Xishuangbanna, China; CEU: Utah Residence with Northern and Western Ancestry; CHB: Han Chinese in Beijing; CHS: Southern Han Chinese; CLM: Colombians from Medellin, Colombia; ESN: Esan in Nigeria; FIN: Finnish in Finland; GBR: British in England and Scotland; GIH: Gujarati Indian from Houston, Texas; GWD: Gambian in Western Divisions in Gambia; IBS: Iberian Population in Spain; ITU: Indian Telugu from the United Kingdom; JPT: Japanese in Tokyo, Japan; KHV: Kinh in Ho Chi Minh City, Vietnam; LWK: Luhya in Webuye, Kenya; MSL: Mende in Sierra Leone; MXL: Mexican Ancestry from Los Angeles, USA; PEL: Peruvians from Lima, Peru; PJL: Punjabi from Lahore, Pakistan; PUR: Puerto Ricans from Puerto Rico; STU: Sri Lankan Tamil from the United Kingdom; TSI: Toscani in Italia; YRI: Yoruba in Ibadan, Nigeria

EM individuals were used to create principal component analysis (PCA) plots by population (Figure 3). By super-population, the EM individuals display six prominent clusters with minimal overlap between AFR and EAS super-populations and considerable spread of the AMR, EUR, and SAS populations across the entire plot. PC1 and PC2 explain greater than 5% of the variance for ten and eight polymorphisms, respectively. The same clustering pattern is observed for sub-populations with little clustering observed within populations (data not shown).



Locus	$Load_{PC1}$	$Load_{PC1}^2$	$Load_{PC2}$	$Load_{PC2}^2$	Functional Relevance?
rs28371730	0.226	0.051	0.006	0	-
rs1081000	0.225	0.051	0.002	0	Intron 1 conversion with CYP2D7
rs28695233	0.225	0.051	0.002	0	Intron 1 conversion with CYP2D7
rs75276289	0.225	0.051	0.002	0	Intron 1 conversion with CYP2D7
rs74644586	0.225	0.051	0.002	0	Intron 1 conversion with CYP2D7
rs1080996	0.225	0.051	0.002	0	Intron 1 conversion with CYP2D7
rs1080995	0.225	0.051	0.002	0	Intron 1 conversion with CYP2D7
rs76312385	0.225	0.051	0.002	0	Intron 1 conversion with CYP2D7
rs28624811	0.225	0.051	0.02	0	-
rs16947	0.225	0.05	0.019	0	2850C>T; C296R
rs4078247	0.091	0.008	0.272	0.074	-
rs28588594	0.093	0.009	0.272	0.074	-
rs1065852	0.092	0.008	0.271	0.074	100C>T; P34S
rs58440431	0.092	0.008	0.271	0.073	-
rs1080989	0.092	0.008	0.271	0.073	-
rs2004511	0.092	0.009	0.271	0.073	-
rs28371738	0.091	0.008	0.271	0.073	-
rs1081003	0.08	0.006	0.227	0.051	1039T>C; F112F

Figure 3. Principal component (PC) analysis of *CYP2D6* extensive metabolizers using genotypes of 418 polymorphisms from 1000 Genomes Project Phase 3. Samples are clustered according to super-population; rs numbers are provided for those loci best explained by PC1 and PC2; functional relevance of the polymorphism is indicated in reference to The Human Cytochrome p450 Allele Nomenclature Table[9] and concordance with variant effect prediction generated by SIFT, PolyPhen-2, PROVEAN, and HSF with green and red cells indicating tolerance and damage, respectively.

UGT2B7, ABCB1, OPRM1, and COMT

Allele frequencies for 613 *UGT2B7* polymorphisms (585 SNPs and 28 INDELs), 5,986 *ABCB1* polymorphisms (5,775 SNPs 210 INDELs, and one CNV), 6,831 *OPRM1* polymorphisms (6,561 SNPs, 267 INDELs, two ALU element insertions, and one CNV), and 1,007 *COMT* polymorphisms (973 SNPs, 33 INDELs, and one CNV) in five super-populations and 26 sub-populations are listed in Supplemental Tables 7 through 10.

The average super-population and sub-population observed and expected heterozygosities are listed in Table 1. A full list of each polymorphism and respective population-specific observed and expected heterozygosities are shown in Supplemental Tables 11 through 14.

A summary of the total number of polymorphisms in each gene and population that deviated from HWE expectations is listed in Table 2. A comprehensive list of HWE p-values for each polymorphism in each population is provided in Supplemental Tables 15 through 18. After Bonferroni correction, *UGT2B7* loci rs541550034 and rs57075995 ($p < 8.16 \times 10^{-5}$), *ABCB1* loci rs546527793 and rs570071012 ($p < 8.35 \times 10^{-6}$), and *OPRM1* loci rs147765820, rs376391508, rs77321666, and rs111829729 ($p < 7.32 \times 10^{-6}$) deviated from HWE expectations in all five super-populations. While no *COMT* loci deviated from HWE expectations in the five super-populations ($p = 4.97 \times 10^{-5}$), it should be noted that the loci rs138433986 and rs11912354 did deviate from HWE expectations in the AMR, EAS, EUR, and SAS populations (p = 0.0009 and 0.0009). One sub-population, CHB, exhibited more deviations from HWE expectations than that due to chance alone (i.e., ~20).

A summary of the total number of pairwise loci comparisons that demonstrated significant LDs are listed in Table 2 and the distribution of LD p-values is shown in

Supplemental Figures 3 through 6. After Bonferroni correction, sub-populations exhibited an average of 4,683 ± 4,004, 9,489 ± 3,368, 33,303 ± 9,716, and 2,154 ± 1,071 significant LDs for *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, respectively. Pairwise LD heat-maps of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* polymorphisms in five major super-populations (Supplemental Figures 7 through 10) show no substantial linkage blocks.

In contrast to *CYP2D6*, the individual MDS plots for *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* show substantial separation for all super-populations (Figure 4). Within super-populations, sub-populations cluster relatively well with minimal overlap between super-populations. Considering the entire dataset of ~15,000 polymorphisms, MDS plots of super-populations follow the pattern observed with single-gene plots. However, sub-populations do not show any clustering within their respective super-populations.

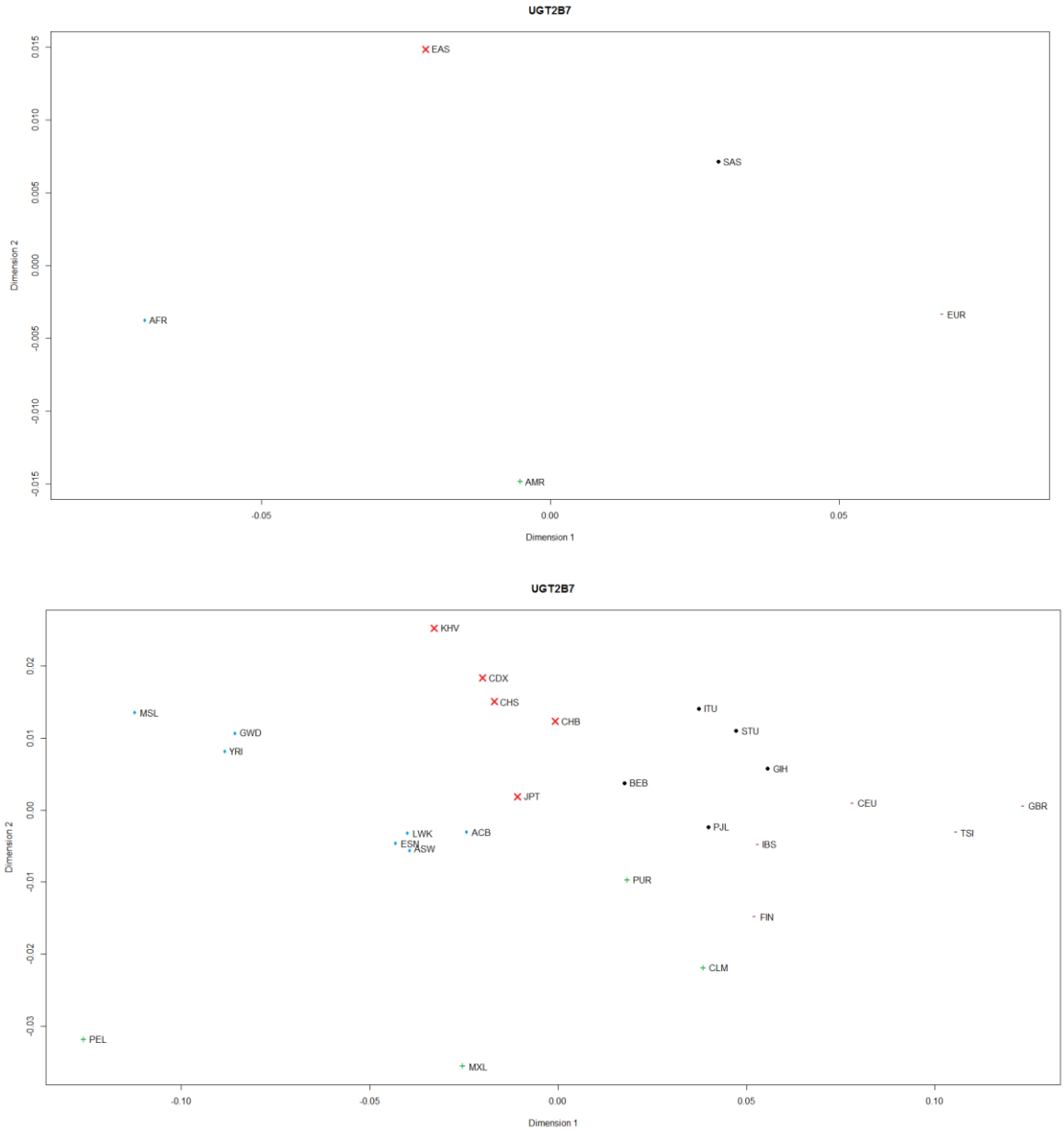


Figure 4. Multidimensional scaling plots of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* polymorphism pairwise genetic distances of five super-populations and 26 sub-populations based on 1000 Genome Project Phase 3 genotype data. African (AFR) populations are marked with a blue diamond, Ad Mixed American (AMR) populations are marked with a green plus sign, East Asian (EAS) populations are marked with a red "X", European (EUR) populations are marked with a purple minus sign, and South Asian (SAS) populations are marked with a solid black circle.

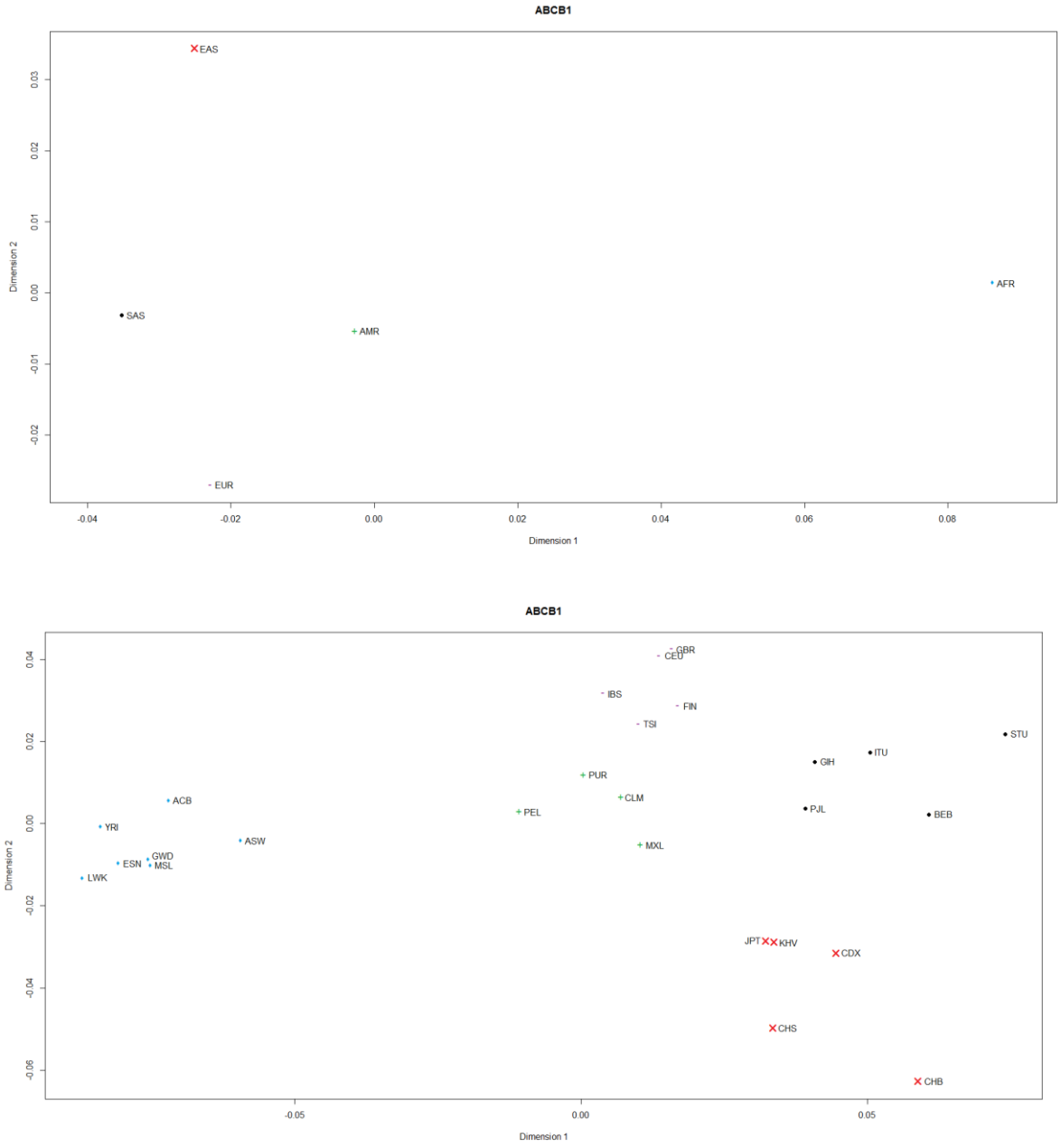


Figure 4 (continued). Multidimensional scaling plots of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* polymorphism pairwise genetic distances of five super-populations and 26 sub-populations based on 1000 Genome Project Phase 3 genotype data. African (AFR) populations are marked with a blue diamond, Ad Mixed American (AMR) populations are marked with a green plus sign, East Asian (EAS) populations are marked with a red "X", European (EUR) populations are marked with a purple minus sign, and South Asian (SAS) populations are marked with a solid black circle.

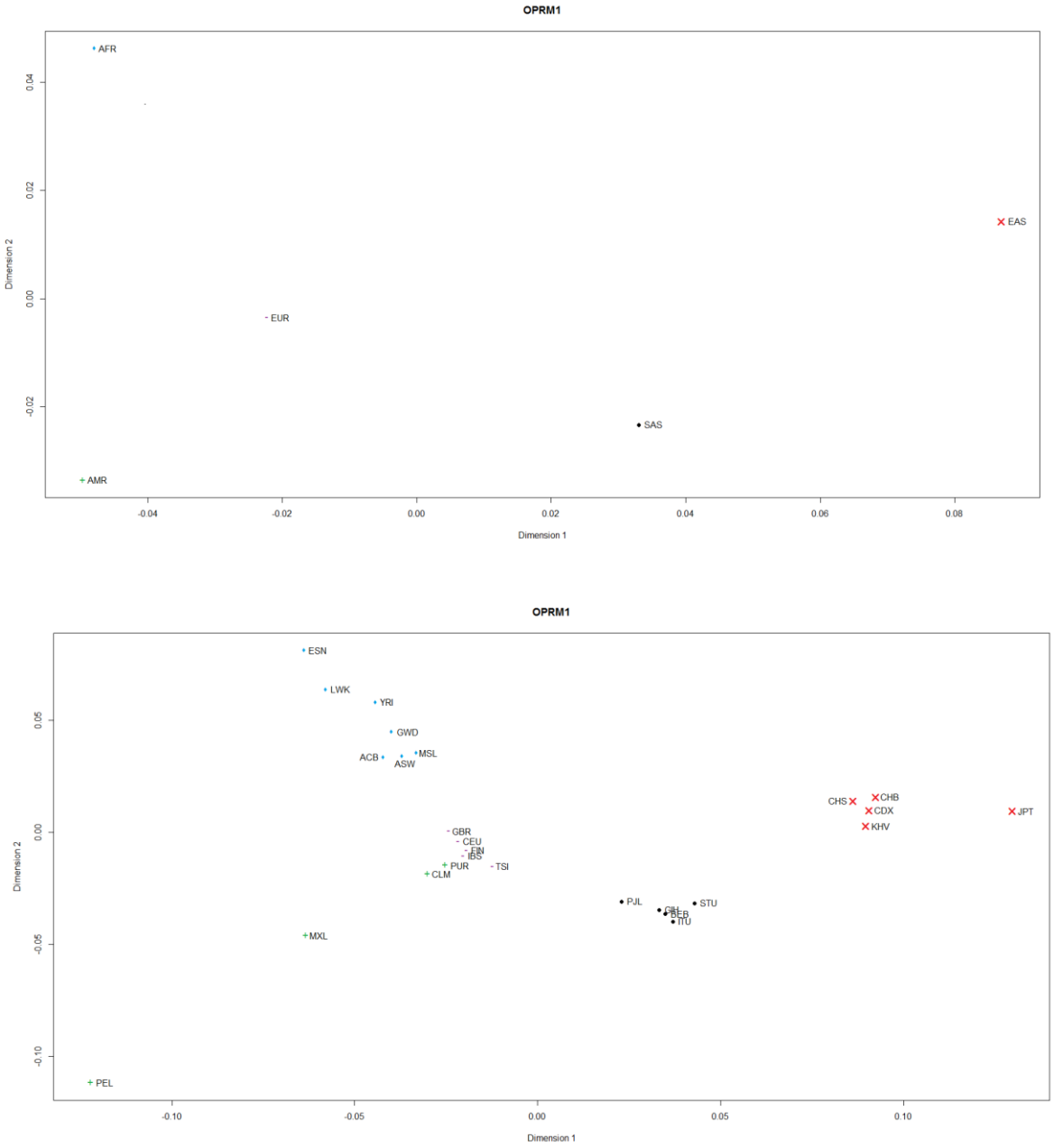


Figure 4 (continued). Multidimensional scaling plots of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* polymorphism pairwise genetic distances of five super-populations and 26 sub-populations based on 1000 Genome Project Phase 3 genotype data. African (AFR) populations are marked with a blue diamond, Ad Mixed American (AMR) populations are marked with a green plus sign, East Asian (EAS) populations are marked with a red "X", European (EUR) populations are marked with a purple minus sign, and South Asian (SAS) populations are marked with a solid black circle.

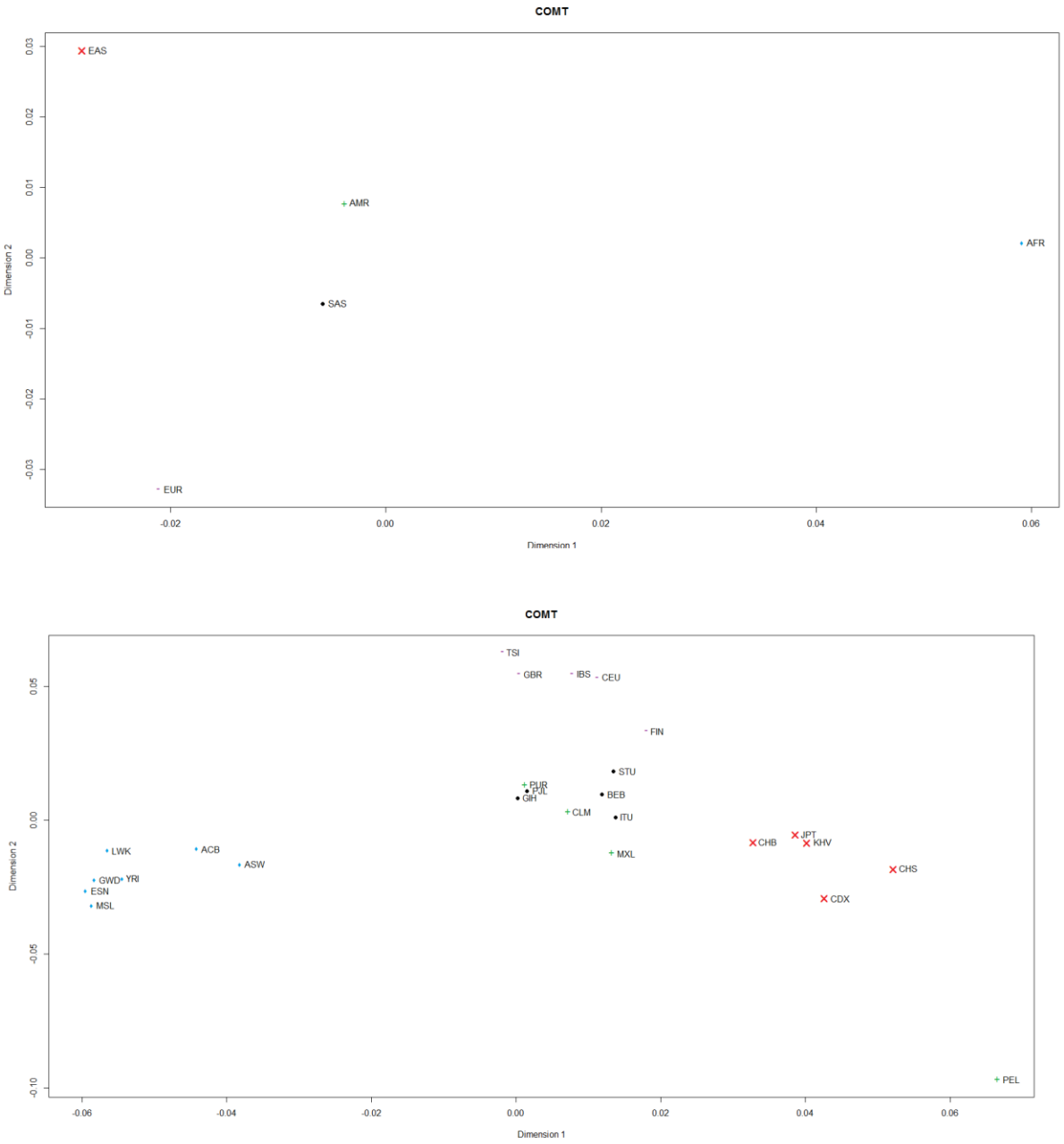


Figure 4 (continued). Multidimensional scaling plots of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* polymorphism pairwise genetic distances of five super-populations and 26 sub-populations based on 1000 Genome Project Phase 3 genotype data. African (AFR) populations are marked with a blue diamond, Ad Mixed American (AMR) populations are marked with a green plus sign, East Asian (EAS) populations are marked with a red "X", European (EUR) populations are marked with a purple minus sign, and South Asian (SAS) populations are marked with a solid black circle.

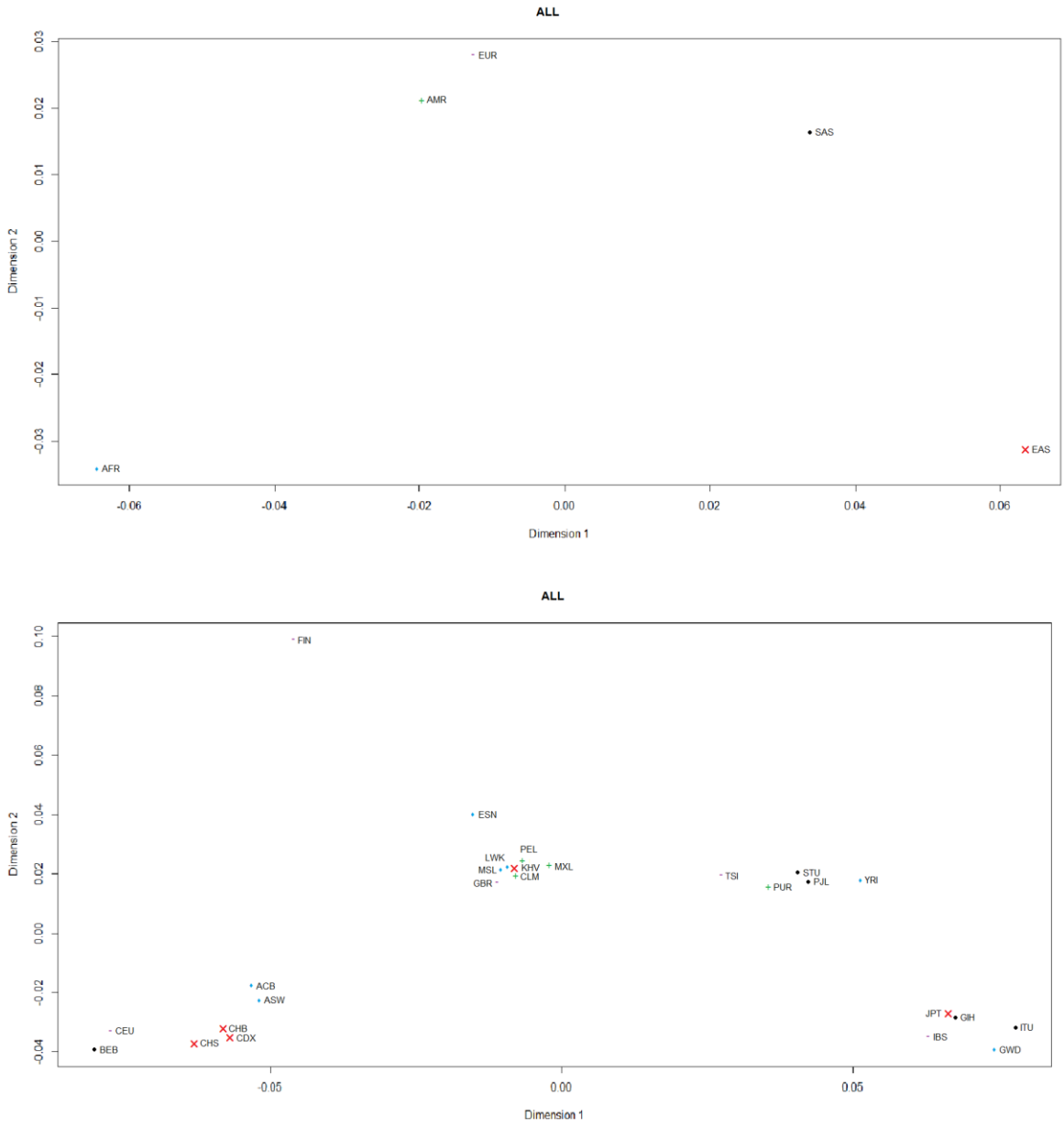


Figure 4 (continued). Multidimensional scaling plots of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* polymorphism pairwise genetic distances of five super-populations and 26 sub-populations based on 1000 Genome Project Phase 3 genotype data. African (AFR) populations are marked with a blue diamond, Ad Mixed American (AMR) populations are marked with a green plus sign, East Asian (EAS) populations are marked with a red "X", European (EUR) populations are marked with a purple minus sign, and South Asian (SAS) populations are marked with a solid black circle.

Variant effect prediction was performed on 613 *UGT2B7*, 5,986 *ABCB1*, 6,831 *OPRM1*, and 1,007 *COMT* polymorphisms to generate SIFT, PolyPhen-2, and PROVEAN scores (Supplemental Tables 19 through 22).[32-41] A summary of the average score and frequency of each variant effect is displayed in Table 3. Of the damaging, or most likely, damaging, exonic polymorphisms in *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, 100% (15/15, 25/25, 17/17, and 5/5 polymorphisms in *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, respectively) are the result of single amino acid changes. Intronic polymorphisms were analyzed further using HSF (Table 4). Those most likely to alter splicing of *UGT2B7*, *OPRM1*, and *COMT* account for < 5% of the total number of polymorphisms scored by HSF. The intronic polymorphisms of *ABCB1* predicted to most likely, or potentially, alter splicing account for over 50% of the total (Table 4). These polymorphisms are distributed across introns one through sixteen, with very few splice-altering polymorphisms occurring after intron sixteen (Figure 2c). Additionally, one *COMT* polymorphism was recognized by the variant effect predictors as a frame-shift mutation (rs563298832) but was not assigned a score by the three algorithms used. Manual inspection of the locus in IGV shows the CATT deletion within intron 5 so assignment as a frame-shift mutation is incorrect. The HSF algorithm did not score this locus either. It is possible that this intronic polymorphism is damaging to the resulting protein, however, this assumption is not supported or refuted by the data presented.

Intergenic Linkage Disequilibria

A total of 1,349 polymorphisms across all five target genes were assigned SIFT, PolyPhen-2, PROVEAN, and/or HSF scores. Tests for pairwise LD were performed on this subset of loci to address potential linkage disequilibria between polymorphisms that may alter

the activity of multiple proteins. After Bonferroni correction (5.50×10^{-8}), 9,573 AFR, 1,328 AMR, 2,517 EAS, 3,134 EUR, and 2,583 SAS significant pairwise LDs were observed between polymorphic loci of different genes ($p < 0.0004$, Supplemental Table 23). The number of significant pairwise LDs is less than that due to chance alone (i.e., ~45,461), however, those that contain two causal polymorphisms may be clinically significant. After removal of significant pairwise LDs containing loci which deviate from HWE expectations, there were 539, 12, 124, 282, and 128 significant pairwise LDs in the AFR, AMR, EAS, EUR, and SAS populations, respectively, between polymorphic loci in different genes that are predicted to be damaging, or most likely damaging to the resulting protein (Figure 5). Two polymorphisms are part of 82.2%, 98.4%, 46.8%, and 85.9% of these significant pairwise LDs within AFR, EAS, EUR, and SAS, respectively (rs5885589 and rs677830). Rs5885589 is an *ABCB1* intronic polymorphism which breaks an existing splice site and activates a cryptic splice site just upstream of exon 17. Rs677830 is found within exon 4 of *OPRM1* and confers glutamine411stop in transcript variant 1B5.[47] The AMR population does not have a substantial percentage of pairwise LDs associated with a single polymorphism.

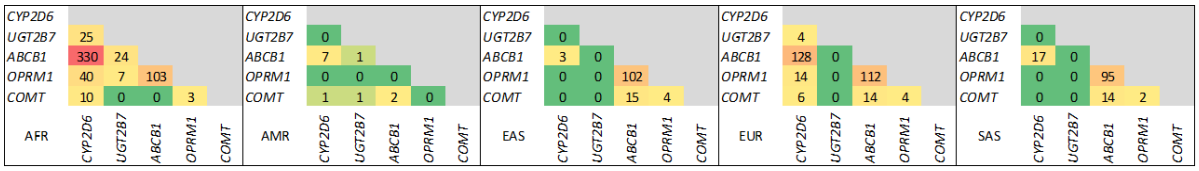


Figure 5. Summary of significant pairwise linkage disequilibria between polymorphisms on different genes in five major super-populations: African (AFR), Ad Mixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS).

Discussion

Our study is limited by two factors. Firstly, the coverage requirement for the 1000 Genomes Project is ~4X, producing an inherent level of missing variants or error in the sequence data. Secondly, due to limited size in each subpopulation, some rare alleles may not be observed due to sample size. When data are generated in-house with greater sub-population samples sizes, greater coverage can be applied that will reduce the level of error and increase the chance of observing rare alleles. However, our analyses add to the population studies on pharmacogenetically interesting genes at global scale.[48-50]

Potential contributors to the number of significant deviations from HWE expectations that were observed for *CYP2D6* and *UGT2B7* polymorphisms in the ACB and CHB populations, respectively, are allele drop-out, the effects of selection, and/or population substructure. For both sub-populations, some degree of substructure has been reported.[51-53] The Barbadian (ACB) population has demonstrated a higher degree of substructure relative to other ancestral African populations.[51,52] The Han Chinese also show some degree of substructure attributed to northern and southern Han populations. It has been shown that the 1000 Genomes CHB population contains individuals from these Han sub-groups.[53]

The 1000 Genomes Project contains self-reported healthy individuals and as such, the prevalence of *CYP2D6* PM, IM, and UM metabolizers may not reflect previously published datasets focusing on cohorts of affected individuals. The PCA plots of EMs explain relatively little variation (5.0% and 3.2%, respectively, for principle components one and two). These data support previous work demonstrating some level of intra-metabolizer status variability as well as intra-sub-population variability, which is supported by MDS plot of each population.

The *CYP2D6* MDS plots show separation of AFR and EAS from the cluster of AMR, EUR, and SAS, supporting previously reported clinical differences between these populations.[54] Lack of tight sub-population (within super-population) clustering supports previous findings that *CYP2D6* activity variation may be greater within than between super-populations.[55] For example, the sub-populations within the EAS super-population (CDX, CHB, CHS, KHV, and JPT) do not cluster tightly. The MDS plot indicates that the Chinese and Vietnamese populations (CDX, CHB, CHS, and KHV) may be different from the Japanese (JPT) population. While minimal, this Asian variability is not novel and may be clinically significant when treating patients of these ancestries.[56] MDS plots of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* show considerably less between super-population clustering, specifically of the SAS, EUR, and AMR populations, suggesting that differences in these genes may be somewhat associated to super-populations. MDS plots of ~15,000 polymorphisms do not show sub-population clustering with their respective super-populations. This observation may be explained by the extreme allele frequency differences between sub-populations of the same super-population. For example, the *OPRM1* SNP, rs66579098, has alternate allele frequencies of 0.27, 0.33, 0.52, and 0.78 in the PUR, CLM, MXL, and PEL sub-populations, respectively (belonging to the AMR super-population).[26,57]

Tests for pairwise LD of damaging, or likely damaging, polymorphisms in all five genes showed association between polymorphisms from all genes. The rs677830 (*OPRM1*) and rs5885589 (*ABCB1*) account for a substantial percentage of significant pairwise LDs in the AFR, EAS, EUR, and SAS populations. These significant LDs may be clinically relevant due to the potential for multilocus interactions[44]. To our knowledge, rs677830 and rs5885589 have not been reported as causal polymorphisms. Interactions between these loci, or others,

may be responsible for compensation when a damaging polymorphism dramatically alters normal protein activity, as suggested by Bartošová, *et al.* 2015[58] and Barratt, *et al.* 2012[59] with *ABCB1* and *OPRM1* polymorphisms shown to alter protein activity *in vivo*.

In conclusion, baseline population summary statistics are presented on five genes involved in opiate metabolism that have been implicated in phenotypic variability leading to idiosyncratic responses in patients. This study demonstrates some genetic association between *CYP2D6* and *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* that will be important for future pharmacogenetic studies and combinatorial genetic approaches for patient care.

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Supplementary Information

Supplemental Table 1. 1000 Genomes Project population codes and descriptions for five super-populations and 26 sub-populations.[26]

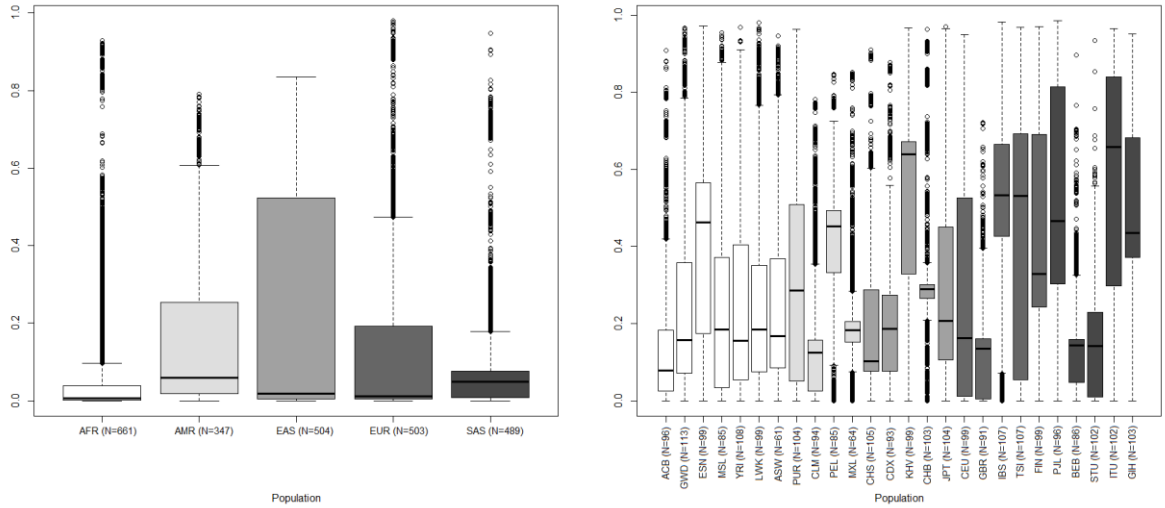
Super-Population (Code)	Sample Size	Population Code	Population Description	Sample Size
African (AFR)	661	YRI	Yoruba in Ibadan, Nigeria	108
		LWK	Luhya in Webuye, Kenya	99
		GWD	Gambian in Western Divisions in Gambia	113
		MSL	Mende in Sierra Leone	85
		ESN	Esan in Nigeria	99
		ASW	American of African Ancestry in Southwest United States	61
		ACB	African Caribbeans in Barbados	96
Ad Mixed American (AMR)	347	MXL	Mexican Ancestry from Los Angeles, USA	64
		PUR	Puerto Ricans from Puerto Rico	104
		CLM	Colombians from Medellin, Colombia	94
		PEL	Peruvians from Lima, Peru	85
East Asian (EAS)	504	CHB	Han Chinese in Beijing China	103
		JPT	Japanese in Tokyo, Japan	104
		CHS	Southern Han Chinese	105
		CDX	Chinese Dai in Xishuangbanna, China	93
		KHV	Kinh in Ho Chi Minh City, Vietnam	99
European (EUR)	503	CEU	Utah Residents (CEPH) with Northern and Western Ancestry	99
		TSI	Toscani in Italia	107
		FIN	Finnish in Finland	99
		GBR	British in England and Scotland	91
		IBS	Iberian Population in Spain	107
South Asian (SAS)	489	GIH	Gujarati Indian from Houston, Texas	103
		PJL	Punjabi from Lahore, Pakistan	96
		BEB	Bengali from Bangladesh	86
		STU	Sri Lankan Tamil from the United Kingdom	102
		ITU	Indian Telugu from the United Kingdom	102

Supplemental Table 2. Allele frequencies and counts for *CYP2D6* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. Multiple alternate alleles and allele frequencies for the same locus are separated by a comma; N is equal to the number of alleles in the respective population. Supplemental Table 2 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

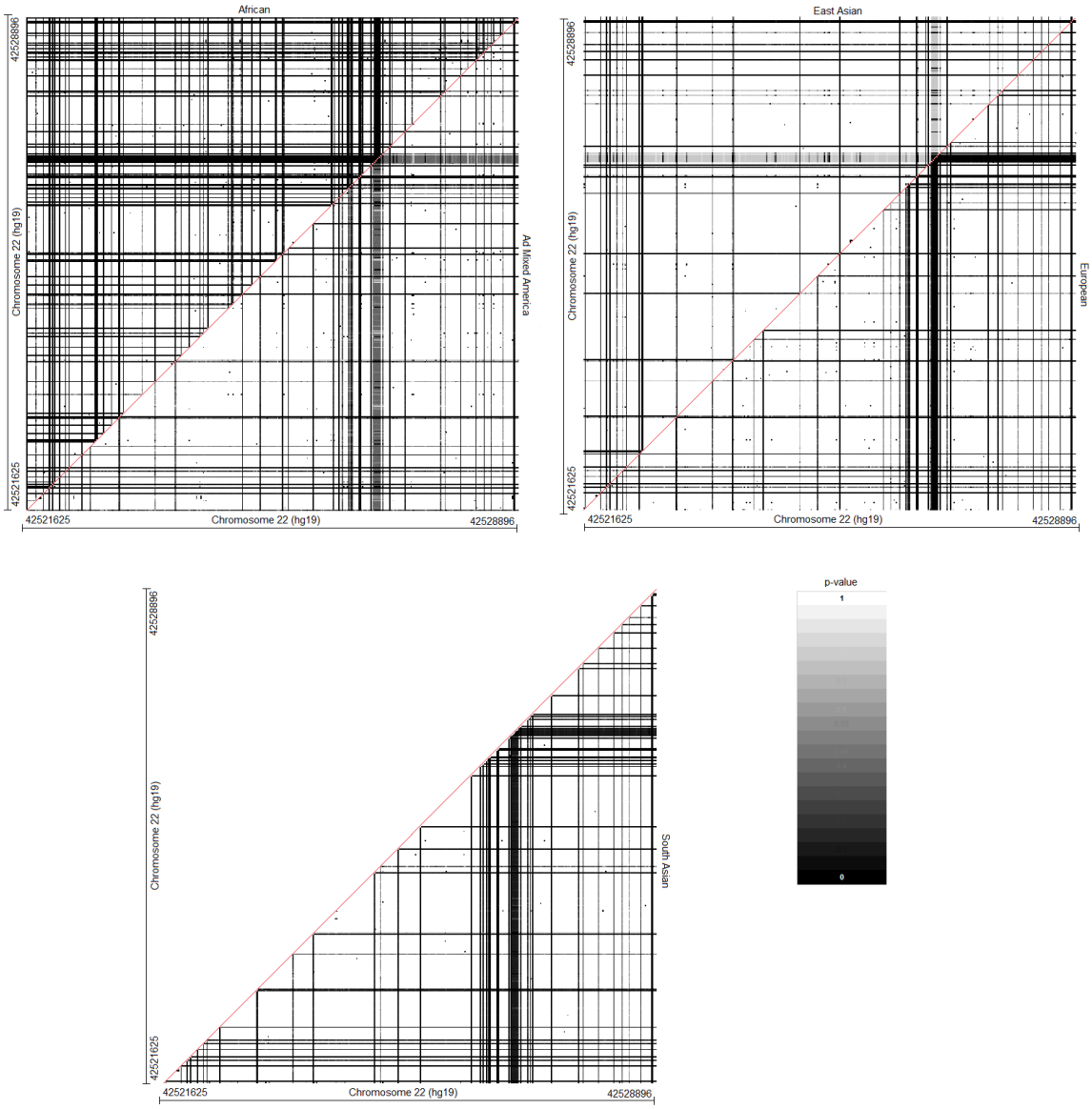
Supplemental Table 3. Observed and expected heterozygosities for *CYP2D6* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. N is equal to the number of individuals in each population. Supplemental Table 3 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 4. Hardy-Weinberg equilibrium p-values for *CYP2D6* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. N is equal to the number of individuals in each population; bolded and italicized values are

significant after Bonferroni correction (p = 0.000120). Supplemental Table 4 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).



Supplemental Figure 1. Distribution of pairwise linkage disequilibrium p-values < 1 for *CYP2D6* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five major global super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. Each boxplot represents a single populations; the center horizontal line represents the mean, the lower and upper boundaries of each box represent the first and third quartiles, respectively, the vertical dashed lines indicate plus/minus three times the interquartile range, and closed circles indicate outliers; N is equal to the number of individuals in each population; p-values for specific pairwise loci comparisons may be shared upon request.



Supplemental Figure 2. Heat map of linkage disequilibrium p-values for *CYP2D6* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations. Super-populations are separated by a diagonal red line.

Supplemental Table 5. Variant effect prediction for 418 polymorphisms in the *CYP2D6* gene region. Supplemental Table 5 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 6. *CYP2D6* star (*) allele frequencies (95% confidence interval) in five super- and 26 sub-populations. Supplemental Table 6 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 7. Allele frequencies and counts for *UGT2B7* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. Multiple alternate alleles for the same locus are separated by a comma; N is equal to the number of alleles in the respective population. Supplemental Table 7 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 8. Allele frequencies and counts for *ABCB1* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. Multiple alternate alleles for the same locus are separated by a comma; N is equal to the number of alleles in the respective population. Supplemental Table 8 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 9. Allele frequencies and counts for *OPRM1* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. Multiple alternate alleles for the same locus are separated by a comma; N is equal to the number of alleles in the respective population. Supplemental Table 9 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 10. Allele frequencies and counts for *COMT* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. Multiple alternate alleles for the same locus are separated by a comma; N is equal to the number of alleles in the respective population. Supplemental Table 10 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 11. Observed and expected heterozygosities for *UGT2B7* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. N is equal to the number of individuals in each population. Supplemental Table 11 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 12. Observed and expected heterozygosities for *ABCB1* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. N is equal to the number of individuals in each population. Supplemental Table 12 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 13. Observed and expected heterozygosities for *OPRM1* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. N is equal to the number of individuals in each population. Supplemental Table 13 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

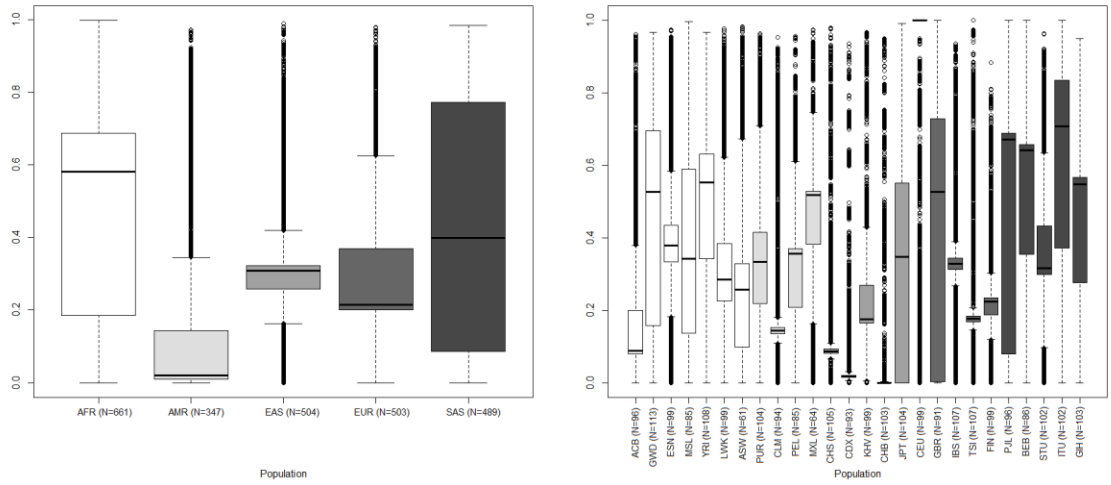
Supplemental Table 14. Observed and expected heterozygosities for *COMT* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. N is equal to the number of individuals in each population. Supplemental Table 14 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 15. Hardy-Weinberg equilibrium p-values for *UGT2B7* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. N is equal to the number of individuals in each population; bolded and italicized values are significant after Bonferroni correction ($p = 8.16 \text{ X } 10^{-5}$). Supplemental Table 15 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

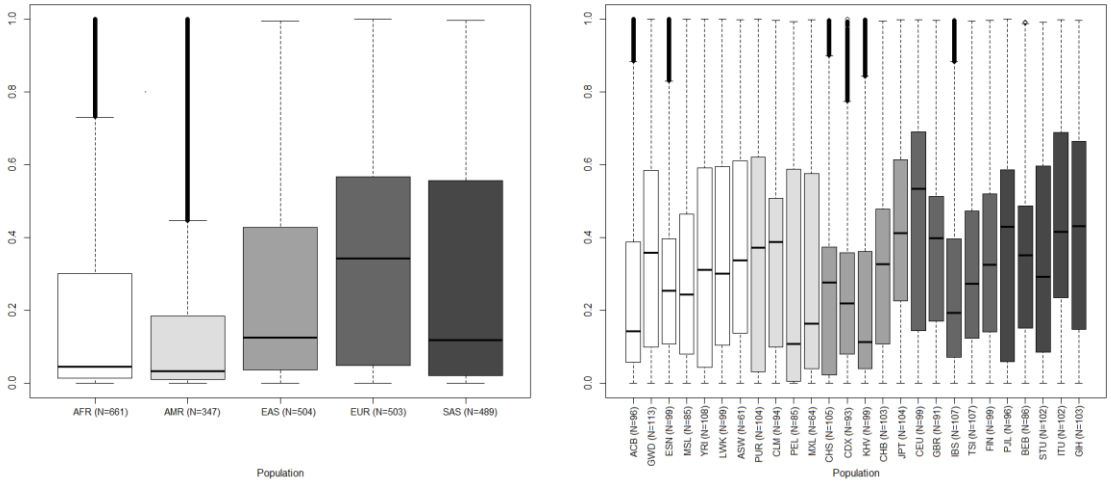
Supplemental Table 16. Hardy-Weinberg equilibrium p-values for *ABCB1* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. N is equal to the number of individuals in each population; bolded and italicized values are significant after Bonferroni correction ($p = 8.35 \text{ X } 10^{-6}$). Supplemental Table 16 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 17. Hardy-Weinberg equilibrium p-values for *OPRM1* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. N is equal to the number of individuals in each population; bolded and italicized values are significant after Bonferroni correction ($p = 7.32 \text{ X } 10^{-6}$). Supplemental Table 17 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 18. Hardy-Weinberg equilibrium p-values for *COMT* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. N is equal to the number of individuals in each population; bolded and italicized values are significant after Bonferroni correction ($p = 4.97 \text{ X } 10^{-5}$). Supplemental Table 18 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).



Supplemental Figure 3. Distribution of pairwise linkage disequilibrium p-values < 1 for *UGT2B7* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five major global super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. Each boxplot represents a single populations; the center horizontal line represents the mean, the lower and upper boundaries of each box represent the first and third quartiles, respectively, the vertical dashed lines indicate plus/minus three times the interquartile range, and closed circles indicate outliers; N is equal to the number of individuals in each population; p-values for specific pairwise loci comparisons may be shared upon request.



Supplemental Figure 4. Distribution of pairwise linkage disequilibrium p-values < 1 for *ABCB1* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five major global super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. Note that tests for pairwise LD were only performed for those loci which deviated from Hardy-Weinberg equilibrium expectations against all other loci. Each boxplot represents a single populations; the center horizontal line represents the mean, the lower and upper boundaries of each box represent the first and third quartiles, respectively, the vertical dashed lines indicate plus/minus three times the interquartile range,

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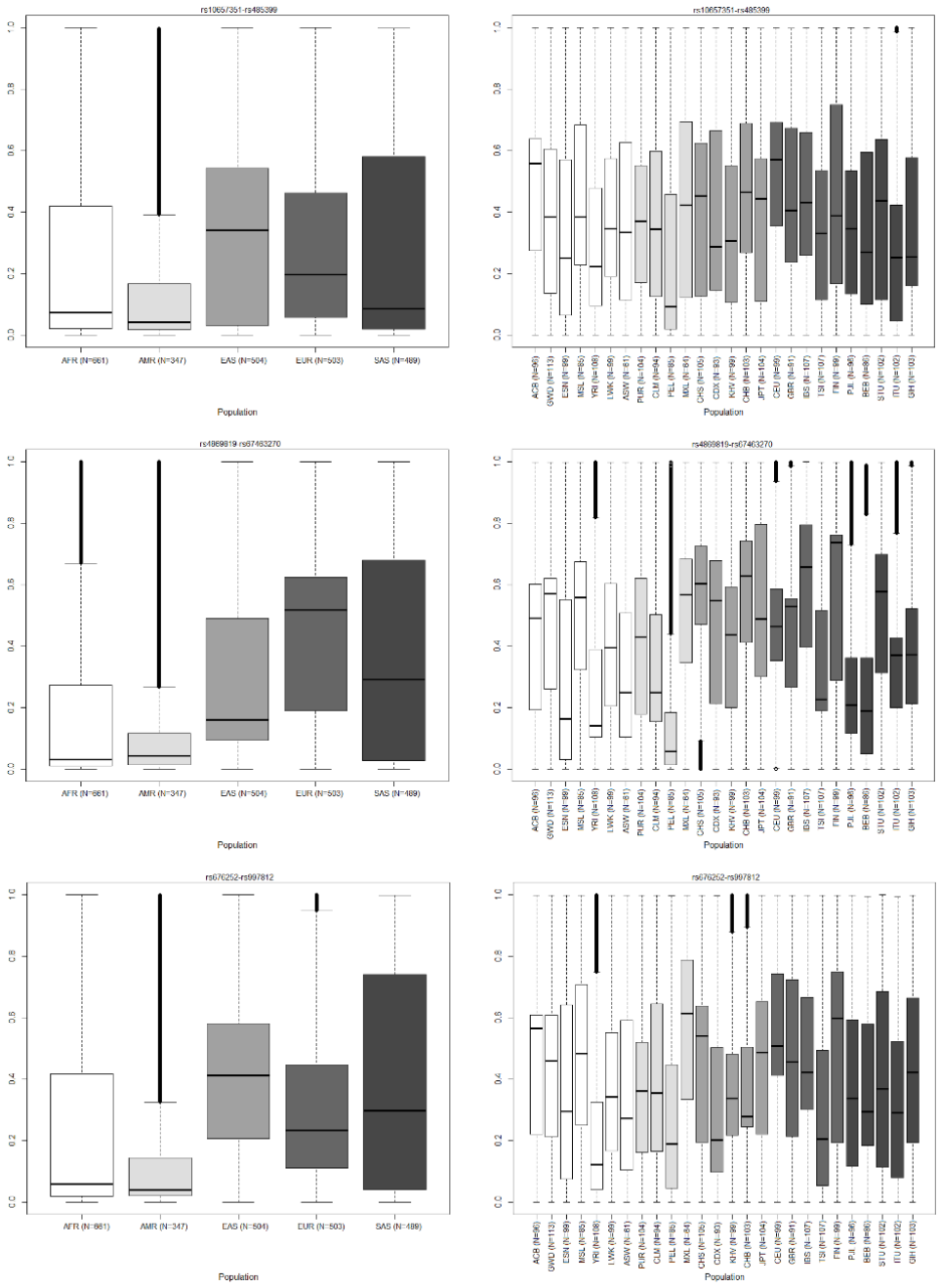
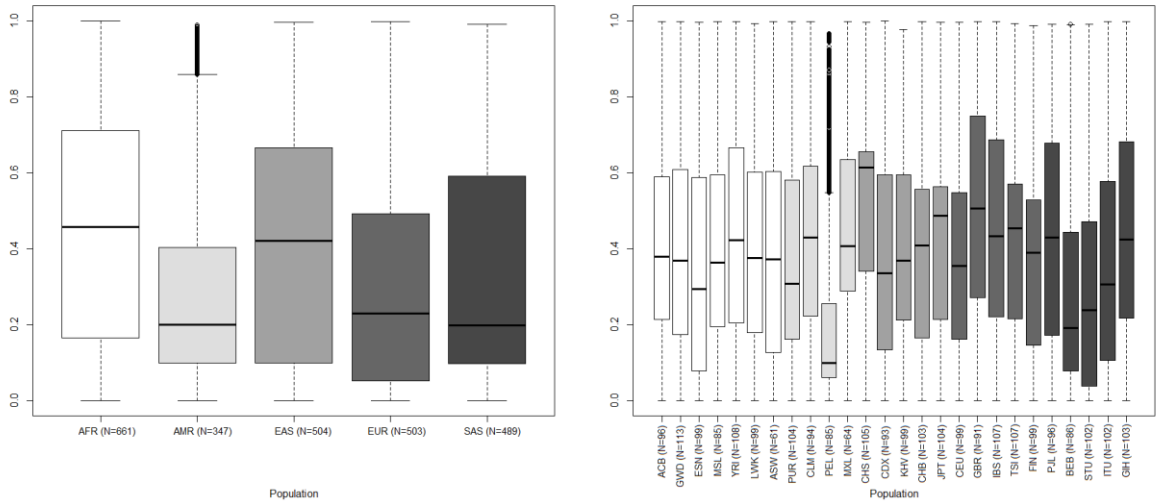
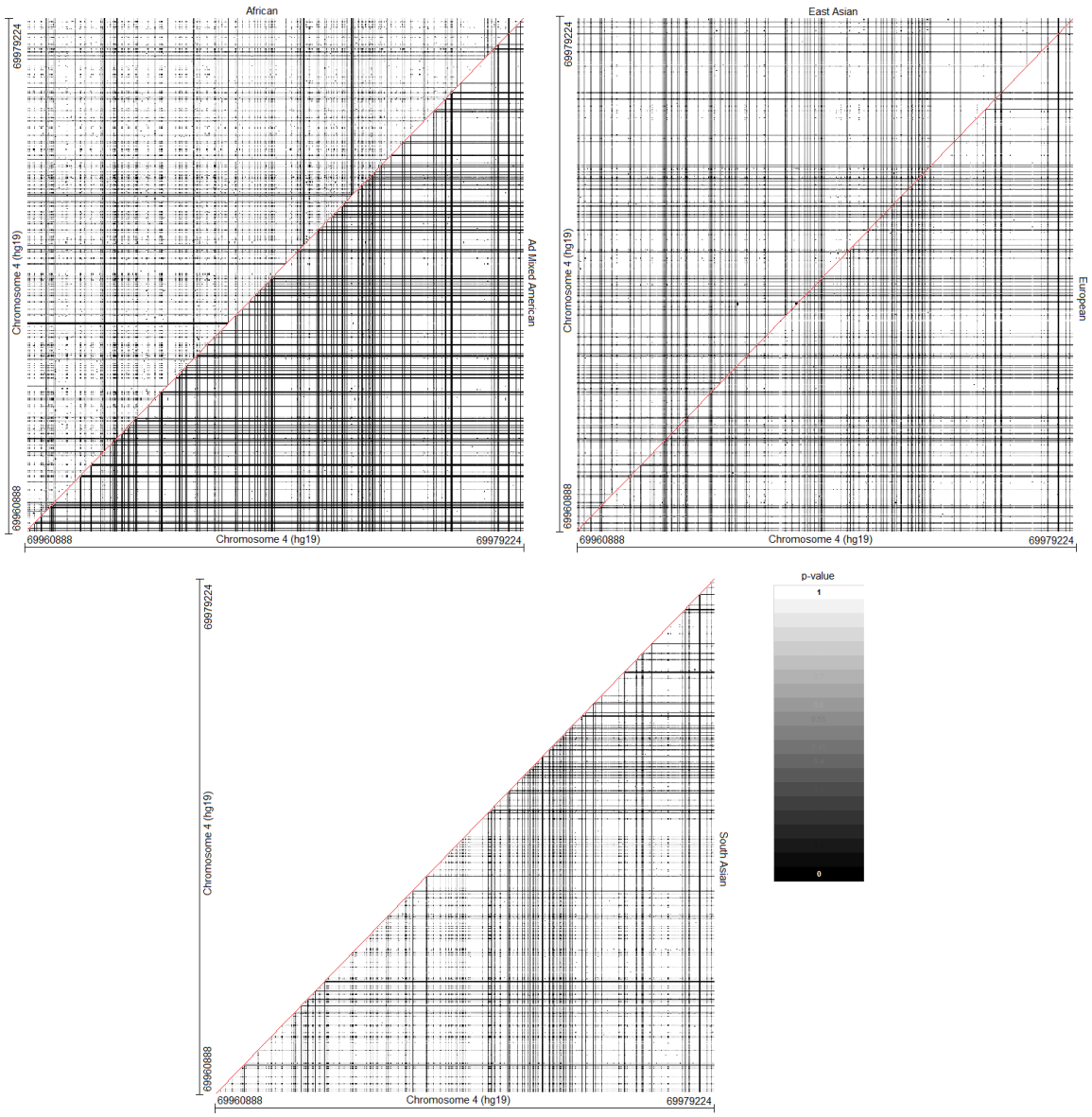


Supplemental Figure 5. Distribution of pairwise linkage disequilibrium p-values < 1 for *OPRM1* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five major global super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. Note that tests for pairwise LD were only performed for those loci which deviated from Hardy-Weinberg equilibrium expectations against all other loci. Due to computational limitations, all pairwise loci comparisons could not be represented in the same boxplot; boxplots are separated according to numerical order of the first locus in

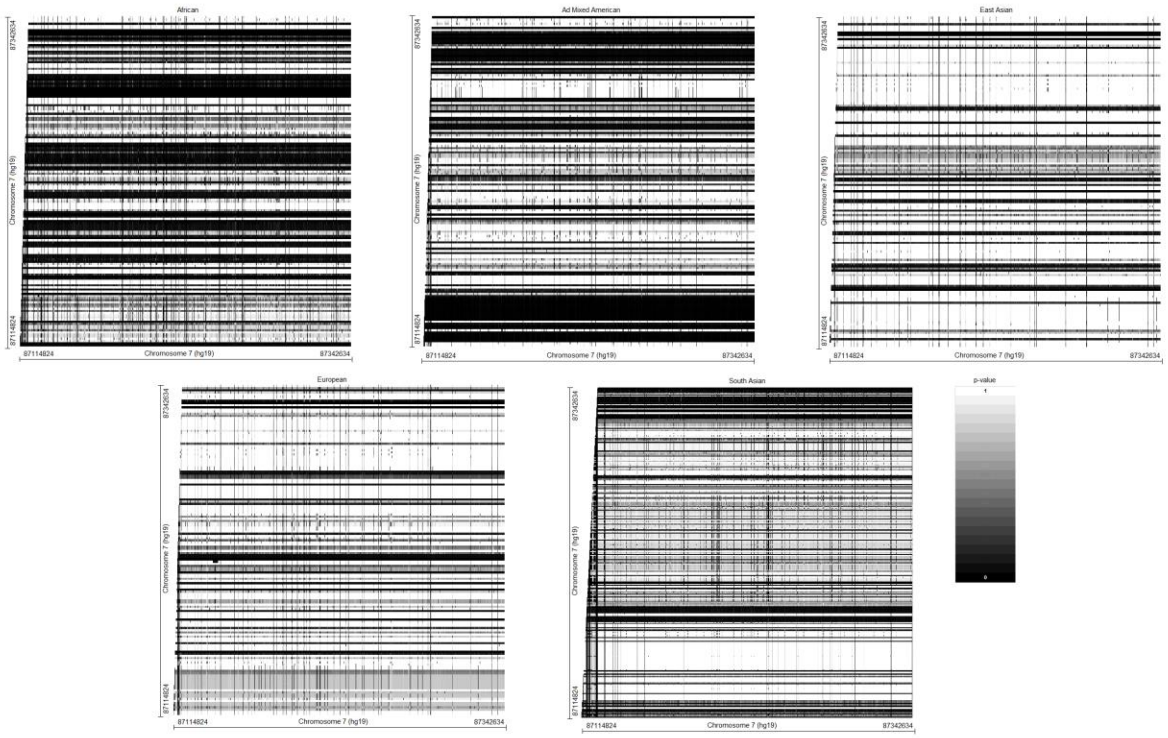
the pairwise comparison. Each boxplot represents a single populations; the center horizontal line represents the mean, the lower and upper boundaries of each box represent the first and third quartiles, respectively, the vertical dashed lines indicate plus/minus three times the interquartile range, and closed circles indicate outliers; N is equal to the number of individuals in each population; p-values for specific pairwise loci comparisons may be shared upon request.



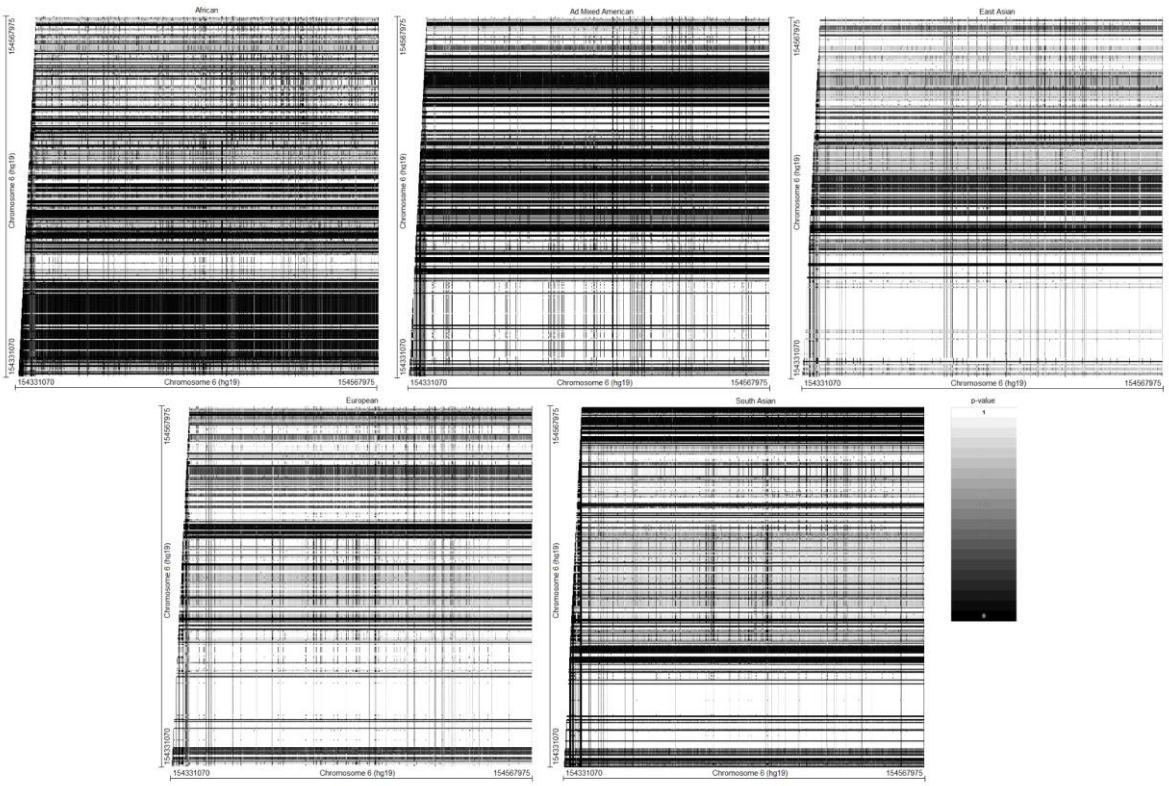
Supplemental Figure 6. Distribution of pairwise linkage disequilibrium p-values < 1 for *COMT* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five major global super-populations and 26 sub-populations based on 1000 Genomes Project Phase 3 genotype data. Each boxplot represents a single populations; the center horizontal line represents the mean, the lower and upper boundaries of each box represent the first and third quartiles, respectively, the vertical dashed lines indicate plus/minus three times the interquartile range, and closed circles indicate outliers; N is equal to the number of individuals in each population; p-values for specific pairwise loci comparisons may be shared upon request.



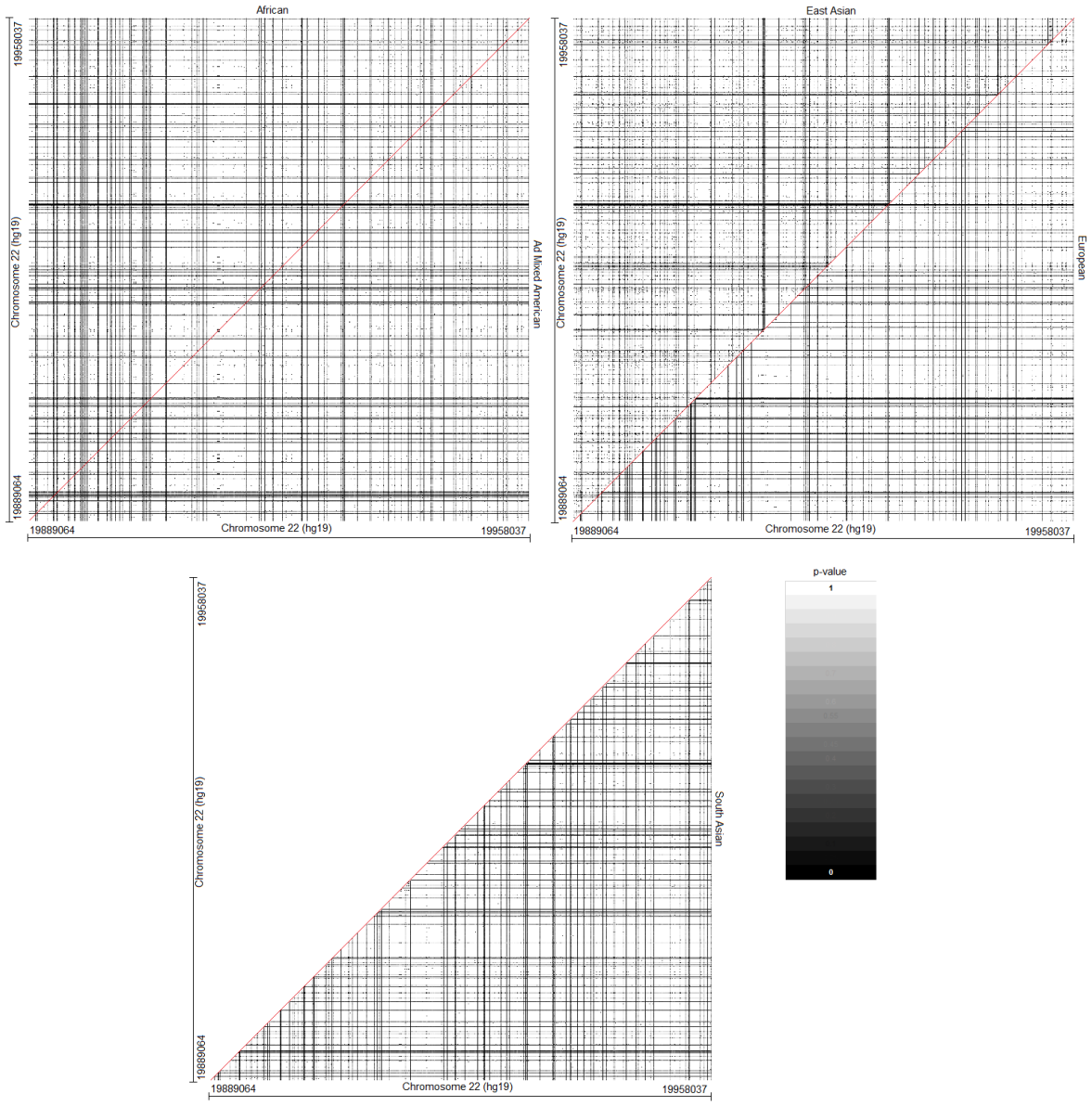
Supplemental Figure 7. Heat maps of pairwise linkage disequilibrium p-values for *UGT2B7* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations. Super-populations are separated by a diagonal red line.



Supplemental Figure 8. Heat map of linkage disequilibrium p-values for *ABCB1* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations. Super-populations are separated by a diagonal red line. Note that pairwise LDs were only performed for those loci which deviated from Hardy-Weinberg equilibrium expectations.



Supplemental Figure 9. Heat map of linkage disequilibrium p-values for *OPRM1* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations. Super-populations are separated by a diagonal red line. Note that pairwise LDs were only performed for those loci which deviated from Hardy-Weinberg equilibrium expectations.



Supplemental Figure 10. Heat map of linkage disequilibrium p-values for *COMT* single nucleotide polymorphisms, insertion/deletion polymorphisms, and copy number variants in five super-populations. Super-populations are separated by a diagonal red line.

Supplemental Table 19. Variant effect prediction for 613 polymorphisms in the UGT2B7 gene region. Supplemental Table 19 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 20. Variant effect prediction for 5,986 polymorphisms in the *ABCB1* gene region. Italicized polymorphisms are found within regions of overlap between *ABCB1* and *RUNDC3B*. Supplemental Table 20 can be viewed at The Pharmacogenomics Journal's

website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 21. Variant effect prediction for 6,831 polymorphisms in the *OPRM1* gene region. Supplemental Table 21 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 22. Variant effect prediction for 1,007 polymorphisms in the *COMT* gene region. Italicized polymorphisms are found within regions of overlap between *COMT* and *TXNRD2* or *ARVCF*. Bolded polymorphisms were assigned SIFT, PolyPhen-2, and/or PROVEAN scores, however, they align with amino acids in *ARVCF*, not *COMT*. Supplemental Table 22 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

Supplemental Table 23. Pairwise linkage disequilibrium p-values for 1,349 polymorphisms across *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* that were assigned SIFT, PolyPhen-2, PROVEAN, and/or HSF scores leading to damaging, or most likely damaging, predictions. Bolded and italicized p-values are significant after Bonferroni correction ($p = 5.50 \times 10^{-8}$). Supplemental Table 23 can be viewed at The Pharmacogenomics Journal's website for this article (https://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201713a.html).

CHAPTER 3

Full-Gene Haplotypes Refine CYP2D6 Metabolizer Phenotype Inferences

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Abstract

CYP2D6 is a critical pharmacogenetic target and polymorphisms in the gene region are commonly used to infer enzyme activity score and predict resulting metabolizer phenotype: poor, intermediate, extensive/normal, or ultrarapid which can be useful in determining cause and/or manner of death in some autopsies. Current genotyping approaches are incapable of identifying novel and/or rare variants so *CYP2D6* star allele definitions are limited to polymorphisms known a priori. While useful for most predictions, recent studies using massively parallel sequencing data have identified additional polymorphisms in *CYP2D6* that are predicted to alter enzyme function but are not considered in current star allele nomenclature. The 1000 Genomes Project data were used to produce full-gene haplotypes, describe their distribution in super-populations, and predict enzyme activity scores. Full-gene haplotypes generated lower activity scores than current approaches due to inclusion of additional damaging polymorphisms in the star allele. These findings are critical for clinical implementation of metabolizer phenotype prediction because a fraction of the population may be incorrectly considered normal metabolizers but actually may be poor or intermediate metabolizers.

Introduction

The cytochrome p450 family 2 subfamily D polypeptide 6 (CYP2D6) enzyme is part of a large family of CYPs responsible for a substantial portion of hepatic Phase I metabolism of foreign compounds and endogenous toxins [1,2]. The enzyme has been implicated in drug metabolism variation of clinical and medico-legal relevance [3,4]. Current methods of pharmacogene analyses employ targeted approaches, such as genome wide association studies of candidate single nucleotide polymorphisms (SNPs) and SNP-targeted massively parallel sequencing (MPS) of known a priori SNPs and/or insertion/deletion polymorphisms (INDELs) [5]. The *CYP2D6* allele nomenclature, in the Human Cytochrome P450 Allele Nomenclature Database (HCYPAND) [6], identifies and defines polymorphisms that confer each *CYP2D6* star (*) allele (the collection of polymorphisms within the gene region). *CYP2D6* * allele genotypes (g), or diplotypes, commonly provide inferences of metabolizer phenotype (MP; poor [gPM], intermediate [gIM], normal/extensive [gNM/gEM], or ultrarapid [gUM] CYP2D6 activity) [1,2,6,7]. It has been demonstrated both clinically and medico-legally that *CYP2D6* information can result in increased prescription efficacy and inference of idiosyncratic effect during accident reconstruction [8-12]. In fact, Koren, *et al.* [8] and Koski, *et al.* [9,10] have used targeted genotyping of *CYP2D6* to make inferences regarding the cause and/or manner of death in a series of medico-legal cases. However, targeted genotyping approaches inherently are incapable of revealing novel polymorphisms that may further refine CYP2D6 * alleles and the associated metabolic differences observed in clinical cases and medico-legal investigations. MPS of the full gene region has the potential to reveal additional polymorphisms and refine predictions of CYP2D6 activity.

Wendt, *et al.* [13] characterized 418 polymorphisms in *CYP2D6* exons, introns, 3' and 5' untranslated regions, and promoter region in the 1000 Genomes Project dataset. 97 (23.2%) of the polymorphisms are currently used by HCYPAND to classify some of the < 150 *CYP2D6* * alleles observed to date. The remaining 321 polymorphisms have a wide range of allele frequencies in the African (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS) super-populations. Most notable are those polymorphisms predicted to damage, or most likely damage, CYP2D6 function. Ignoring these loci when determining *CYP2D6* * alleles may lead to inaccurate predictions of enzyme function and incorrect conclusions for drug therapy or potential cause and/or manner of death investigations. The HCYPAND database has established inclusion criteria for newly observed *CYP* alleles [14] which put more emphasis on enzyme-altering polymorphisms for the sake of providing minimalist nomenclature. However, in medico-legal autopsy cases where incident reconstruction and cause and/or manner of death may be inferred from toxicology and genetic data [8-10], a more comprehensive and inclusive nomenclature may be necessary. Herein, all typed loci from the 1000 Genomes Project data were used to generate and characterize full-gene *CYP2D6* haplotypes. These data indicate that the phenotypic impact of some previously defined *CYP2D6* * alleles may have been mischaracterized due to damaging polymorphisms occurring elsewhere in the gene relative to a HCYPAND causal SNP or INDEL. Mischaracterizations based on targeted genotyping and traditional * allele nomenclature may have clinical and medico-legal consequences, as a fraction of 1000 Genomes Project samples may be inaccurately placed into MP categories.

Materials and Methods

Polymorphisms in the *CYP2D6* gene region (introns, exons, 5' and 3' untranslated regions [UTRs], and promoter) were downloaded from Phase 3 of the 1000 Genomes Project [15,16] and analyzed individually in 5 super- and 26 sub-populations (Table S1) according to Wendt, *et al.* 2017 [13]. 1000 Genomes Project *CYP2D6* haplotypes containing reportedly phased polymorphisms [17] were aligned to the hg38 and hg19 reference genomes and the M33388 GenBank accession reference sequence (Table S2) for ease of community comparison [18-21]. CYP2D6 full-gene haplotypes were named relative to the reverse DNA strand of three reference sequences with the following nomenclature format: reference sequence (genome name or GenBank Accession Number)- HCYPAND CYP2D6* allele designation-polymorphism rs number, if known, followed by the base at that position. Note that if an rs number is not provided for a specific location, the nucleotide position and base change, relative to the indicated reference, are provided. For example, haplotype 1 is named M33388-*CYP2D6*: 5157insCCCACCCCTT, hg19-*CYP2D6*: rs28439297A; rs28680494G; rs1080983G; rs1080985C; rs28735595A; rs28624811C; rs28633410G; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; rs28371699G; rs28371701C; rs28371702T; rs1058164G; rs16947C; rs28371730G; rs1135840G; rs116390392G; rs71184866insACA; rs35028622T; rs34386013T, and hg38-*CYP2D6*: None, relative to the M33388, hg19, and hg38 reference genomes, respectively.

Full-gene *CYP2D6* haplotypes and diplotypes for 2,504 individuals in five super- and 26 sub-populations were created using excel-based workbooks. Private mutations (those polymorphisms observed once in the 1000 Genomes dataset), except those considered clinically relevant by HCYPAND and those predicted by Wendt, *et al.* 2017 [13] to damage,

or most likely damage, the resulting protein, were removed from haplotype formation to simplify downstream analyses. 1000 Genomes Project haplotypes were named according to the same convention described above. Genetic Data Analysis [22] was used to determine haplotype and diplotype frequencies, observed (Ho) and expected (He) heterozygosities, pairwise genetic distances, and perform tests for detection of departures from Hardy-Weinberg Equilibrium (HWE). TreeView Version 1.6.6 Build 7601 [23,24] and RStudio® [25] were used to create phylogenetic trees and multidimensional scaling (MDS) plots, respectively. Network analyses were performed using Population Analysis with Reticulate Trees (PopART) [26]. For comparison to HCYPAND CYP2D6 * alleles, full-gene haplotypes lacking amino acid changes and damaging intronic sequences are considered derivatives of CYP2D6*1 and full-gene haplotypes conferring R296C (or C296R for hg19-based haplotypes) and S486T (or T486S for hg19-based haplotypes) but no other amino acid changes or damaging intronic polymorphisms were considered derivatives of CYP2D6*2.

Activity scores were assigned to each allele (i.e., 0, 0.5, 1, or 2) and individual (i.e., 0, 0.5, 1, 1.5, 2, or 3) in two ways: (1) Full-gene haplotypes were assigned a most similar HCYPAND -recognized allele which was then assigned an activity score based on Gaedigk, et al. [27] without considering the impact of additional polymorphisms not recognized by HCYPAND [6]; (2) Considering all polymorphisms, a best- and worst-case activity score were assigned to each full-gene haplotype. For example, haplotype 33 (M33388-*CYP2D6*: 310T; 843G; 1067G; 5157insCCCACCCCTT) received an activity score of 1 based on absence of HCYPAND causal polymorphisms only (resembling a normally active * allele). The presence of non-HCYPAND intronic polymorphism rs78854695, 1067G, damages splicing [13] but its

specific impact on CYP2D6 has not been confirmed empirically. So haplotype 33 was assigned best- and worst-case activity scores of 0.5 and 0, respectively.

Results

Histograms of SIFT [28-33], PolyPhen-v2 [28,34,35], and PROVEAN [36-38] scores from Wendt, *et al.* [13] for HCYPAND-recognized and non-HCYPAND polymorphisms (Figure 1) indicate that 29, 20, and 30 polymorphisms, respectively, from the 1000 Genomes Project dataset for *CYP2D6* are predicted to negatively impact protein function. After removal of 138 private mutations, except those considered causal by HCYPAND and those considered damaging or most likely damaging based on Wendt, *et al.* [13], 446 unique full-gene haplotype string sequences were observed (Table S2). Full-gene *CYP2D6* haplotypes 11, 3, and 1 are identical to reference sequences M33388, hg19, and hg38, respectively. A majority of haplotypes were observed once in the global population so the average global frequency of full-gene *CYP2D6* haplotypes was quite low (0.00224 ± 0.0115 with a range of 0.165 (haplotype 1) to 0.000200 (haplotypes 205 through 446)). Haplotypes 1 through 18, had global frequencies ≥ 1%, with an average frequency of 0.0394 ± 0.0438 (Table 1 and Figure 2). The average super-population frequencies for haplotypes 1 through 18 were 0.0348 ± 0.0382 in AFR, 0.0508 ± 0.0832 in AMR, 0.0110 ± 0.0169 in EAS, 0.0539 ± 0.0559 in EUR, and 0.0638 ± 0.102 in SAS.

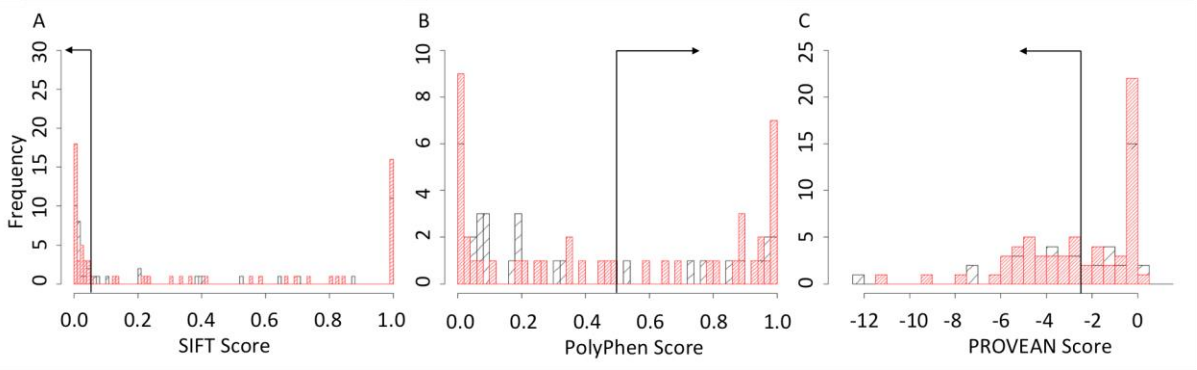


Figure 1. Distribution of variant effect prediction for Clinical Pharmacogenetics Implementation Consortium polymorphisms and those not used for *CYP2D6* nomenclature. Distribution of Sort Intolerant From Tolerant (SIFT) (A) [28-33], Polymorphism Phenotyping v2 (PolyPhen-v2) (B) [28,34,35], and Protein Variant Effect Analyzer (PROVEAN) (C) [36-38] scores from Wendt, et al. [13] for The Human CYP Allele Nomenclature Database recognized polymorphisms (black bars) and polymorphisms not considered by the database (red bars). Arrows indicate the threshold applied to scores from each algorithm to predict the damaging or benign effect a polymorphism has on protein function; scores < 0.05, > 0.5, < -2.5 for SIFT, PolyPhen-v2, and PROVEAN, respectively, may impact protein function.

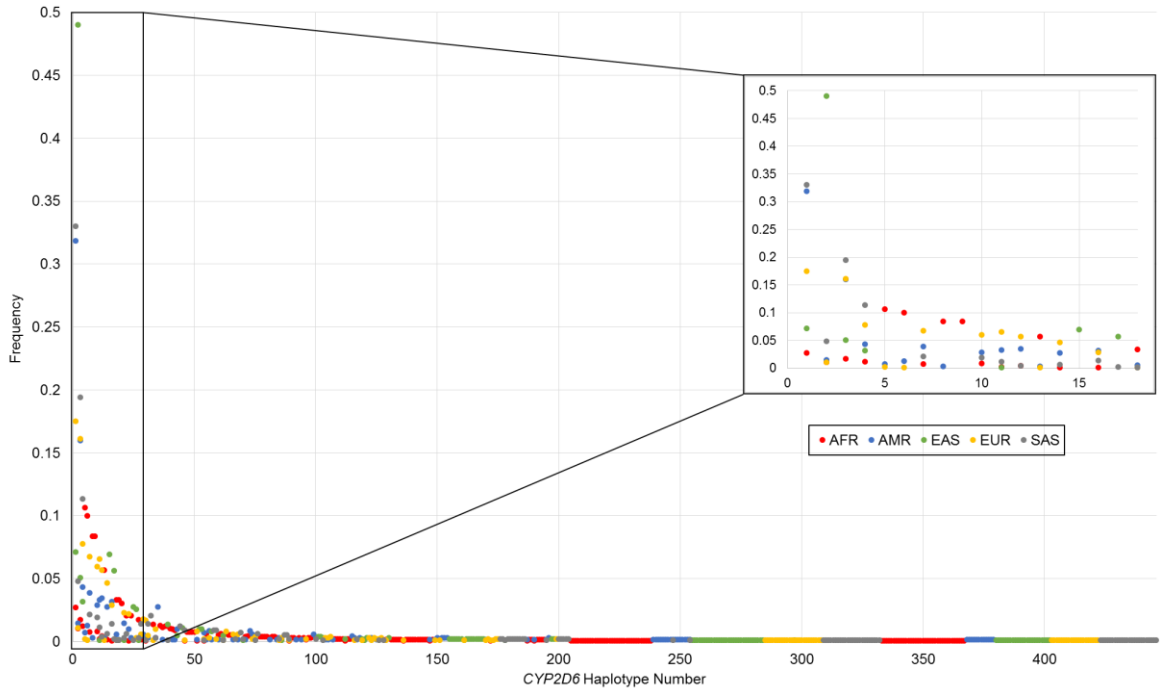


Figure 2. *CYP2D6* haplotype frequencies. Observed frequencies of 446 full-gene *CYP2D6* haplotypes in five major super-populations (African [AFR], Admixed American [AMR], East Asian [EAS], European [EUR], and South Asian [SAS]). The inset graph shows the frequency of those haplotypes with greater than 30 observations globally.

Table 1. Full-gene *CYP2D6* haplotypes with ≥ 1% global frequency. Eighteen cytochrome p450 family 2, subfamily D, polypeptide 6 (*CYP2D6*) full-gene haplotypes with global allele frequencies ≥ 1% in the 1000 Genomes Project dataset. Italicized nucleotide positions and rs numbers indicate polymorphisms that change the amino acid sequence relative to the indicated reference genome; underlined nucleotide positions and rs numbers alter CYP2D6 function [6,27,39-41].

Haplotype Number	Most Similar CYP2D6 * Allele	Reported Activity	Gaedigk, *et al.* Activity Score	Full-gene Best Case Activity Score	Full-gene Worst Case Activity Score	M33388 Nomenclature	M33388 Amino Acid Changes	Hg19 Nomenclature	Hg19 Amino Acid Changes	Hg38 Nomenclature	Hg38 Amino Acid Changes
1	1	Normal	1	1	1	M33388-*CYP2D6* : 5157insCCCACCCCTT	-	hg19-*CYP2D6* : rs28439297A; rs28680494G; rs1080983G; rs1080985C; rs28735595A; rs28624811C; rs28633410G; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; rs28371699G; rs28371701C; rs28371702T; rs1058164G; *rs16947C* ; rs28371730G; *rs1135840G* ; rs116390392G; rs71184866insACA; rs35028622T; rs34386013T	Splice Defect; C296R; T486S	hg38-*CYP2D6* : None	-
2	4	None	0	0	0	M33388-*CYP2D6* : -2060G; -2053T; -1426T; -1235G; -1000A; *100T* ; 310T; 843G; 1039T; 1661C; 2097G; 3582G; *4180C* ; 4401T; 4719G; 4808G; 4864C; 5157insCCCACCCCTT	P34S; Splice Defect; S486T	hg19-*CYP2D6* : rs1080983G; rs1080985C; rs28588594T; rs1080989A; rs28624811C; rs28633410G; *rs1065852T* ; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; rs28371701C; rs1081003T; rs58440431G; *rs16947C* ; rs2004511G; rs28371730G; rs28371738T; rs116390392G; rs71184866insACA; rs4078247G	P34S; C296R	hg38-*CYP2D6* : rs28439297G; rs28680494T; rs28588594T; rs28735595G; rs1080989A; *rs1065852T* ; rs28371699T; rs28371702G; rs1081003T; rs1058164C; rs58440431G; rs2004511G; *rs1135840C* ; rs28371738T; rs35028622G; rs4078247G; rs34386013C	P34S; Splice Defect; S486T
3	2	Normal	1	1	1	M33388-*CYP2D6* : -2060G; -2053T; -1770A; -1584G; -1235G; -740T; -678A; 214C; 221A; 223G; 227C; 232C; 233C; 245G; 310T; 746G; 843G; 1661C; *2850T* ; 3584A; *4180C* ; 4481A; 4655delACA; 4719G; 4864C; 5157insCCCACCCCTT	Splice Defect; R296C; S486T	hg19-*CYP2D6* : None	-	hg38-*CYP2D6* : rs28439297G; rs28680494T; rs1080983A; rs1080985G; rs28735595G; rs28624811T; rs28633410A; rs1808995C; rs1080996A; rs74644586G; rs76312385C; rs75276289C; rs28695233C; rs1081000G; rs28371699T; rs28371701G; rs28371702G; rs1058164C; *rs16947T* ; rs28371730A; *rs1135840C* ; rs116390392A; rs71184866delACA; rs35028622G; rs34386013C	Splice Defect; R296C; S486T
4	2	Normal	1	1	1	M33388-*CYP2D6* : -2060G; -2053T; -1770A; -1235G; -740T; -678A; 214C; 221A; 223G; 227C; 232C; 233C; 245G; 310T; 746G; 843G; 1661C; *2850T* ; 2988A; 3584A; *4180C* ; 4481A; 4655delACA; 4719G; 4864C; 5157insCCCACCCCTT	Splice Defect; R296C; Splice Defect; S486T	hg19-*CYP2D6* : rs1080985C; rs28371725A	Splice Defect	hg38-*CYP2D6* : rs28439297G; rs28680494T; rs1080983A; rs28735595G; rs28624811T; rs28633410TA; rs1808995C; rs1080996A; rs74644586G; rs76312385C; rs75276289C; rs28695233C; rs1081000G; rs28371699T; rs28371701G; rs28371702G; rs1058164C; *rs16947T* ; rs28371725A; rs28371730A; *rs1135840C* ; rs116390392A; rs71184866delACA; rs35028622G; rs34386013C	Splice Defect; R296C; Splice Defect; S486T
5	17	Decreased	0.5	0.5	0.5	M33388-*CYP2D6* : -2060G; -2053T; -1235G; -740T; 214C; 221A; 223G; 227C; 232C; 233C; 245G; 310T; 843G; *1023A* ; 1661C; *2850T* ; 3584A; *4180C* ; 4709A; 4719G; 4766A; 4864C; 5157insCCCACCCCTT	Splice Defect; T107I; R296C; S486T	hg19-*CYP2D6* : rs1080983G; rs1080985C; rs28633410G; rs28371701C; *rs28371706T* ; rs116390392G; rs71184866insACA; rs4078249A; rs4078248A	T107I	hg38-*CYP2D6* : rs28439297G; rs28680494T; rs28735595G; rs28624811T; rs1808995C; rs1080996A; rs74644586G; rs76312385C; rs75276289C; rs28695233C; rs1081000G; rs28371699T; rs28371702G; *rs28371706T* ; rs1058164C; *rs16947T* ; rs28371730A; *rs1135840C* ; rs4078249A; rs35028622G; rs4078248A; rs34386013C	Splice Defect; T107I; R296C; S486T
6	1	Normal	1	1	1	M33388-*CYP2D6* : -43insG; 4928A; 5157insCCCACCCCTT	-	hg19-*CYP2D6* : rs28439297A; rs28680494G; rs1080985C; rs28735595A; rs28624811C; rs28633410G; rs75085559insG; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; rs28371699G; rs28371701C; rs28371702T; rs1058164G; *rs16947C* ; rs28371730G; *rs1135840G* ; rs116390392G; rs71184866insACA; rs35028622T; rs34386013T; rs112866416A	Splice Defect; C296R; T486S	hg38-*CYP2D6* : rs75085559insG; rs112866416A	-
7	4	None	0	0	0	M33388-*CYP2D6* : -2060G; -2053T; -1426T; -1235G; -1000A; *100T* ; 310T; 746G; 843G; *974A* ; *984G* ; 997G; 1661C; 1846A; 2097G; 3582G; *4180C* ; 4401T; 4719G; 4808G; 4864C; 5157insCCCACCCCTT	P34S; L91M; H94R; Splice Defect; Splice Defect; S486T	hg19-*CYP2D6* : rs1080983G; rs1080985C; rs28588594T; rs1080989A; rs28624811C; rs28633410G; *rs1065852T* ; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; *rs28371703A* ; *rs28371704G* ; rs28371705G; rs3892097A; rs58440431G; *rs16947C* ; rs2004511G; rs28371730G; rs28371738T; rs116390392G; rs71184866insACA; rs4078247G	P34S; L91M; H94R; Splice Defect; C296R	hg38-*CYP2D6* : rs28439297G; rs28680494T; rs28588594T; rs28735595G; rs1080989A; *rs1065852T* ; rs28371699T; rs28371701G; rs28371702G; *rs28371703A* ; *rs28371704G* ; rs28371705G; rs1058164C; rs3892097A; rs58440431G; rs2004511G; *rs1135840C* ; rs28371738T; rs35028622G; rs4078247G; rs34386013C	P34S; L91M; H94R; Splice Defect; Splice Defect; S486T
8	29	Decreased	0.5	0.5	0	M33388-*CYP2D6* : -2060G; -2053T; -1594C; -1418A; -1408A; -1235G; -740T; -176A; 310T; 744delC; 746G; 843G; *1659A* ; 1661C; 2123T; 2215G; 2292A; *2850T* ; *3183A* ; *4180C* ; 4719G; 4864C; 5157insCCCACCCCTT	Splice Defect; V136I; R296C; V338M; S486T	hg19-*CYP2D6* : rs1080983G; rs1080984C; rs1080985C; rs1080986A; rs1080987A; rs28633410G; rs1080993A; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; rs267608275delC; *rs61736512A* ; rs76327133T; rs80262685G; rs75203276A; *rs59421388A* ; rs28371730G; rs116390392G; rs71184866insACA	Splice Defect; V136I; V338M	hg38-*CYP2D6* : rs28439297G; rs28680494T; rs1080984C; rs1080986A; rs1080987A; rs28735595G; rs28624811T; rs1080993A; rs28371699T; rs267608275delC; rs28371701G; rs28371702G; *rs61736512A* ; rs1058164C; rs76327133T; rs80262685G; rs75203276A; *rs16947T* ; *rs59421388A* ; *rs1135840C* ; rs35028622G; rs34386013C	Splice Defect; V136I; R296C; V338M; S486T
9	17	Decreased	0.5	0.5	0.5	M33388-*CYP2D6* : -2060G; -2053T; -1235G; -740T; 214C; 221A; 223G; 227C; 232C; 233C; 245G; 310T; 654T; 843G; *1023A* ; 1661C; *2850T* ; 3584A; *4180C* ; 4709A; 4719G; 4766A; 4864C; 5157insCCCACCCCTT	Splice Defect; T107I; R296C; S486T	hg19-*CYP2D6* : rs1080983G; rs1080985C; rs28633410G; rs376217512T; rs28371701C; *rs28371706T* ; rs116390392G; rs71184866insACA; rs4078249A; rs4078248A	T107I	hg38-*CYP2D6* : rs28439297G; rs28680494T; rs28735595G; rs28624811T; rs1808995C; rs1080996A; rs74644586G; rs76312385C; rs75276289C; rs28695233C; rs1081000G; rs28371699T; rs376217512T; rs28371702G; *rs28371706T* ; rs1058164C; *rs16947T* ; rs28371730A; *rs1135840C* ; rs4078249A; rs35028622G; rs4078248A; rs34386013C	Splice Defect; T107I; R296C; S486T

Table 1 (continued). Full-gene *CYP2D6* haplotypes with ≥ 1% global frequency. Eighteen cytochrome p450 family 2, subfamily D, polypeptide 6 (*CYP2D6*) full-gene haplotypes with global allele frequencies ≥ 1% in the 1000 Genomes Project dataset. Italicized nucleotide positions and rs numbers indicate polymorphisms that change the amino acid sequence relative to the indicated reference genome; underlined nucleotide positions and rs numbers alter CYP2D6 function [6,27,39-41].

Haplotype Number	Most Similar CYP2D6 * Allele	Reported Activity	Gaedigk, *et al.* Activity Score	Full-gene Best Case Activity Score	Full-gene Worst Case Activity Score	M33388 Nomenclature	M33388 Amino Acid Changes	Hg19 Nomenclature	Hg19 Amino Acid Changes	Hg38 Nomenclature	Hg38 Amino Acid Changes
10	4	None	0	0	0	M33388-*CYP2D6* : -2060G; -2053T; -1426T; -1235G; -1000A; *100T* ; 310T; 746G; 843G; *974A* ; *984G* ; 997G; 1661C; 1846A; 2097G; 3582G; *4180C* ; 4401T; 4719G; 4808G; 4864C	P34S; L91M; H94R; Splice Defect; Splice Defect; S486T	hg19-*CYP2D6* : rs1080983G; rs1080985C; rs28588594T; rs1080989A; rs28624811C; rs28633410G; *rs1065852T* ; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; *rs28371703A* ; *rs28371704G* ; rs28371705G; rs3892097A; rs58440431G; *rs16947C* ; rs2004511G; rs28371730G; rs28371738T; rs116390392G; rs71184866insACA; rs4078247G; rs536156813delCCCACCCCTT	P34S; L91M; H94R; Splice Defect; C296R	hg38-*CYP2D6* : rs28439297G; rs28680494T; rs28588594T; rs28735595G; rs1080989A; *rs1065852T* ; rs28371699T; rs28371701G; rs28371702G; *rs28371703A* ; *rs28371704G* ; rs28371705G; rs1058164C; rs3892097A; rs58440431G; rs2004511G; *rs1135840C* ; rs28371738T; rs35028622G; rs4078247G; rs34386013C; rs536156813delCCCACCCCTT	P34S; Splice Defect; Splice Defect; L91M; H94R; Splice Defect; S486T
11	1	Normal	1	1	1	M33388-*CYP2D6* : None	-	hg19-*CYP2D6* : rs28439297A; rs28680494G; rs1080983G; rs1080985C; rs28735595A; rs28624811C; rs28633410G; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; rs28371699G; rs28371701C; rs28371702T; rs1058164G; *rs16947C* ; rs28371730G; *rs1135840G* ; rs116390392G; rs71184866insACA; rs35028622T; rs34386013T; rs536156813delCCCACCCCTT	Splice Defect; C296R; T486S	hg38-*CYP2D6* : rs536156813delCCCACCCCTT	-
12	1	Normal	1	1	1	M33388-*CYP2D6* : 1170A; 5157insCCCACCCCTT	-	hg19-*CYP2D6* : rs28439297A; rs28680494G; rs1080983G; rs1080985C; rs28735595A; rs28624811C; rs28633410G; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; rs28371699G; rs28371701C; rs28371702T; rs1081004A; rs1058164G; *rs16947C* ; rs28371730G; *rs1135840G* ; rs116390392G; rs71184866insACA; rs35028622T; rs34386013T	Splice Defect; C296R; T486S	hg38-*CYP2D6* : rs1081004A	-
13	1	Normal	1	1	1	M33388-*CYP2D6* : 310T; 843G; 1067G	Splice Defect; Splice Defect	hg19-*CYP2D6* : rs28439297A; rs28680494G; rs1080983G; rs1080985C; rs28735595A; rs28624811C; rs28633410G; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; rs28371701C; rs78854695G; rs1058164G; *rs16947C* ; rs28371730G; *rs1135840G* ; rs116390392G; rs71184866insACA; rs35028622T; rs34386013T; rs536156813delCCCACCCCTT	Splice Defect; C296R; T486S	hg38-*CYP2D6* : rs28371699T; rs28371702G; rs78854695G; rs536156813delCCCACCCCTT	Splice Defect; Splice Defect
14	35	Normal	1	1	1	M33388-*CYP2D6* : -2060G; -2053T; -1770A; -1584G; -1235G; -740T; -678A; *31A* ; 214C; 221A; 223G; 227C; 232C; 233C; 245G; 310T; 746G; 843G; 1661C; *2850T* ; 3584A; *4180C* ; 4481A; 4655delACA; 4719G; 4864C; 5157insCCCACCCCTT	V11M; Splice Defect; S486T	hg19-*CYP2D6* : *rs769258A*	V11M	hg38-*CYP2D6* : rs28439297G; rs28680494T; rs1080983A; rs1080985G; rs28735595G; rs28624811T; rs28633410A; *rs769258A* ; rs1808995C; rs1080996A; rs74644586G; rs76312385C; rs75276289C; rs28695233C; rs1081000G; rs28371699T; rs28371701G; rs28371702G; rs1058164C; *rs16947T* ; rs28371730A; *rs1135840C* ; rs116390392A; rs71184866delACA; rs35028622G; rs34386013C	V11M; Splice Defect; R296C; S486T
15	1	Normal	1	1	1	M33388-*CYP2D6* : -498A; 5154T; 5157insCCCACCCCTT	-	hg19-*CYP2D6* : rs28439297A; rs28680494G; rs1080983G; rs1080985C; rs28735595A; rs28624811C; rs28633410G; rs74966855A; rs1808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; rs28371699G; rs28371701C; rs28371702T; rs1058164G; *rs16947C* ; rs28371730G; *rs1135840G* ; rs116390392G; rs71184866insACA; rs35028622T; rs34386013T; rs374153932T	Splice Defect; C296R; T486S	hg38-*CYP2D6* : rs74966855A; rs374153932T	-
16	1	Normal	1	1	1	M33388-*CYP2D6* : 270A; 5157insAAGGGGTGGG	-	hg19-*CYP2D6* : rs28439297T; rs28680494C; rs1080983C; rs1080985G; rs28735595T; rs28624811G; rs28633410C; rs1808995C; rs1080996G; rs74644586G; rs76312385A; rs75276289C; rs28695233T; rs1081000T; rs29001678A; rs28371699C; rs28371701G; rs28371702A; rs1058164C; *rs16947G* ; rs28371730C; *rs1135840C* ; rs116390392C; rs71184866insTGT; rs35028622A; rs34386013A	Splice Defect; C296R; T486S	hg38-*CYP2D6* : rs29001678A	-
17	1	Normal	1	1	1	M33388-*CYP2D6* : 270A; 5157insAAGGGGTGGG	-	hg19-*CYP2D6* : rs28439297T; rs28680494C; rs1080983C; rs1080985G; rs28735595T; rs28624811G; rs28633410C; rs1808995C; rs1080996G; rs74644586G; rs76312385A; rs75276289C; rs28695233T; rs1081000T; rs29001678A; rs28371699C; rs28371701G; rs28371702A; rs1058164C; *rs16947G* ; rs28371730C; *rs1135840C* ; rs116390392C; rs71184866insTGT; rs35028622A; rs34386013A	Splice Defect; C296R; T486S	hg38-*CYP2D6* : rs29001678A	-
18	1	Normal	1	1	1	M33388-*CYP2D6* : 5154A; 5157insAAGGGGTGGG	-	hg19-*CYP2D6* : rs28439297T; rs28680494C; rs1080983C; rs1080985G; rs28735595T; rs28624811G; rs28633410C; rs1808995C; rs1080996G; rs74644586G; rs76312385A; rs75276289C; rs28695233T; rs1081000T; rs28371699C; rs28371701G; rs28371702A; rs1058164C; *rs16947G* ; rs28371730C; *rs1135840C* ; rs116390392C; rs71184866insTGT; rs35028622A; rs34386013A; rs374153932A	Splice Defect; C296R; T486S	hg38-*CYP2D6* : rs374153932A	-

One haplotype observed in this study was consistent with HCYPAND *CYP2D6* * allele reference list (*CYP2D6**1A,5 M33388-CYP2D6: None, hg19-*CYP2D6*: rs28439297A; rs28680494G; rs1080983G; rs1080985C; rs28735595A; rs28624811C; rs28633410G; rs10808995G; rs1080996C; rs74644586C; rs76312385T; rs75276289G; rs28695233A; rs1081000A; rs28371699G; rs28371701C; rs28371702T; rs1058164G; rs16947C; rs28371730G; rs1135840G; rs116390392G; rs71184866insACA; rs35028622T; rs34386013T; rs536156813delCCCACCCCTT, hg38-*CYP2D6*: rs536156813delCCCACCCCTT). Though not specifically reported in the HCYPAND *CYP2D6* * allele table, 407 (91.3%) haplotypes could be associated with at least one * allele based on the presence of defining amino acid changes and causal polymorphisms, however, 38 (i.e., 8.52%) of them could not be associated. These 38 haplotypes were observed 125/5008 times (2.50%) in the 1000 Genomes Project and contain combinations of functionally relevant polymorphisms [6]. Figure 3 and Figure S1 represent the variant composition of haplotypes 1 through 18 and all 446 haplotypes, respectively. The average number of polymorphisms per haplotype was 15 ± 10, 20 ± 10, and 14 ± 10 as designated by comparison with the M33388, hg19, and hg38 reference sequences, respectively. The majority of each haplotype is functionally irrelevant polymorphic sites; however, 326, 328, and 326 haplotypes harbor a damaging, or most likely damaging, variant relative to the M33388, hg19, and hg38 reference genomes, respectively.

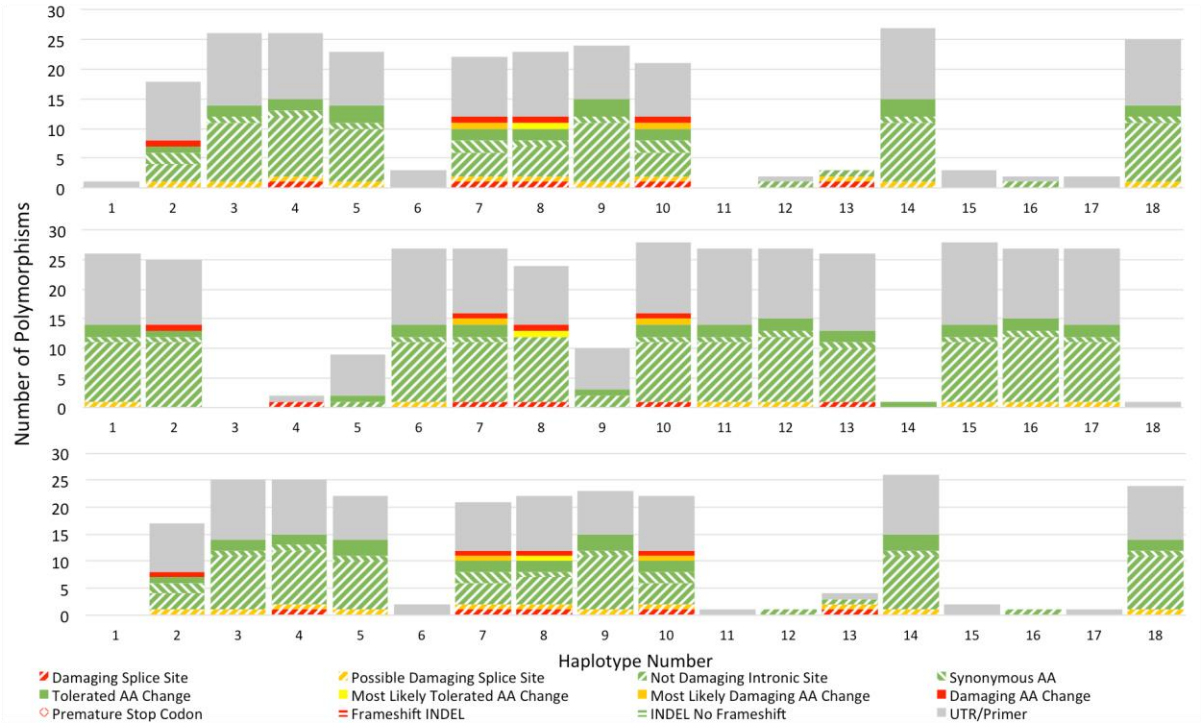


Figure 3. *CYP2D6* haplotype composition. Haplotype composition of 18 full-gene *CYP2D6* star alleles, with global frequencies ≥ 1%, aligned to GenBank accession M33388 (A), hg19 (B), and hg38 (C). Variant effect predictions performed by Wendt, *et al.* [13] using Sort Intolerant From Tolerant (SIFT) [28-33], Polymorphism Phenotyping v2 (PolyPhen-v2)[28,34,35] Protein Variant Effect Analyzer (PROVEAN) [36-38], and Human Splicing Finder [42].

Network analysis was performed to determine the relatedness of two sets of haplotypes: (1) haplotypes having ≥ 1% global haplotype frequency (haplotypes 1-18; Figure 4), and (2) haplotypes observed more than once in the entire 1000 Genomes Project dataset (haplotypes 1-204; Figure S2). In Figure 4 and Figure S2, the haplotypes with relatively low global frequencies appear to be derived from the major haplotypes (1, 2, and 3). All major haplotypes except 15 and 17 were observed in the AFR super-population, though the frequency is relatively low due to the AFR population having the widest haplotype spread (Figure S2). Haplotype 9 is exclusive, and haplotypes 5, 6, 9, 13, and 18 are almost exclusive, to the AFR super-population. The clustering of rare haplotypes suggests that these may be specific to one

super-population, such as AFR (minor haplotypes stemming from haplotypes 5, 6, 8, and 9) or EAS (minor haplotypes stemming from haplotypes 2, 15, and 17).

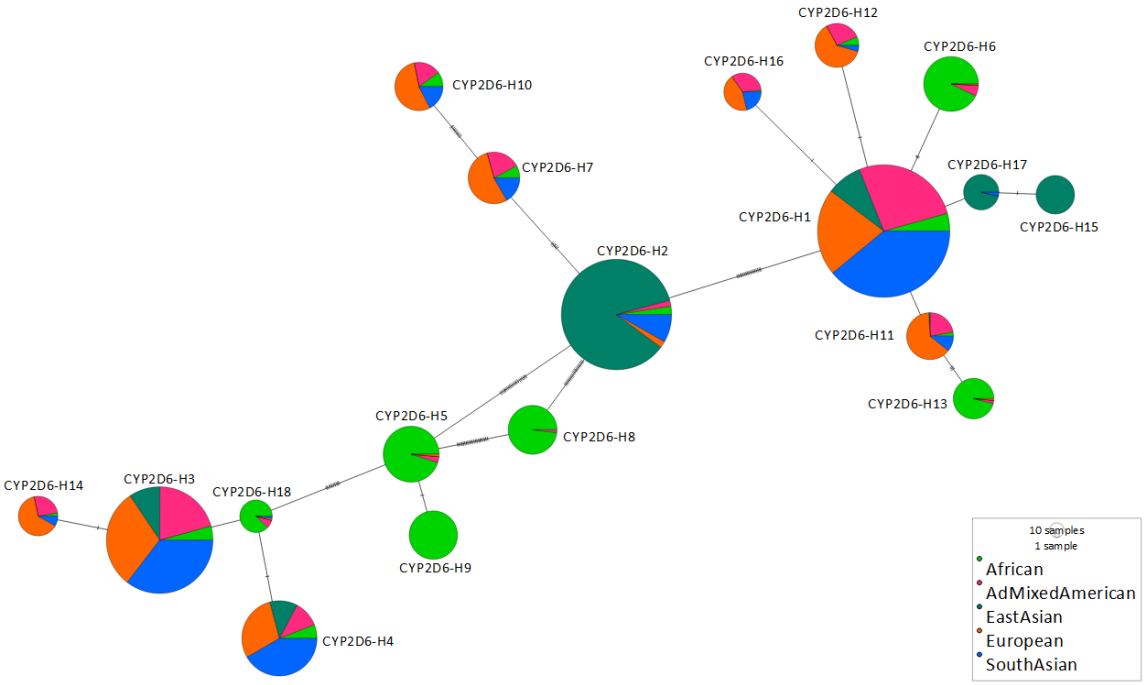


Figure 4. Network analysis of *CYP2D6* haplotypes. Network analysis of *CYP2D6* full-gene haplotypes 1 through 18. The size of each circle is proportional to the global frequency of each haplotype, segments within each circle are proportional to the super-population haplotype frequency, and lines connecting circles are dashed with the number of mutations separating two haplotypes.

There were 961 unique diplotypes observed across 2,504 individuals. The average global diplotype frequency was 0.00104 ± 0.00336. Ten diplotypes had global frequencies ≥ 1%, with an average global frequency of 0.0275 ± 0.0177 (Table 1). The average diplotype frequency in the AFR, AMR, EAS, EUR, and SAS super-populations was 0.00253 ± 0.00277, 0.00587 ± 0.0133, 0.00658 ± 0.0227, 0.00466 ± 0.00688, and 0.00568 ± 0.0142, respectively (Figure 5). The average global Ho and He of *CYP2D6* were 0.820 ± 0.0898 and 0.861 ± 0.0923, respectively. Before Bonferroni correction ($p < 0.05$), *CYP2D6* deviated from HWE

expectations in three super-populations (AFR, AMR, and EUR) and nine sub-populations (ASW, GWD, LWK, MSL, YRI, CLM, CDX, CHS, and GBR) (Figure 6). After Bonferroni correction ($p < 0.00161$), *CYP2D6* deviated from HWE expectations in the AFR super-population and the ASW and LWK sub-populations.

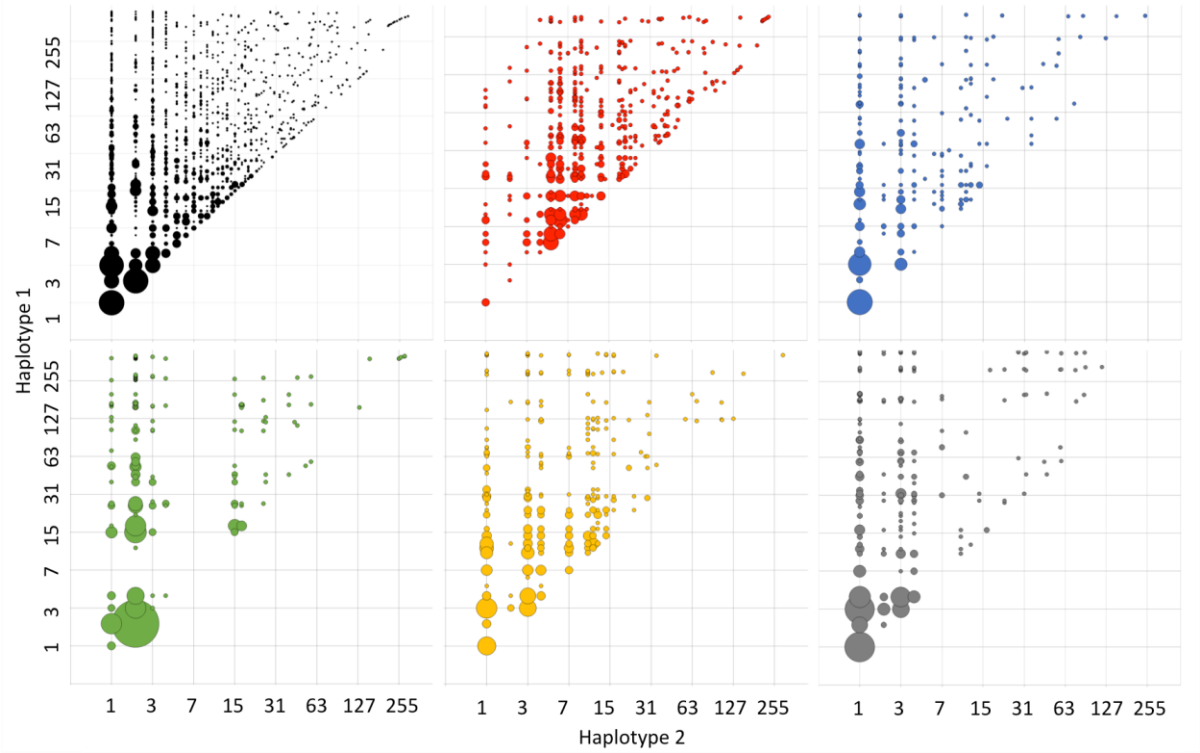


Figure 5. *CYP2D6* diplotype frequencies. Relative *CYP2D6* diplotype frequencies in the global population (A), African (B), Admixed American (C), East Asian (D), European (E), and South Asian (F) super-populations. The x- and y-axes indicate the first and second haplotype, respectively, of an individual diplotype; the size of each solid circle is proportional to the frequency of that diplotype.

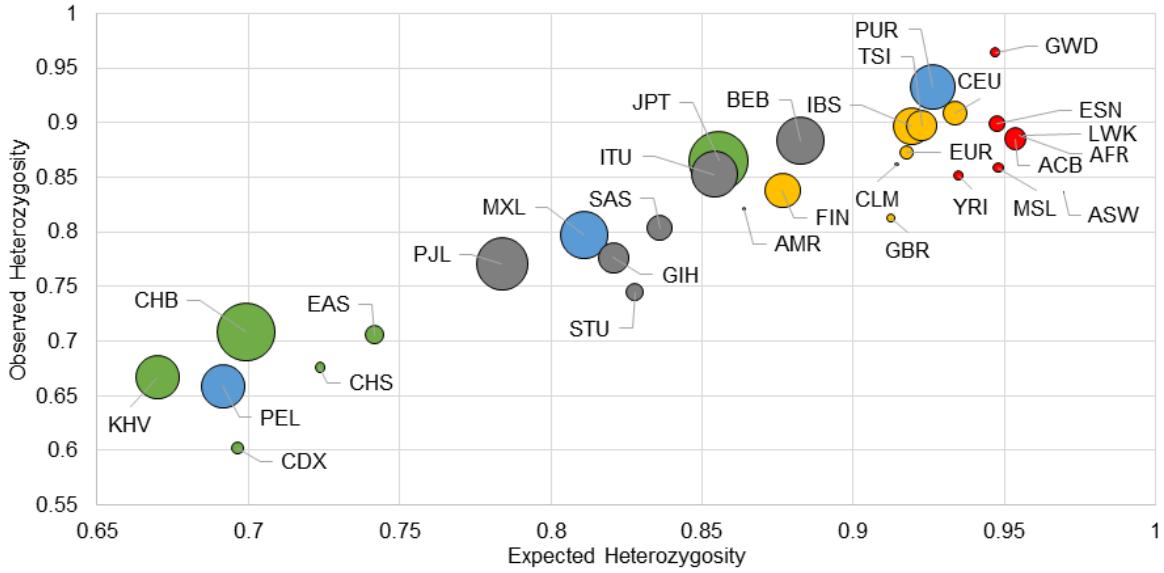


Figure 6. Heterozygosity and Hardy-Weinberg Equilibrium summary. Observed and expected heterozygosity of *CYP2D6* in five major super- and twenty-six sub-populations. Super-populations and their associated sub-populations are color coded (red for African [AFR], blue for Admixed American [AMR], green for East Asian [EAS], yellow for European [EUR], and grey for South Asian [SAS]); the size of each data point corresponds to the Hardy-Weinberg Equilibrium (HWE) p-value for the locus within that population. The AFR super-population and the Luhya in Webuye, Kenya (LWK) and American of African Ancestry in Southwest United States (ASW) sub-populations deviated significantly from HWE expectations after Bonferroni correction ($p < 0.00161$).

Activity scores were assigned to each individual using the functional consequence of the most closely related HCYPAND-recognized * allele to each full-gene haplotype. 282 individuals harbor full-gene haplotypes that, by HCYPAND nomenclature, should confer normal activity enzymes (activity score = 1) but full-gene data reveal additional causal polymorphisms that were predicted to damage enzyme function (Figure 7). Twenty-two of these individuals (21 AFR and 1 AMR) have diplotypes where two full-gene haplotypes produce conflicting activity scores relative to the HCYPAND approach. The average individual activity scores were 1.40 ± 0.644, 1.36 ± 0.638, and 1.30 ± 0.675 based on HCYPAND guidelines, full-gene best- (Student's t-test; $p < 0.05$ relative to the HCYPAND

approach), and full-gene worst-case (Student's t-test; $p < 0.001$ relative to the HCYPAND approach) haplotype activity score designation. Haplotype 8 (M33388-*CYP2D6*: -2060G; -2053T; -1594C; -1418A; -1408A; -1235G; -740T; -176A; 310T; 744delC; 746G; 843G; 1659A; 1661C; 2123T; 2215G; 2292A; 2850T; 3183A; 4180C; 4719G; 4864C; 5157insCCCACCCCTT) is responsible for the majority of conflicting MP predictions (111 AFR and 2 AMR individuals). By HCYPAND nomenclature, this haplotype would be assigned an activity score of 0.5 based on similarity to *CYP2D6**29 [43]; however, full-gene haplotype data reveal the presence of non-HCYPAND INDEL rs267608275delC (744delC). Due to lack of empirical observation of the influence rs267608275delC has on CYP2D6 function, worst- and best-case activity scores of 0 and 0.5, respectively, were assigned for full-gene haplotypes, indicating that rs267608275delC may or may not further decrease CYP2D6 function. This significant decrease in average activity score suggests that by current *CYP2D6* * allele and activity score designation, ~11% of the individuals in this dataset may be wrongly considered gNM-F, gNM-S, or gIM when they likely belong in the gNM-S, gIM, and gPM categories, respectively.

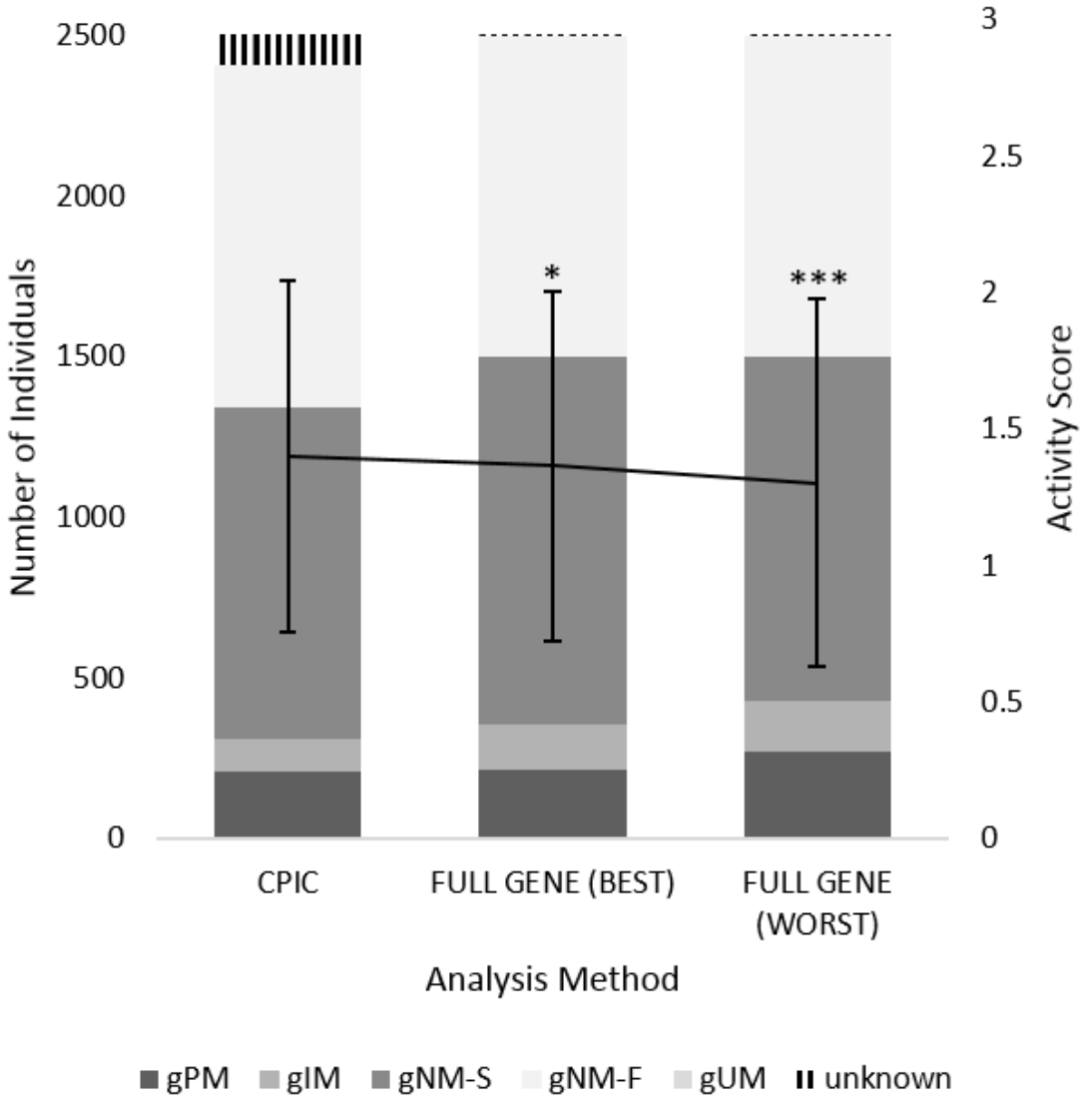
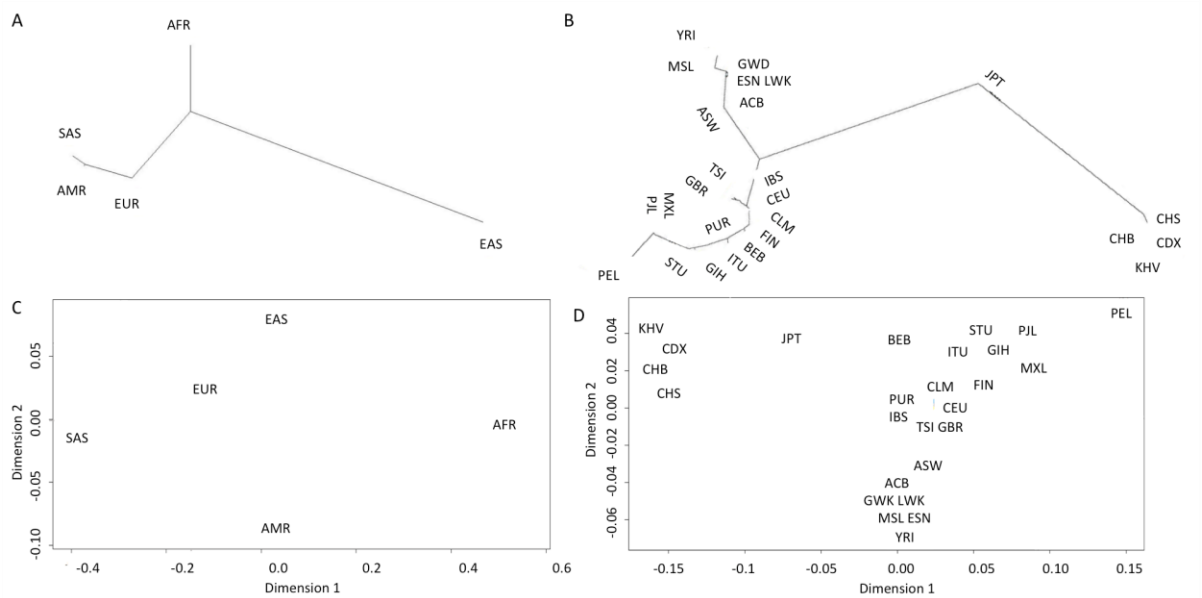


Figure 7. Activity score predictions using Clinical Pharmacogenetics Implementation Consortium star allele nomenclature and full-gene *CYP2D6* haplotypes. Genotype-inferred (g) CYP2D6 MP (gPM: poor; gIM: intermediate; gNM-S: normal/extensive-slow; gNM-F: normal/extensive-fast; gUM: ultrarapid) distribution and average activity scores using The Human CYP Allele Nomenclature Database (HCYPAND) [6] recognized *CYP2D6* * alleles and full-gene haplotypes for 2,504 1000 Genomes Project self-reported healthy individuals. Asterisks indicate significant difference in average activity score (Student's t-test; * $p < 0.05$; *** $p < 0.001$) compared with HCYPAND nomenclature; vertical black bars indicate the average activity score ± one standard deviation; individuals with combinations of causal HCYPAND polymorphisms were not assigned to a MP using HCYPAND nomenclature and were assigned to the "unknown" MP category.

MDS plots and unrooted phylogenetic trees (Figure 8) of super-populations show distant separation of the AFR and EAS populations while EUR, AMR, and SAS cluster relatively close together. Considering sub-populations, those belonging to the AFR and EAS super-populations cluster together according to super-population affiliation. Sub-populations belonging to the AMR, EUR, and SAS super-populations have considerable overlap with one another.



AFR: African; AMR: Ad Mixed American; EAS: East Asian; EUR: European; SAS: South Asian; ACB: African Caribbean in Barbados; ASW: American of African Ancestry in Southwest USA; BEB: Bengali from Bangladesh; CDX: Chinese Dai in Xishuangbanna, China; CEU: Utah Residence with Northern and Western Ancestry; CHB: Han Chinese in Beijing; CHS: Southern Han Chinese; CLM: Colombians from Medellin, Colombia; ESN: Esan in Nigeria; FIN: Finnish in Finland; GBR: British in England and Scotland; GIH: Gujarati Indian from Houston, Texas; GWD: Gambian in Western Divisions in Gambia; IBS: Iberian Population in Spain; ITU: Indian Telugu from the United Kingdom; JPT: Japanese in Tokyo, Japan; KHV: Kinh in Ho Chi Minh City, Vietnam; LWK: Luhya in Webuye, Kenya; MSL: Mende in Sierra Leone; MXL: Mexican Ancestry from Los Angeles, USA; PEL: Peruvians from Lima, Peru; PJL: Punjabi from Lahore, Pakistan; PUR: Puerto Ricans from Puerto Rico; STU: Sri Lankan Tamil from the United Kingdom; TSI: Toscani in Italia; YRI: Yoruba in Ibadan, Nigeria

Figure 8. Population comparisons using full-gene *CYP2D6* haplotypes. Neighbor-joining trees (A and B) and multidimensional scaling plots (C and D) for five super- (A and C) and twenty-six sub-populations (B and D) in the 1000 Genomes Project using pairwise genetic distances based on full-gene *CYP2D6* haplotype assignment.

Discussion

Full-gene *CYP2D6* haplotypes may be able to refine MP predictions, ultimately identifying more gIM and gPM individuals than the HCYPAND haplotype nomenclature. The analyses presented here may be limited by the relative low depth of sequence coverage per sample within the 1000 Genomes project database, small sample size for each sub population,

and the precision of variant effect prediction algorithms. These factors impact detection of rare variants that may contribute to CYP2D6 function. In fact, the splice defects defining three * alleles (*CYP2D6**4, *CYP2D6**11, and *CYP2D6**41) were not identified by the software analyses performed in Wendt, et al. and the 843G SNP was incorrectly identified as damaging [6], emphasizing the importance of using variant effect predictors with caution and employing multiple prediction algorithms to identify single nucleotide variants of interest [44]. Additional rare variants will continue to be discovered for PM, IM, and/or UM individuals and/or isolated populations such as Finns or Ashkenazi Jews. While potentially contributing significantly to phenotype, variant effect prediction is not possible; however, the analysis herein may allow for some prediction of phenotype using a number of previously unexploited polymorphisms [45-48]. Additional research is needed (e.g. functional enzyme studies, targeted mutagenesis, and/or quantitative trait analyses) to empirically characterize the phenotype generated from rare polymorphisms, combinations of rare/deleterious polymorphisms in the same haplotype, combinations of deleterious polymorphisms in different genes that may influence one another, and their distributions in under-represented populations.

Copy number variation (CNV) of some *CYP2D6* * alleles and *CYP2D7* pseudogene conversion do occur in some individuals, namely UMs, and may influence the HWE and LD results [49]. It is likely that some 1000 Genomes Project individuals from the AFR super-population carry CNVs based on deviations from HWE expectations [49] but the project does not explore CNV in detail due to limitations of short read sequencing [50,51]. The data presented herein have been analyzed as though only two copies of *CYP2D6* are present in each individual so unless an individual contains the SNP rs1135823G>T (1617G>T), the UM phenotype was not identified. A number of unique haplotypes have been identified that may

be true haplotype observations but may also be attributed to duplication of two common haplotypes and/or *CYP2D7* pseudogene conversions [52,53]. This phenomenon is particularly true for African populations which exhibit relatively frequent gene duplications (up to 30%) [54,55]. The development of continuous read single-molecule DNA sequencing strategies, such as nanopore technology [56], may help reduce ambiguity in sequencing regions with a high degree of structural variation.

Unique haplotypes have been identified from the full-gene region of *CYP2D6*, including introns, exons, 5' and 3' UTRs, and the promoter region. While comprehensively assessing the gene itself, there are a number of distant regulatory elements that may impact enzyme function. Wang, *et al.* [5] identified long-range haplotypes that include polymorphisms within enhancer regions that may refine these haplotype definitions. However, inclusion of such regulatory elements in *CYP2D6*-based MP predictions may need to be explored further due to potential regulation of other enzymes, potentially confounding MP prediction. Additionally, private mutations not predicted to damage the resulting protein have been removed (note that those considered for HCYPAND-recognized * alleles have been included) from this analysis; however, if incorporated, may produce finer granularity of haplotype definition but likely would not alter activity score unless empirically shown to alter enzyme function.

Full-gene *CYP2D6* data have provided additional resolution to the MP compared to predictions used to date, possibly resolving some medico-legal autopsy negative cases. Although empirical data are required to confirm their enzyme activity, approximately 11% of the healthy individuals in this study may be wrongly identified as NMs according to traditional *CYP2D6* genotyping and activity score predictions of MP. Clinically, these individuals likely

would be classified as IM or PM and be treated accordingly. Enhanced predictive capabilities of MP may be made with comprehensive *CYP2D6* diplotype information and/or incorporation of a longer-read sequencing platform into the *CYP2D6* interrogation workflow.

The case described by Koren, *et al.* [8] of an application of *CYP2D6* genotyping to assist in a medico-legal investigation is a classic example of ultra-rapid metabolism of codeine to morphine. In such cases the medicaments were delivered as a pro-drug (inactive) that must be metabolized in order to deliver the intended effect (e.g., codeine or tamoxifen) [1,2]. Given the prevalence of UM in various populations and the current use of these drugs, it is anticipated that similar cases will occur and molecular autopsies may shed light on the cause and/or manner of death. At the opposite end of the metabolizer phenotype spectrum are PMs and IMs. If considering codeine to morphine metabolism, *CYP2D6* genotyping post-mortem may not be informative. However, many antidepressants (e.g., nortriptyline) are active upon administration and depend on CYP2D6 to deactivate the drug. PMs and IMs, based on their *CYP2D6* variants, may experience adverse reactions to antidepressants which include, but are not limited to, delayed propagation of myocardium depolarization leading to cardiac arrhythmia, myocardial infarction, and death [11]. In the context of the data presented in this study, ~11% of individuals may be incorrectly classified as NMs or IMs as their full-gene haplotype data indicate one category lower (i.e., NM by targeted approach is an IM by full-gene approach; IM by targeted approach is a PM by full-gene approach). As such, understanding *CYP2D6* haplotype information of all metabolizer phenotypes can be quite relevant to the medico-legal community.

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Supplementary Information

Table S1. Population codes. 1000 Genomes Project population codes and descriptions for five super-populations and 26 sub-populations [15,16]. Table from Wendt, *et al.* 2017 [13].

Super-Population (Code)	Sample Size	Population Code	Population Description	Sample Size
African (AFR)	661	YRI	Yoruba in Ibadan, Nigeria	108
		LWK	Luhya in Webuye, Kenya	99
		GWD	Gambian in Western Divisions in Gambia	113
		MSL	Mende in Sierra Leone	85
		ESN	Esan in Nigeria	99
		ASW	American of African Ancestry in Southwest United States	61
		ACB	African Caribbeans in Barbados	96
Ad Mixed American (AMR)	347	MXL	Mexican Ancestry from Los Angeles, USA	64
		PUR	Puerto Ricans from Puerto Rico	104
		CLM	Colombians from Medellin, Colombia	94
		PEL	Peruvians from Lima, Peru	85
East Asian (EAS)	504	CHB	Han Chinese in Beijing China	103
		JPT	Japanese in Tokyo, Japan	104
		CHS	Southern Han Chinese	105
		CDX	Chinese Dai in Xishuangbanna, China	93
		KHV	Kinh in Ho Chi Minh City, Vietnam	99
European (EUR)	503	CEU	Utah Residents (CEPH) with Northern and Western Ancestry	99
		TSI	Toscani in Italia	107
		FIN	Finnish in Finland	99
		GBR	British in England and Scotland	91
		IBS	Iberian Population in Spain	107
South Asian (SAS)	489	GIH	Gujarati Indian from Houston, Texas	103
		PJL	Punjabi from Lahore, Pakistan	96
		BEB	Bengali from Bangladesh	86
		STU	Sri Lankan Tamil from the United Kingdom	102
		ITU	Indian Telugu from the United Kingdom	102

Table S2. *CYP2D6* full-gene haplotypes aligned to reference genomes. Cytochrome p450 full-gene star allele string sequences (forward strand on the top, reverse strand on the bottom) aligned to and named according to the hg19 and hg38 reference genomes and GenBank accession M33388 sequence. Individual bases are colored for visual clarity; nucleotide numbers are in reference to the start codon of M33388 sequence for consistency with The Human Cytochrome P450 Allele Nomenclature Database nomenclature guidelines; amino acid changes are colored to indicate predicted severity of impact on resulting protein function [28-38,42]; intronic regions between exons of the amino acid string sequence are dark grey; black boxes highlight differences between the four references sequences used; HCYPAND causal polymorphisms not observed in the 1000 Genomes Project are considered invariable relative to the hg19 reference genome. Supplementary Table 2 can be viewed on the publisher's website: https://link.springer.com/article/10.1007/s00414-017-1709-0.

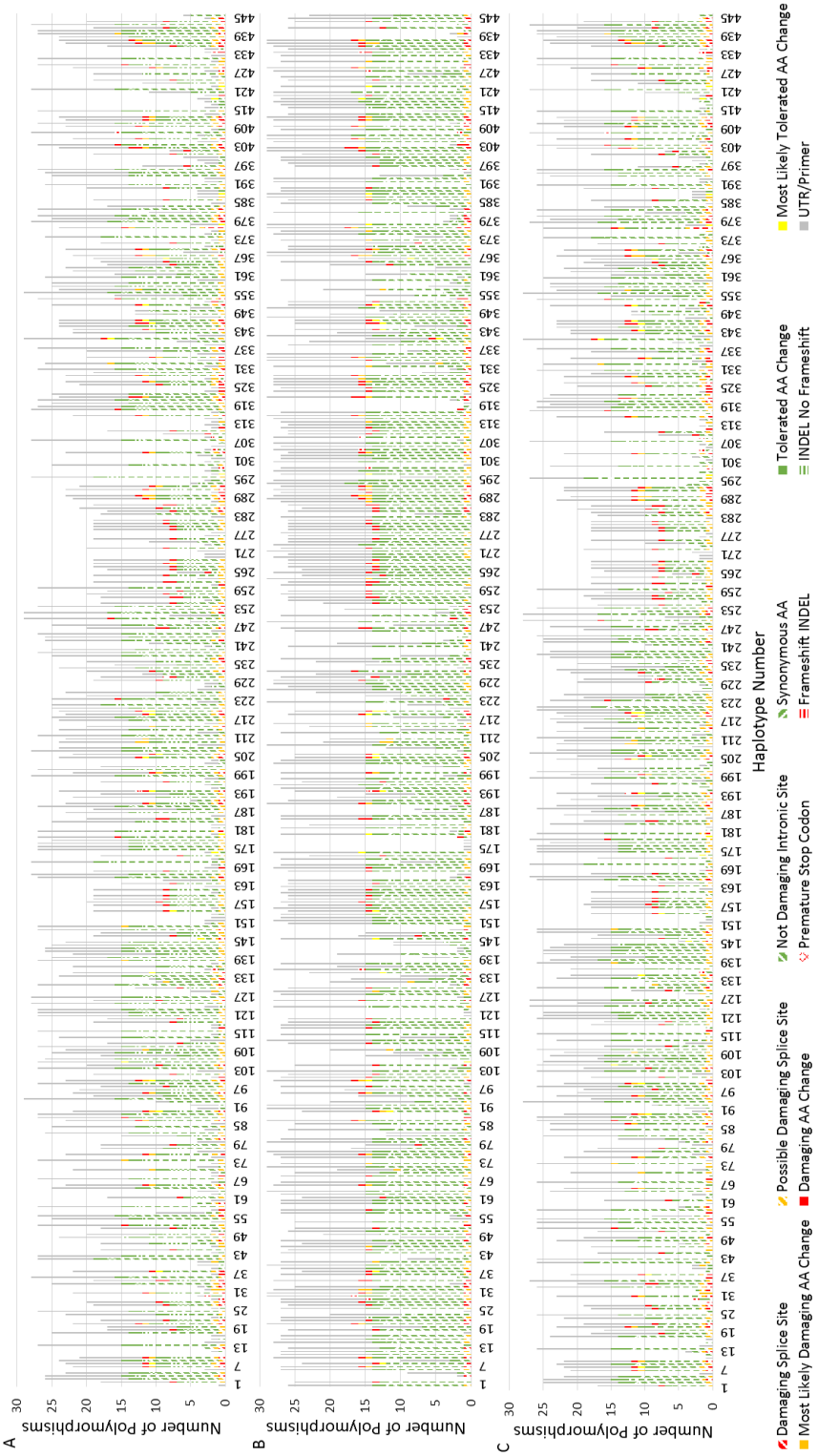

Figure S1. *CYP2D6* full-gene haplotype composition. Haplotype composition of 446 full-gene *CYP2D6* star alleles aligned to GenBank accession M33388 (A), hg19 (B), and hg38 (C). Variant effect predictions described by Wendt, *et al.* [13] using Sort Intolerant From Tolerant [28-33], Polymorphism Phenotyping v2 [28,34,35], Protein Variant Effect Analyzer [36-38], and Human Splicing Finder [42].

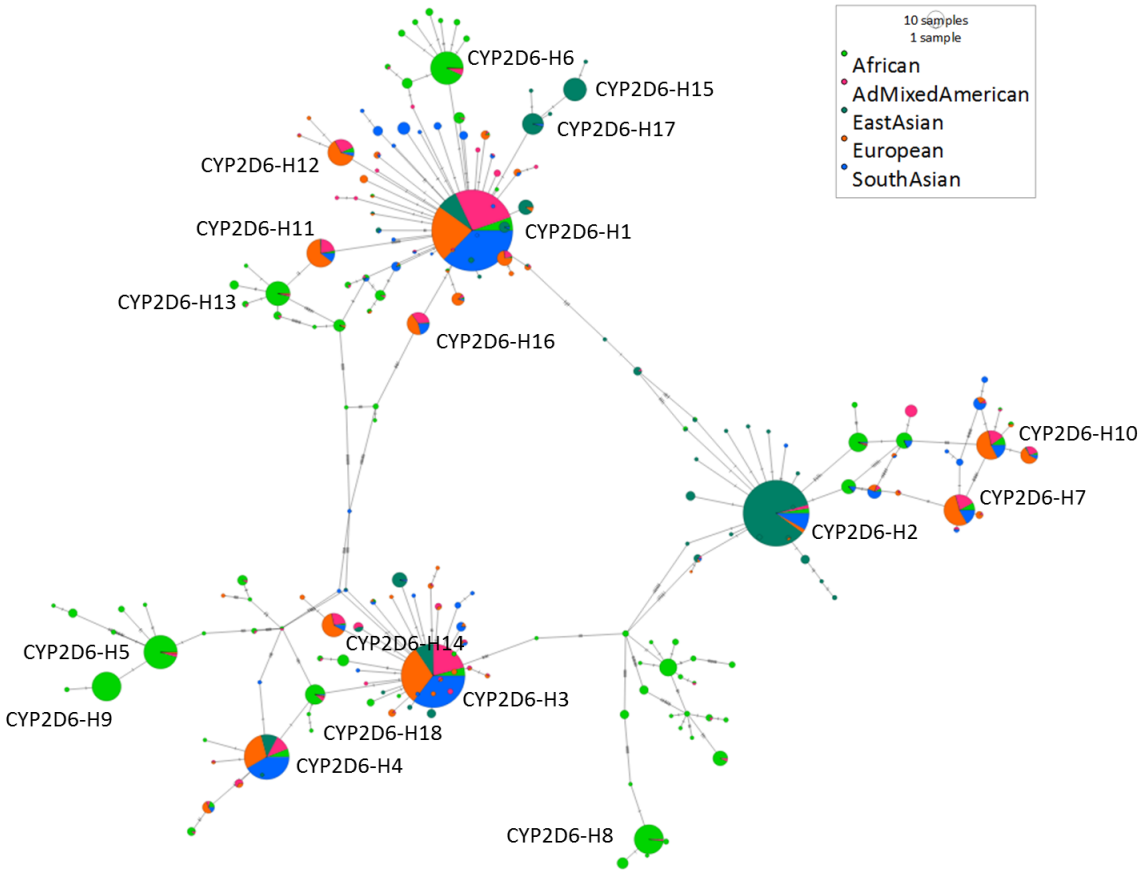

Figure S2. Network analysis of *CYP2D6* full-gene haplotypes observed more than once. Network analysis of *CYP2D6* full-gene haplotypes 1 through 204. Haplotypes with global frequencies ≥ 1% are labeled, the size of each circle is proportional to the global frequency of each haplotype, segments within each circle are proportional to the super-population haplotype frequency, and lines connecting circles are dashed with the number of variants separating two haplotypes. Haplotypes observed once in the global population (haplotypes 205 through 446) were removed prior to network analysis.

CHAPTER 4

Predicted Activity of **UGT2B7, ABCB1, OPRM1, and COMT** *using full-gene haplotypes and their association with the CYP2D6-inferred metabolizer phenotype*

Forensic Science International Genetics. 2017 Nov 26;33:48-58. doi: 10.1016/j.fsigen.2017.11.012. [Epub ahead of print] PubMed PMID: 29190510.

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Abstract

The pharmacogene, *CYP2D6,* is commonly used to infer metabolizer phenotype of many marketed drugs and endogenous toxins in ante- and post-mortem patients but only represents the efficiency of phase 1 metabolism. Downstream metabolic enzymes encoded by *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* also have been implicated in variable individual response to drugs due to their activity at different stages of the tramadol ADME (absorption, distribution, metabolism, and excretion) process. While commonly studied as single genes using targeted genotyping approaches, a more comprehensive tramadol metabolism profile has not been evaluated. 1000 Genomes Project data for *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* were used to characterize full-gene haplotypes and their effect on protein function using in-house excel-based workbooks, PopART, and TreeView. Population genetic summary statistics and intergenic analyses associated these haplotypes with full-gene *CYP2D6*-inferred metabolizer phenotype. The findings suggest that *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* may contribute to predicted metabolizer phenotype as opposed to relying solely on *CYP2D6*.

Introduction

The cytochrome p450 family 2, subfamily D, polypeptide 6 (CYP2D6) enzyme is responsible for phase I metabolism of approximately 30% of marketed drugs and endogenous toxins [1,2]. *CYP2D6* is a highly variable pharmacogene with well documented allele distributions that vary by demography [3-6]. Constellations of individual single nucleotide (SNPs) or insertion/deletion (INDELs) polymorphisms in *CYP2D6* define star (*) alleles (i.e. a haplotype [operationally defined by a set of SNPs]) which may be used to predict the metabolizer phenotype (e.g. poor [PM], intermediate [IM], extensive/normal [EM/NM] and ultrarapid [UM]) of an individual using their *CYP2D6* diplotype (i.e. combination of two *CYP2D6* * alleles) information and associated activity scores. These data have demonstrated value for guiding individualized prescription medication practices and even post-mortem investigations [7-10].

The *CYP2D6*-inferred metabolizer phenotype describes only one phase of the tramadol (T) ADME (absorption, distribution, metabolism, and excretion) process and does not explain all genotypic contribution of an individual's phenotypic expression [11]. Numerous polymorphisms in the downstream metabolic enzymes uridine diphosphate glucuronosyltransferase, family 1, polypeptide B7 (UGT2B7), adenosine triphosphate (ATP) binding cassette, subfamily B, number 1 (ABCB1), opioid receptor mu 1 (OPRM1), and catechol-O-methyltransferase (COMT) also have been implicated in idiosyncratic response to drugs. These ADME proteins are less well characterized and typically are interrogated in single-gene studies that associate relatively few SNPs/INDELs to rate of drug metabolism and/or enzyme activity [12-17]. It has been demonstrated that combinatorial pharmacogenetic profiles (i.e., data from multiple genes) improved patient outcomes in response to antidepressants [18,19] and opiates [20]. Therefore, a higher confidence in predicting a metabolizer phenotype may be realized if information from

multiple enzymes in an ADME pathway, such as CYP2D6, UGT2B7, ABCB1, OPRM1, and COMT, are included in the analysis. For example, a *CYP2D6**4/*CYP2D6**4 homozygote is considered a PM and may be prescribed a higher dose of pro-drug (e.g., T) to reach the therapeutic window. However, that same individual may harbor an *ABCB1* diplotype which confers decreased efflux of O-desmethyltramadol (M1, the primary active metabolite of T) across the blood brain barrier, enabling a relatively large concentration of M1 to reach OPRM1 and stimulate analgesia propagation. Ultimately, a patient with this pair of diplotypes at *CYP2D6* and *ABCB1* should experience the desired, and safe, degree of pain relief, but relying solely on *CYP2D6* information for this patient would support increasing the tramadol dose which potentially could cause hyperalgesia.

While combinatorial studies have been performed, they rely on targeted genotyping approaches to interrogate *a priori* SNPs and/or INDELs [13,15,20-24]. Consequently, novel polymorphism(s) cannot be identified that refine estimates of enzyme activity [25]. Massively parallel sequencing (MPS) of the full gene region increases the potential to discover polymorphisms that are currently excluded from phenotype predictions [26].

Herein, the SNP and INDEL variant effect prediction data presented by Wendt, *et al.* [27] are expanded upon using the phased data of the 1000 Genomes Project [28]. Full-gene haplotypes of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* were characterized in self-reported healthy individuals. When compared to *CYP2D6*-predicted metabolizer phenotype for the same individuals [25], it was demonstrated that NMs by *CYP2D6* genotyping may possess poorly active downstream metabolic enzymes. Logistic regression suggests that phenotype predictions using *CYP2D6*-inferences alone do not explain all phenotypic variability as there may be contribution from polymorphisms in *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*.

Materials and Methods

Polymorphisms in the *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* gene regions, including introns, exons, 5′ and 3′ untranslated regions (UTRs), and promoters, were downloaded from Phase 3 of the 1000 Genomes Project and analyzed individually in 5 super- and 26 sub-populations (Table S1) according to Wendt, *et al*. [27]. Haplotypes for each gene were produced according to Table 1 and individual haplotypes are listed in Table S2. Certain polymorphisms characterized were removed from haplotype formation to simplify downstream analyses but capture meaningful levels of variation within each gene. Those excluded variants differ for each gene based on gene size, number of polymorphic sites within each gene, and the consensus variant effect prediction of each polymorphism. In general, polymorphisms that were not scored by Sort Intolerant From Tolerant (SIFT) [34-39], Polymorphisms Phenotyping v2 (PolyPhen-v2) [34,40,41], Protein Variant Effect Analyzer (PROVEAN) [42-44], or Human Splicing Finder (HSF) [45], were removed. Private mutations (SNPs or INDELs observed once in the 1000 Genomes Project) were included/excluded on a gene-by-gene basis. *ABCB1* was divided into four haplotype blocks based on Sai, *et al.* [30,31]. Herein, haplotype block *ABCB1-Block-1* has been extended to include untranslated exon 1 (Figure 1).

Table 1. Haplotype production approach for *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*. Private mutations are defined as those observed once in the global population (all 2,504 1000 Genomes Project individuals).

Gene	Total Polymorphisms	Full-Gene Haplotypes	Processing Notes	Polymorphisms Removed	Polymorphisms Included	Final Haplotypes
UGT2B7	613	887	Removal of private mutations except those predicted damaging or most likely damaging [27,29]	246	367	641
ABCB1	5,986	>3,000	Removal of all unscored polymorphisms [27]; gene broken into haplotype blocks [30,31]	5,310	676 Total (51 Block 3; 511 Block 2; 106 Block 1; 8 Block -1)	98 Block 3; 754 Block 2; 208 Block 1; 9 Block -1
OPRM1	6,831	> 3,000	Removal of all unscored polymorphisms [27]	6,627	204	527
COMT	1,007	2,131	Removal of all unscored polymorphisms [27]	924	83	377

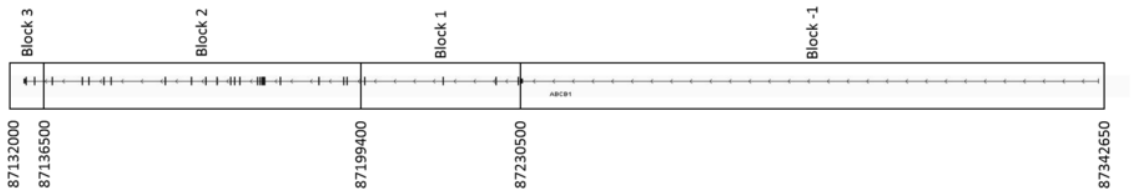

Figure 1. *ABCB1* haplotype blocks. Image modified from Integrative Genomics Viewer [32,33] indicated chromosome 7 coordinates are relative to the hg19 reference genome.

Using in-house Excel-based workbooks, haplotypes were aligned to the hg19 and hg38 reference genomes. Haplotypes were named with the following nomenclature format: reference sequence (genome name)-community recognized star allele (if known)-list of polymorphism rs numbers, if known, and the base at each position. Note that within text haplotypes were referenced using numeric identifiers relative to their frequency in the global population of all 2,504 1000 Genomes Project individuals (Table S2).

Population genetic summary statistics for five super- and 26 sub-populations, including haplotype and diplotype frequencies (analogous to allele and genotype frequencies), observed (H_o)

and expected (H_e) heterozygosities, pairwise genetic distances, and tests for detection of departures from Hardy Weinberg Equilibrium (HWE) and linkage disequilibrium were performed using Genetic Data Analysis (GDA) [46] and the RStudio® package ggplot2 [47]. TreeView Version 1.6.6 Build 7601 [48,49] was used to create phylogenetic trees; haplotype network analyses were performed using Population Analysis with Reticulate Trees (PopART) using the ancestral parsimony setting [50].

Enzyme activity was predicted using commonly typed and previously described polymorphisms for each gene [13,17,29-31,51-53]. Due to lack of empirical data for each polymorphism, additional damaging or most likely damaging polymorphisms in a gene were assumed to completely eliminate enzyme function. Logistic regression was used to explore possible relationships between the well-characterized *CYP2D6*-inferred metabolizer phenotype, represented as an activity score (a qualitative measure of phenotype derived from the activity conferred by each * allele an individual carries [54]) and the predicted activity of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*. These data were then used to interpret the potential utility of a combinatorial pharmacogenetic profile.

Results and Discussion

UGT2B7, ABCB1, OPRM1, and COMT

A total of 641, 98, 754, 208, 9, 527, and 377 string sequences were observed for *UGT2B7*, *ABCB1-Block 3*, *ABCB1-Block 2*, *ABCB1-Block 1*, *ABCB1-Block -1*, *OPRM1*, and *COMT*, respectively (Table 1 and Figure 2). *ABCB1-Block 3* haplotype 1, *ABCB1-Block 2* haplotype 191, *ABCB1-Block 1* haplotype 8, *ABCB1-Block -1* haplotype 3, and *COMT* haplotype 1, respectively, were identical to the hg19/hg38 reference genomes. No *UGT2B7* and *OPRM1* haplotypes were

identical to the hg19/hg38 reference sequences. A majority of haplotypes were observed once in the global population so the average global frequency of haplotypes for each gene was quite low (0.00156 ± 0.00690 for *UGT2B7*, 0.0102 ± 0.0566 for *ABCB1-Block 3*, 0.00133 ± 0.00699 for *ABCB1-Block 2*, 0.00481 ± 0.0243 for *ABCB1-Block 1*, 0.111 ± 0.222 for *ABCB1-Block -1*, 0.00190 ± 0.00873 for *OPRM1*, and 0.00265 ± 0.00900 for *COMT*). *UGT2B7* haplotypes 1-20, *ABCB1-Block 3* haplotypes 1-7, *ABCB1-Block 2* haplotypes 1-17, *ABCB1-Block 1* haplotypes 1-16, *ABCB1-Block -1* haplotypes 1-3, *OPRM1* haplotypes 1-18, and *COMT* haplotypes 1-21 had global alleles frequencies ≥ 1% (Figure 2), with average frequencies of 0.0284 ± 0.0278 for *UGT2B7*, 0.127 ± 0.186 for *ABCB1-Block 3*, 0.0293 ± 0.0371 for *ABCB1-Block 2*, 0.0516 ± 0.0748 for *ABCB1-Block 1*, 0.331 ± 0.229 for *ABCB1-Block -1*, 0.0371 ± 0.0311 for *OPRM1*, and 0.0298 ± 0.0255 for *COMT*.

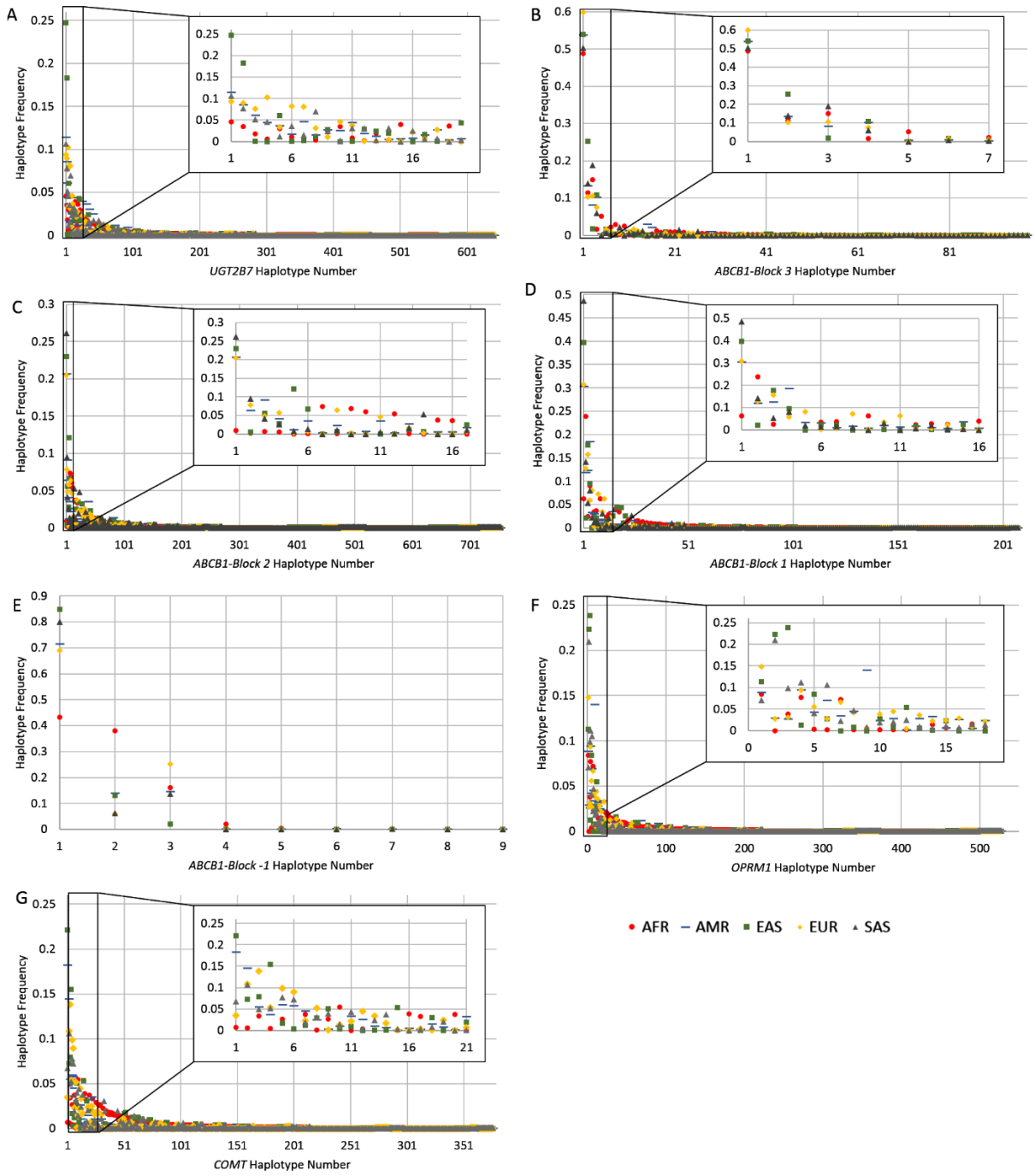

Figure 2. Haplotype frequencies for *UGT2B7* (A), *ABCB1-Block 3* (B), *ABCB1-Block 2* (C), *ABCB1-Block 1* (D), *ABCB1-Block -1* (E), *OPRM1* (F), and *COMT* (G) in five super-populations (African [AFR; circles], Admixed American [AMR; horizontal lines], East Asian [EAS; squares], European [EUR; diamonds], and South Asian [SAS; triangles]).

Variant compositions for the most common haplotypes of each gene and for all haplotypes are displayed in Figures 3 and S1, respectively. Empirical data are not present for the large number of haplotypes observed so for the descriptive purposes of this work, the presence of one damaging, or most likely damaging [27,34-45], polymorphism in the haplotype is considered sufficient to decrease enzyme function. The average number of polymorphisms per haplotype was 59.8 ± 27.6 for *UGT2B7,* 3.56 ± 1.01 for *ABCB1-Block -1*, 4.50 ± 1.97 for *ABCB1-Block 1*, 16.5 ± 7.00 for *ABCB1-Block 2*, 3.08 ± 1.21 for *ABCB1-Block 3*, 11.3 ± 2.62 for *OPRM1*, and 4.89 ± 1.99 for *COMT*. Due to limited studies of the polymorphic nature of these four genes and inclusion of additional interrogated regions, none of the observed sequences herein were identical to previously reported star (*) alleles (a haplotype of polymorphisms along the length of the gene region) for *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*. It should be noted that a substantial number of SNPs/INDELs found in each haplotype (Figures 3 and S1) are found in intronic or 5′ and 3′ untranslated regions and may have no individual impact on protein function but my play roles in regulating splice variation, rate of transcription, or have epistatic effects.

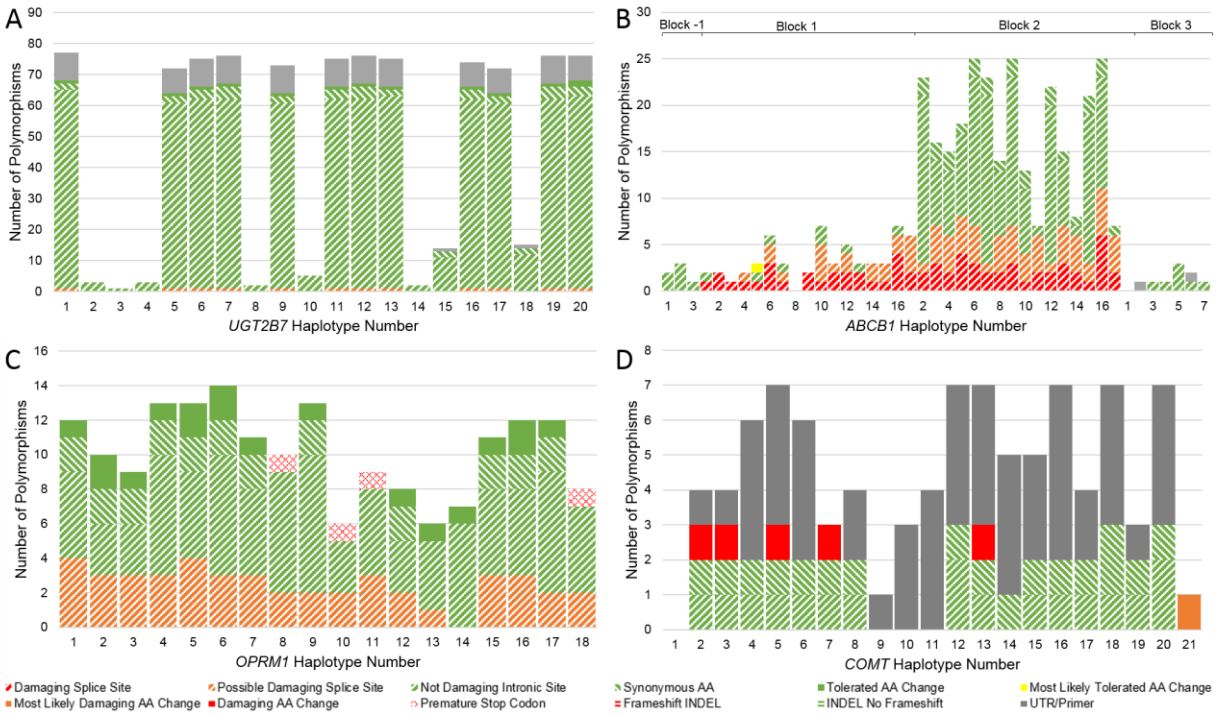

Figure 3. Haplotype composition of 19, 3, 16, 17, 7, 18, and 21 haplotypes in *UGT2B7* (A), *ABCB1*-Block -1 (B), *ABCB1*-Block 1 (B), *ABCB1*-Block 2 (B), *ABCB1*-Block 3 (B), *OPRM1* (C), and *COMT* (D), respectively, with global frequencies ≥ 1%. Variant effect predictions presented by Wendt, *et al.* [27] using Sort Intolerant From Tolerant [34-39], Polymorphism Phenotyping v2 [34,40,41], Protein Variant Effect Analyzer [42-44], and Human Splicing Finder [45].

Network analysis was performed to determine the relatedness of two sets of haplotypes for each gene of interest: (1) haplotypes having >1% global haplotype frequency (Figure 4), and (2) haplotypes observed more than once in the 1000 Genomes Project dataset (Figure S2). Networks for *UGT2B7*, *ABCB1-Block 3*, *ABCB1-Block 2*, and *ABCB1-Block-1* haplotypes (Figure S2) appear to have more clearly defined haplotype relationships, less looping (multiple haplotypes may have multiple relationships with nearby haplotypes), and/or less reticulation (the degree of "webbing" in the network) than those of *OPRM1* and *COMT*. This observation is possibly attributable to the relatively few number of polymorphisms separating *OPRM1* and *COMT* haplotypes or be an artifact of deleting private mutations which may sufficiently differentiate the

relationships between haplotypes; alternatively, the substantial reticulation in the *OPRM1* and *COMT* haplotype networks might also suggest some degree of recombination between the regions of interest. Most major haplotypes in all four genes were observed in all five super-populations while many minor haplotypes were unique to one super-population, namely African (i.e., *UGT2B7* haplotypes stemming from *UGT2B7*-H19). This observation may be due to population-specificity and/or sampling effects.

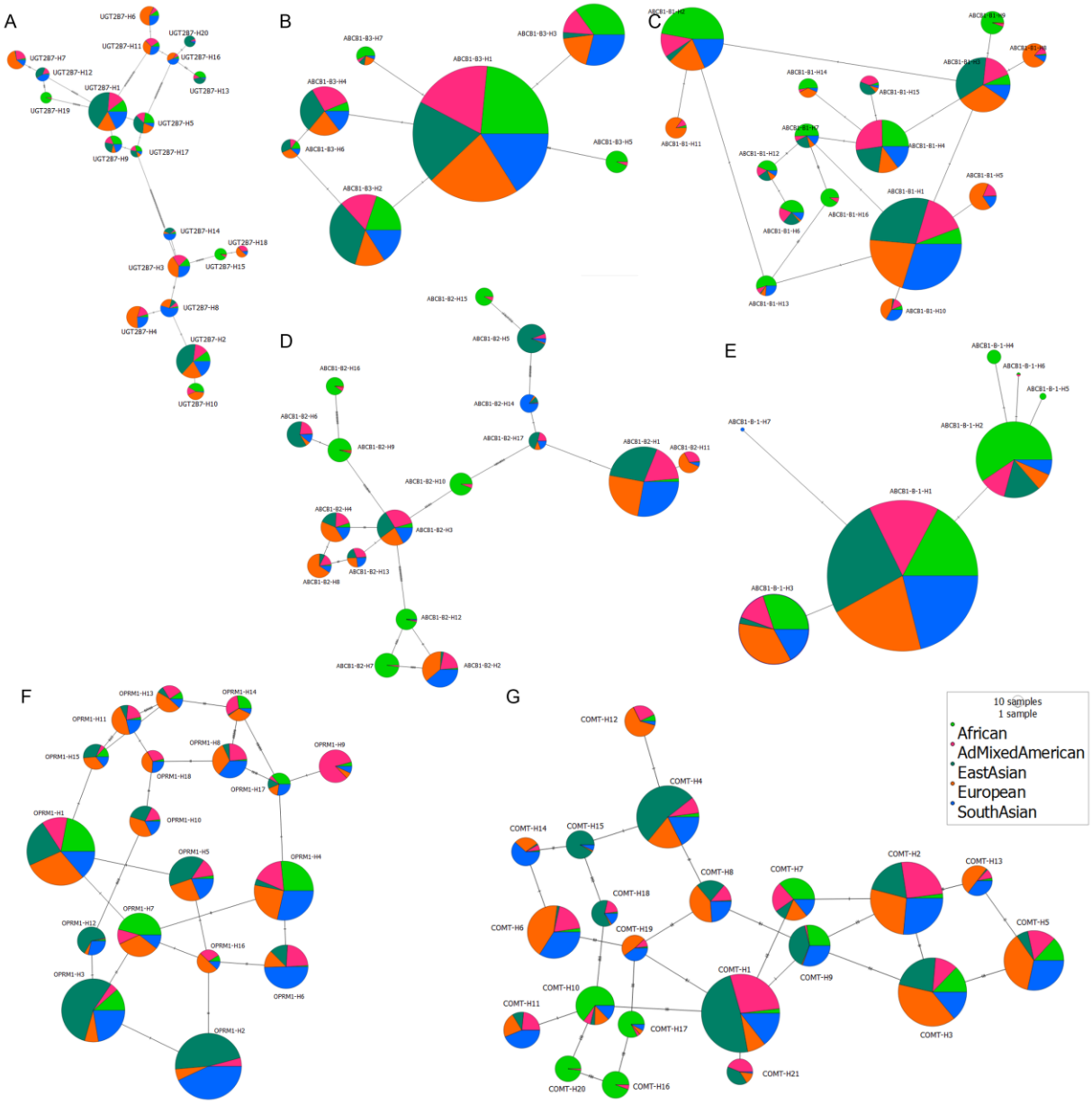

Figure 4. Network analysis of *UGT2B7* haplotypes 1-20 (A), *ABCB1*-Block 3 haplotypes 1-7 (B), *ABCB1*-Block 2 haplotypes 1-17 (C), *ABCB1*-Block 1 haplotypes 1-16 (D), *ABCB1*-Block -1 haplotypes 1-9 (E), *OPRM1* haplotypes 1-18 (F), and *COMT* haplotypes 1-21 (G). The size of each circle is proportional to the global frequency of each haplotype, segments within each circle are proportional to the super-population haplotype frequency, and lines connecting circles are dashed with the number of mutations separating two haplotypes.

There were 1,414, 225, 1,530, 567, 17, 1,219, and 1,267 unique *UGT2B7*, *ABCB1-Block 3*, *ABCB1-Block 2*, *ABCB1-Block 1*, *ABCB1-Block -1*, *OPRM1*, and *COMT* diplotypes, respectively, observed across 2,504 individuals. The average global diplotype frequencies were $7.07 \times 10^{-4} \pm 0.00151$ for *UGT2B7*, 0.00444 ± 0.0234 for *ABCB1-Block 3*, $6.534 \times 10^{-4} \pm 0.00149$ for *ABCB1-Block 2*, 0.00176 ± 0.00685 for *ABCB1-Block 1*, 0.0588 ± 0.125 for *ABCB1-Block -1*, $8.20 \times 10^{-4} \pm 0.00211$ for *OPRM1*, and $7.96 \times 10^{-4} \pm 0.00142$ for *COMT*. Population-specific diplotype frequencies are displayed in Figure S5. The average observed diplotype heterozygosity was 0.850 ± 0.129, 0.745 ± 0.172, 0.690 ± 0.224, 0.753 ± 0.170 0.687 ± 0.191 for the African (AFR), Ad Mixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS) super-populations, respectively. Prior to Bonferroni correction ($p < 0.05$), *UGT2B7*, *OPRM1*, and *COMT* deviated significantly from HWE expectations in all five, two (AFR and EAS), and one (AMR) super-populations, respectively. After Bonferroni correction ($p < 0.00714$), *UGT2B7* and *OPRM1* deviated significantly from HWE expectations in four (AMR, EAS, EUR, and SAS) and one (EAS) super-populations, respectively, out of the five total super-populations (Figure 5).

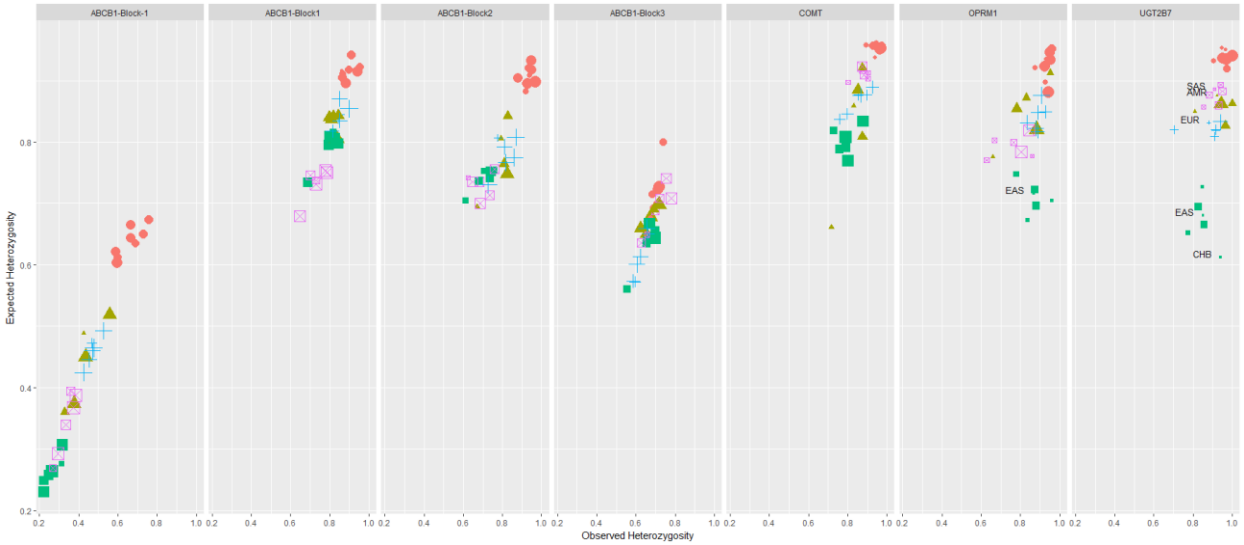

Figure 5. Observed and expected heterozygosity of *ABCB1*-Block -1, *ABCB1*-Block 1, *ABCB1*-Block 2, *ABCB1*-Block 3, *COMT*, *OPRM1*, and *UGT2B7* haplotypes in five super-populations (African [AFR] in solid circles; Admixed American [AMR] in solid triangles; East Asian [EAS] in squares; European [EUR] in plus signs; South Asian [SAS] in "X"-filled squares) and the 26 sub-populations within each super-population. The size of each data point represents the Hardy-Weinberg Equilibrium p-value for each population; labeled populations indicate significance after Bonferroni correction ($p < 0.00714$).

Intergenic Analyses

Unrooted neighbor-joining trees (Figure S4) of super- and sub-populations using each gene individually (*ABCB1* is a combination of all four haplotype blocks) tend to show separation more so of the AFR and EAS populations while the AMR, EAS, and SAS populations cluster closer together. Considering all five genes (Figure 6) the same super-population trend is seen. Generally, the sub-populations within each super-population were grouped closely together; however, the Gujarati Indian from Houston, Texas (GIH) and the Peruvians from Lima, Peru (PEL) populations plot separately from the group of AMR, EUR, and SAS sub-populations.

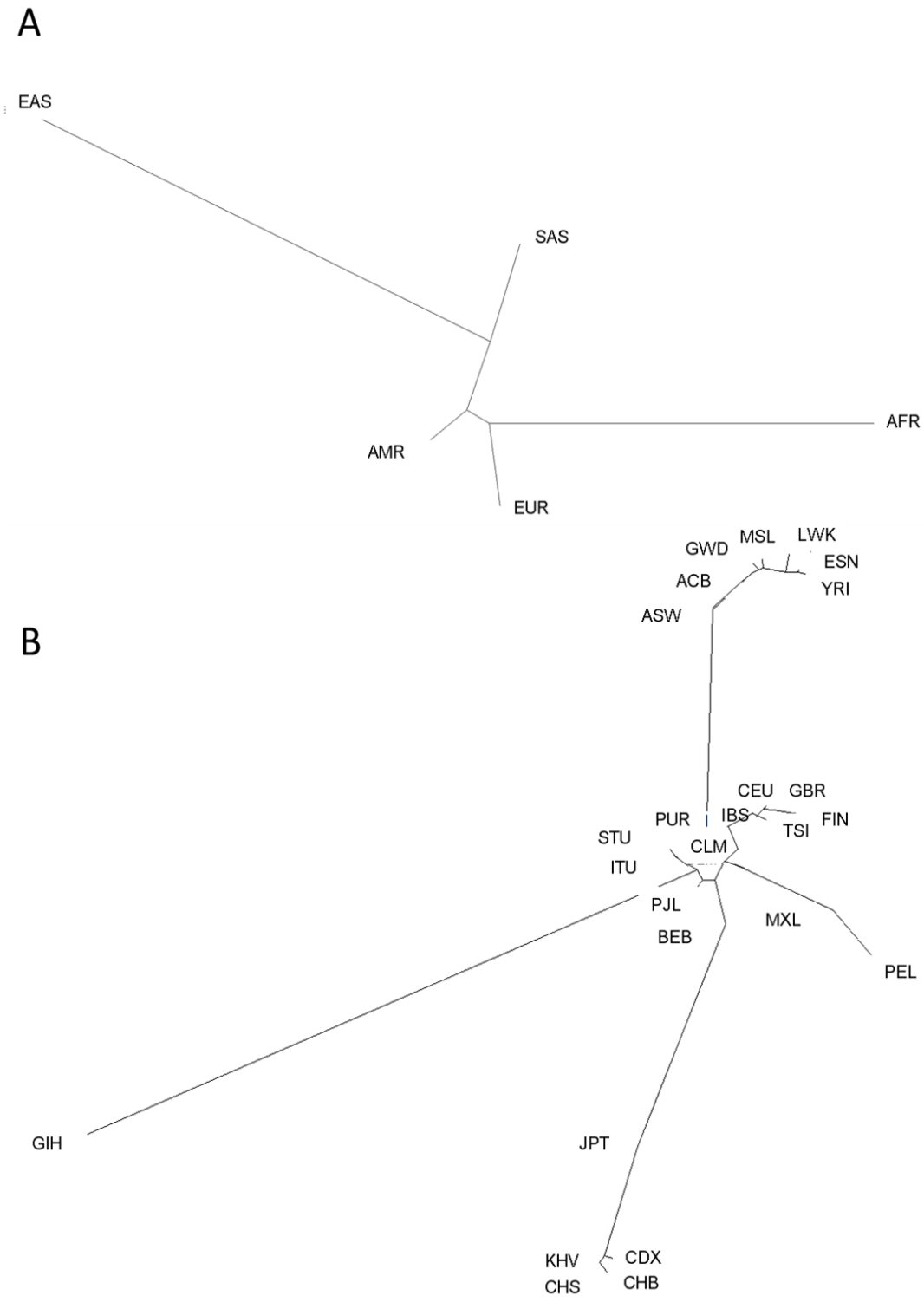

Figure 6. Neighbor-joining trees for five super- (A) and twenty-six sub-populations (B) in the 1000 Genomes Project using pairwise genetic distances based on *CYP2D6* [25], *UGT2B7*, *ABCB1-Block 3, ABCB1-Block 2, ABCB1-Block 1, ABCB1-Block -1, OPRM1, and COMT* haplotype assignments.

Intergenic pairwise LD was tested using full-gene haplotypes for *CYP2D6* [25], *UGT2B7*, *ABCB1-Block 3*, *ABCB1-Block 2*, *ABCB1-Block 1*, *ABCB1-Block -1*, *OPRM1*, and *COMT* to identify associations between metabolically relevant genes. Prior to Bonferroni correction ($p < 0.05$) and after removal of significant associations between *ABCB1* haplotype blocks, there were ten, 16, eight, five, and ten significant pairwise LDs in the AFR, AMR, EAS, EUR, and SAS super-populations, respectively (Figures 7 and S5). After Bonferroni correction ($p < 0.00179$), there were six, five, one, two, and one significant pairwise LDs in the AFR, AMR, EAS, EUR, and SAS super-populations, respectively, most of which contain *CYP2D6* and an additional downstream metabolic enzyme. The AFR super-population exhibited more LDs than any other super-population (though the significant correlations are weak [average Pearson's $r = 0.0181$]) and those increased LDs are detected in the AFR sub-populations as well. These data are contrary to the expectations of lower LD in AFR populations compared with other population groups [55] but were observed with the individual SNP data as well so this observation is not surprising [27]. However, the effect may be artifactual and possibly explained by the highly polymorphic nature of these genes in the AFR population which results in an overall low frequency of each haplotype (Figure 2). Consequently, a large number of diplotypes may be observed only once in the AFR super-population, making the comprised haplotypes appear to be in LD due to scant observations of each haplotype. When compressed to minimize the impact of rare diplotypes using the "collapse less-frequent alleles" function in GDA, significant LDs were observed between *CYP2D6* and *UGT2B7*, *ABCB1-Block -1, ABCB1-Block 1, ABCB1-Block 2, ABCB1-Block 3, OPRM1* and *COMT*, with Pearson's r-values ranging from -0.0562 to 0.0610 for AFR and -0.0903 to 0.129 for AMR. Though not observed across the whole ADME process, there were some significant LDs between *CYP2D6* and other downstream enzymes in the EAS, EUR, and SAS populations as well.

Of particular interest are the significant pairwise LDs between *CYP2D6/UGT2B7* (-0.0562 [AFR] to 0.0934 [AMR]) and *CYP2D6/COMT* (-0.0902 [EUR] to 0.129 [AMR]) in all five super-populations, which may represent associations between their functional impact. The *COMT* locus is found in a one megabase (Mb) region of chromosome 22 with a relatively high average recombination rate (2.40 ± 1.56 centimorgans/Mb) which may artificially inflate the LD pattern involving this locus [55-59]. These empirical data have not yet been explored and more research is needed to support whether an effect is real.

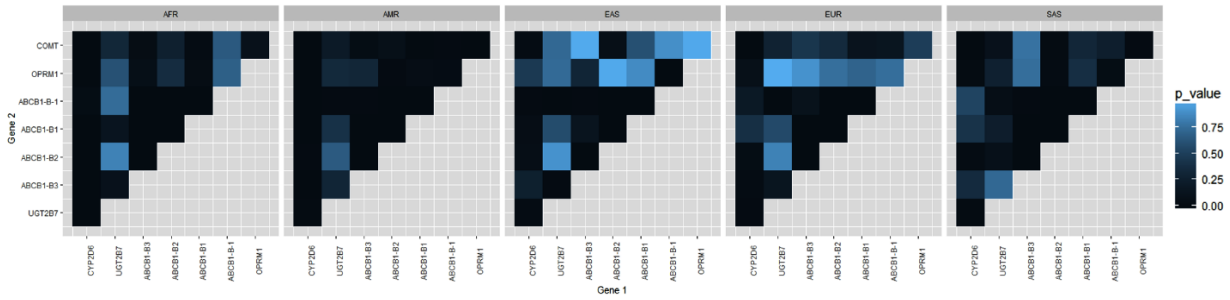

Figure 7. Heat maps of pairwise linkage disequilibrium p-values using *CYP2D6* [25], *UGT2B7*, *ABCB1-Block 3*, *ABCB1-Block 2*, *ABCB1-Block 1*, *ABCB1-Block -1*, *OPRM1*, and *COMT* diplotype in the African (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS) super-populations.

Using previously identified genotype-phenotype data [13,17,29-31,51-53] and additional polymorphisms characterized by Wendt, *et al.* [27], the activities of UGT2B7, ABCB1, OPRM1 and COMT were predicted for each 1000 Genomes Project individual. When grouped by *CYP2D6*-inferred metabolizer phenotype as a global cohort (2,504 self-reported healthy individuals), there was no association detected between metabolizer phenotype and the diplotype-predicted activity of the selected downstream metabolically-relevant enzymes. Positive and negative correlations were observed between *COMT* ($p = 0.0223$) and *UGT2B7* ($p = 0.0389$) and *CYP2D6* activities, respectively; however the variance at *CYP2D6* activity score of 3 is quite large and may have

influenced the significance of this relationship (Figure 8A shaded regions). CYP2D6 activity score of 3 was only detected in one Toscani in Italia individual who carries one normally active and one increased activity *CYP2D6* * allele (*CYP2D6**1/*53). On the super-population level, there were more obvious trends, again between *UGT2B7* and *COMT* activities and the *CYP2D6* activity score. Two super-populations showed significant associations between *CYP2D6* and other enzyme activity: AMR and *UGT2B7* ($p = 0.0340$), and EAS and *OPRM1* ($p = 0.0361$). The remaining super-populations and genes did not exhibit significant associations between the *CYP2D6*-inferred metabolizer phenotype and diplotype-predicted downstream metabolic activity. Variant effect predictions [34-45] suggested that all 1000 Genomes Project self-reported healthy individuals possess an *ABCB1* diplotype that confers abnormal transporter activity. This observation may be misleading due to inaccuracies of the variant effect prediction programs used [27]. The functional consequences of individual *ABCB1* polymorphisms, the combined impact of multiple *ABCB1* polymorphisms, and the interaction between the effects of multiple polymorphisms in different genes are unavailable for comparison in this study but eventually will be needed to be empirically evaluated in affected, or drug-exposed, populations. If these observations are correct, the relative abundance of these splice-altering polymorphisms suggests that decreased ATP-dependent efflux efficiency may be the norm for self-reported healthy individuals. For example, rs2235027 has an alternate allele frequency of 0.517, 0.516, 0.383, 0.509, and 0.397 in the AFR, AMR, EAS, EUR, and SAS super-populations, respectively [27]. It can be hypothesized that affected, or drug-exposed, individuals possess additional polymorphisms, or are enriched for those identified here, that further alter transporter function and play a role in the idiosyncratic drug response phenotype [60-63]. Also epistatic interactions between multiple ABCB1 SNPs/INDELs have been demonstrated to influence antiepileptic drug resistance [64]. Possibly a similar phenomenon is

observed in self-reported healthy individuals who have either 1) not been exposed to a drug with which the epistasis-associated phenotype is observed or 2) are expressing a low level phenotype below level of personal discomfort and reporting.

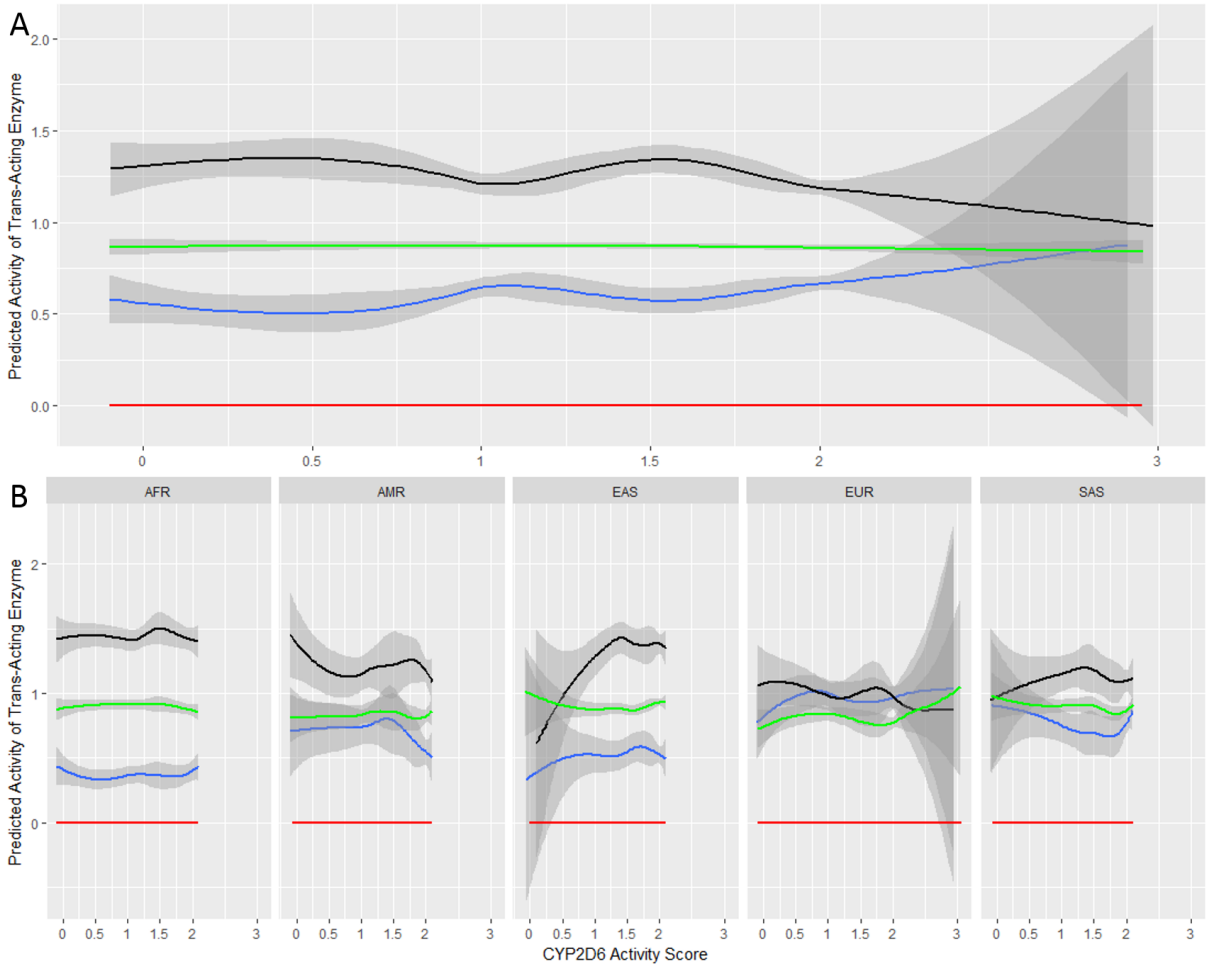

Figure 8. Regression analysis between CYP2D6 metabolizer phenotype [25] and predicted activity of downstream metabolic enzymes *UGT2B7* (blue), *ABCB1* (red), *OPRM1* (green), and *COMT* (black) in the global population of 2,504 1000 Genomes Project individuals (A) and by super-populations (B). Predicted activity of each trans-acting metabolic enzyme is based on the sum of predicted haplotype activities and ranges from zero to two (inactive to normally active, respectively).

Conclusions

Full-gene haplotypes of four genes encoding trans-acting T-metabolism proteins, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, were defined and characterized using substantially more polymorphic sites than previously employed in pharmacogenetic studies. In doing so, a large number of haplotypes were observed. The data presented demonstrate significant LDs between full-gene haplotypes of *CYP2D6* and those of *UGT2B7* and *COMT*; however, the functional effects of these findings need to be determined empirically. The relatively low frequency of each haplotype and associated diplotype may confound LD estimates simply because each haplotype was only observed in combination with one other haplotype. This study also proposed an extended *ABCB1-Block -1*, which included distal untranslated exon 1, and did not substantially increase acquired information over the truncated *Block -1* reported by Sai, *et al.* [30,31]. Most individual haplotypes identified in this study were quite rare; however, relatively common haplotypes (≥ 1% global frequency) were identified which contain at least one damaging, or most likely damaging, polymorphism. It should be noted that copy number variation and *CYP2D6/CYP2D7* gene conversion do occur in some individuals, primary UMs and may alter the presented LD and regression patterns [65]. These events were not considered herein for determining of CYP2D6 activity [11] due to the limitations of short read sequences that comprise 1000 Genomes Project data [66,67]. It is likely that ongoing developments in longer read sequencing technologies will provide more confident interpretation of structural variation from existing short-read sequences [68-71].

The variant effects of many polymorphisms included in these haplotype definitions have not been empirically evaluated by the pharmacogenetics/pharmacogenomics community. There are obvious limitations to using an algorithmic approach to variant effect [72]; however, the

predicted implications on phenotype should not be overlooked, instead they can be used to narrow the pool of potentially causal variants/haplotypes to explore empirically The inclusion of only self-reported healthy individuals in the 1000 Genomes Project means that additional functionally-relevant haplotypes may be selected against being represented in this dataset. This limiting factor may impact the analyses performed above. It is likely that additional polymorphisms and/or specific haplotypes may be enriched, or selected for, in affected, or T-exposed, cohorts [73-75]. As such, there potentially are additional damaging haplotypes in these affected groups that have not been observed herein so a full-gene interrogation of affected cohorts may provide greater resolution to damaging haplotype population distribution. This possibility lends support to utilizing a comprehensive genotyping approach, such as relatively long-read MPS or continuous-read nanopore technology in pharmacogenetic/pharmacogenomic interrogations [70,71,76].

Though limited to a large cohort of self-reported healthy individuals, associations between individual genes have been identified which may be clinically significant. Though slight, there is a relationship between the *CYP2D6*-inferred metabolizer phenotype and the diplotype-predicted activities of UGT2B7, ABCB1, OPRM1, and COMT. This association highlights the need for comprehensive functional evaluation of the impact of polymorphisms in all five genes, and/or combinations of two, three, or four of these genes, on drug metabolism in the same individuals. It is reasonable to hypothesize that empirical evaluation of these targets will reveal the advantage of combinatorial pharmacogenetic profiles in regards to increased patient efficacy and even assisting with medico-legal accident reconstruction [18-20]. Currently, these data remain relatively scarce in the literature. The data presented herein provide a basis to interrogate the highly polymorphic T-metabolism pathway, defining full-gene haplotypes for, and characterizing the association between, five pharmacogenes that can be utilized in clinical pharmacogenetic evaluations and post-

mortem molecular autopsy using gene-targeted MPS. It is likely that these data can be expanded upon, by interrogating additional ADME gene haplotypes, for broad applicability for predicting metabolizer phenotype following exposure to other opioid drugs.

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Supplementary Information

Table S1. Population codes. 1000 Genomes Project population codes and descriptions for five super-populations and 26 sub-populations. Table from Wendt, *et al.* 2017 [27].

Super-Population (Code)	Sample Size	Population Code	Population Description	Sample Size
African (AFR)	661	YRI	Yoruba in Ibadan, Nigeria	108
		LWK	Luhya in Webuye, Kenya	99
		GWD	Gambian in Western Divisions in Gambia	113
		MSL	Mende in Sierra Leone	85
		ESN	Esan in Nigeria	99
		ASW	American of African Ancestry in Southwest United States	61
		ACB	African Caribbeans in Barbados	96
Ad Mixed American (AMR)	347	MXL	Mexican Ancestry from Los Angeles, USA	64
		PUR	Puerto Ricans from Puerto Rico	104
		CLM	Colombians from Medellin, Colombia	94
		PEL	Peruvians from Lima, Peru	85
East Asian (EAS)	504	CHB	Han Chinese in Beijing China	103
		JPT	Japanese in Tokyo, Japan	104
		CHS	Southern Han Chinese	105
		CDX	Chinese Dai in Xishuangbanna, China	93
		KHV	Kinh in Ho Chi Minh City, Vietnam	99
European (EUR)	503	CEU	Utah Residents (CEPH) with Northern and Western Ancestry	99
		TSI	Toscani in Italia	107
		FIN	Finnish in Finland	99
		GBR	British in England and Scotland	91
		IBS	Iberian Population in Spain	107
South Asian (SAS)	489	GIH	Gujarati Indian from Houston, Texas	103
		PJL	Punjabi from Lahore, Pakistan	96
		BEB	Bengali from Bangladesh	86
		STU	Sri Lankan Tamil from the United Kingdom	102
		ITU	Indian Telugu from the United Kingdom	102

Table S2. Short haplotype numbers, full-gene haplotype nomenclature, amino acid change, and predicted activity scores for UGT2B7, ABCB1-Block 3, ABCB1-Block 2, ABCB1-Block 1, ABCB1-Block -1, OPRM1, and COMT relative to the hg19 and hg38 reference genomes. Table S2 can be viewed on the Forensic Science International: Genetics website for this article (https://www.fsigenetics.com/article/S1872-4973(17)30260-0/abstract).

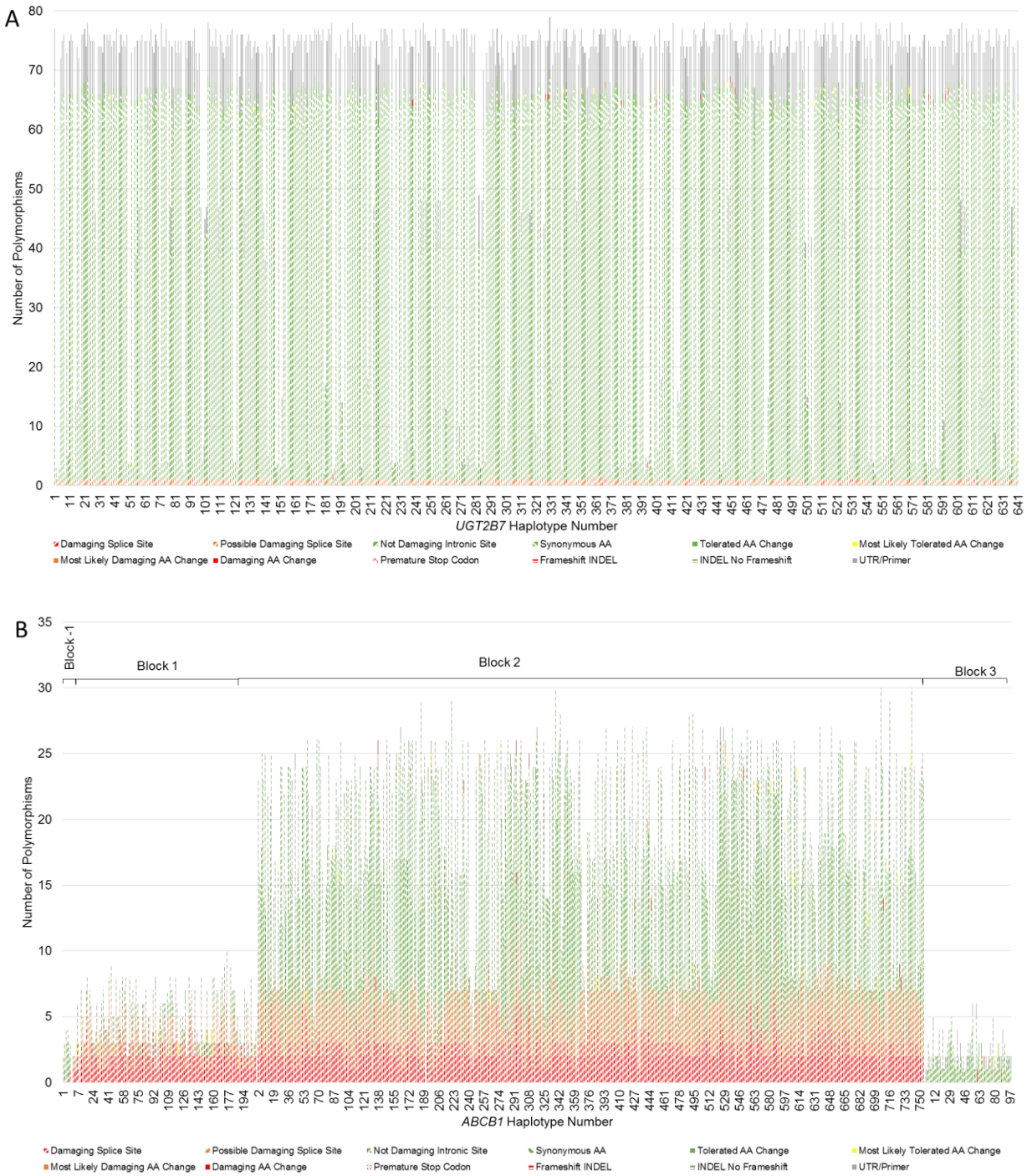


Figure S1. Haplotype composition of 641, 9, 208, 754, 98, 527, and 377 haplotypes in *UGT2B7* (A), *ABCB1-Block -1* (B), *ABCB1-Block 1* (B), *ABCB1-Block 2* (B), *ABCB1-Block 3* (B), *OPRM1* (C), and *COMT* (D), respectively, with global frequencies ≥ 1%. Variant effect predictions presented by Wendt, *et al*. 2017 [27] using Sort Intolerant From Tolerant [34-39], Polymorphism Phenotyping v2 [34,40,41], Protein Variant Effect Analyzer [42-44], and Human Splicing Finder [45].

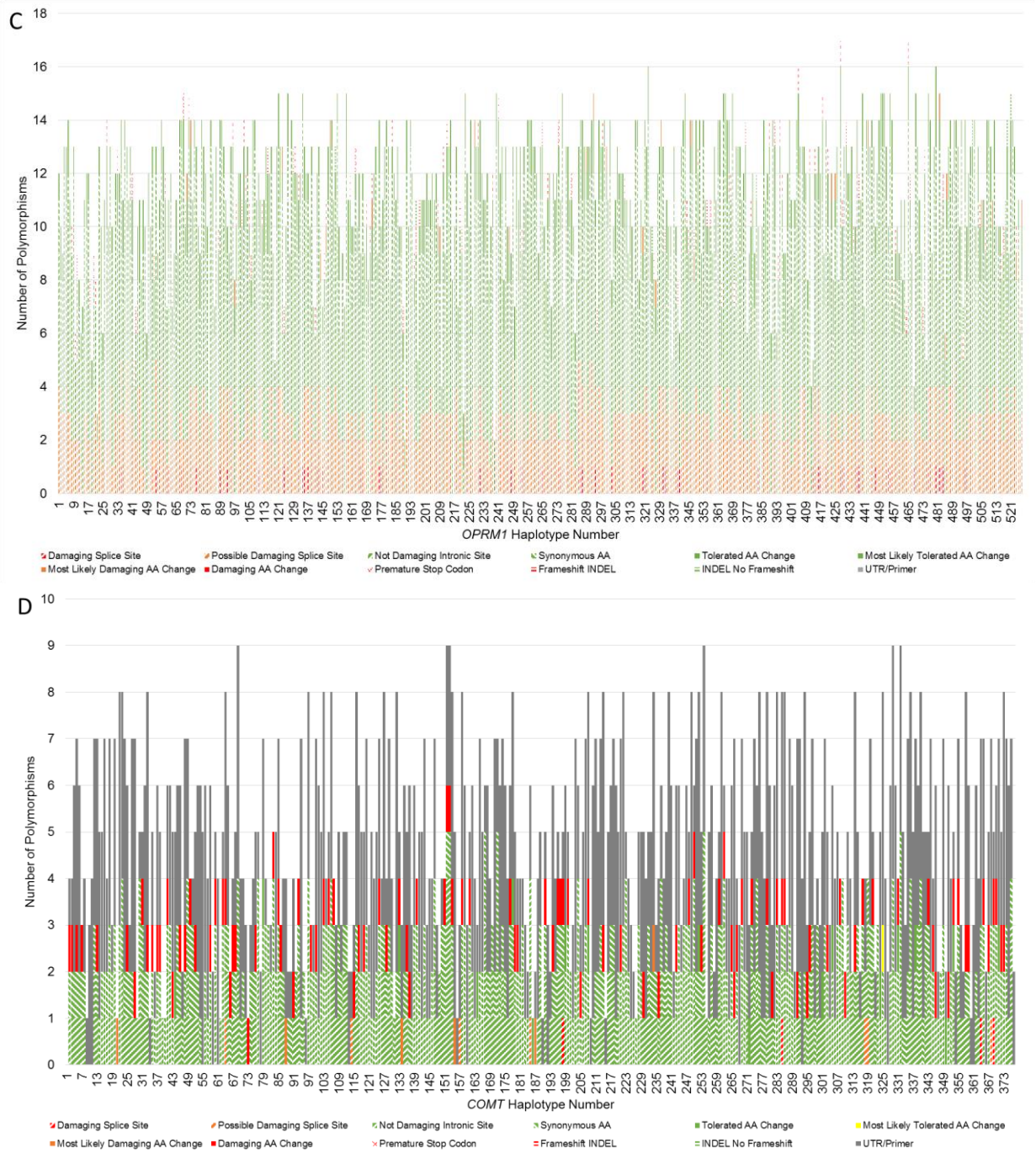


Figure S1 (continued). Haplotype composition of 641, 9, 208, 754, 98, 527, and 377 haplotypes in *UGT2B7* (A), *ABCB1-Block -1* (B), *ABCB1-Block 1* (B), *ABCB1-Block 2* (B), *ABCB1-Block 3* (B), *OPRM1* (C), and *COMT* (D), respectively, with global frequencies ≥ 1%. Variant effect predictions presented by Wendt, *et al*. 2017 [27] using Sort Intolerant From Tolerant [34-39], Polymorphism Phenotyping v2 [34,40,41], Protein Variant Effect Analyzer [42-44], and Human Splicing Finder [45].

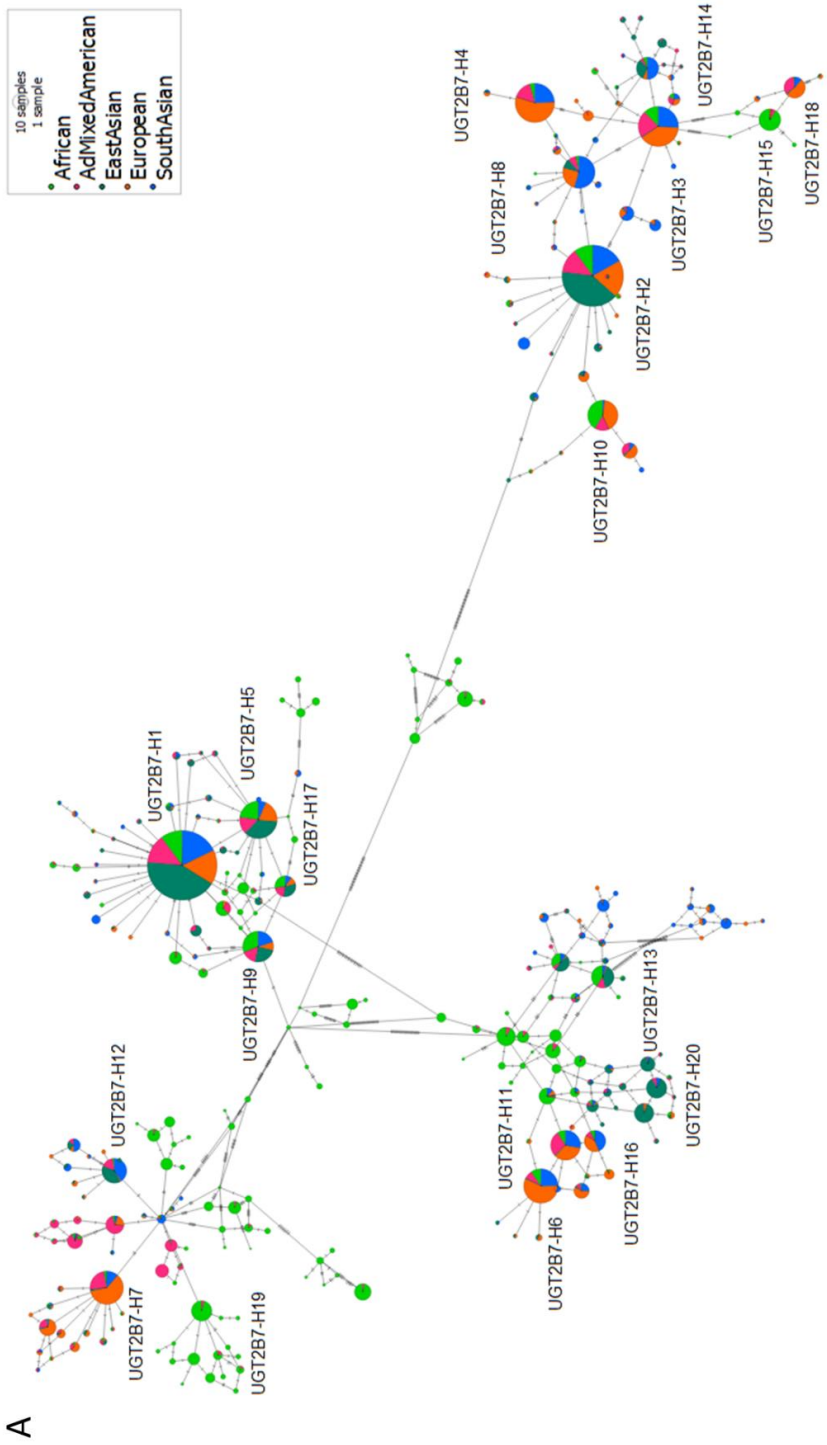


Figure S2. Network analysis of haplotypes observed more than once in the global population for *UGT2B7* (haplotypes 1-285; A), ABCB1-Block 3 (haplotypes 1-53; B), *ABCB1-Block 2* (haplotypes 1-271; C), *ABCB1-Block 1* (haplotypes 1-102; D), *OPRM1* (haplotypes 1-223; E), and *COMT* (haplotypes 1-215; F). Haplotypes with global frequencies ≥ 1% are labeled, the size of each circle is proportional to the global frequency of each haplotype, segments within each circle are proportional to the super-population haplotype frequency, and lines connecting circles are dashed with the number of mutations separating two haplotypes.

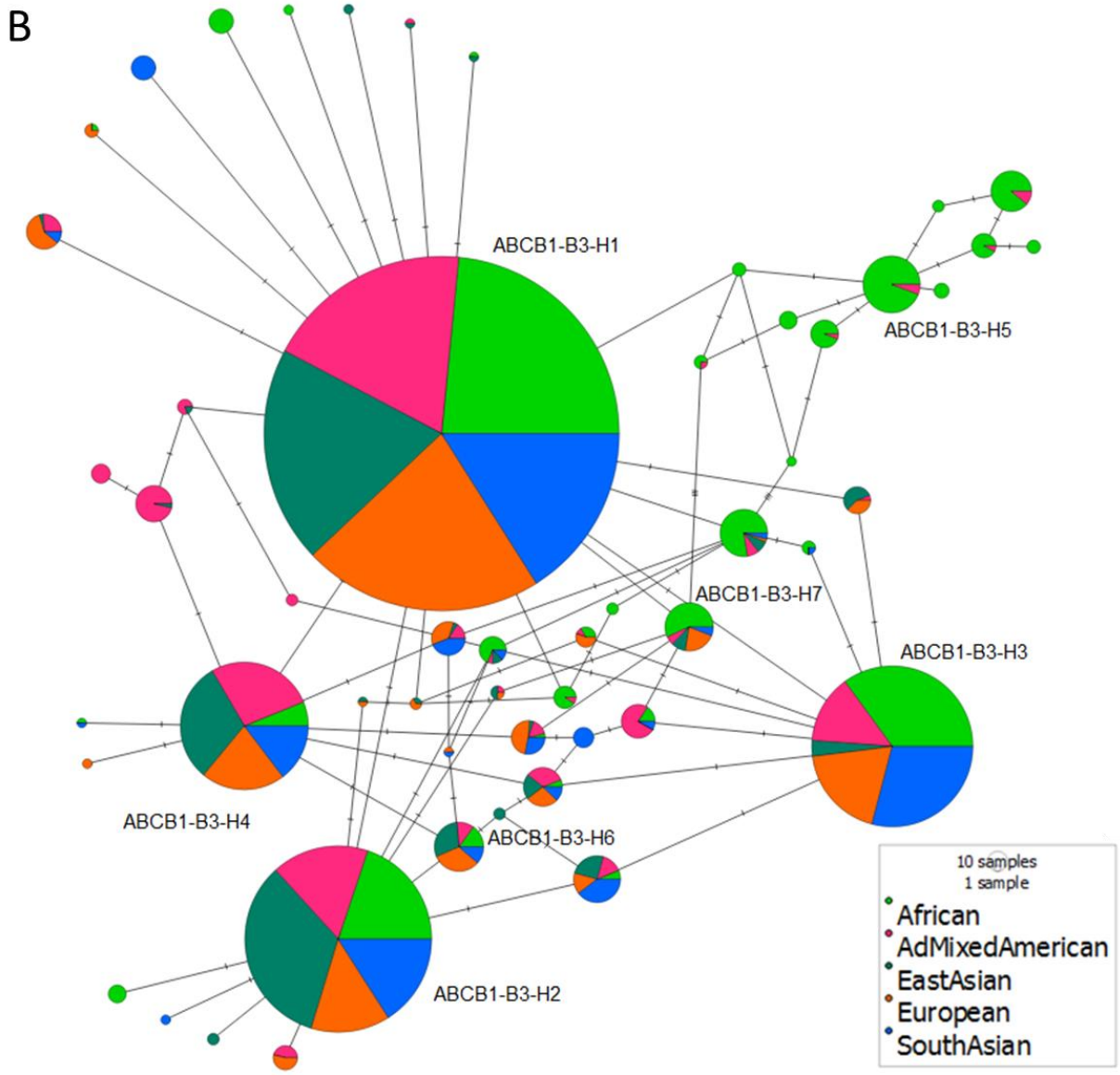
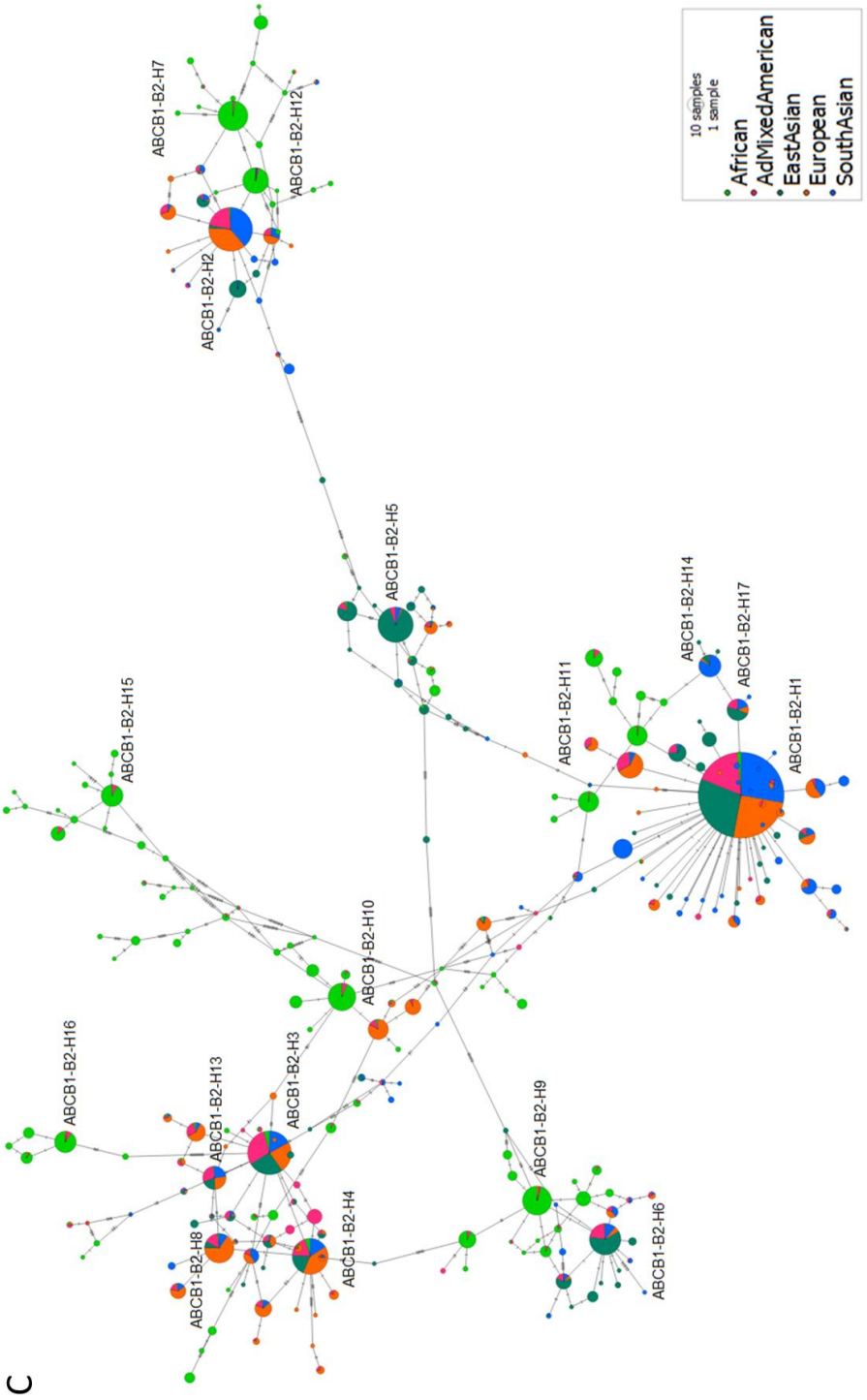


Figure S2 (continued). Network analysis of haplotypes observed more than once in the global population for *UGT2B7* (haplotypes 1-285; A), ABCB1-Block 3 (haplotypes 1-53; B), *ABCB1-Block 2* (haplotypes 1-271; C), *ABCB1-Block 1* (haplotypes 1-102; D), *OPRM1* (haplotypes 1-223; E), and *COMT* (haplotypes 1-215; F). Haplotypes with global frequencies ≥ 1% are labeled, the size of each circle is proportional to the global frequency of each haplotype, segments within each circle are proportional to the super-population haplotype frequency, and lines connecting circles are dashed with the number of mutations separating two haplotypes.



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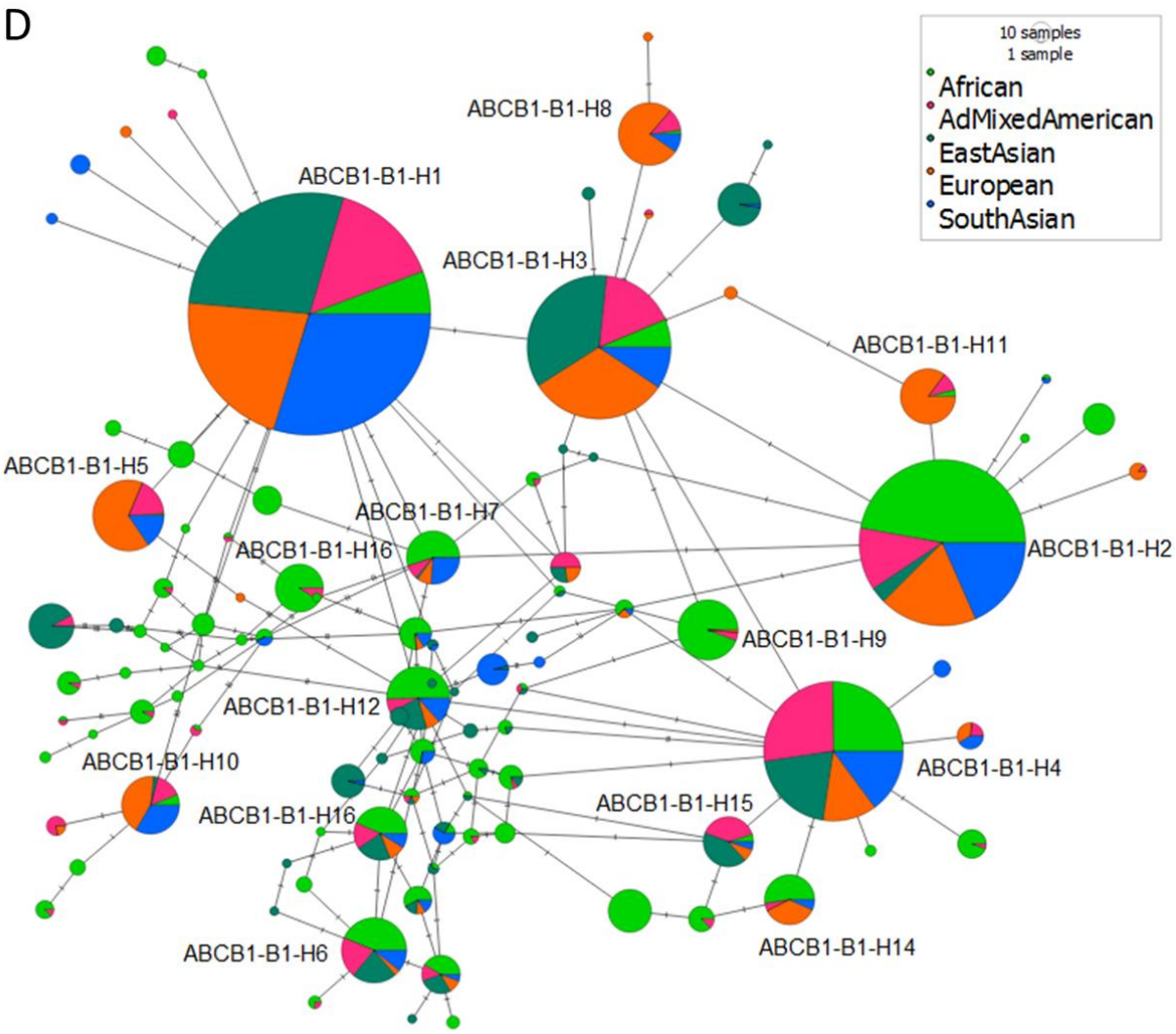

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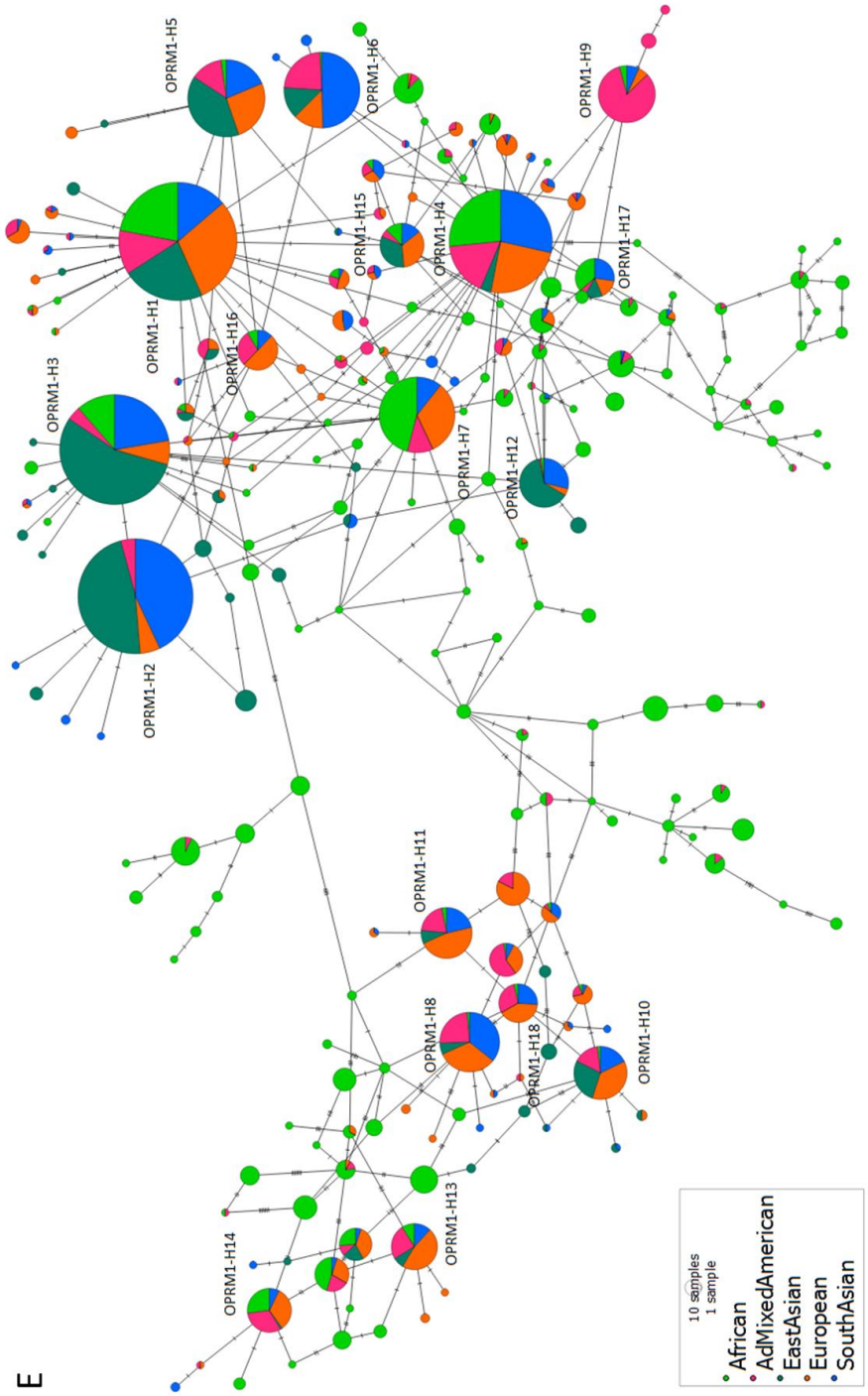

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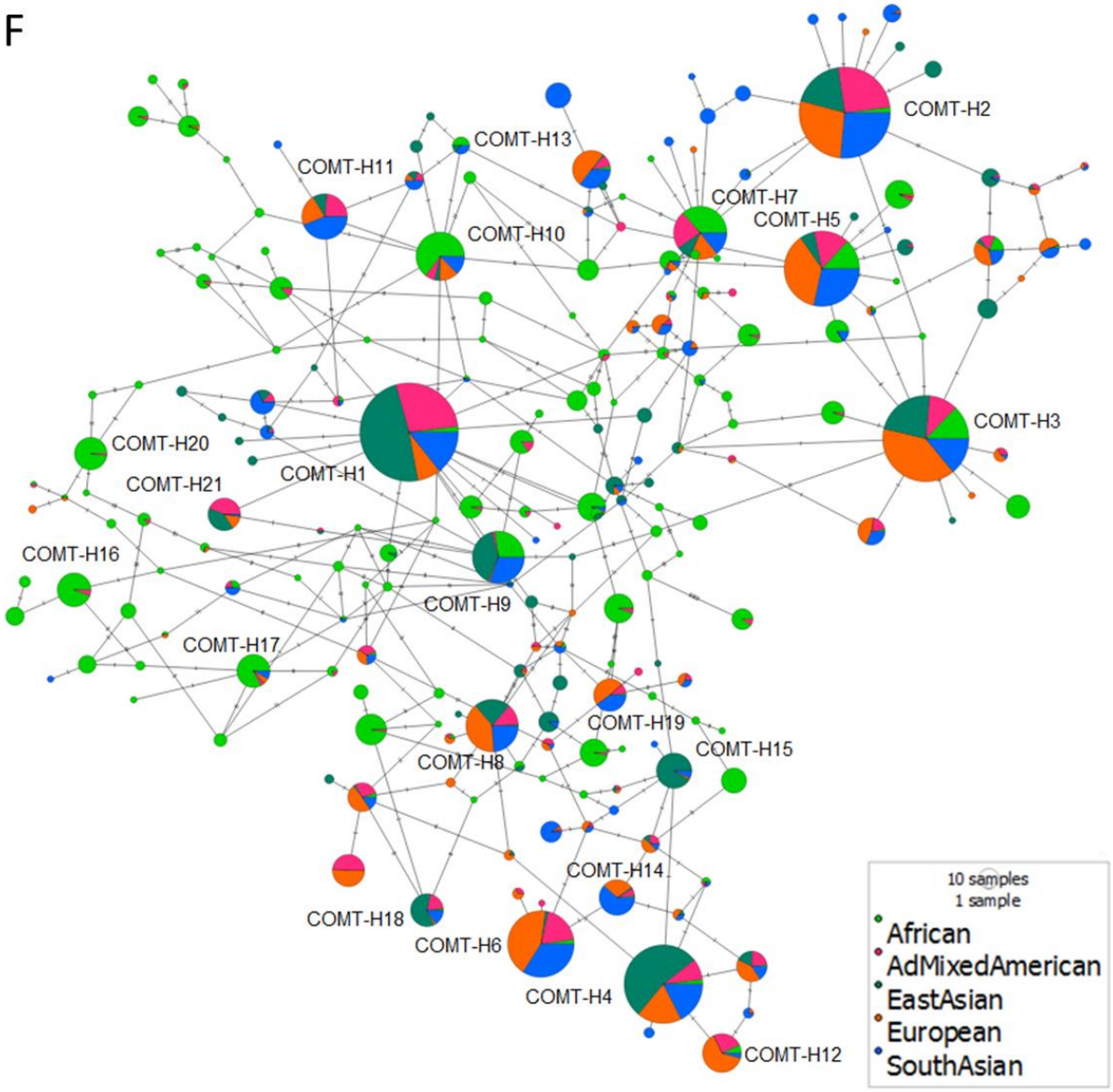

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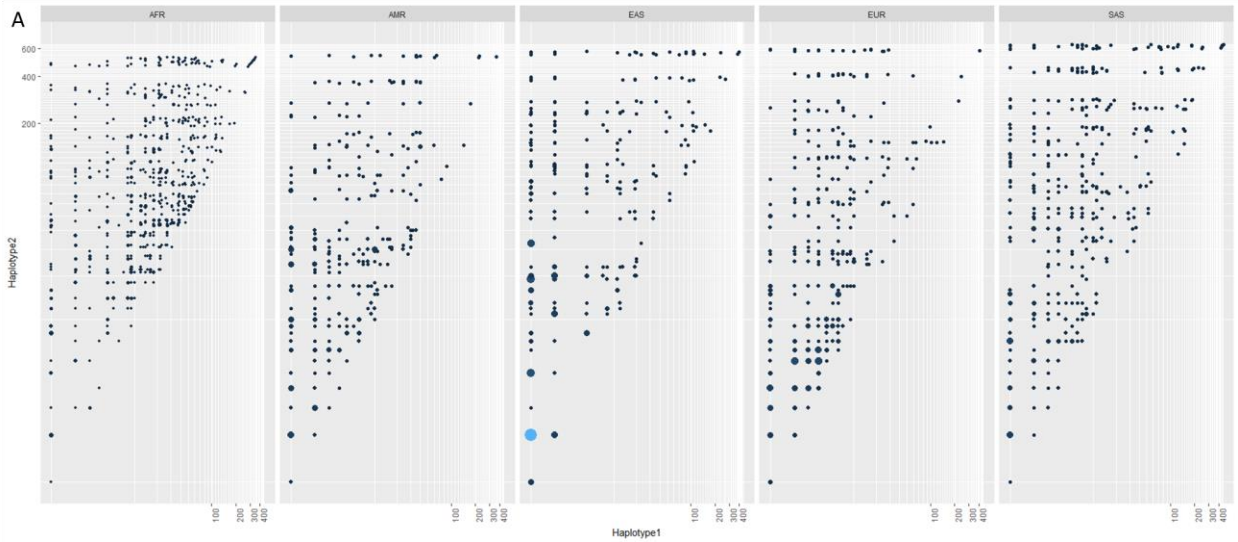

Figure S3. *UGT2B7* (A), *ABCB1-Block 3* (B), *ABCB1-Block 2* (C), *ABCB1-Block 1* (D), *ABCB1-Block -1* (E), *OPRM1* (F), and *COMT* (F) diplotype frequencies in the African (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS) super-populations. The x- and y- axes are the first and second haplotype number, respectively, of and individual diplotype plotted on a log10 scale; the size and color of each circle is proportional to the frequency of that diplotype with larger, bright data points indicating more frequent diplotypes.

Figure S3 (continued). *UGT2B7* (A), *ABCB1-Block 3* (B), *ABCB1-Block 2* (C), *ABCB1-Block 1* (D), *ABCB1-Block -1* (E), *OPRM1* (F), and *COMT* (F) diplotype frequencies in the African (AFR), Admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS) super-populations. The x- and y- axes are the first and second haplotype number, respectively, of and individual diplotype plotted on a log10 scale; the size and color of each circle is proportional to the frequency of that diplotype with larger, bright data points indicating more frequent diplotypes.

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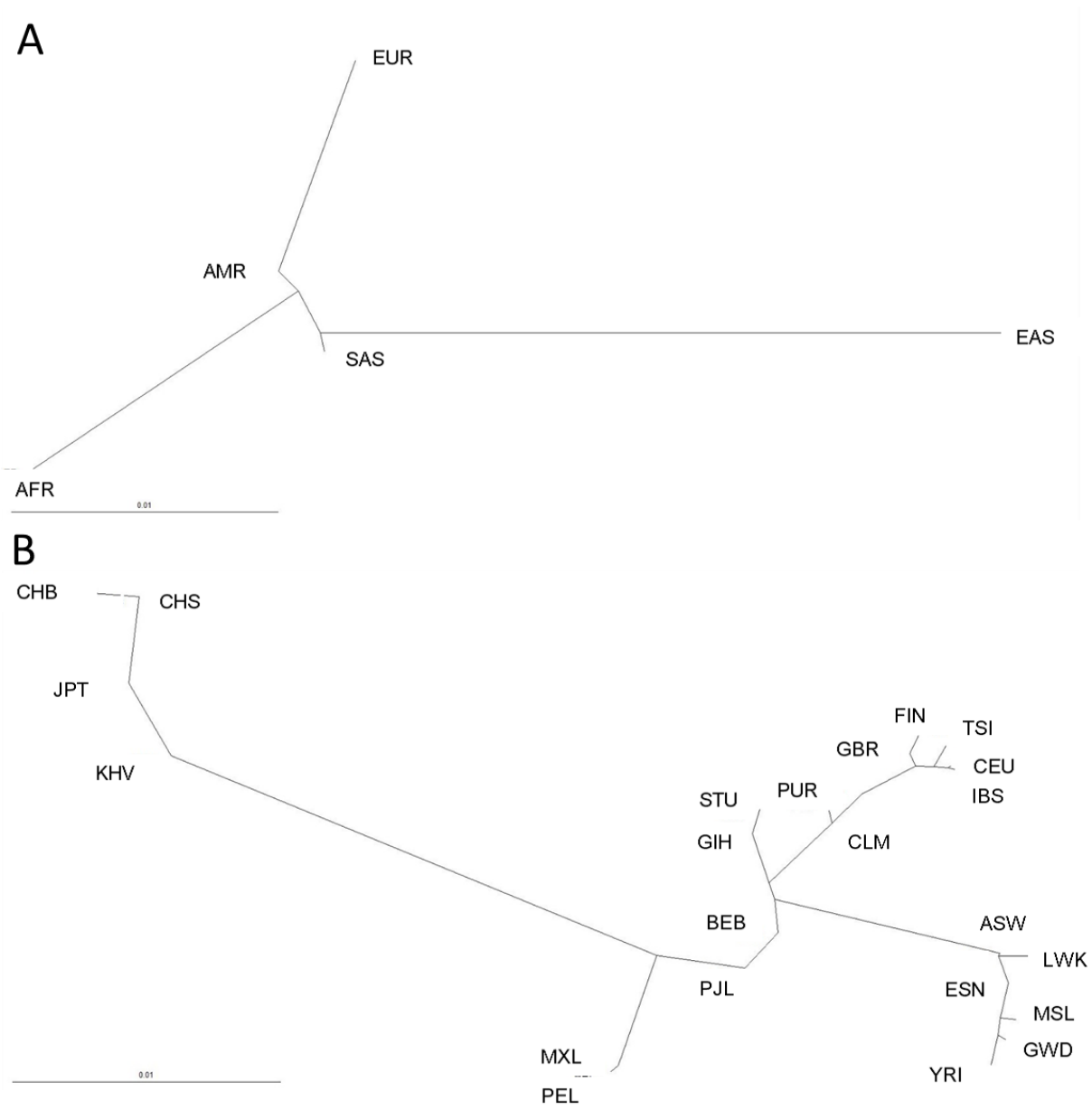


Figure S4. Neighbor-joining trees for five super- and twenty-six sub-populations in the 1000 Genomes Project using pairwise genetic distances based on *UGT2B7* (A and B), *ABCB1* (C and D), *OPRM1* (E and F), and *COMT* (G and H) haplotype assignments. The *ABCB1* neighbor joining trees utilize diplotype information from all four haplotype blocks.

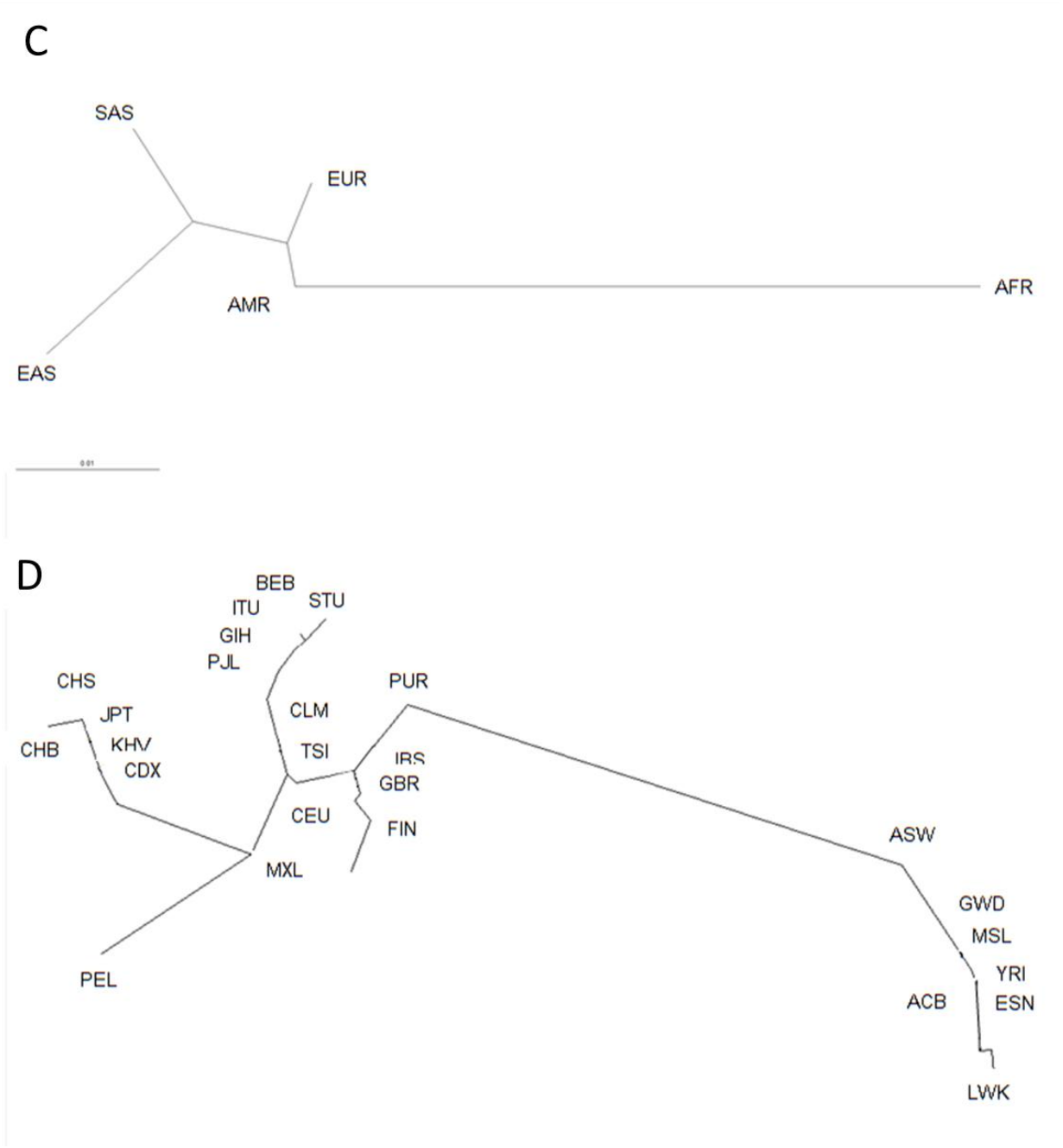
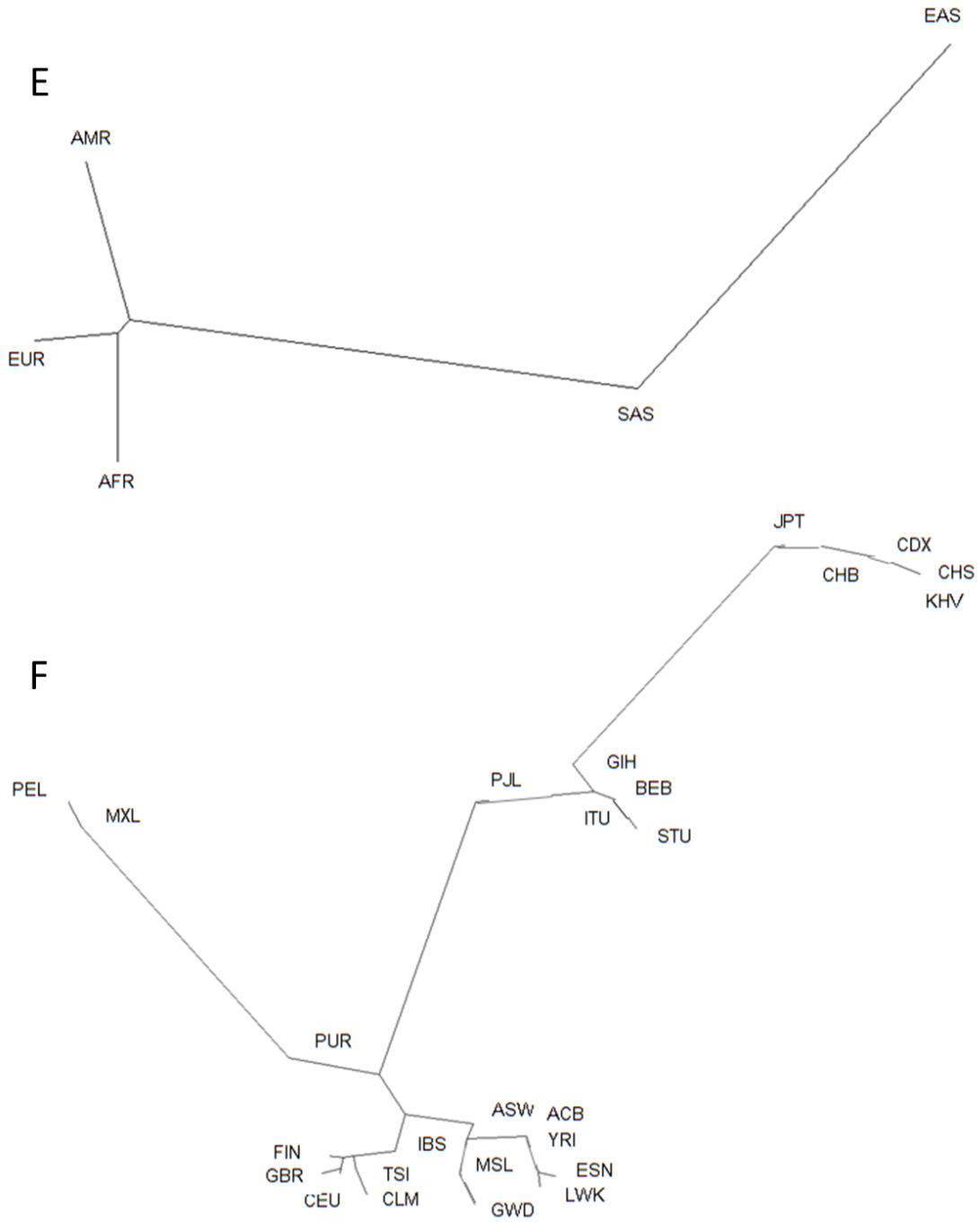


Figure S4 (continued). Neighbor-joining trees for five super- and twenty-six sub-populations in the 1000 Genomes Project using pairwise genetic distances based on *UGT2B7* (A and B), *ABCB1* (C and D), *OPRM1* (E and F), and *COMT* (G and H) haplotype assignments. The *ABCB1* neighbor joining trees utilize diplotype information from all four haplotype blocks.



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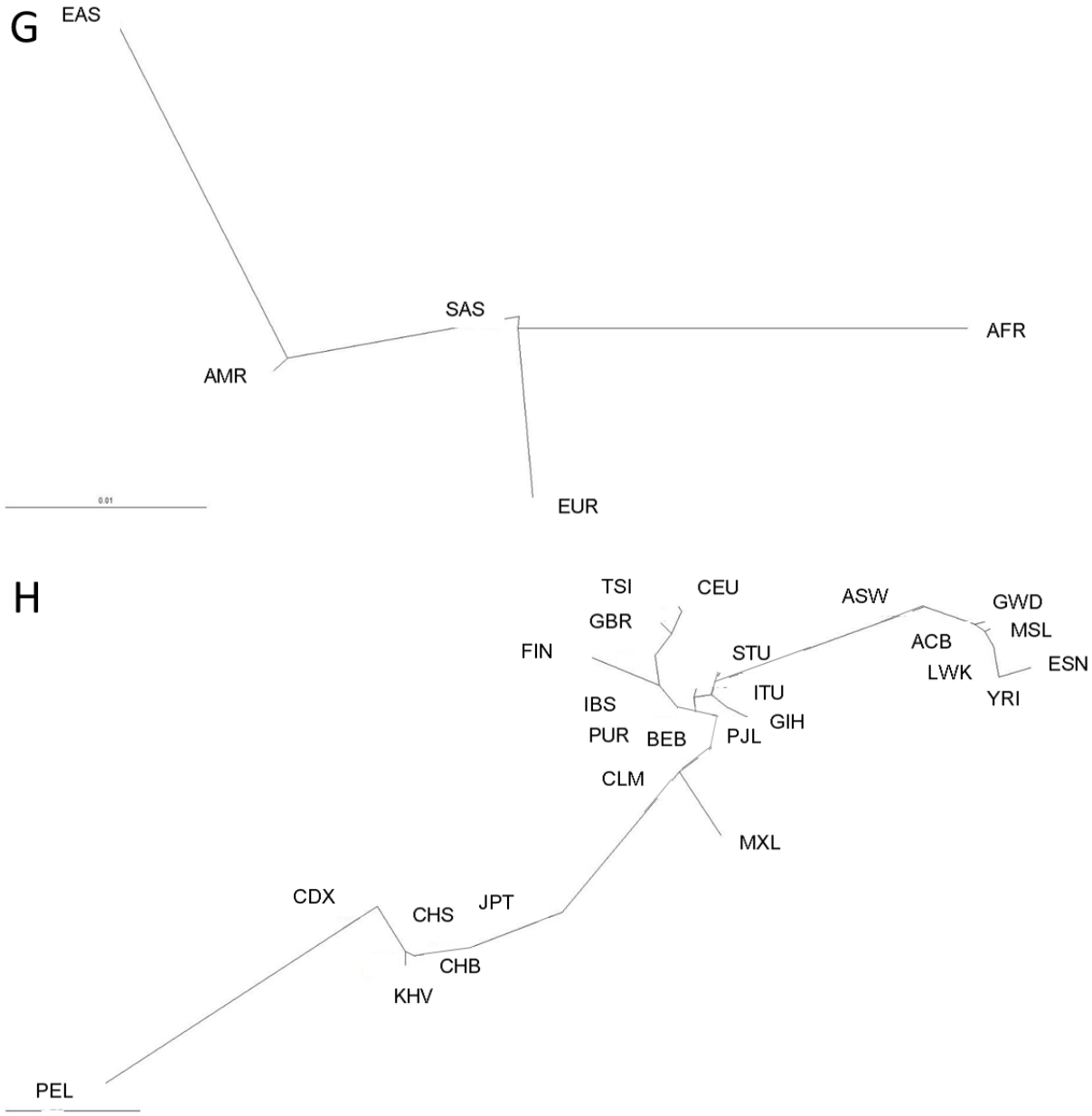

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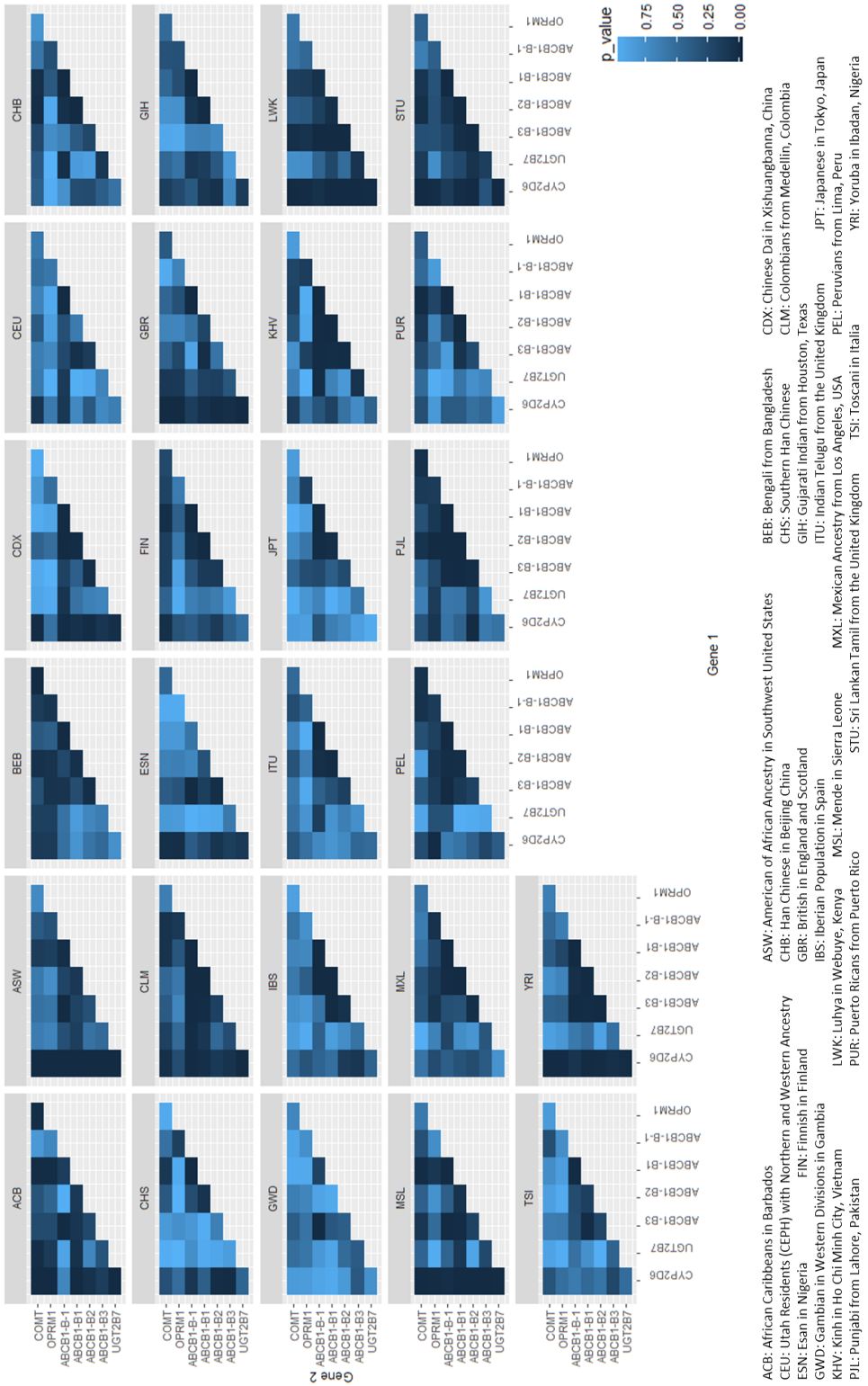

Figure S5. Heat maps of pairwise linkage disequilibrium p-values using *CYP2D6* (Wendt FR, manuscript in review), *UGT2B7*, *ABCB1-Block 3*, *ABCB1-Block 2*, *ABCB1-Block 1*, *ABCB1-Block -1*, *OPRM1*, and *COMT* diplotype in twenty-six sub-populations from the 1000 Genomes Project.

PART 3

DESIGN AND IMPLEMENTATION OF

A MASSIVELY PARALLEL SEQUENCING LIBRARY

PREPARATION PANEL FOR

PREDICTING OPIATE METABOLIZER PHENOTYPE

CHAPTER 5

Supervised Classification of CYP2D6 Metabolizer Phenotype with Tramadol-Exposed Finns

Submitted for publication in
International Journal of Legal Medicine

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Nicole MM Novroski
Anna-Liina Rahikainen
Antti Sajantila
Bruce Budowle

Abstract

The cytochrome p450 family 2, subfamily D, polypeptide 6 (*CYP2D6*) may be used to infer the metabolizer phenotype (MP) of an individual as poor, intermediate, extensive/normal, or ultra-rapid. MPs can guide prescription medication dosing to avoid idiosyncratic responses to a drug, such as tramadol, a commonly-prescribed synthetic opioid agonist used to treat moderate-to-severe post-operative pain. Application of *CYP2D6* information has relied on long-range amplification of the locus and restriction enzyme digestion to detect single nucleotide variants (SNVs) associated with MPs. This process can be cumbersome and requires knowledge of genotype phase (i.e., the arrangement of alleles across genotypes indicating their position on the same DNA strand). Phase may be achieved using long-read DNA sequencing and/or computational methods; however, both can be error prone, which may make it difficult or impractical for implementation into clinical practice. *CYP2D6* was interrogated in Finns using supervised machine learning and feature selection to identify a subset of SNVs indicative of MP and/or rate of tramadol O-demethylation (T:M1). A subset of 18 *CYP2D6* SNVs could predict MP/T:M1 with up to 96.3% accuracy given phased data. These data indicate that phase contributes to classification accuracy when using *CYP2D6* data. Of these 18 SNVs, three are novel loci putatively associated with T:M1. These findings may enable design of small multiplexes for easy clinical application of MP prediction.

Introduction

Tramadol (T) is a synthetic opioid agonist and serotonin/norepinephrine reuptake inhibitor commonly used to relieve moderate to severe pain.[1, 2] Administered as a racemic mixture of (+) and (-) enantiomers, tramadol is demethylated primarily by cytochrome p450 family 2, subfamily D, polypeptide 6 (CYP2D6) to O-desmethyltramadol (M1).[1, 2] M1, (+) tramadol, and (-) tramadol contribute to the analgesic effect of the drug;[3] however, *CYP2D6* diplotypes have demonstrated significant influence on M1 pharmacokinetics (PK) in tramadol-treated patients. This variability in PK may result in idiosyncratic responses, including death.[4, 5]

CYP2D6 is an extensively studied pharmacogene whose protein product is responsible for phase I metabolism of approximately 30% of marketed drugs, including tramadol, and a number of endogenous toxins.[6-10] Current clinical uses of *CYP2D6* genetic information rely on long-range amplification of the gene by the polymerase chain reaction (PCR) and subsequent restriction enzyme cleavage to detect the presence or absence of relevant polymorphisms or multiplexed SNaPshot assays.[11-18] *CYP2D6* genotype data are commonly arranged into star (*) alleles (i.e., a collection/haplotype of single nucleotide [SNPs] and/or insertion/deletion [INDELs] polymorphisms in the gene region) which, when combined into a diplotype (i.e., a genotype of two haplotypes), have been positively associated with the metabolizer phenotype (poor [PM], intermediate [IM], extensive/normal [EM/NM], and ultrarapid [UM]) of clinical patients and in post-mortem settings.[19, 20] Though they have predictive capabilities, *CYP2D6* diplotypes currently require information beyond that of individual SNV genotypes, including their haplotype phase, predicted by either computational phasing or long-range PCR and subsequent long-read sequencing.[21, 22]

There are several ways to phase data for related and unrelated cohorts;[23] however, they have limitations. First, computational approaches are potentially limited by sample size, degree of sample relatedness, marker density, population substructure, and associated allele frequency differences.[24, 25] Large genes which currently rely on variant phase for phenotype analyses (e.g., pharmacogenes) are regularly analyzed as a haplotype, sometimes covering thousands of bases (see https://www.pharmacogenomics.pha.ulaval.ca/wp-content/uploads/2015/04/HAP-UGT2B7.html).[26-28] Haplotype analyses of these genes may be incorrect due to limitations of the computational/statistical phasing algorithm(s) used. Second, physically observed SNV phase may be achieved with long-read DNA sequencing chemistries which are theoretically a better solution to *CYP2D6* and other pharmacogene studies; however, the read quality and error rates of short-read platforms are much better characterized and long-read and/or single-molecule chemistries are largely still under development.[29-32]

It is conceivable that a minimal set of maximally informative unphased SNV loci exist which can predict *CYP2D6* MP with comparable accuracy as current approaches. By minimizing the number of loci required to predict a patient's response to a drug, the multiple amplification approach may be replaced by a multiplexed reaction whose products may serve as input for short-read massively parallel sequencing (MPS) chemistries or Sanger sequencing, which have been through extensive clinical and applied studies to characterize error rate and accuracy.[33-36] An approach to pharmacogenetic predictions using *CYP2D6*, which does not rely on cumbersome restriction enzyme digestion and/or long-range amplification reactions, may prove advantageous in clinical application of pharmacogenetic data. Additionally, if predictions can be made in the absence of genotype phase, clinical utility of the *CYP2D6* locus may be improved.

Herein, supervised machine learning was used to classify tramadol-exposed individuals from a Finnish population into their respective *CYP2D6* MPs using a subset of maximally informative genotypes (i.e., selected features/attributes). Application of these data may reduce the need for long-range amplification of the *CYP2D6* locus by focusing on a reduced subset of seven to 12 SNV loci that can predict the rate of tramadol O-demethylation and resulting MP category in clinical applications with accuracies as high as 96.3%.

Materials and Methods

Subjects

A total of 208 whole blood samples were collected from medico-legal autopsies performed on Finnish individuals between 2001 and 2012 according to the ethical handling of human subjects review processes at the University of Helsinki and the University of North Texas Health Science Center (Institutional Review Board protocol #2016-051) and stored on Whatman® FTA® cards (GE Healthcare Life Sciences, Marlborough, MA, USA).[17] Note that sample size was determined by sample availability and not to achieve a specific predictive power.

Toxicological Analysis

Summary statistics, including age and sex distribution, mean drug concentration information, and manner of death (MoD) distribution were performed in RStudio® version 1.0.136 (RStudio: Integrated Development for R. http://www.rstudio.com). Model-based clustering was performed in RStudio® using the package `mclust` version 5.2.3[37, 38] and empirically-determined tramadol:O-desmethyltramadol (T:M1) ratios to define the most likely number of components (i.e., MPs) within the dataset, place each sample within one of the identified components based on

T:M1 ratio, determine the error of sample assignment to a component, and display the distribution of each T:M1 ratio.

DNA Extraction and Quantitation

DNA was extracted from FTA® cards using the QIAamp® DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's recommended protocol.[39] Each DNA extract was eluted in a final DNA extract in approximately 100 µl of elution buffer.

The quality and quantity of extracted DNA were determined using the Quantifiler™ Trio DNA Quantification Kit (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's recommended protocol.[40] The samples used in this study have been stored on FTA cards and those maintained for long time periods may be subject to degradation and inhibitors, which may complicate downstream amplification of relatively long targets.[17] DNA degradation and inhibition were evaluated using the degradation index (DI; ratio of small autosomal target DNA concentration to large autosomal target DNA concentration) and the internal PCR control cycle threshold (IPC C_t) indicator, respectively. Possible inhibition was detected using an IPC C_t threshold of 30, with sample IPC C_t values > 30 indicating an inhibited sample. DNA extracts also were quantified on the Qubit® 2.0 Fluorometer (Invitrogen, Carlsbad, CA, USA) with the Qubit® double-stranded DNA Broad Range Assay according to the manufacturer's recommended protocol.[41] Qubit® quantification results were used to normalize all DNA extracts to 2.5 ng/µl.

CYP2D6 Long-PCR

CYP2D6, *CYP2D6* duplications, and *CYP2D7P/CYP2D6* hybrid genes (i.e., *CYP2D6**13 and subtypes; see https://www.pharmvar.org/gene-support/Variation_CYP2D6.pdf) were

amplified using the KAPA LongRange HotStart PCR Kit (KAPA Biosystems, Inc., Wilmington, MA, USA) with the KAPA triplex reaction. The resulting PCR products were expected to be ~6.6 kb, ~3.5 kb, and ~5 kb (Fragments A, B, and H, respectively; Table 1). Amplification was performed in 25 µl reaction volumes using 10 ng genomic DNA, 1X KAPA LongRange Buffer, 1.5 mM $MgCl_2$, 0.2 mM each dNTP, 0.625 U KAPA LongRange HotStart DNA Polymerase, 5% DMSO, 0.5 µM KAPA Fragment A Forward primer, 0.5 µM KAPA Fragment A Reverse primer, 0.5 µM KAPA Fragment B Forward primer, 0.5 µM KAPA Fragment B Reverse primer, and 0.5 µM KAPA Fragment H Forward primer. PCR cycling included an initial denaturation at 95 °C for 3 minutes followed by 35 cycles of denaturation at 95 °C for 15 seconds and annealing/extension at 68 °C for 7 minutes and 30 seconds. All PCR products were visualized using the Agilent 2200 TapeStation (Agilent Technologies, Waldbronn, Germany) with the Agilent 2200 Genomic DNA ScreenTape Assay using 10 µl sample buffer and 1 µl sample/ladder. PCR products were quantified using the Qubit 2.0 Fluorometer with the Qubit® double-stranded DNA Broad Range Assay according to the manufacturer's recommended protocol.[41] All PCR products were normalized to 0.2 ng/µl. Note that the *CYP2D6* *5 deletion was detected using the KAPA *5 primer pair and internal control primers using the same reaction and cycling conditions described previously.

Table 1. Primer sequences (KAPA Biosystems, Inc.) used to amplify different structural variations of the *CYP2D6* locus on chromosome 22.

Primer Description	Sequence (5'→3')	Expected Product Size (kb)	Description
Fragment A Forward	ATGGCAGCTGCCATACAATCCACCTG	6.6	Indicates presence of at least one wild type *CYP2D6* allele, as determined by size.
Fragment A Reverse	CGACTGAGCCCTGGGAGGTAGGTAG		
Fragment B Forward	CCATGGAAGCCCAGGACTGAGC	3.5	Indicates presence of at least one gene duplication.
Fragment B Reverse	CGGCAGTGGTCAGCTAATGAC		
Fragment H Forward	TCCGACCAGGCCTTTCTACCAC	5	Indicates presence of at least one *CYP2D7P/CYP2D6* hybrid
*CYP2D6**5 Forward	CTCCAGCCTCCACCAGTCCAG	2.9	Indicates deletion of *CYP2D6*
*CYP2D6**5 Reverse	CAGGCATGAGCTAAGGCACCCAGAC		
Internal Control Forward	GCATGCACAGCTCAGCACTGC	3.8	Indicates a successful PCR reaction
Internal Control Reverse	GCCACCCTGATGTCTCAGTTTCG		

Library Preparation and Sequencing

One nanogram (0.2 ng/µl) of *CYP2D6* triplex long-PCR product was used as input for Nextera XT (Illumina, Inc., San Diego, CA, USA) library preparation using enzymatic fragmentation and adapter ligation according to the manufacturer's recommended protocol.[42] Library traces were spot-checked using the Agilent 2200 TapeStation with the Agilent 2200 High Sensitivity D1000 ScreenTape System using 2 µl reaction buffer and 2 µl sample/ladder. Positive and negative controls were included in the post-clean-up library check. Successfully prepared libraries were visualized as having broad size distribution from approximately 250 to 1250 bp. Pooled and normalized libraries were loaded into a MiSeq Reagent Kit v2 (500 cycles; 2 x 250 bp read length); sequencing was performed on the MiSeq (Illumina, Inc.) according to the manufacturer's recommended protocol.[43] Note that PhiX (12.5 pM) was included in all sequencing runs.

Alignment, Variant Analysis, and Machine Learning

Fastq files were locally aligned to the hg19/GRCh37 reference genome using the Burrows-Wheeler Aligner (BWA) `mem` command and the Sequence Alignment/Map Tools (SAMtools) `view`, `sort`, and `index` commands.[44-46] The resulting sorted batch alignment/map (.sorted.bam) files were input for the Genome Analysis Toolkit (GATK).[47] The resulting variant call format (.vcf) files were used as input for VCFtools,[48] PLINK,[49] Genome-wide Complex Trait Analysis (GCTA),[50] and in-house Excel-based workbooks.

CYP2D6 locus phase was inferred using the IMPUTE2[51] `-phase` command with reference to the hg19/GRCh37 genome. Phased loci recognized by the Pharmacogene Variation (PharmVar) Consortium Human Cytochrome P450 Allele Nomenclature database (see

https://www.pharmvar.org/gene/CYP2D6; accessed 16JAN2018) relevant for * allele assignment were analyzed using the *CYP2D6* VCF Translator.[52] Output from the translator was used to infer *CYP2D6* * alleles, genotypes, and an associated genetically-inferred metabolizer phenotype (g-MP) for each individual based on the recommendations of Gaedigk, *et al.*[53] However, this approach fails to utilize the entirety of generated sequence data (i.e., targeted genotyping of specific SNVs within *CYP2D6* at the exclusion of all other SNVs within the gene) so subsequent analysis of the .vcf file was performed using supervised machine learning techniques and the entire collection of genotypes from the *CYP2D6* full-gene region.

Supervised machine learning makes predictions of an *a priori* response variable given highly dimensional input data (e.g., genotypes).[54] Supervised classification was used in two ways: 1) to predict MP in a sample of Finns in a post-mortem setting given full-gene *CYP2D6* genotype data and 2) to predict MP of the same cohort using a subset of selected loci that would provide comparable prediction accuracy as the whole set of SNVs. Four classification approaches were used with and without attribute/feature selection depending on the variable being predicted (described below) which were 1) regularized multinomial logistic regression (RMLR), 2) 1-nearest neighbor (1NN), 3) random forests (RF), and 4) linear regression (LR). Briefly, RMLR predicts a non-binary categorical variable (e.g., MP) using logistic regression that has been regularized to improve generalization (i.e., improve classifier performance when applied to new, unseen data).[55-58] The 1NN classifier assigns a categorical variable (e.g., MP or T:M1) of an unknown by finding its closest neighbor among a set of training points or data.[56, 57, 59, 60] RF classifiers predict an outcome variable (e.g., MP or T:M1) by constructing a series of decision trees using input features. LR models use a combination of explanatory variables (e.g., SNV loci) to predict a numerical outcome variable (e.g., T:M1). Note that while RMLR and LR were used exclusively for

categorical and numerical variable prediction, respectively, the RF and 1NN classifiers can be used for categorical or numerical variable prediction, both of which were used in this study. Using the full set of genotypes, classification was performed in WEKA as follows: Logistic classifier attributes set to `weka.classifiers.functions.Logistic -R 1.0E-8 -M -1 -num-decimal-places 4` (RMLR), IBk classifier attributes set to `weka.classifiers.lazy.IBk -K 1 -W 0 -A "weka.core.neighboursearch.LinearNNSearch -A \"weka.core.EuclideanDistance -R first-last\""` (1NN), RandomForest classifier attributes set to `weka.classifiers.trees.RandomForest -P 100 -I 100 -num-slots 1 -K 0 -M 1.0 -V 0.001 -S 1` (RF), and the LinearRegression classifier attributes set to `weka.classifiers.functions.LinearRegression -S 0 -R 1.0E-8 -num-decimal-places 4` (LR).

Cross validation was used to evaluate classifier accuracy using n-1 cross validation where n is the number of instances (e.g., samples) for which variables (e.g., genotypes) were observed. In doing so, the size of the training set is maximized while minimizing the effects of over-fitting the data upon which the classifier is trained.[56, 57] A second test set also is produced which includes a single instance of all variables with which the model is tested. By performing n-fold cross validation, the model is tested once for each instance within a dataset (i.e., all instances in n are used to test the model designed with n-1 instances). Unless otherwise noted, 43-fold cross validation was used for the work described herein.

Feature selection identifies a subset of variables/attributes/features which provide comparable predictive power to the entire set of variables. Consequently, feature selection reduces noise, eliminates features that provide minimal meaning for classifier performance, and minimizes the

effects of over-fitting.[61, 62] Feature selection was performed using the Select Attributes function of WEKA, the CfsSubsetEval attribute evaluator with its default settings `weka.attributeSelection.CfsSubsetEval -P 1 -E 1` and default search method settings `weka.attributeSelection.GreedyStepwise -T -1.7976931348623157E308 -N -1 -num-slots 1`.

Results

Sample Demography, Toxicology, and Quality

The average age of the 208 deceased individuals used in this study was 60.0 years ± 18.3 (n = 81) and 52.2 years ± 17.9 (n = 127) for females and males, respectively. All subjects expired in Finland and were assumed to be of Finnish ancestry. All individuals were assigned an alphanumeric International Classification of Diseases, Tenth Revision (ICD-10) cause of death (CoD) code at the time of medico-legal autopsy (see International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10]-WHO Version for 2016. http://apps.who.int/classifications/icd10/browse/2016/en#/I; accessed 21APR2017) (Figure S1).

The average measured concentrations of tramadol and M1 and T:M1 ratio were 4.04 mg/l ± 5.94, 0.447 ± 0.769 mg/l, and 11.6 ± 18.3, respectively (Figure 1). Differences in the concentrations of tramadol and M1 or T:M1 between pairwise combinations of MoD groups or between males and females within and between MoD groups were tested using one-way analysis of variance (ANOVA) and Tukey's Honest Significant Difference test. Significant differences were observed between the concentration of tramadol in suicide and trauma ($p = 1.00 \times 10^{-7}$) and suicide and disease ($p = 7.65 \times 10^{-5}$) MoDs and the T:M1 ratios for suicide and disease ($p = 6.20 \times 10^{-4}$) MoDs.

Parent compound to metabolite ratios were used to infer the natural clustering of individuals in the cohort. These clusters were associated with a corresponding toxicologically-inferred metabolizer phenotype (t-MP).[63, 64] Here, T:M1 ratios were used for model-based clustering of each subject into a t-MP category using `mclust` (Figure 1).[37, 38] Assuming unequal variance, the sample set was divided into five components consistent with PM (5; orange; T:M1 $\geq$ 50; N = 5), IM (4; purple; 50 > T:M1 $\geq$ 20; N = 20), NM-S (3; green; 20 > T:M1 $\geq$ 8; N = 67), NM-F (2; red; 8 > T:M1 $\geq$ 3; N = 91), and UM (1; blue; 3 > T:M1 $\geq$ 1; N = 25) phenotype resolution reported in Gaedigk, *et al.*[53] It should be noted that the `mclust` package selected five as the most probable number of components due to it having the least negative Bayesian information criterion (BIC). As expected, there was a spike in classification inaccuracy where two classes meet due to ambiguity of threshold assignment between them.

Quantifiler™ Trio (Quant Trio) results were used to determine the presence of degradation and/or inhibition in the autopsy samples used for this study. The average DI was 1.47 ± 0.631 and ranged from 0.796 (sample collected in 2012) to 7.76 (sample collected in 2003) (Figure 1). Only four samples triggered the IPC C_t flag and had DI values > 1 indicating degradation and/or inhibition. These four samples had average DI and IPC C_t values of 1.26 ± 0.220 and 31.3 ± 1.19, respectively. While DI tends to be lower in newer samples, this cohort did not show a significant relationship between sample age and DI or quantity of DNA obtained from the storage medium.

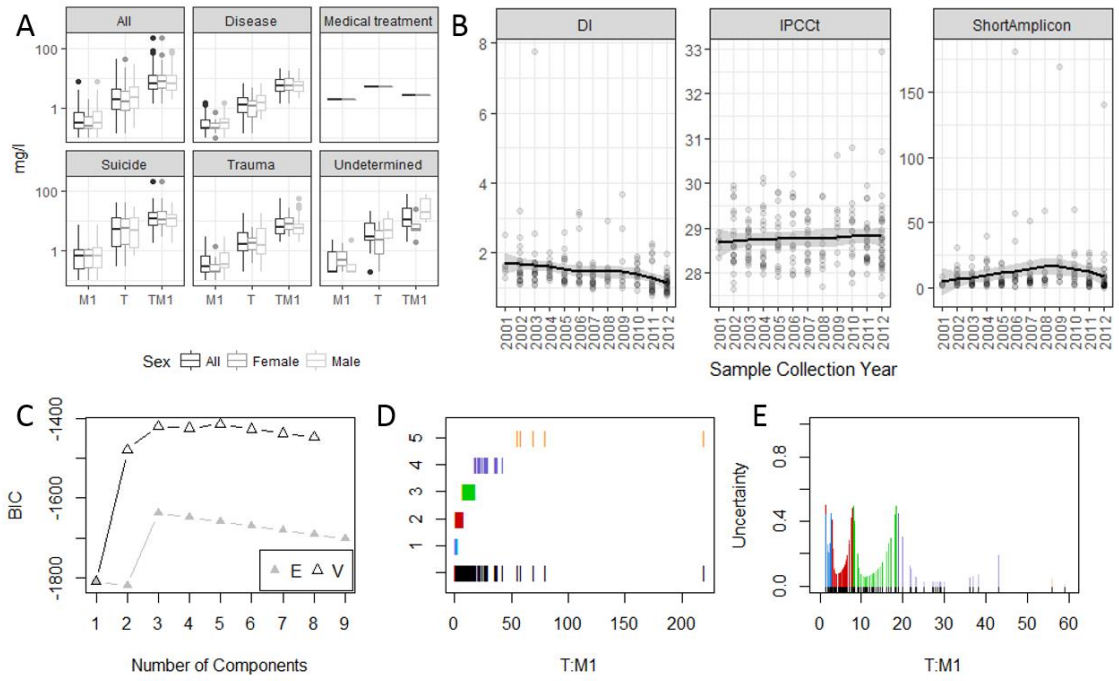

Figure 1. Summaries of sample information. A) Concentration (mg/l) of tramadol, O-desmethyltramadol and ratio of tramadol:O-desmethyltramadol in 208 deceased, tramadol-exposed Finns stratified by sex and autopsy-determined manner of death. Note the $\log_{10}$ scale of the y-axis. B) Scatterplots of the degradation index (DI), mean cycle threshold for the internal PCR control (IPC Ct), and sample quantity (ShortAmplicon; ng/µl) by sample collection year. The relative color intensity of each data point represents the number of samples at a given x,y coordinate with darker data points indicating greater sample abundance. Local polynomial regression (e.g., loess) curves (black lines) and standard error (grey shading) show general trends. C-E) Model-based clustering output of 208 deceased tramadol-exposed Finns using the tramadol/O-desmethyltramadol (T:M1) ratio. C) The most likely number of clusters assuming equal (E) and unequal (V) variance; D) distribution of all samples (black) and their assigned clusters (different colors); E) error associated with sample assignment to each cluster. Note that the x-axis of image C is trimmed to exclude cluster 5 (orange) as to provide greater resolution of sample assignment from $0 \leq$ T:M1 ≤ 60.

CYP2D6 Structural Analyses

Long-range PCR was used to identify the presence of normal *CYP2D6*, by length, CNV, and/or *CYP2D7P/CYP2D6* hybrids in each sample. Sample *CYP2D6* diplotype data is presented in Table S1. Indeed, the DI and IPC C_t values did not indicate overall degradation or inhibition, respectively, of the samples in this study; however, the relative amplification success of 7 kb

fragments was quite low (i.e., the total number of amplification failures was 169/208). This lower success rate has been observed[17] and highlights the need for methods which rely on smaller size targets. It also should be noted that testing for sample degradation using a long (>200 bp) and short amplicon (75-80 bp) ratio, as is done with Quant Trio, may not be a good indicator of amplification success for much longer amplicons. Rahikainen, *et al.*[17] noted that a DI ≥ 1 was indicative of poor *CYP2D6* amplification. Here, poor amplification is confirmed on a larger sample set and a slight, though not significant, negative linear relationship between the Quant Trio DI value and the quantity of amplified *CYP2D6* ($p = 0.0693$; Pearson's $r = -0.259$) is observed. To expand upon the Rahikainen, *et al.* findings, it may be reasonable to consider that as a sample DI approaches 1, *CYP2D6* amplification is likely and as the sample DI exceeds 1, *CYP2D6* amplification success will be lower.

The samples in which *CYP2D6* amplified represented twenty ICD-10 CoDs with no significant relationship between CoD and T:M1 (ANOVA; $p = 0.999$), suggesting that the high observation of ICD-10 T36 (Poisoning by, adverse effect of, and under-dosing of systemic antibiotics) had no impact on T:M1. These 44 successfully amplified *CYP2D6* products were subjected to MPS and the resultant data to machine learning to identify possible maximally informative target SNVs for *CYP2D6* genetic interrogation compared with full-gene capabilities (see *Metabolizer Phenotype Classification and Feature Selection*).

Sequencing Performance

Three MPS runs were performed to generate *CYP2D6* full-gene sequence data with average cluster density and clusters passing filter of 952 k/mm^2 ± 496 and 88.2% ± 6.20, respectively. After application of a 20X read depth threshold, the average sample read depth was 452X ± 505 (range 25.2X to 2,925X).

CYP2D6 Single Nucleotide Variants

Raw *CYP2D6* SNV .vcf files were analyzed with VCFtools to generate general population genetic summary statistics based on a locus read depth threshold of 20X. A total of 1,875 SNVs were detected with an average read depth of 361X ± 211 (range 21X to 2,020X). All detected sites are listed in Table S1. The average alternate allele frequency for the 571 observed heterozygous sites was 0.136 ± 0.213. After Bonferroni correction ($p_{adj} = 2.69 \times 10^{-5}$), there were no significant deviations from expectations of Hardy-Weinberg Equilibrium in this deceased Finnish cohort. After correction for multiple testing ($p_{adj} = 2.67 \times 10^{-5}$), no SNVs exhibited significant association on T:M1 (data not shown).

Heritabilities (h^2) of T:M1 and t-MP were evaluated using the full set of 1,875 SNVs using the `--reml` command in PLINK. Given the wide-spread application of *CYP2D6* SNV and diplotype information for MP prediction, the phenotypic variance in this cohort was minimally explained and not significant ($h^2_{t\text{-}MP}$: 0.0929, p = 0.458; $h^2_{T:M1}$: 3.00×10^{-6}, p = 0.500) with the observed variants (Table 2). Indeed, this finding on phenotypic variance using full-gene information may be indicative that the sample size is not sufficient for detecting the true heritability of phenotype and/or full-gene data may not contribute substantially to maximize explainable phenotypic variance. Hence, a subset of loci within the gene likely contribute more so to phenotype relative to all others.

Table 2. Heritability (h^2) summary for the variance of rate of tramadol O-demethylation (T:M1) and the resulting toxicologically-inferred metabolizer phenotype (t-MP) in 44 samples.

Phenotype	h^2	Standard error (h^2)	p-value
T:M1	3×10^{-6}	0.787	0.500
t-MP	0.0929	0.887	0.458

Polypharmacy

Sample polypharmacy was a potential confounding variable that may have influenced the observed concentrations of tramadol and M1, especially for co-administered CYP2D6 substrates that may compete for enzyme active sites. The drug cocktails in the 44 samples used herein were assessed using the database Transformer.[65] All samples used in this study had at least one additional CYP2D6 substrate detected in their toxicology screens with no detectable patterns of commonly co-administered additional drugs or drug classes. Additionally, there were no significant correlations detected between tramadol, M1, or M1 measurements and the concentration or presence/absence of specific additional compounds. For these reasons, samples were subjected to machine learning as a single cohort of tramadol-exposed Finns, and polypharmacy was not considered a significant confounding variable for this sample cohort.

Metabolizer Phenotype Classification and Feature Selection

The MP category and numerical T:M1 measurement (see Materials and Methods *Alignment, Variant Analysis, and Machine Learning* and Results *Sample Demography, Toxicology, and Quality*) assigned to each individual were used as the output variable for machine learning in WEKA in two phases: 1) classification with phased *CYP2D6* data using the hg19/GRCh37 reference genome, and 2) classification with unphased *CYP2D6* genotype data. Both iterations were performed with and without feature selection using 1NN, LR/RMLR (depending on predicted outcome variable), and RF classifiers.

The 44 successfully amplified and sequenced *CYP2D6* samples represented four t-MPs based on T:M1. In the absence of phased genotype data for *CYP2D6* and assuming four t-MPs, the evaluated models modestly predicted t-MP, regardless of the supervised machine learning

algorithm (Figure 2). The average classification accuracy using all SNVs was 22.0% ± 3.47 for all three prediction algorithms used. Computational phase with the hg19/GRCh37 reference genome was performed in IMPUTE2. The overall concordance between phased and input genotypes was 95.4%, indicating reliable performance of the phasing algorithm. When phase was incorporated, the mean prediction accuracy increased slightly to 25.0% ± 0; however, the increase was not significant. Feature selection increased the mean classification accuracy depending on the stringency applied during feature inclusion. Inclusion of only those features used in greater than 12%, 50%, and 75% of cross validation folds significantly increased classification accuracies to 42.4% ± 3.47, 46.2% ± 3.47, and 48.5% ± 4.73, respectively ($p = 0.0237$, 0.00881, and 0.0351, respectively); however, individual classifiers had relatively low prediction performance as the feature selection stringency increased. The maximum mean classification accuracy observed in this study was 52.3% after using phased genotype data and the RMLR classifier. When considering individual t-MP categories independently, t-NM-F individuals were classified well regardless of the algorithm used (mean 70.0% ± 4.10; 2.94-fold greater accuracy than by random chance). However, classification accuracy was low for the other three t-MPs observed in this cohort. In fact, the t-UM and t-NM-S individuals were consistently misclassified. These inaccuracies overwhelmingly represented scenarios where one t-MP was misclassified as the adjacent t-MP. For example, 83% of the misclassified t-NM-F samples were classified as t-UM or t-NM-S. This observation is likely a consequence of binning the continuous T:M1 variable into discrete categories or classes commonly used to represent CYP2D6 function (Figure 1E). However, using phased data, the t-UMs, t-NM-Ss, and t-IMs were classified with accuracies 1.35- (32.3%), 1.53- (36.4%), and 1.40-fold (33.3%) better than random chance alone, respectively.

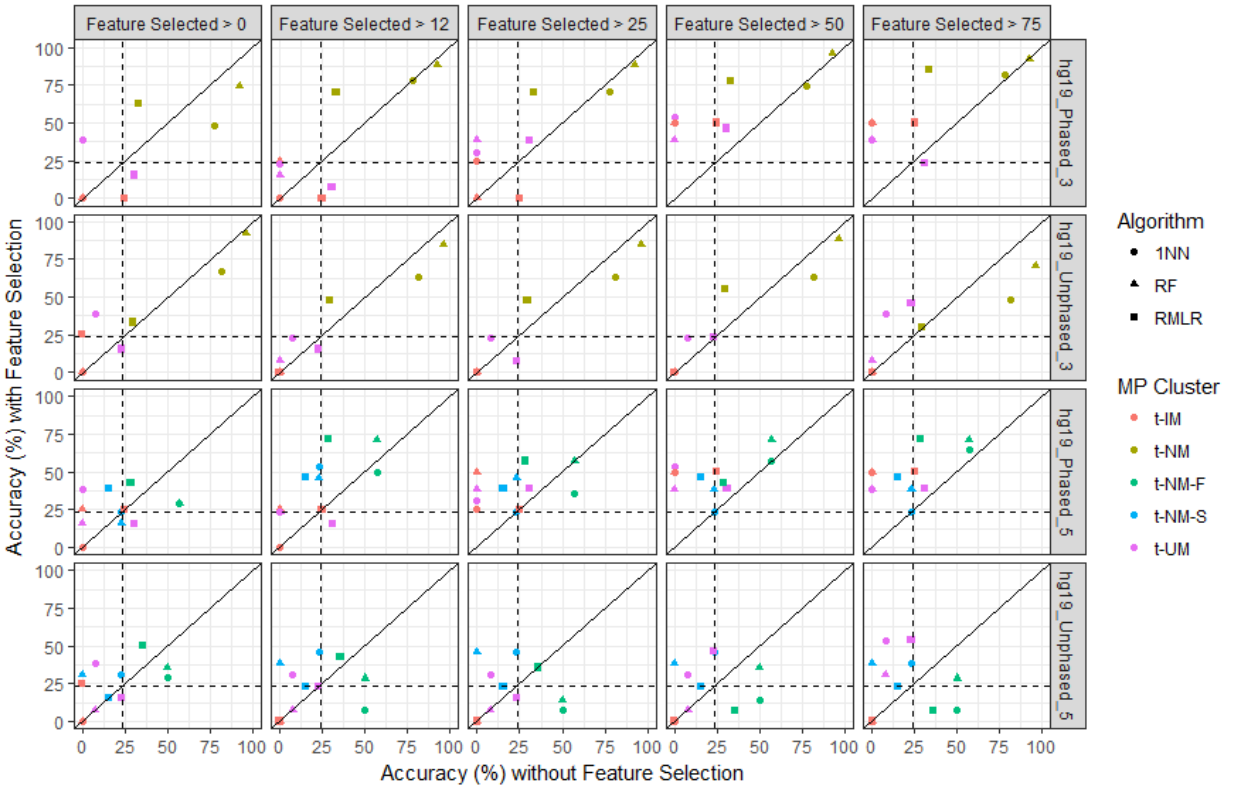

Figure 2. Summary of machine learning classification accuracies for four metabolizer phenotype (MP) clusters (t-UM = ultra-rapid; t-NM-F = normal/extensive [fast]; t-NM = normal/extensive ([fast] and [slow] inclusive); t-NM-S = normal/extensive [slow]; and t-IM = intermediate) using phased and unphased *CYP2D6* data aligned to the hg19/GRCh37 reference genome for varying feature selection stringencies (features used in 0%, 12%, 25%, 50%, and 75% of cross-validation folds) compared to the accuracy of the model using all genotype data from *CYP2D6*. Three machine learning algorithms are depicted: 1-nearest neighbor (1NN), random forest (RF), and regularized multinomial logistic regression (RMLR); dashed lines represent the average predictive accuracy due to random chance (23.8%; 10%-trimmed mean). Note that the number of clusters relative to Figure 1C are also indicated (e.g., hg19_Phased_5 and hg19_Phased_3 indicate the use of five and three clusters, respectively, for prediction).

To evaluate the influence of binning error on the predictions observed in Figure 2, additional bins were created at the boundaries of each MP. In doing so, a sample may be classified as one of the four observed MP clusters (t-UM, t-NM-F, t-NM-S, or t-IM) or as a boundary-type, indicating that ambiguity exists in classifying that individual into one of the four main categories (Figure 1E), but the sample may belong to one of two categories separated by the boundary (t-UM/t-NM-F, t-

NM-F/t-NM-S, or t-NM-S/t-IM). The RLMR, 1NN, and RF classifiers were used in the same manner as above with five levels of feature inclusion stringency. Using phased and unphased genotype data, the addition of extra bins decreased classification accuracy such that the maximum achievable accuracy was 25% with the RMLR classifier using the phased genotypes feature selected to include SNVs involved in > 50 folds (data not shown). Alternatively, capturing only clinically relevant-differences in MP by allowing for classification of a single sample into t-UM, t-NM (inclusive of fast [F] and slow [S] while not penalizing the inaccuracy of deciding between the two), or t-IM[53] (Figures 1C and 1E) increased mean classification accuracies of all three MPs to 33.7% ± 8.89, 86.4% ± 5.65, and 50% ± 0 for t-UM, t-NM (inclusive of fast and slow), and t-IM, respectively (Figure 2). As seen with finer MP resolution above, using phased genotype data significantly increased mean classification accuracies for inclusion of features used in > 25%, 50%, and 75% of cross-validation folds ($p = 0.0136$, 4.82×10^{-4}, and 9.74×10^{-3}, respectively). Interestingly, using unphased genotypes without feature selection and the RF classifier predicted NMs with a maximum accuracy of 96.3%. This level of accuracy was not significantly affected with the introduction of phased genotypes and increased feature inclusion stringency.

The LR, 1NN, and RF classifiers were used to predict the T:M1 continuous variable. Using all unphased SNVs, predictions with all three algorithms were modestly inaccurate with an average difference in actual and predicted T:M1 (ΔT:M1) of -0.117 ± 13.8, indicating slight under-estimation of T:M1 (Figure 3). There were no significant differences between the actual and predicted values of T:M1 due to choice of machine learning algorithm given all unphased SNVs. Incorporation of phased genotype information significantly exacerbated the underestimation of T:M1 by decreasing the mean ΔT:M1 to -6.71 ± 34.8 ($p = 0.0186$). The 1NN and RF classifiers did not exhibit differences between actual and predicted T:M1; however, the LR classifier

produced significantly lower predictions of T:M1 relative to the actual value ($p = 0.0228$) if given phased data to the *CYP2D6* locus. Feature selection was performed by assessing the same five thresholds for feature inclusion as the categorical variable predictions described above (> 0%, > 12%, > 25%, >50%, and >75%). Unlike the increased accuracies observed in Figure 2 for feature selected t-MP predictions, there were no significant changes in ΔT:M1 given attribute selected loci, indicating prediction accuracies no better than random chance for any of the five feature inclusion thresholds.

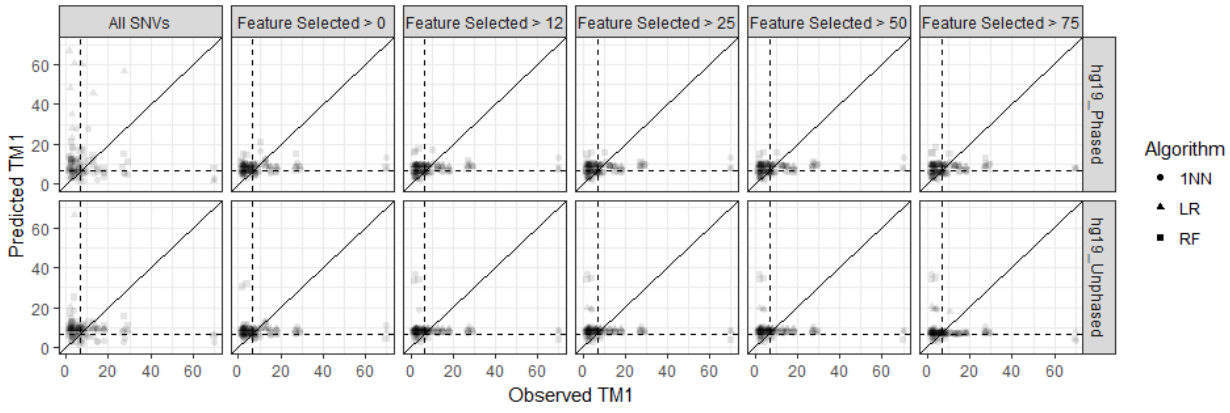

Figure 3. Summary of machine learning predicted tramadol:O-desmethyltramadol (T:M1) ratios using phased and unphased *CYP2D6* data aligned to the hg19/GRCh37 reference genome for varying feature selection stringencies (features used in 0%, 12%, 25%, 50%, and 75% of cross-validation folds) compared to the observed toxicologically determined T:M1. The shading of data points is scaled to represent the relative abundance of data points along the x=y diagonal; dashed lines represent the average predictive accuracy due to random chance (6.67; 10%-trimmed mean).

To evaluate how few SNV loci could be used to predict t-MP and T:M1, five different thresholds were applied to the data during feature selection; these thresholds included features involved in > 0%, > 12%, > 25%, > 50%, and > 75% of the folds performed during cross-validation. By incorporating features used in > 75% of the cross validation folds, the mean accuracy in predicting t-MP was significantly greater than that of the entire set of SNVs in the *CYP2D6* region ($p < 0.0351$). This finding suggests that instead of using the entire set of 1,875

SNVs detected in the *CYP2D6* gene region to predict MP of this study cohort, it may be reasonable to type only seven loci (i.e., a 268-fold reduction in the number of loci required to make a prediction), while also considering biological sex (Table 3). The loci are NC_000022.10:c.*428G>A, NC_000022.10:c.*264G>A, NC_000022.10:c.352+308G>A, NC_000022.10:c.181-347A>G, NC_000022.10:c.-43insG, NC_000022.10:c.-560A>G, and NC_000022.10:c.-1431C>T (Table 3). For predicting T:M1, there were no significant differences between ΔT:M1 for phased versus unphased data, RF versus LR versus 1NN classifiers, or classification accuracies using various feature inclusion criteria. For T:M1, it may be reasonable to reduce the number of loci by 150-fold. Predicting the T:M1 phenotype can be achieved using presence/absence information for fragments A and H and genotype information for the following 12 loci: NC_000022.10:c.*378T>A, NC_000022.10:c.*264G>A, NC_000022.10:c.1441T>C, NC_000022.10:c.1316-1G>A, NC_000022.10:c.1315+32T>C, NC_000022.10:c.1117G>A, NC_000022.10:c.1094G>A, NC_000022.10:c.837-18G>C, NC_000022.10:c.755A>G, NC_000022.10:c.666+118A>C, NC_000022.10:c.-194C>T, and NC_000022.10:c.-1243A>G (Table 3). Interestingly, the common gene duplication detected with fragment B was not meaningful for predicting T:M1 in this cohort.

Table 3. Selected features used in more than 75% of the cross validation folds to predict toxicologically inferred metabolizer phenotype (t-MP) and/or tramadol:O-desmethyltramadol ratio (T:M1). Relevant additional information is provided for each locus, including conferred amino acid change, relative position on two other relevant reference sequences (hg38/GRCh38 and M33388), the Finnish minor allele frequency (MAF) observed in this sampling of deceased Finns, and the global MAF.

Locus rs Number	DNA Sequence Change*	Hg19/GRCh37 Coordinate	hg19/GRCh37 Reference Allele	Amino Acid Change	Hg38/GRCh38 Coordinate	M33388 Coordinate	MAF	Global MAF	Used to predict
-	c.*428G>A	42522148	G	-	42126146	4645	0.0147	0.00	t-MP
-	c.*378T>A	42522198	T	-	42126196	4595	0.0156	0.00	T:M1
rs116390392 / rs12169962†	c.*264G>A	42522312	G	-	42126310	4481	0.545	0.239	t-MP and T:M1
rs1135838	c.1441T>C	42522629	T	F481V	42126627	4164	0.0147	0.00	T:M1
-	c.1316-1G>A	42522755	G	Intron	42126753	4038	0.0152	0.00	T:M1
-	c.1315+32T>C	42522821	T	Intron	42126819	3972	0.0152	0.00	T:M1
rs150552908†	c.1117G>A	42523505	G	G373G	42127503	3288	0.0156	0.00	T:M1
rs1058172	c.1094G>A	42523528	G	R365H	42127526	3265	0.0156	0.00	T:M1
-	c.837-18G>C	42524003	G	Intron	42128001	2790	0.0152	0.00	T:M1
-	c.755A>G	42524264	A	D252V	42128262	2529	0.0152	0.00	T:M1
-	c.666+118A>C	42524669	A	Intron	42128667	2124	0.156	0.00	T:M1
-	c.352+308G>A	42525431	G	Intron	42129429	1363	0.0151	0.00	t-MP
-	c.181-347A>G	42526258	A	Intron	42130256	536	0.03125	0.00	t-MP
rs75085559†	c.-43insG	42526836	-	-	42130834	-43	0.0114	0.0435	t-MP
-	c.-194C>T	42526987	C	-	42130985	-194	0.0469	0.00	T:M1
-	c.-560A>G	42527353	A	-	42131351	-560	0.0156	0.00	t-MP
-	c.-1243A>G	42528036	A	-	42132029	-1238	0.0667	0.00	T:M1
rs28588594†	c.-1431C>T	42528224	C	-	42132217	-1426	0.148	0.240	t-MP
Fragment H (Presence or Absence)	NA	NA	NA	NA	NA	NA	NA	NA	T:M1

*Nucleotide numbering is based on the negative DNA strand of reference sequence NC_000022.10 (hg19/GRCh37).
†Locus is recognized in *CYP2D6* haplotype definitions reported by PharmVar.

Student's t-tests were used to compare the mean T:M1 between genotypes at each locus in Table 3 in a pairwise manner for only those loci with more than one observation of each genotype in the sample set (i.e., NC_000022.10:c.*264G>A, NC_000022.10:c.-1243A>G, and NC_000022.10:c.-1431C>T; Figure S2). There were no significant differences between T:M1 for pairwise combinations of genotypes at NC_000022.10:c.*264G>A or NC_000022.10:c.-1431C>T; however, there was a significantly lower mean T:M1 for those individuals carrying the G allele at NC_000022.10:c.-1243A>G (N = 3; p = 0.00137; Figure S2). This locus is not currently

reported by PharmVar as a defining locus for *CYP2D6* haplotypes and while these data suggest the downstream variant impacts function, a larger sample size may be needed to validate the impact of the locus on CYP2D6 activity with respect to tramadol O-demethylation. It should be noted that additional, potentially damaging loci were detected in this cohort: NC_000022.10:c.1094G>A (SIFT: Damaging [0.00]; PROVEAN: Deleterious [-3.46]) and NC_000022.10:c.755A>G (SIFT: Tolerated [0.0647]; PROVEAN: [-4.81]) Only four loci identified for t-MP and T:M1 prediction are currently recognized by PharmVar as part of *CYP2D6* haplotypes: NC_000022.10:c.*264G>A (M33388:4481G>A; *CYP2D6**2, *11, *31, *65, *69, *84, and *102-*105), NC_000022.10:c.1117G>A (M33388:G>A; *CYP2D6**6), NC_000022.10:c.-43insG (M33388; undetermined but detected), and NC_000022.10:c.-1431C>T (M33388C>T; *CYP2D6**4, *10, *21, *36, *47, *49, *52, *56, *58, *64, *68, *69, *72, and *99-*101). Note that while causal loci conferring abnormal CYP2D6 activity (i.e., conferring g-PM, g-IM, or g-UM) are not represented in Table 3, there was significant enrichment of the NC_000022.10:c.*264A allele in the autopsied Finns relative to the global minor allele frequency from the 1000 Genomes Project ($p = 3.76 \times 10^{-8}$). The inverse observation is true for the NC_000022.10:c.-1431T allele ($p = 0.0331$).

CYP2D6 Haplotype

Phased genotype variant call files were used as input for the *CYP2D6* VCF Translator. The output of the translator was used to infer *CYP2D6* * allele assignments for each individual consistent with PharmVar recognized haplotypes (www.PharmVar.com; i.e., only those loci recognized by PharmVar were analyzed). Due to the relatively small sample size of this study, *CYP2D6* * allele frequencies are not reported but full-gene haplotypes are provided in Supplemental Table 2. Individuals exhibiting hybrid- and/or duplication-positive amplicons by

long-range PCR were excluded from estimates of haplotype diversity as similarity of the regions of *CYP2D6* and *CYP2D7* may contribute to producing a hybrid locus or private mutations unique to a single *CYP2D6* duplicate. In the 33 samples positive for Fragment A only (i.e., these individuals lack *CYP2D7P/CYP2D6* hybrids and *CYP2D6* duplications), there were 51/66 unique haplotypes. The *CYP2D6* full-gene haplotype diversity was 0.972.

Distributions of g-MP and t-MP were compared using a chi-squared goodness of fit test. There were significant differences between the two MP distributions ($p = 3.31 \times 10^{-15}$) indicating genotype-phenotype discordance. The magnitude of this difference; however, is similar with previous reports of various global populations,[13, 66-68] but to our knowledge, this is the first report in Finns. Most of this discordance was due to differences in classifying individuals into the fast (NM-F) and slow (NM-S) designations of the NM phenotype class. Using genetic data (g-MP), 28/44 and 8/44 samples were considered NM-F and NM-S, respectively, while using toxicology data (t-MP), these categories contained 14/44 and 13/44 samples, respectively.

Discussion

The *CYP2D6* locus, and indeed many pharmaco- and immunogenes, can be challenging to amplify by long PCR, and thus sequence and interpret using current restriction digestion and subsequent computational methods. This study successfully amplified the full *CYP2D6* region in a subset of a deceased Finnish cohort. Though not a significant confounding variable, overall poor amplification success was possibly due to the degree of degradation observed in samples stored on FTA paper, generally confirming the observations of Rahikainen, *et al.*[17] These studies suggest that large targets are quite difficult to amplify from FTA-deposited substrates, an important observation for medico-legal autopsy, bio-banking, and clinical diagnostics.

The goal of this study was to identify a minimal set of maximally informative *CYP2D6* SNVs and evaluate the necessity of phased genotype information for predicting phenotype. Full-gene haplotype information was generated using short-read DNA sequencing and subsequent computational phasing. To our knowledge, there are few reports of full-gene information for the *CYP2D6* locus[69, 70] but these data are useful for expanding the pharmacogenomics and personalized medicine community's knowledge of how full-gene interrogation of various genes may impact the understanding of the genotype-phenotype relationship.[71] Generally, phased genotyping information from *CYP2D6* predicted MP with substantially greater accuracy than raw genotypes, especially for non-NM individuals. This finding is unsurprising but emphasizes a limitation of interrogating pharmaco- and immunogenes for predicting a number of metabolically relevant phenotypes.

Using current approaches by identifying key *CYP2D6* star-allele defining variants has proven inaccurate in some populations.[13, 66-68] While somewhat inaccurate, there is a tradeoff involved with obtaining more, possibly uninformative full-gene genotype data and maximizing assay real estate, specifically in terms of short-read DNA sequencing library preparation panel development. For example, obtaining full-gene *CYP2D6* information for some populations may provide slightly increased phenotype prediction accuracy, but limits sequencing throughput and for archived samples, full-gene amplification and subsequent typing success may be quite low. Conversely, a core set of seven loci, identified and evaluated herein using supervised machine learning techniques, may predict MP with increased accuracy relative to random chance and comparable with that of full-gene information, thereby increasing the typing success of many archived samples. These findings potentially enable creation of SNV-targeted MPS library preparation panels

specific to pharmacogenetics population studies and promote easy and cost effective clinical applications of *CYP2D6* data.

Subsequent evaluations of the capability to predict the actual ratio of parent compound to metabolite (T:M1) also were performed with modest success depending on the method employed. Interestingly, the LR, RF, and 1NN machine learning algorithms could not accurately predict the T:M1 ratio any better than random chance, and required knowledge of whether an individual contains a hybrid allele (detected by fragment H). However, predicting the exact ratio of parent drug to primary metabolite may not be the most clinically relevant application of *CYP2D6* genotype information as individuals are currently binned into general classes of MP describing a range of ratios (e.g., T:M1). Consequently, while the actual and predicted values of T:M1 were quite different and indeed biologically relevant, the clinical significance of poor T:M1 prediction may be uninformative.

Seven and 12 loci (with one overlapping SNV) out of 1,875 SNVs (a 103-fold reduction in loci) were selected to predict T:M1 and t-MP, respectively, in this cohort of Finnish individuals. Interestingly, the nonpathogenic, downstream *CYP2D6* variant NC_000022.10:c.*264G>A (also known as rs116390392, rs12169962, M33388:4481G>A) was a key feature for predicting both t-MP and T:M1 in Finns at the highest level of feature inclusion stringency (i.e., the locus was used in >75% of cross-validation folds). In fact, this SNV also was one of only four PharmVar loci identified after application of the maximum feature inclusion stringency threshold (including NC_000022.10:c.1117G>A, NC_000022.10:c.-43insG and NC_000022.10:c.-1431C>T). These four SNVs are located in the 5' and 3' untranslated regions (UTRs) or are not known to be causal; however, according to PharmVar, the NC_000022.10:c.1117G>A locus has only been reported in an allele conferring an inactive CYP2D6 enzyme (*CYP2D6*6*). The *CYP2D6*6*:1707delT variant

is considered the defining variant of this haplotype because it produces a deleterious frameshift mutation, making the presence of NC_000022.10:c.1117G>A meaningless. However, NC_000022.10:c.1117G>A may additionally contribute to enzyme inactivity in other haplotypes as suggested by the deceased Finns. Though only three samples had the alternate allele at NC_000022.10:c.-1243A>G, which appears to be a putatively identified novel variant in the 3' UTR. In this cohort of deceased Finns, the presence of the G allele was associated with a faster rate of tramadol O-demethylation, as indicated by a decrease in T:M1. There were general trends observed at the remaining 17 loci, but in the absence of more than one observation of the alternate allele/genotype, conclusions regarding their functional impact are not presented. While these loci offered predictive power in a cohort of deceased Finns, the application of that power in non-Finnish European, other global populations, and non-tramadol opioid users must be evaluated.

The relative absence of PharmVar loci after application of the most stringent feature selection threshold is quite interesting; however, the majority of successful *CYP2D6* amplifications were indicated as normal metabolizers, which could explain the relative lack of clinically relevant SNV enrichment. Alternatively, there are a number of relatively infrequent SNVs which confer variable CYP2D6 activity. The lack of these loci as most meaningful for phenotype classification my supervised machine learning may be an artifact of global rarity and unsteady presence/absence in the extreme *CYP2D6*-inferred MPs. In other words, the clinical relevance of the SNVs detected here should not influence the relative usefulness of each locus for predicting phenotype by these machine learning algorithms.

The samples used in this study are from medico-legal autopsies which raises two key limitations: 1) each sample had detectable concentrations of other compounds in their blood, and 2) the T:M1 ratio may not accurately reflect the rate of tramadol O-demethylation in clinical

patients due to post-mortem redistribution and/or time between tramadol administration and death. It is reasonable to hypothesize that polypharmacy (i.e., the administration or use of more than one medication or drug for at least one medical condition or recreation[72]) would negatively impact the predictability of the MP, especially when multiple CYP2D6 substrates are co-administered at or above the recommended dose. Polypharmacy would likely manifest as inaccurate and/or discordant MP predictions when using genetic and toxicological data. Though not a readily apparent confounding variable in this study, polypharmacy will require more systematic controls and large sample sizes to detect and accurately characterize specific interactions between combinations of two, three, four, or more compounds.[72]

Significant differences in t-MP and g-MP distributions were observed, indeed representing diplotype-phenotype discordance, especially for the NM-S versus NM-F MPs. The measurement of t-MP using T:M1 is a key limitation that may have contributed to this difference in distribution as there was no knowledge or control of the tramadol concentration delivered to each sample, post-mortem tramadol and/or O-desmethyltramadol redistribution, or the time between tramadol dosing and O-desmethyltramadol detection. This discordance also might be influenced by limited data. It is known that drug ADME (absorption, distribution, metabolism, and excretion) and response are pathway-dependent processes; however, most clinical applications use only *CYP2D6*. Given the relatively low heritability described here, it is likely that a combinatorial genetic predictive model will increase classification accuracies by explaining a greater proportion of phenotypic variance and providing a more complete picture of tramadol ADME and response.

The opioid analgesic tramadol was used as a model drug to identify and evaluate a set of maximally predictive *CYP2D6* loci. Predicting tramadol without full-gene *CYP2D6* data is highly desirable and may provide a level of accuracy, depending on the MP in question. However, the

model may not apply to non-tramadol opiates, or other CYP2D6 substrates. Future work should evaluate the efficacy of a minimal collection of SNVs on other, non-tramadol opiates, and more broad classes of CYP2D6 substrates to identify if the subset of features identified here are equally informative of codeine to morphine conversion, for example. In doing so, a predictive model may be constructed which incorporates SNVs from multiple candidate genes to predict response to a battery of drugs and toxins.

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Supplementary Information

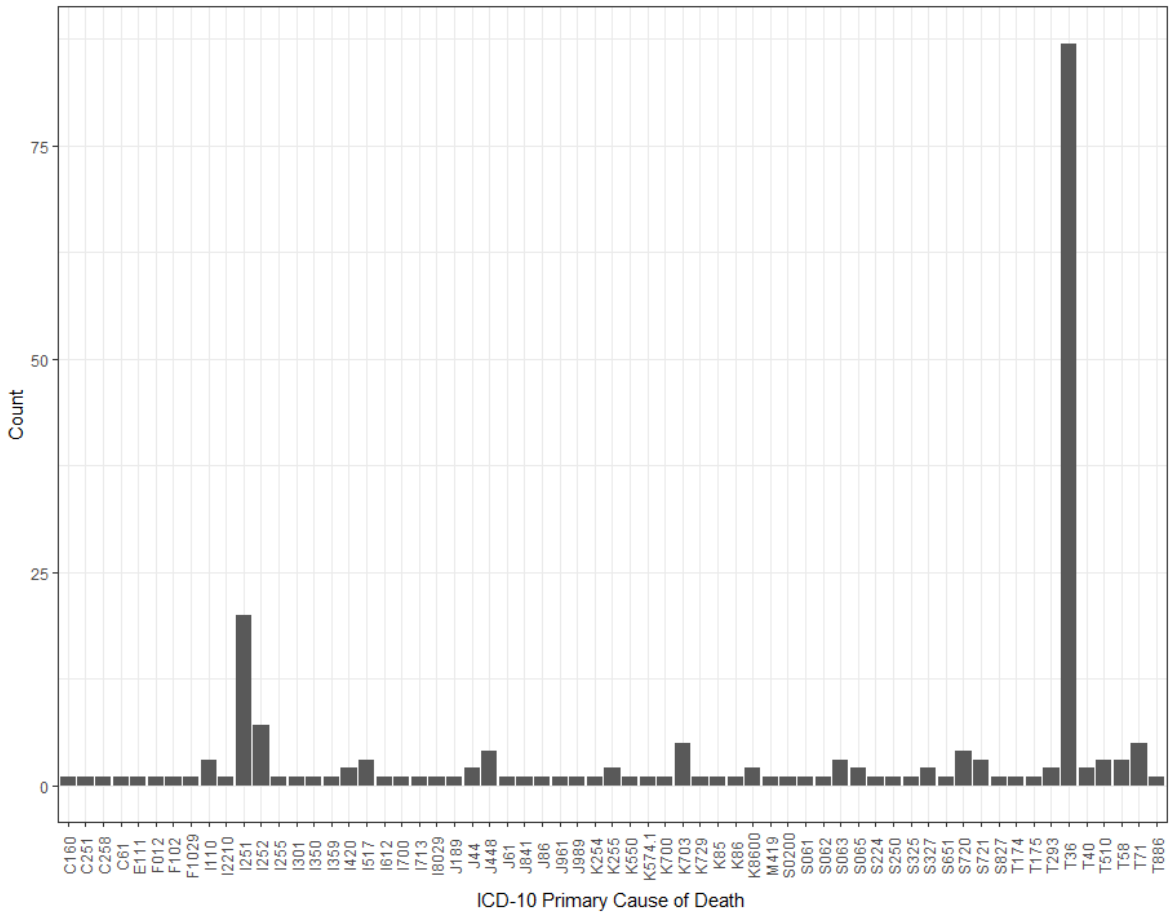

Figure S1. International Classification of Disease, Tenth Revision (ICD-10; see International Statistical Classification of Diseases and Related Health Problems 10th Revision - WHO Version for 2016. http://apps.who.int/classifications/icd10/browse/2016/en#/I; accessed 21APR2017) cause of death code counts for 208 deceased tramadol-exposed Finns.

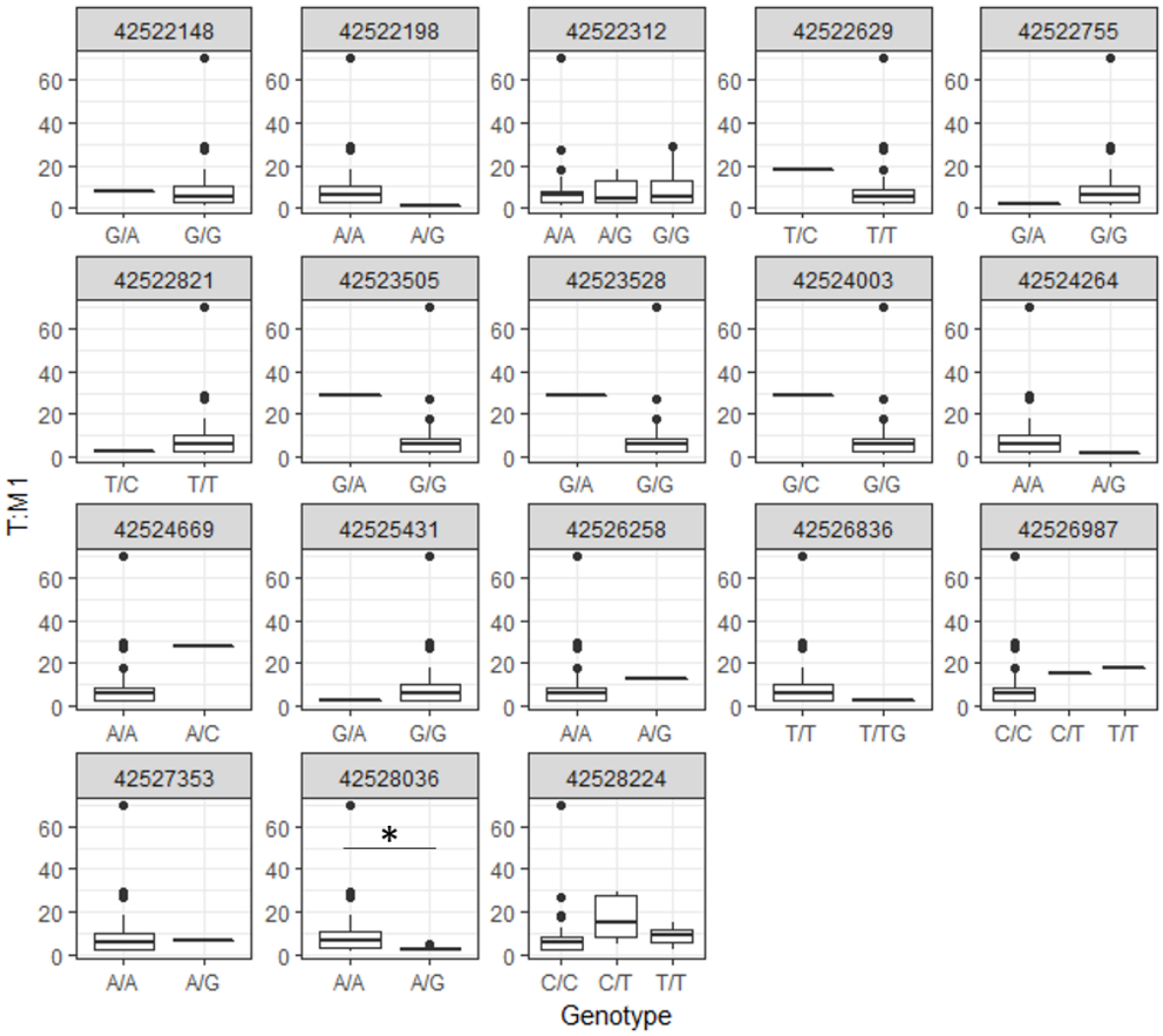

Figure S2. Association between genotype at 18 *CYP2D6* loci (Table 4) and the ratio of tramadol to O-desmethyltramadol (T:M1) for N = 44 Finns. Each boxplot represents a single genotype relative to the negative DNA strand of the indicated hg19/GRCh37 chromosome 22 position; the center horizontal line represents the median, the lower and upper boundaries of each box represent the first and third quartiles, respectively; the top and bottom vertical lines indicate plus and minus three times in the interquartile range, respectively; black bots indicate boxplot outliers. A student's t-test was used to compare the mean M1:T ratio between the homozygous-reference genotype at each locus and all other genotypes observed more than once with asterisks (*) indicating $p < 0.05$.

Table S1. Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42522066	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522075	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522077	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522080	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522090	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522093	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522097	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522102	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522107	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522108	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522115	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522116	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522117	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522119	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522123	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522126	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522129	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522133	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522134	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522136	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522137	C	CTGT	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 1	1 1	0 1	1 1	0 0	1 1	0 0	1 1	1 1	1 1	1 1	1 1	0 0	0 0	0 0	1 1	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	0 1	0 0	1 1	1 1
42522138	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522140	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522142	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522145	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522146	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522148	C	T	0 0	0 0	? ?	? ?	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522153	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522156	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522158	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522163	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522164	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522169	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522172	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522189	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522198	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 1	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522213	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522217	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522227	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522230	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522235	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522236	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522244	T	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 1	? ?	? ?	? ?
42522251	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522255	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522260	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522308	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522312	T	C	0 0	1 1	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	1 1	0 0	1 1	0 0	1 1	0 0	1 1	1 1	1 1	1 1	1 1	0 0	0 0	0 0	1 1	1 1	1 0	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	0 1	0 0	1 1	1 1
42522338	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522365	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522373	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522375	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522389	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522392	G	A	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	1 1	0 0	1 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	1 1
42522393	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522401	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522403	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522408	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522421	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522427	A	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 1	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522436	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522447	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522448	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522464	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 1	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522466	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522470	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522485	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522486	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522494	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522498	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522499	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522502	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522505	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522506	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522519	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522526	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522534	A	G	0 1	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522538	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 1	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522540	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522549	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522550	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522561	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522568	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522569	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522572	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522574	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522575	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522577	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522582	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522585	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522586	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522587	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42522588	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522591	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522592	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522593	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522594	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522595	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522598	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522600	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522602	AG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522608	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522609	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522610	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522613	G	C	0 0	1 1	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	1 0	1 1	0 1	1 1	0 0	1 1	0 0	1 0	1 1	0 1	1 1	0 1	0 0	0 0	0 0	0 0	1 1	0 1	1 0	1 1	0 0	0 0	1 1	0 0	1 1	0 0	0 0	1 1	0 0	1 0	0 0	1 1	0 0
42522614	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522616	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522622	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522624	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522627	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522628	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522629	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 1	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522631	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522633	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522655	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522657	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522660	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522662	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522664	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522665	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522667	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522669	C	T	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42522671	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522673	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522677	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522682	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522685	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522688	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522695	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522698	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522700	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522701	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522703	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522704	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522706	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522710	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522712	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522715	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522727	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522733	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522739	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522744	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522755	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42522756	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522758	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522763	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522768	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522771	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522775	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522776	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522779	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522781	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522785	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522789	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522796	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522798	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522800	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522805	T	C	0 1	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522807	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522808	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522809	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522811	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522813	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522815	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522816	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522820	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522821	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 1	0 0	? ?	? ?	? ?
42522826	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522828	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522832	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522840	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522841	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522842	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522843	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522845	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522847	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522851	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522857	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522859	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522863	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522867	A	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522870	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522871	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522876	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																										
42522883	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522891	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522897	TG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522903	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522906	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522910	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522914	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522921	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522924	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522925	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522928	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522930	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522931	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522933	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42522936	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522937	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522945	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522946	C	T	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522951	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522953	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522954	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522957	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522960	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522963	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522965	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522970	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522972	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522981	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522984	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522986	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522991	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522992	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42522996	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523001	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523003	A	G	0 0	1 1	? ?	? ?	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 1	1 1	0 0	1 1	? ?	? ?	0 0	1 1	0 1	1 1	? ?	1 1	0 0	? ?	0 0	? ?	1 1	0 1	1 1	1 1	0 0	0 0	? ?	1 1	1 1	1 1	0 0	? ?	1 1	0 1	? ?	? ?	? ?
42523004	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523006	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523016	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523018	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523025	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523029	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523030	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523032	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523038	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523046	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523051	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523058	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523060	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523062	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523064	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523065	CG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523071	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523073	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523075	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523087	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523089	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523091	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523097	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523099	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523101	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523103	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523105	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523106	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523109	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523111	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523122	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523124	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523125	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523128	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523133	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523140	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523142	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523144	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523146	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523156	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523163	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523165	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523167	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523169	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523171	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523172	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523174	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523176	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523182	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523185	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523186	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523188	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523190	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523196	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523199	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523203	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523204	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42523206	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523209	T	C	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 1	0 0	1 0	1 1	0 1	1 1	0 0	1 1	0 0	1 1	1 1	1 1	1 1	1 1	0 0	0 0	0 0	0 0	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	1 0	0 0	1 1	1 1
42523211	T	C	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	1 1	0 0	1 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	1 1
42523216	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523219	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523223	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523226	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523227	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523233	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523236	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523242	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523243	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523244	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523246	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523258	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523266	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523271	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523296	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523301	AC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523309	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523315	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523320	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523324	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523328	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523330	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523344	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523358	G	T	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523359	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523360	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523364	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523366	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523377	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523382	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523389	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523393	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523406	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 1	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523409	G	T	0 0	1 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 1	1 1	0 1	1 1	? ?	? ?	0 0	0 1	1 1	0 1	? ?	0 1	0 0	? ?	0 0	? ?	1 1	0 1	0 1	1 1	0 0	1 1	? ?	0 0	1 1	1 1	0 0	? ?	0 0	0 1	? ?	? ?	? ?
42523412	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 1	? ?	? ?	? ?
42523415	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523418	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523420	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523428	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523447	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523463	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523464	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 1	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523468	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523473	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523480	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523487	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523490	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523499	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523501	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523503	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523505	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523513	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523514	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523517	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523526	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523528	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523531	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523532	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 1	0 0	? ?	? ?	? ?
42523534	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523537	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523539	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523542	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523544	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523546	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523550	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523551	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523558	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523569	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523741	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523742	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523743	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523744	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523745	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523747	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523749	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523751	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523752	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523754	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523755	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523757	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523758	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523759	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523764	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523767	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523769	TC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523773	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523776	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523777	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523778	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	**Reference Allele (0)**	**Alternate Allele (1)**																																										
42523780	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523781	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523783	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523784	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523786	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523787	GC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523789	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523790	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523792	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523793	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523794	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523795	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523797	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523798	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523799	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523803	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 1	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523804	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523805	C	T	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	1 1	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523807	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523811	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523812	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523813	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523814	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523815	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523817	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523819	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523821	CA	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523822	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523823	CTGT	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523824	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523826	T	G	0 0	0 0	? ?	? ?	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523827	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523828	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523832	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523834	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523836	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523838	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523840	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 1	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523841	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523843	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523846	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523849	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523850	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523851	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523852	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523855	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523857	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523861	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523864	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523865	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523870	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523873	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523876	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523883	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523887	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523888	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523892	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523893	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523898	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523901	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523904	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523906	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523909	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523910	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523917	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523918	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523919	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523921	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523922	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523923	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523924	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523928	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523930	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523943	A	G	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 1	0 0	1 0	1 1	0 1	1 1	0 0	1 1	0 0	1 1	1 1	1 1	1 1	1 1	0 0	0 0	0 0	0 0	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 0	0 0	1 1	1 1	1 0	0 0	1 1	1 1
42523945	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523948	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523949	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523951	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523954	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523955	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523956	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42523957	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523960	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523961	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523967	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523969	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523971	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523975	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523976	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523982	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523987	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42523989	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42523992	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524001	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524003	C	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524004	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524009	C	CAG	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524014	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524017	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524018	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524035	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524037	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524040	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524045	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524048	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524051	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524054	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524056	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524058	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524065	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524066	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524068	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524072	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524076	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524080	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524082	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524083	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524086	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524088	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524091	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524098	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524100	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524110	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524118	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524119	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524120	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524127	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524129	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524130	C	T	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524132	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524133	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524136	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524138	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524140	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524142	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524143	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524148	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524149	GC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524152	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524153	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524156	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524159	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524164	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524168	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524169	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524172	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524174	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524175	CCTT	C	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524178	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524180	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524183	A	T	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524184	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524186	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524187	C	T	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524192	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524195	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524196	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524201	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524203	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524205	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524207	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 1	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524210	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524212	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524213	CG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524214	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524216	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524218	G	T	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524219	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524220	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524222	TG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524223	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524224	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524225	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 1	? ?	0 0	0 0	? ?	? ?	? ?
42524227	TG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524228	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524229	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524235	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524238	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524240	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524241	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524249	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524251	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524258	A	G	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524264	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																											
42524265	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 1	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524274	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524276	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524279	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524280	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524281	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524285	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524286	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524287	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524291	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524292	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524294	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524296	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524297	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524299	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524300	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524303	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524304	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524307	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524310	C	A	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524312	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524315	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524317	TG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524321	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524322	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524323	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524324	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524327	A	G	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524330	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524333	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524339	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524340	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524341	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524344	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524345	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524346	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524347	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524348	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524349	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524351	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524355	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524357	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524358	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524360	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524362	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524364	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524366	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524367	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524368	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524369	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524373	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524375	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524377	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524379	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524382	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524383	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524385	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524388	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524391	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524393	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524397	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524398	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524399	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524400	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524401	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524403	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524406	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524408	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524409	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524411	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524413	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524415	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524417	GC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524421	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524422	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524426	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524427	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524429	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524432	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524434	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524435	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524436	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524438	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524439	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524444	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524448	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524452	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524454	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524457	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524464	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524466	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524469	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42524471	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524475	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524476	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524477	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524478	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524481	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524487	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524489	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524490	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524491	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524493	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524496	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524499	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524500	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524502	C	T	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524504	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524505	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524506	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524508	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524511	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524513	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524517	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524519	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524521	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524522	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524524	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524526	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524531	A	G	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524532	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524533	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524534	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524535	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524537	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524538	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524539	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524540	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524542	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524544	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524545	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524546	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524548	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524552	AT	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524553	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524554	A	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524557	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524560	T	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 1	0 0	? ?	? ?	? ?
42524563	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524565	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524567	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524571	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524572	G	A	0 0	0 0	? ?	? ?	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524576	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524578	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524580	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524581	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524584	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524585	GC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524591	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524593	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524601	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524603	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524606	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524608	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524611	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524612	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524615	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524619	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524621	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 1	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524625	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524627	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524630	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524632	CCCT	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524635	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524638	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524641	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524644	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524650	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524651	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524653	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524654	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524655	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524657	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524659	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524663	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524664	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524666	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524669	T	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 1	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524672	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524673	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524675	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524676	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524679	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 1	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	**Reference Allele (0)**	**Alternate Allele (1)**																																												
42524680	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524681	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524684	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524685	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524686	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524687	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524692	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524694	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524696	T	C	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	1 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 1	0 0	1 1	0 0	1 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	1 1
42524699	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524700	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524701	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524702	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524705	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524707	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524708	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 1	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 1	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524710	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524711	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524713	C	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524715	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524717	GC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524722	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524724	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524728	GC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524733	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524736	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524739	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524741	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524743	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 1	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524744	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524746	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524749	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524750	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524755	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524758	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524759	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524760	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524762	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524763	CT	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524764	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524767	TCGG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524771	TCTCTC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524773	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524775	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524779	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524784	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524787	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524789	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524793	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524795	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524796	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524797	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524799	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 1	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524803	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524805	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524808	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524811	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524814	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524815	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524816	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524820	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 1	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524823	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524825	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524832	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524838	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524844	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524847	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524848	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524852	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524856	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524859	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524865	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524868	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524869	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524878	C	T	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524881	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524884	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524886	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524890	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524893	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 1	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524895	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524896	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524898	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524901	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524902	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524905	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524906	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524907	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524912	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524913	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524916	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524917	C	T	0 0	0 0	? ?	? ?	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42524919	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524920	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524922	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524924	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 1	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524931	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 1	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524935	GA	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524936	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524941	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524942	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524945	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524947	C	T	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0
42524950	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524951	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524952	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524953	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524955	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524956	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524957	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524960	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524964	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524968	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524971	G	A	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524973	G	A	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42524975	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524978	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524980	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524981	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524982	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524985	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524986	TC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524992	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524995	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524996	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42524999	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525000	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525002	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525003	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525004	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525008	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 1	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42525009	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525010	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525013	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525016	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525018	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525019	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525021	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525022	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525023	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525024	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525025	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525026	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525027	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525029	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525030	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42525033	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525038	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525039	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525040	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525043	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525044	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525047	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525049	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525050	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525057	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525060	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525061	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525073	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525076	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525080	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525091	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525093	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525094	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525096	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525098	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525100	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525101	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525103	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525104	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525105	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525107	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525108	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525109	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525113	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525114	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525115	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42525118	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 1	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42525124	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525125	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525128	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525130	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	1 1	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42525131	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525132	G	C	0 0	1 1	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	1 0	1 1	0 1	1 1	0 0	1 1	0 0	1 0	1 1	0 1	1 1	0 1	0 0	0 0	0 0	0 0	1 1	0 1	0 1	1 1	0 0	0 1	1 1	0 0	1 1	0 0	0 0	1 1	0 0	1 0	0 0	1 1	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																										
42525133	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525137	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525139	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525140	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525146	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525148	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525151	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525158	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525176	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525178	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525181	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525182	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525184	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525189	TG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525191	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525195	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525199	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525203	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525205	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525208	T	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 1	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525210	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525214	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525215	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525223	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525227	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525228	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525230	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525232	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525236	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525239	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525243	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525246	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525250	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525255	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525256	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525259	CTA	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	? ?
42525261	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525262	T	TGGC	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	? ?
42525265	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525268	C	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	? ?
42525270	C	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	? ?
42525271	T	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525274	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525282	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525284	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525289	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525292	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525294	T	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525296	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525305	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525307	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525318	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525320	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525321	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525322	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525324	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525325	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525327	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525328	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525330	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525331	A	G	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525333	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525338	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525342	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525345	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525346	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525352	CA	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525358	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525360	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525366	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525372	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525378	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525381	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525382	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525387	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525398	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525400	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525402	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525406	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525407	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525409	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525411	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525431	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 1	? ?	0 0	0 0	? ?	? ?	? ?
42525432	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525434	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525438	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525441	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525442	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525443	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525445	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525449	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525450	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43		44	
TM1			6.2		2.7		6.3		2		8		15		6.3		9.5		5.7		7.1		1.8		2.1		2.4		3.5		13		4		1.5		4		4.6		4.8		29		3		28		6.2		6		3.5		7.9		13		18		8		2		1.3		11		27		15		5.6		2.8		2.8		70		2.5		2.8		18		8		2.8	
t-MP			NM-F		UM		NM-F		UM		NM-S		NM-S		NM-F		NM-S		NM-F		NM-S		UM		UM		UM		NM-F		NM-S		NM-F		UM		NM-F		NM-F		NM-F		PM		NM-F		PM		NM-F		NM-F		NM-F		NM-S		NM-S		NM-S		NM-S		UM		UM		NM-S		PM		NM-S		NM-F		UM		UM		PM		UM		UM		NM-S		NM-S		UM	
g-MP			NM-F		NM-F		UM		UM		NM-F		PM		NM-F		NM-F		NM-F		NM-F		NM-F		NM-F		NM-S		NM-F		NM-F		NM-S		NM-F		NM-F		IM		NM-F		NM-S		NM-F		NM-F		NM-S		NM-F		NM-F		NM-S		NM-F		NM-F		IM		NM-F		NM-F		NM-F		NM-F		IM		NM-F		NM-F		NM-F		NM-F		NM-S		NM-F		NM-F		UM		NM-F	
AGE			47		76		57		68		38		65		57		59		64		46		32		26		60		39		62		60		69		94		88		30		33		57		49		70		82		91		66		54		55		54		46		59		44		71		60		52		29		28		56		89		33		46		83		76	
SEX			Male		Male		Male		Male		Male		emal		Male		emal		emal		Male		Male		Male		Male		Male		emal		Male		emal		Male		emal		Male		Male		Male		Male		emal		emal		Male		emal		Male		Male		emal		emal		emal		emal		emal		emal		Male		Male		Male		Male		Male		emal		emal		emal		Male	
A			Y		Y		N		N		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		N		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		N		Y		Y		Y		N		N	
B			N		N		Y		Y		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		Y		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		Y		Y	
H			N		N		N		Y		N		N		N		N		N		N		N		N		Y		N		N		Y		N		N		N		N		N		N		Y		N		N		Y		N		N		N		N		N		N		Y		N		N		N		N		N		Y		N		N		N		N		N	
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																																																																										
42525453	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525461	C	T	0	0	0	0	?	?	?	?	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	0	0	?	?	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?
42525462	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525463	GC	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525465	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525466	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525467	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525470	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525472	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525473	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525476	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525477	CACCGGATTCCA	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525478	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525483	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525485	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525488	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525490	CTGGGAA	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525495	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525496	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525498	TGCGC	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525499	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525501	G	A	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	?	?	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?
42525508	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525510	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525515	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525521	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525522	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525524	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525526	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525528	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525531	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525533	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525538	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525543	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525544	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525545	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525546	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525549	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525550	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525553	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525554	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525556	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525558	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525560	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525561	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525562	GC	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525564	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525565	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525566	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525568	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525569	C	T	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	0	0	?	?	0	0	0	0	0	0	0	1	0	0	0	0	?	?	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?
42525570	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525575	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525576	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525578	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525580	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525583	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525585	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525587	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525589	C	T	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	0	0	?	?	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?
42525590	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525591	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525594	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525595	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525597	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525600	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525603	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525606	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525608	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525609	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525610	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525615	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525619	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525621	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525625	C	T	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
42525628	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525629	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525635	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525637	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525639	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525640	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525641	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525644	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525646	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525648	C	T	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	?	?	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	0	0	?	?	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?
42525649	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525650	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525652	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525656	C	T	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	?	?	0	0	1	1	?	?	0	0	?	?	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?
42525657	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525664	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42525665	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42525667	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525668	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525670	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525672	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525675	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525676	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525679	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525682	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525685	GTCA	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525686	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 1	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525689	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525691	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525692	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525695	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525702	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525706	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525711	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525712	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 1	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525713	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525715	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525717	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525719	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525721	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525722	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525723	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525725	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525728	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525730	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525733	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525746	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525748	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525754	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525757	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525758	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525759	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525764	G	A	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525767	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525772	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525773	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525781	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525783	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525793	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525798	G	C,T	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 1	0 2	0 1	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 1	0 0	0 0	0 0	? ?	1 1	0 0	0 0	0 0	? ?	1 1	0 0	? ?	? ?	? ?
42525800	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525802	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525803	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525811	T	C	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0
42525814	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 1	? ?	0 0	0 0	? ?	? ?	? ?
42525815	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525821	G	T	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0
42525826	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525846	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525850	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525853	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525856	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525859	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525860	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525866	TC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525877	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525887	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525889	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525892	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525898	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525922	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525923	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42525926	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525949	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525950	TC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525952	C	A	0 0	1 1	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	1 0	1 1	0 0	1 1	0 0	1 1	0 0	0 1	1 1	0 1	1 1	0 1	0 0	0 0	0 0	0 0	1 1	0 1	1 0	1 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	1 1	0 0	0 1	0 0	1 1	0 0
42525959	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525962	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525967	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525970	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525973	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525976	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525978	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525979	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525980	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525983	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525986	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525987	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525990	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42525993	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526004	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526006	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526011	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526013	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526015	A	G	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526021	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526031	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526033	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526036	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42526037	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526041	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 1	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526042	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526043	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526044	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526046	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526047	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526049	C	G	0 0	1 1	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	1 0	1 1	0 1	1 1	0 0	1 1	0 0	1 0	1 1	0 1	1 1	1 1	0 0	0 0	0 0	1 1	1 1	1 0	0 1	1 1	0 0	1 1	1 1	0 0	1 1	0 0	0 0	1 1	0 0	0 1	0 0	1 1	1 1
42526055	CG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526062	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526085	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526100	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526107	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526109	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526111	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526118	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526124	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526125	A	G	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	? ?	0 0	0 1	? ?	? ?	? ?
42526126	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526128	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526131	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526137	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526140	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526147	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526158	A	G	0 1	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	? ?	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526162	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	? ?	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526168	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526175	T	C	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	? ?	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526177	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526193	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526200	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526218	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526221	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526222	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526224	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526227	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526232	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526251	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526258	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 1	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526262	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526263	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526264	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526275	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526280	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526284	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 1	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526291	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526293	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 1	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526296	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526298	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526299	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526304	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526309	A	G	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526311	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526316	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526320	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526324	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526326	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526334	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526335	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526337	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526343	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526348	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	? ?	0 0	0 0	0 0	0 1	? ?	0 0	0 0	? ?	? ?	? ?
42526363	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526374	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526378	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526393	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526399	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526402	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526405	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526420	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526423	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526425	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526431	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526435	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526440	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526441	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526442	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526443	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526444	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526447	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526449	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526452	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526453	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526456	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526460	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526463	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526467	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526468	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526470	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526480	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526484	A	C	0 0	1 1	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 1	1 1	0 1	1 1	0 0	1 1	0 0	0 1	1 1	0 1	1 1	1 0	0 0	0 0	0 0	0 0	1 1	1 0	1 0	1 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	1 1	0 0	1 0	0 0	1 1	0 0
42526485	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42526486	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526490	C	A	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526493	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526494	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526497	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526500	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526501	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526506	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526507	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526509	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526514	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526525	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526532	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526537	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526538	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526549	C	T	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 1	0 0	0 1	1 1	1 0	1 1	0 0	1 1	0 0	1 1	1 1	1 1	1 1	1 1	0 0	0 0	0 0	0 0	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	1 0	0 0	1 1	1 1
42526558	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526560	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526561	G	T	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 1	0 0	1 0	1 1	1 0	1 1	0 0	1 1	0 0	1 1	1 1	1 1	1 1	1 1	0 0	0 0	0 0	0 0	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	0 1	0 0	1 1	1 1
42526562	G	C	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 1	0 0	0 1	1 1	1 0	1 1	0 0	1 1	0 0	1 1	1 1	1 1	1 1	1 1	0 0	0 0	0 0	0 0	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	1 0	0 0	1 1	1 1
42526564	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526566	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526567	G	A	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 1	0 0	0 1	1 1	1 0	1 1	0 0	1 1	0 0	1 1	1 1	0 1	1 1	1 1	0 0	0 0	0 0	0 0	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	1 0	0 0	1 1	1 1
42526569	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526570	GCAT	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526571	C	G	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 1	0 0	1 0	1 1	1 0	1 1	0 0	1 1	0 0	1 1	1 1	0 1	1 1	1 1	0 0	0 0	0 0	0 0	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	0 1	0 0	1 1	1 1
42526572	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526573	T	G	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 1	0 0	0 1	1 1	1 0	1 1	0 0	1 1	0 0	1 1	1 1	0 1	1 1	1 1	0 0	0 0	0 0	0 0	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	1 0	0 0	1 1	1 1
42526574	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526576	TCA	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526579	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526580	G	C	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 1	0 0	1 0	1 1	1 0	1 1	0 0	1 1	0 0	1 1	1 1	0 1	1 1	1 1	0 0	0 0	0 0	0 0	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	0 1	0 0	1 1	1 1
42526584	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526589	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526594	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526600	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526606	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526615	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 1	? ?	0 0	0 0	? ?	? ?	? ?
42526622	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526627	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526632	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526634	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526636	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526637	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526639	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 1	0 0	? ?	? ?	? ?
42526642	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526643	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526648	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526649	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42526650	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526651	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526654	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526656	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526657	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526660	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526661	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526675	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526681	AG	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526685	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526687	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526692	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526694	G	A	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	1 1	0 0	0 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	1 1
42526696	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526697	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526701	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526704	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526707	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526708	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526709	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526714	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42526723	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526726	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526727	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526729	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526732	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526735	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526738	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526741	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526744	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526747	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526748	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526750	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526751	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526758	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526760	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526762	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526763	C	T	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526764	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 1	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42526767	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526771	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526774	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42526779	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42526782	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526783	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526785	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526794	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526797	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526806	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526809	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526810	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526811	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526817	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526820	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526823	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526825	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526827	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526829	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526832	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526833	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526836	A	AC	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526837	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526842	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526847	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526850	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526854	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526856	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526858	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526861	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526863	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 1	0 0	0 0	? ?	? ?
42526864	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526868	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526871	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526873	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526875	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526877	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526879	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526882	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526884	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526886	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526888	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526894	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526895	G	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42526896	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526900	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526901	T	C	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42526905	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526906	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526909	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526910	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526911	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526915	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526920	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526921	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526923	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526924	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526925	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526929	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526930	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526931	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526936	T	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42526938	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42526941	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526945	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526947	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526948	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526949	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526950	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526953	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526956	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526958	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526960	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526961	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526962	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526963	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526970	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526976	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526980	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526982	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42526987	G	A	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	1 1	? ?	? ?
42526999	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527001	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527009	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527014	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527017	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527018	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527022	G	A	1 1	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527027	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527030	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527031	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527034	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527037	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527040	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527047	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527048	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42527067	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527077	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527081	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527084	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527086	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527088	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527096	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527101	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527110	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527113	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527115	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527116	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527120	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527123	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527125	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527126	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527129	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527132	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527136	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527138	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527139	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527146	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527147	T	C	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527155	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527157	C	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527161	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527164	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527170	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527174	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527177	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527182	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527185	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527186	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527188	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527197	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527198	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527200	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527202	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527204	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527205	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527207	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527213	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527215	C	T	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527218	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527219	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527221	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527228	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527233	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527240	AC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527243	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527246	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527254	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527256	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527263	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527265	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527268	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527269	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527271	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527274	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527281	T	A	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527283	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527285	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527287	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527292	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527293	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527295	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527297	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527300	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42527301	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527302	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527303	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527307	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527311	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527314	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527316	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42527319	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527322	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527325	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527331	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42527332	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527337	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527338	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527341	T	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 1	0 0	0 0	? ?	? ?
42527342	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527344	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527348	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527349	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527351	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527353	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42527354	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527356	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527359	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42527360	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527363	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527365	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527368	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527369	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527370	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527372	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527373	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527376	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527380	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527384	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527389	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527391	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527393	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527398	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527402	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527410	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527422	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527428	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527430	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527435	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527438	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527443	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42527444	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527454	AG	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42527455	G	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 1	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42527463	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527464	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527471	T	C	0 0	1 1	1 1	0 0	0 0	1 0	0 0	0 0	0 0	0 1	0 0	0 1	1 1	1 0	1 1	0 0	1 1	0 0	1 1	1 1	1 1	1 1	1 1	0 0	0 0	0 0	1 1	1 1	0 1	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 1	0 0	1 1	1 1	1 0	0 0	1 1	1 1
42527472	G	A	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527474	A	G	0 1	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42527477	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527479	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527492	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527494	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527497	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527501	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527504	C	T	0 0	0 0	? ?	? ?	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42527505	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527508	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527517	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527521	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527533	A	G	0 0	1 1	1 1	0 0	0 0	0 1	0 0	0 0	0 0	0 1	0 0	1 0	1 1	0 1	1 1	0 0	1 1	0 0	1 1	1 1	1 1	1 1	1 1	0 0	0 0	0 0	0 0	1 1	1 0	1 1	1 1	0 0	1 1	1 1	1 1	1 1	0 0	0 0	1 1	1 1	0 1	0 0	1 1	1 1
42527537	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527542	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527544	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527546	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527548	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527556	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527561	TCA	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 1	0 0	0 0	? ?	0 0	0 0	0 0	? ?	? ?
42527565	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527567	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527584	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527599	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527614	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527617	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527618	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527619	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527624	G	A	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527630	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527635	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527638	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527640	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527645	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527652	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527669	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527670	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527678	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527695	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527696	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527698	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527706	A	T	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527707	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527709	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527716	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527717	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527723	A	G	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 1	0 0	? ?	? ?	? ?
42527726	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527729	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527730	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527743	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527744	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527750	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527751	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527761	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527763	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527765	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527767	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527770	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527771	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 1	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527774	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527782	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 1	0 0	? ?	? ?	? ?

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	emal	Male	emal	emal	Male	Male	Male	Male	Male	emal	Male	emal	Male	emal	Male	Male	Male	Male	emal	emal	Male	emal	Male	Male	emal	emal	emal	emal	emal	emal	Male	Male	Male	Male	Male	emal	emal	emal	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N
Chromosome 22 Position	**Reference Allele (0)**	**Alternate Allele (1)**																																											
42527786	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527788	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527792	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527793	C	T	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 0	0 0	0 0	1 1	0 0	1 1	0 0	0 0	0 0	0 0	1 1	0 0	0 0	0 0	1 1
42527795	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527798	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527800	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527801	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527806	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527809	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527810	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527813	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527818	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527820	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527826	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527828	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527830	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527835	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527837	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527840	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527843	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527844	G	A	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42527847	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527848	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527851	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527854	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527857	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527860	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527861	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527864	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527865	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527866	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527868	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527869	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527871	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527873	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527874	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527876	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527879	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527880	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527881	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527883	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527886	AT	A	1 1	1 0	0 0	0 0	0 1	0 1	0 1	1 0	0 1	0 1	0 1	0 1	0 1	0 1	0 1	0 0	0 0	0 1	1 0	1 0	1 0	0 0	0 0	0 1	0 0	0 0	0 0	1 0	1 0	0 1	1 0	0 1	0 0	0 0	0 1	0 1	0 0	0 1	0 0	0 1	1 0	0 0	0 0	0 0
42527887	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527888	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527889	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527890	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527891	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527894	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527895	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527896	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527898	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527902	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527905	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527909	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527911	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527915	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527920	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527932	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527934	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42527937	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528013	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528019	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528020	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528026	ATCCTTTTT	A,ATT,ATTT	0 0	1 2	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 3	0 0	1 3	2 3	0 2	1 2	? ?	? ?	0 0	0 1	1 2	0 3	? ?	1 1	0 0	? ?	? ?	? ?	1 3	0 2	0 0	1 2	0 0	2 2	? ?	0 0	1 2	? ?	0 0	? ?	0 0	0 1	? ?	? ?	? ?
42528027	TCC	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528029	CTTTTTT	C,CTTTTT	0 1	0 0	? ?	? ?	0 2	1 2	0 1	1 2	1 2	0 0	1 2	0 0	0 0	0 0	0 0	? ?	? ?	1 2	0 1	0 0	0 1	? ?	0 0	1 2	? ?	? ?	? ?	0 0	0 0	0 1	0 0	1 2	0 0	? ?	1 1	0 0	? ?	0 1	? ?	0 1	0 0	? ?	? ?	? ?
42528031	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528032	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528033	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528034	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 1	0 1	0 1	? ?	? ?	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 1	0 0	0 0	0 0	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 1	? ?	? ?	? ?
42528035	T	C	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 1	? ?	? ?	0 0	0 0	0 1	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 1	0 1	0 0	0 1	0 0	1 1	? ?	0 0	0 1	? ?	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42528036	T	C	0 0	0 1	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 0	? ?	? ?	0 0	0 1	0 0	0 0	? ?	0 0	0 0	? ?	? ?	? ?	0 0	0 0	0 0	0 1	0 0	0 0	? ?	0 0	0 0	? ?	0 0	? ?	0 0	0 0	? ?	? ?	? ?
42528037	T	C	0 0	0 0	? ?	? ?	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 1	0 0	0 1	0 1	? ?	? ?	0 0	0 1	0 1	0 0	? ?	0 1	0 0	? ?	? ?	? ?	0 1	0 0	0 0	0 1	0 0	0 0	? ?	0 0	0 1	? ?	0 0	? ?	0 0	0 1	? ?	? ?	? ?
42528038	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528039	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528040	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528041	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528042	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528043	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528045	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528046	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528047	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528048	T	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528058	GAGA	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528059	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528060	G	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528061	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528062	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528065	A	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528071	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
42528074	C	.	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43		44	
TM1			6.2		2.7		6.3		2		8		15		6.3		9.5		5.7		7.1		1.8		2.1		2.4		3.5		13		4		1.5		4		4.6		4.8		29		3		28		6.2		6		3.5		7.9		13		18		8		2		1.3		11		27		15		5.6		2.8		2.8		70		2.5		2.8		18		8		2.8	
t-MP			NM-F		UM		NM-F		UM		NM-S		NM-S		NM-F		NM-S		NM-F		NM-S		UM		UM		UM		NM-F		NM-S		NM-F		UM		NM-F		NM-F		NM-F		PM		NM-F		PM		NM-F		NM-F		NM-F		NM-S		NM-S		NM-S		NM-S		UM		UM		NM-S		PM		NM-S		NM-F		UM		UM		PM		UM		UM		NM-S		NM-S		UM	
g-MP			NM-F		NM-F		UM		UM		NM-F		PM		NM-F		NM-F		NM-F		NM-F		NM-F		NM-F		NM-S		NM-F		NM-F		NM-S		NM-F		NM-F		IM		NM-F		NM-S		NM-F		NM-F		NM-S		NM-F		NM-F		NM-S		NM-F		NM-F		IM		NM-F		NM-F		NM-F		NM-F		IM		NM-F		NM-F		NM-F		NM-F		NM-S		NM-F		NM-F		UM		NM-F	
AGE			47		76		57		68		38		65		57		59		64		46		32		26		60		39		62		60		69		94		88		30		33		57		49		70		82		91		66		54		55		54		46		59		44		71		60		52		29		28		56		89		33		46		83		76	
SEX			Male		Male		Male		Male		Male		emal		Male		emal		emal		Male		Male		Male		Male		Male		emal		Male		emal		Male		emal		Male		Male		Male		Male		emal		emal		Male		emal		Male		Male		emal		emal		emal		emal		emal		emal		Male		Male		Male		Male		Male		emal		emal		emal		Male	
A			Y		Y		N		N		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		N		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		Y		N		Y		Y		Y		N		N	
B			N		N		Y		Y		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		Y		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		N		Y		Y	
H			N		N		N		Y		N		N		N		N		N		N		N		N		Y		N		N		Y		N		N		N		N		N		N		Y		N		N		Y		N		N		N		N		N		N		Y		N		N		N		N		N		Y		N		N		N		N		N	
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																																																																									
42528077	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528091	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528161	T	C	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	1	?	?	0	0	0	0	0	0	0	1	?	?	0	0	0	0	0	0	?	?	?	?
42528224	G	A	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	1
42528249	A	G	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?
42528327	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528328	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528332	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528333	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528335	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528336	G	A	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	1	?	?	?	?	?	?
42528338	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528339	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528341	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528344	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528347	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528349	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528350	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528352	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528354	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528356	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528357	T	A	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	?	?	0	0	0	1	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?
42528358	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528359	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528360	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528365	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528366	AT	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528367	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528368	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528369	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528370	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528371	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528372	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528375	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528377	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528379	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528382	C	G	0	0	1	1	1	1	0	0	0	1	1	0	0	0	1	1	0	0	0	1	0	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0	0	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	0	0	1	1	1	1
42528385	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528386	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528388	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528389	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528390	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528395	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528396	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528398	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528401	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528402	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528405	TG	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528408	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528410	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528411	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528412	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528413	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528414	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528416	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528422	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528423	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528424	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528426	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528427	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528429	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528431	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528432	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528435	T	C	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?	0	0	0	0	0	0	0	1	0	0	0	0	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?
42528437	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528439	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528440	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528442	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528444	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528447	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528448	T	C	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	?	?	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	?	?	0	0	0	0	?	?	?	?	?	?
42528452	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528453	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528454	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528455	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528456	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528459	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528463	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528464	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528465	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528466	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528467	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528468	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528469	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528475	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528476	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528479	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528481	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528483	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528485	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528486	C	T	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	0	0	0	0	0	0	?	?	0	0
42528487	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table S1 (continued). Computationally phased *CYP2D6* full-gene haplotype information for 44 tramadol-exposed post-mortem Finns and their associated ratio of tramadol to O-desmethyltramadol (T:M1), toxicologically-determined phenotype group (t-MP) as determined by model-based clustering (Figure 1C-E), CYP2D6 genotype-inferred metabolizer phenotype (g-MP), age, sex, and amplicon success using primers listed in Table 1 with Y and N indicating successful and unsuccessful amplification of the target, respectively.

Sample			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
TM1			6.2	2.7	6.3	2	8	15	6.3	9.5	5.7	7.1	1.8	2.1	2.4	3.5	13	4	1.5	4	4.6	4.8	29	3	28	6.2	6	3.5	7.9	13	18	8	2	1.3	11	27	15	5.6	2.8	2.8	70	2.5	2.8	18	8	2.8
t-MP			NM-F	UM	NM-F	UM	NM-S	NM-S	NM-F	NM-S	NM-F	NM-S	UM	UM	UM	NM-F	NM-S	NM-F	UM	NM-F	NM-F	NM-F	PM	NM-F	PM	NM-F	NM-F	NM-F	NM-S	NM-S	NM-S	UM	UM	NM-S	PM	NM-S	NM-F	UM	UM	PM	UM	UM	NM-S	NM-S	UM
g-MP			NM-F	NM-F	UM	UM	NM-F	PM	NM-F	NM-F	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	NM-S	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	IM	NM-F	NM-F	NM-F	NM-F	NM-S	NM-F	NM-F	UM	NM-F
AGE			47	76	57	68	38	65	57	59	64	46	32	26	60	39	62	60	69	94	88	30	33	57	49	70	82	91	66	54	55	54	46	59	44	71	60	52	29	28	56	89	33	46	83	76
SEX			Male	Male	Male	Male	Male	Male	emale	Male	emale	emale	Male	Male	Male	Male	Male	emale	Male	emale	Male	emale	Male	Male	Male	Male	emale	emale	Male	emale	emale	emale	emale	emale	emale	emale	emale	Male	Male	Male	Male	Male	emale	emale	emale	Male
A			Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
B			N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
H			N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	Y	N	N	N	N	N	N
Chromosome 22 Position	Reference Allele (0)	Alternate Allele (1)																																												
42528488	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528491	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528493	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528495	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528502	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528503	T	C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	?	?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528505	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528507	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528509	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528510	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528513	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528516	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528518	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528520	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528521	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528522	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528527	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528529	T	C	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?	?	1	1	0	0	0	0	0	1	0	1	0	0	0	0	1	0	0	0	1	0	0	0
42528532	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528533	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528536	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528540	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528548	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528553	A	G	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	?	?	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
42528567	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528568	T	C	0	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0	0	0	1	1	0	0	1	0	0	1	0	1	0	1	1	1	1	1	1	0	1	0	0	1
42528569	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528572	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528581	T	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528583	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528588	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528591	A	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528596	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528598	G	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42528601	C	.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

CHAPTER 6

A Pathway-Driven Predictive Model of Tramadol Pharmacogenetics

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Abstract

Predicting metabolizer phenotype (MP) is typically performed using data from a single gene. Cytochrome p450 family 2 subfamily D polypeptide 6 (CYP2D6) is considered the primary gene for predicting MP in reference to approximately 30% of marketed drugs and endogenous toxins. CYP2D6 predictions have proven clinically effective but also have well-documented inaccuracies due to relatively high genotype-phenotype discordance in certain populations. Herein, a pathway-driven predictive model employs genetic data from uridine diphosphate glucuronosyltransferase, family 1, polypeptide B7 (UGT2B7), adenosine triphosphate (ATP) binding cassette, subfamily B, number 1 (ABCB1), opioid receptor mu 1 (OPRM1), and catechol-O-methyltransferase (COMT) to predict the tramadol to primary metabolite ratio (T:M1) and the resulting toxicologically-inferred MP (t-MP). These data were then combined with CYP2D6 data to evaluate performance of a fully combinatorial model relative to CYP2D6 alone. These data identify UGT2B7 as a potentially significant explanatory marker for T:M1 variability in a population of tramadol-exposed individuals of Finnish ancestry. Supervised machine learning and feature selection were used to demonstrate that a set of 16 loci from 5 genes can predict t-MP with over 90% accuracy, depending on t-MP category and algorithm, which was significantly greater than predictions made by CYP2D6 alone.

Introduction

Pharmacogenetic studies typically rely on targeted monogenic genotyping approaches (i.e. detection of targeted single nucleotide variants (SNVs) from one gene) to characterize the way populations or individuals respond to drugs (1-4). The cytochrome p450 family 2, subfamily D, polypeptide 6 (*CYP2D6*) locus is a gene routinely used to predict metabolism of various compounds due to its involvement in phase I metabolism of approximately 30% of marketed drugs and endogenous toxins (3,5-8). *CYP2D6* genotype-phenotype correlations have demonstrated relatively high efficacy in various clinical applications, however, notable genotype-phenotype discordance is documented (9-11). It is understood that drug ADME-R (absorption, distribution, metabolism, excretion, and response) are dependent upon protein pathways, not the activity of a single protein. Consequently, one-gene one-phenotype predictive models do not utilize extended ADME-R information. Altar*, et al.* demonstrated that combinatorial approaches (i.e. genetic data from multiple proteins) to predicting metabolizer phenotype (MP) have significantly more efficacious patient outcomes when compared to a single-gene single-phenotype model for psychiatric compounds (12,13). Pathway-driven pharmacogenetic studies have been performed in relatively few drug classes and typically utilize relatively few loci (i.e., genes or SNVs) (14-16), but the success of this type of model has not been evaluated for extended metabolic pathways (e.g., one or two genes versus multiple genes representing various stages of ADME-R).

CYP2D6 is readily implicated in O-demethylation of tramadol to form O-desmethyltramadol (M1). Tramadol is among the most widely prescribed opioid analgesics in the United States and as such contributes to the critical public health opioid usage and distribution crisis (17,18). Given the overwhelmingly high number of tramadol prescriptions

in the United States, it is essential that predictive models include as much data as possible to address the degree of CYP2D6 genotype-phenotype discordance observed in individuals and in some populations. It is reasonable to hypothesize that a combinatorial predictive model of tramadol metabolism using genetic information from proteins representative of phase II metabolism, active metabolite distribution, and neurotransmitter and analgesia propagation would provide a more complete picture of how an individual responds to tramadol.

Supervised machine learning identifies underlying relationships describing the interaction between a known outcome variable (i.e., MP) and highly dimensional explanatory variables (i.e., genotypes). To our knowledge, machine learning is not readily used to identify loci for predicting patient MP but may offer considerable advantages for pathway-driven pharmacogenetic analyses via feature selection. Herein, a pathway-driven predictive model of tramadol ADME-R was evaluated to identify features (i.e., single nucleotide [SNPs] and/or insertion/deletion [INDELs] polymorphisms) capable of classifying members of a deceased, tramadol-exposed Finnish population into toxicologically-inferred MP (t-MP) categories. The genetic data from uridine diphosphate glucuronosyltransferase, family 1, polypeptide B7 (*UGT2B7*), adenosine triphosphate (ATP) binding cassette, subfamily B, number 1 (*ABCB1*), opioid receptor mu 1 (*OPRM1*), and catechol-O-methyltransferase (*COMT*) were used in combination with *CYP2D6* data (19) and demonstrate increased prediction accuracy and correlation coefficients for the t-MP and T:M1 outcome variables, respectively. These predictions were made using a substantially reduced number of loci (16 and 33 for t-MP and T:M1, respectively) offering promise for design and clinical implementation of accurate and reproducible tramadol response models.

Subjects and Methods

Subjects

A total of 208 DNA samples from deceased, tramadol-exposed individuals of Finnish ancestry were used in this study. Samples were collected in Finland between 2001 and 2012 according to the ethical handling of human subjects policies at the University of Helsinki and transferred to the University of North Texas Health Science Center (Institutional Review Board protocol 2016-051). Detailed information on sample collection, toxicological analyses, and DNA extraction and quantitation were described by Wendt, *et al.* (19).

Marker Selection, Library Preparation, and Massively Parallel Sequencing

A TruSeq® Custom Amplicon (TSCA) Low Input library preparation panel (Illumina®, Inc.) was designed using the Illumina DesignStudio™ (see https://www.illumina.com/informatics/sample-experiment-management/custom-assay-design.html; Accessed June 2017). The exons of four pharmacogenes (*UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*) were targeted for kit design (Table 1). Library preparation was performed using 10 ng of genomic DNA and followed the manufacturer's recommended protocol. Two modifications were made to the TSCA Low Input protocol: 1) during the Remove Unbound Oligos step, sample purification beads were allowed to dry for only one minute instead of the indicated five minutes, and 2) prior to library cleanup, the hybridization plate was placed on a magnetic stand for two minutes before 45 μL of supernatant were transferred to the cleanup plate. Cleaned-up library traces were spot-checked using the Agilent 2200 TapeStation (Agilent Technologies, Waldbronn, Germany) using the Agilent 2200 High Sensitivity D1000 ScreenTape System according to the manufacturer's recommended protocol (see

https://support.illumina.com/content/dam/illumina-support/documents/documentation/chemistry_documentation/samplepreps_truseq/truseqcustomamplicon/truseq-custom-amplicon-low-input-reference-guide-1000000002191-04.pdf; Accessed July 2017). Sample libraries were normalized and pooled in batches of 32 and sequenced on the MiSeq (Illumina) using the MiSeq Reagent kit v2 (500 cycles) with 2 x 250 bp read length.

Alignment, Variant Analysis, and Machine Learning

Resulting .fastq files were locally aligned to the hg19/GRCh37 reference genome using the Burrows-Wheeler Aligner `mem` command and the SamTools `view`, `sort`, and `index` commands (20-22). Variant calling was performed in Genome Analysis ToolKit (GATK) (23) using the `HaplotypeCaller` command. Resulting .vcf files were, or were converted to, standard input for VCFtools (24), Genome-wide Complex Trait Analysis (GCTA) (25), PLINK (26) IMPUTE2 v2.3.2 (ref. 27), and various in-house Excel-based workbooks.

Supervised machine learning was performed in the Waikato Environment for Knowledge Analysis (WEKA) as described previously (28,29) using four classifiers: regularized multinomial logistic regression (RMLR; for t-MP only), 1-nearest neighbor (1NN; for t-MP and T:M1), random forest (RF; for t-MP and T:M1), and linear regression (LR, for T:M1 only). Feature selection and leave-one-out cross validation were used to reduce the size of the model and assess model accuracy, respectively. Note that specific descriptions of all WEKA functions used herein have been detailed previously by Wendt, *et al.* (19) and Schmedes, *et al.* (28,29). Unless otherwise stated, sample n-1 (i.e., 207-fold) cross-validation was performed.

Results

Samples

The cohort in this study represents a larger sampling of deceased tramadol-exposed individuals of Finnish ancestry than reported previously (19). The mean ratio of tramadol to M1 (T:M1) for 208 Finns was 11.6 ± 18.3. There was no significant difference in mean T:M1 between males (12.8 ± 25.0; N = 127; mean age 52.2 years ± 17.9) and females (10.9 ± 12.3; N = 81; mean age 60.0 years ± 18.3).

The R `mclust` package (30) for RStudio was used to evaluate the natural clustering of the dataset (19). Five clusters were identified and used to sort each sample into a t-MP category based on the following thresholds: poor metabolizers (PM; T:M1 ≥ 50; N = 5), intermediate metabolizers (IM; 50 > T:M1 ≥ 20; N = 20), slow normal metabolizers (NM-S; 20 > T:M1 ≥ 8; N = 67), fast normal metabolizers (NM-F; 8 > T:M1 ≥ 3; N = 91), and ultra-rapid metabolizers (UM; 3 > T:M1 ≥ 1; N = 25).

Library Preparation Panel and Sequencing Performance

The massively parallel sequencing (MPS) panel targeted 216 exonic amplicons with a probe-based chemistry (Tables S1 and S2). Based on requirements for probe placement, some intronic regions also were obtained. The average amplicon length was 177 bases ± 6.84. Note that *ABCB1* and *COMT* had small gaps after panel design (Table 1) resulting in lack of genotype data for two exonic SNPs (NC_000007.13:g.87133763A>G and NC_000007.13:g.87145971C>G) in *ABCB1*, each with the alternate allele observed only once in the Exome Aggregation Consortium and 1000 Genomes Project databases (1kGP) (31,32).

Sort Intolerant From Tolerant (SIFT) and Polymorphism Phenotype v-2 (PolyPhen v2) scores indicate possibly damaging consequences of NC_000007.13:g.87145971C>G (SIFT: 0; PolyPhen v2: 0.995) (refs. 33,34). With publically available data, there has not been any reported genetic variation in the design gap in *COMT*.

Table 1. Design strategy for a TruSeq Custom Amplicon Low Input library preparation panel targeting the exons of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*. Design resulted in 98% overall coverage of desired targets. A full list of amplicons is provided in Supplemental Table __; note that due to optimal amplicon sizing, certain intronic regions may have been captured within an amplicon.

Gene	Chromosome	Amplicons*	Coverage (%)	Gaps Coordinates	Gap Details
UGT2B7	4	24	100	-	-
ABCB1	7	90		87,197,059-87,197,105 87,198,648-87,198,648 87,191,244-87,191,244 87,180,975-87,180,975 87,145,948-87,145,986 87,133,754-87,133,770	Transcript NM_000927 Intron 6, Transcript NM_000927 Intron 6, Transcript NM_000927 Intron 8, Transcript NM_000927 Intron 10, Transcript NM_000927 Exon 25, Transcript NM_000927 Exon 29
OPRM1	6	74	100	-	-
COMT	22	28		19,938,573-19,938,580	Transcript NM_001135161 Exon 1

*One pair of probes designed to target each amplicon

The average cluster density and clusters passing filter were 1 159 k/mm^2 ± 290 and 86.5% ± 5.02, respectively. Positive and negative controls performed as expected. After application of a 10X locus read-depth threshold, 8 546 SNVs from *UGT2B7*, *ABCB1*, *OPRM1* and *COMT* were used for feature selection and t-MP and T:M1 prediction with an average locus read-depth of 16.4X ± 3.60.

Single Nucleotide Variants

Raw .vcf files were analyzed in VCFtools to generate population genetic summary statistics based on a minimum read-depth threshold of 10X. The average alternate allele frequency of 8 546 SNVs was 0.0300 ± 0.0876. After Bonferroni correction ($p_{adj\_heterozygous\_loci}$

= 3.59 x 10^{-5}; ~70 deviations expected due to chance alone), 8 loci significantly deviated from expectations of Hardy-Weinberg Equilibrium (NC_000004.11:g.69964180C>T, NC_000004.11:g.69978750C>T, NC_000006.11:g.154414563A>G, NC_000006.11:g.154414573C>T, NC_000006.11:g.154428702A>C, NC_000007.13:g.87178626C>T, NC_000007.13:g.87180198A>C, and NC_000022.10:g.19956781G>A), all of which exhibited significant excess heterozygosity in this Finnish population. This suggests that there was relatively little population substructure in this cohort (mean difference between observed and expected heterozygotes of 30.2 ± 8.16).

Linkage disequilibrium (LD) was evaluated in VCFtools using the genotype pairs from SNVs within *UGT2B7*, *ABCB1*, *OPRM1*, *COMT*, and *CYP2D6* (N = 10 421). Note that *CYP2D6* genotype data used in this study are those generated by Wendt, *et al.* (19) for a subset of the 208 Finns (N = 44) described here and are not analyzed independently herein. A total of 2 252 significant pairwise LDs between SNVs in different genes was observed (p_{adj} = 9.21 x 10^{-10}); of these, 8 SNV pairs had ≥ 25 individuals (i.e., 50 alleles) contributing to the LD pattern with r^2 values ≥ 0.65 (Table 2; mean r^2 = 0.957 ± 0.122).

Table 2. Significant pairwise linkage disequilibria (LD; p_{adj} < 9.21 x 10^{-10}) between single nucleotide variants (SNVs) in different genes of interest for only those pairs of SNVs with at least 25 genotypes (i.e., 50 alleles) contributing to the LD pattern and r^2 values ≥ 0.65.

Locus 1 (hg19/GRCh37)	rs Number (Locus 1)	Locus 2 (hg19/GRCh37)	rs Number (Locus 2)	r^2
NC_000004.11:g.69962282G>A	-	NC_000006.11:g.154360666C>T	rs199648369	0.656
NC_000004.11:g.69978303C>G	-	NC_000007.13:g.87214698A>G	-	1
NC_000004.11:g.69962733C>T	-	NC_000006.11:g.154412616T>A	-	1
NC_000004.11:g.69962733C>T	-	NC_000006.11:g.154360678C>A	rs1297476429	1
NC_000004.11:g.69962676C>T	rs14712761	NC_000007.13:g.87224929T>C	-	1
NC_000004.11:g.69963152T>C	rs1386213886	NC_000007.13:g.87214721G>A	-	1
NC_000004.11:g.69963152T>C	rs1386213886	NC_000006.11:g.154412881A>C	-	1
NC_000004.11:g.69962733C>T	-	NC_000007.13:g.87224962 T>C	-	1

Individual SNVs were correlated with T:M1 using Pearson's correlation (Figure 1A) with genotype imputation for missing loci. After correction for multiple testing (p_{adj}=2.42 x 10^{-6}), 14 SNVs were significantly associated with the rate of tramadol O-demethylation (Table 3). Two pairs of loci exhibited significant LDs (NC_000007.13:g.87229006T>G/NC_000022.10:g.19938432G>A [N=164 and 147 genotypes, respectively] and NC_000004.11:g.69972849T>C/ NC_000022.10:g.19938432G>A [N=150 and 147 genotypes, respectively]).

The heritability (h^2) of t-MP and T:M1 was inferred using the `--reml` command in GATK with individual and pairwise combinations of two, three, four, and all five genes (Figure 1B). In general, the variability of t-MP was poorly explained regardless of gene or gene combination. However, after correction for multiple testing (p_{adj} = 0.00161), the SNVs from *UGT2B7* ($h^2_{T:M1}$ = 0.821; p = 1.22 x 10^{-6}) and the combination of SNVs from *CYP2D6/UGT2B7* ($h^2_{T:M1}$ = 0.786; p = 4.04 x 10^{-4}) significantly explained relatively large proportions of the variation in T:M1 with relatively little error (0.0594 and 0.0758 for *UGT2B7* and *CYP2D6/UGT2B7*, respectively).

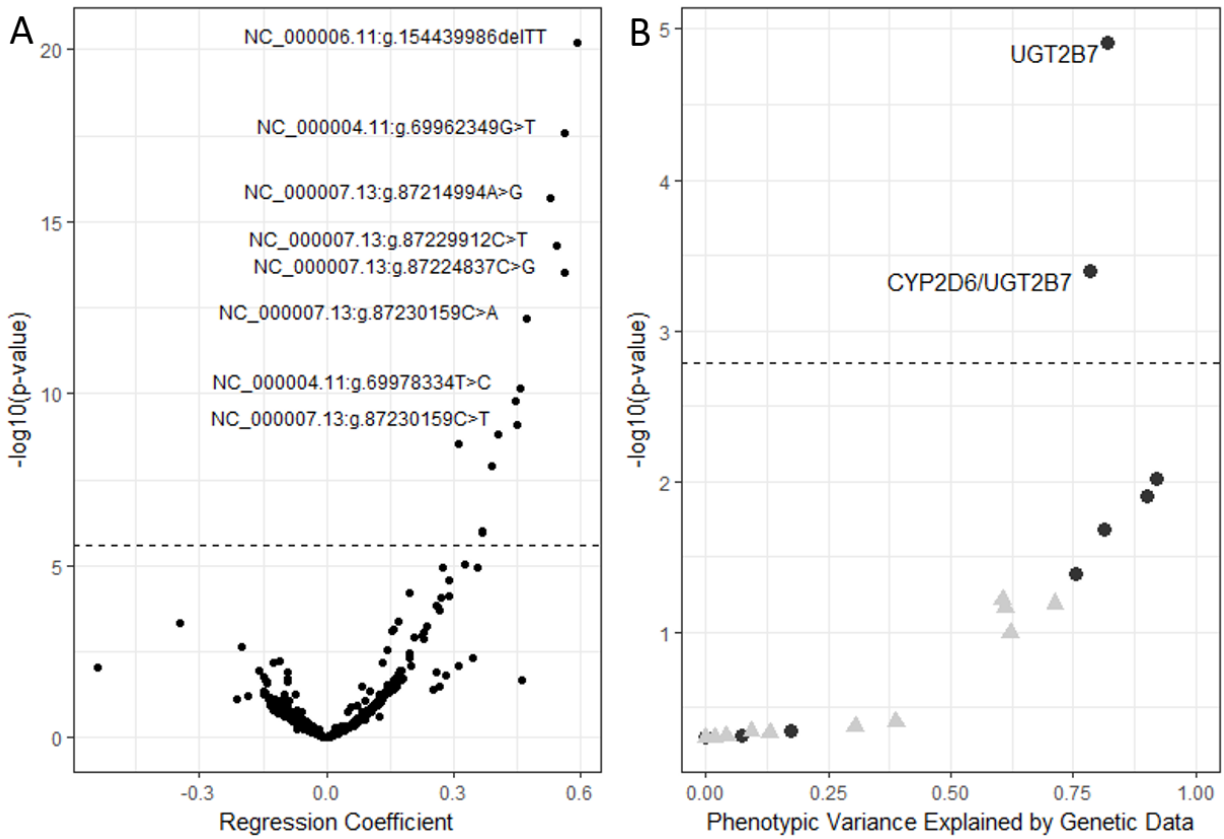

Figure 1. (A) Association between the tramadol to O-desmethyltramadol ratio (T:M1) for individual genotypes at *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*. A dashed horizontal line indicates the threshold for significance after correction for multiple testing ($-\log_{10}(p_{adj}) = 5.62$); loci are labeled if they exceed the significance threshold and have regression coefficients ≥ 0.45 (arbitrarily selected to avoid locus label overlap). (B) Heritability summary of restricted maximum likelihood (`--reml` in GCTA) analyses, with the first 20 eigenvectors as covariates, of the T:M1 (solid black circles) and the associated toxicologically-inferred metabolizer-phenotype (t-MP; solid grey triangles) phenotypes. A dashed horizontal line indicates the threshold for significance after correction for multiple testing ($-\log_{10}(p_{adj}) = 2.79$); two data points are labeled, indicating that the individual (*UGT2B7*) and combined (*CYP2D6*/*UGT2B7*) genotype information significantly explained a relatively high proportion of phenotypic variance.

Table 3. Relevant locus information for fourteen loci significantly associated with the tramadol to O-desmethyltramadol ratio (T:M1) in 208 autopsied individuals from a Finnish population sample.

Chr (Gene)	rs	hg19/GRCh37	cDNA Position	hg38/GRCh38	cDNA Position	Δ Base (Ref>Alt)	Δ Amino Acid	Pearson's r ± s.e. (95% CI)	p	CADD (Phred)	SIFT (Score)	PolyPhen (Score)
4 (*UGT2B7*)	rs1255338508	NC_000004.11:g.69962349	XM_005265702.1:c.-26-1909; NM_001074.2:c.111	NC_000004.12:g.69096631	NM_001074.3:c.111; NM_001330719.1:c.111; XM_011532229.2:c.111	G>T	M>I	0.563 ± 0.0585 (0.448-0.678)	2.56×10^{-18}	0.00400	Tolerated (0.990)	Benign (0.0100)
4 (*UGT2B7*)	-	NC_000004.11:g.69978334	XM_005265702.1:c.723; NM_001074.2:c.1470	NC_000004.12:g.69112616	NM_001074.3:c.1470; NM_001330719.1:c.*140	T>C	S>S	0.458 ± 0.0661 (0.328-0.587)	7.09×10^{-11}	0.00500	-	-
4 (*UGT2B7*)	-	NC_000004.11:g.69972849	XM_005265702.1:c.256-44; NM_001074.2:c.1003-44	NC_000004.12:g.69107131	-	T>C	Intron	0.367 ± 0.0720 (0.226-0.508)	1.02×10^{-6}	1.01	-	-
6 (*OPRM1*)	-	NC_000006.11:g.154439986	NM_001008503.1:c.1164+27379; NM_000914.3:c.*130; NM_001145287.1:c.*130; XM_005267003.1:c.*130	NC_000006.12:g.154118851	NM_001145279.3:c.*130; NM_001145280.3:c.*130; NM_001145281.2:c.*130; NM_000914.4:c.*130; NM_001285522.1:c.*165; NM_001285524.1:c.*130; XM_017010906.2:c.*130; NM_001145287.2:c.*130; NM_001285526.1:c.*130	delTT	-	0.593 ± 0.0564 (0.483-0.704)	6.08×10^{-21}	9.00	-	-
7 (*ABCB1*)	-	NC_000007.13:g.87214994	NM_000927.4:c.120	NC_000007.14:g.87585678	NM_001348944.1:c.120; NM_000927.4:c.120; NM_001348945.1:c.330; NM_001348946.1:c.120	A>G	F>F	0.531 ± 0.0593 (0.415-0.647)	1.97×10^{-16}	15.7	-	-
7 (*ABCB1*)	-	NC_000007.13:g.87229912	NM_000927.4:c.-7+159	NC_000007.14:g.87600596	-	C>T	-	0.544 ± 0.0633 (0.420-0.668)	4.71×10^{-15}	11.4	-	-
7 (*ABCB1*)	-	NC_000007.13:g.87224837	NM_000927.4:c.117+245	NC_000007.14:g.87595521	-	C>G	-	0.562 ± 0.0587 (0.447-0.677)	3.07×10^{-24}	2.46	-	-
7 (*ABCB1*)	-	NC_000007.13:g.87230159	NM_000927.4:c.-95	NC_000007.14:g.87600843	NM_000927.4:c.-95; NM_001348946.1:c.-95	C>A	-	0.473 ± 0.0616 (0.352-0.593)	6.8×10^{-13}	13.1	-	-
7 (*ABCB1*)	rs569567574	NC_000007.13:g.87178819	NM_000927.4:c.1570	NC_000007.14:g.87549503	NM_001348944.1:c.1570; NM_000927.4:c.1570; NM_001348945.1:c.1780; NM_001348946.1:c.1570	C>T	V>I	0.446 ± 0.0659 (0.317-0.575)	1.66×10^{-10}	28.3	Deleterious (0)	Probably Damaging (0.878)
7 (*ABCB1*)	rs1380760525	NC_000007.13:g.87229006	NM_000927.4:c.68+427	NC_000007.14:g.87599690	-	T>G	-	0.452 ± 0.0692 (0.316-0.587)	7.73×10^{-10}	0.747	-	-
7 (*ABCB1*)	-	NC_000007.13:g.87179532	NM_000927.4:c.1305	NC_000007.14:g.87550216	NM_001348944.1:c.1305; NM_000927.4:c.1305; NM_001348945.1:c.1515; NM_001348946.1:c.1305	T>C	T>T	0.405 ± 0.0639 (0.280-0.530)	1.52×10^{-9}	0.0330	-	-
7 (*ABCB1*)	-	NC_000007.13:g.87135183	NM_000927.4:c.3636+30	NC_000007.14:g.87505867	-	A>G	-	0.311 ± 0.0475 (0.218-0.404)	2.75×10^{-9}	9.01	-	-
7 (*ABCB1*)	-	NC_000007.13:g.87179342	NM_000927.4:c.1379	NC_000007.14:g.87550026	NM_001348944.1:c.1379; NM_000927.4:c.1379; NM_001348945.1:c.1589; NM_001348946.1:c.1379	G>T	T>N	0.390 ± 0.0656 (0.261-0.518)	1.29×10^{-8}	18.8	Tolerated (0.0900)	Benign (0.0217)
22 (*COMT*)	-	NC_000022.10:g.19938432	-	NC_000022.11:g.19950909	-	G>A	-	0.367 ± 0.0726 (0.225-0.510)	1.14×10^{-6}	1.28	-	-

Predicting t-MP

Predictions of t-MP and T:M1 were performed in two phases: 1) classification of MP using combined unphased genotype data from *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, and 2) classification with computationally phased genotypes from the same four genes. In general, unphased genotypes predicted t-MP and T:M1 variables with less accuracy and lower correlation coefficients than the phased genotype models. The results presented herein focus on predictions of t-MP and T:M1 using phased genotype data.

The 208 tramadol-exposed individuals of Finnish ancestry used for classification represent five classes of t-MP. Using three supervised machine learning models, t-MP prediction accuracies were relatively low with mean accuracies of 19.2% ± 39.7 (RF), 20.4% ± 23.0 (1NN), and 25.2% ± 15.6 (RMLR) which are not better than random chance (20.9%, 10%-trimmed mean). These accuracies represent poor prediction of all five t-MPs, with lack of a true positive prediction for the t-IM and t-PM categories in all three models. Overall, the RMLR classifier predicted t-MP with significantly higher accuracies than the 1NN or RF classifiers ($p < 0.001$).

Feature selection was used to evaluate classification accuracies as a reduced number of SNVs are provided for each model. The models were evaluated with features used in >0%, >12%, >25%, >50%, and >75% of cross-validation folds (Figure 2). Classification accuracies generally increased for all five t-MP categories with the RMLR classifier outperforming the LR and 1NN models. RMLR predicted the t-MP variable with mean accuracies for t-UM, t-NM-F, t-NM-S, and t-IM that were 1.22- (25.6% ± 2.19), 3.35- (70.1% ± 2.38), 2.64- (55.2% ± 4.47) and 2.01-fold (42.0% ± 2.74) greater than random chance (20.9%; 10%-trimmed mean), respectively. Note that t-PMs were not reliably predicted with any algorithm.

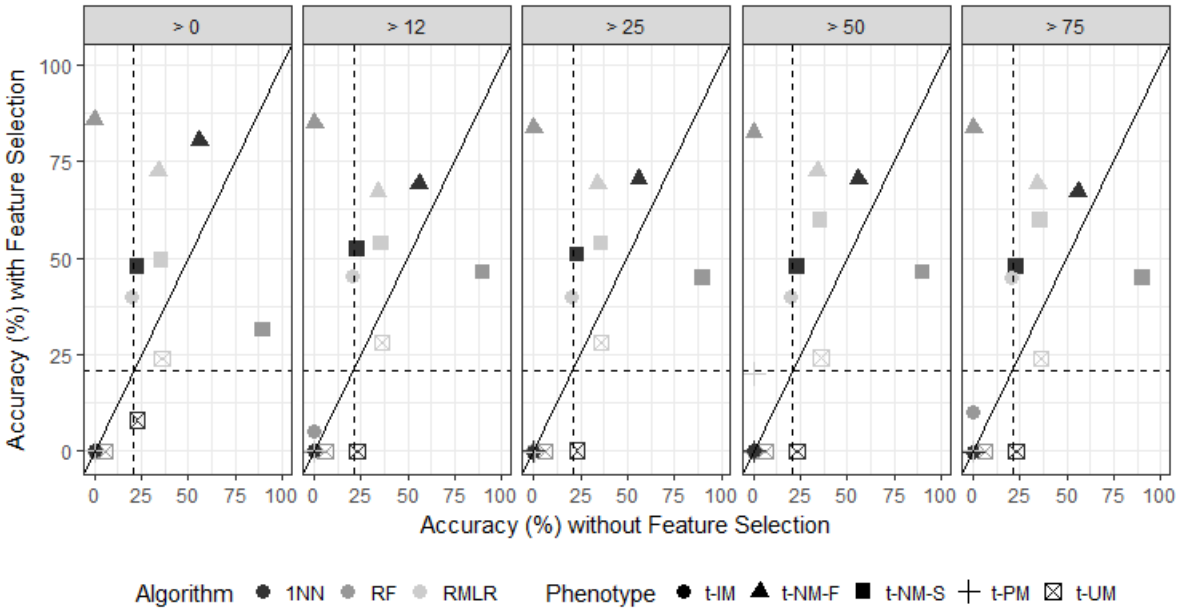

Figure 2. Summary of machine learning classification accuracies for four metabolizer phenotype clusters (t-UM = ultra-rapid; t-NM-F = normal/extensive [fast]; t-NM-S = normal/extensive [slow]; and t-IM = intermediate) using phased *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* data aligned to the hg19/GRCh37 reference genome for varying feature selection stringencies (features used in greater than 0%, 12%, 25%, 50%, and 75% of cross-validation folds) compared to the accuracy of the model using all genotype data from *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*. Three machine learning algorithms are depicted: 1-nearest neighbor (1NN), random forest (RF), and regularized multinomial logistic regression (RMLR); dashed lines represent the average predictive accuracy due to random chance (20.9%; 10%-trimmed mean).

Wendt, *et al.* (19) previously described t-MP classification using *CYP2D6* alone. That study analyzed a subset of the current sample set (N = 44/208 individuals) which had genetic data for a fully comprehensive t-MP prediction. Note that because of limited sampling, this cohort represented only four MP categories (i.e., t-PMs were not observed) and used 43-fold cross validation. Using a comprehensive, pathway-driven model with all 10 421 SNVs from *CYP2D6* (19), *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, performance of the RF, 1NN, and RMLR classifiers modestly increased to 27.3%, 27.3%, and 20.5%, respectively. Feature selection increased these classification accuracies with the RMLR classifier again

outperforming the 1NN and RF models in overall accuracy (mean of 60.6% ± 19.1 overall; 61.5% for t-UM, 75.0% for t-NM-F, 72.7% for t-NM-S, and 33.3% for t-IM; Figure 3A). Relative to the *CYP2D6* predictions, the pathway-driven model using *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* together provided significantly higher classification accuracies for t-MP ($p = 0.0190$; paired t-test). The maximum classification accuracy reached 93.8% using only 16 SNVs.

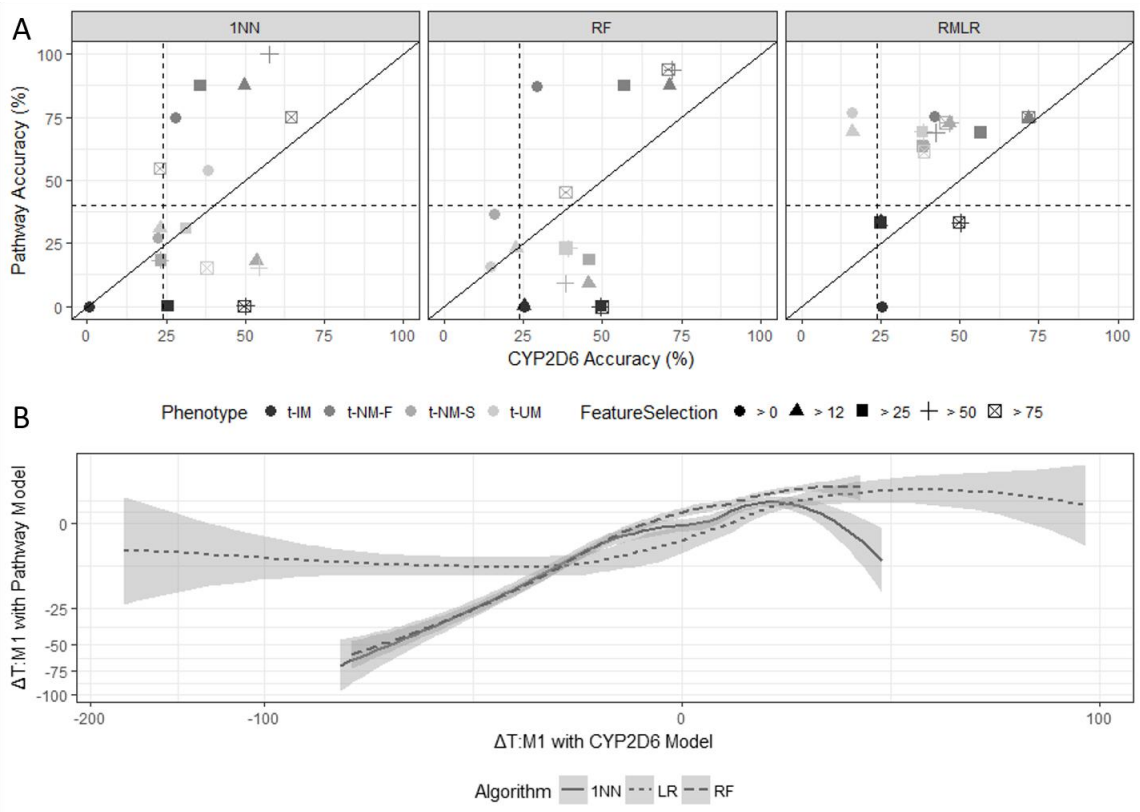

Figure 3. Summary of machine learning classification accuracies for metabolizer phenotype (t-UM = ultra-rapid; t-NM = normal/extensive, and t-IM = intermediate; panel A) and the tramadol to O-desmethyltramadol ratio (T:M1; panel B) using phased *CYP2D6* (unpublished data), *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* data aligned to the hg19/GRCh37 reference relative to using *CYP2D6* alone. In panel A, varying feature selection stringencies (i.e., features used in greater than 0%, 12%, 25%, 50%, and 75% of cross-validation folds) and supersized machine learning algorithms (i.e., 1-nearest neighbor (1NN), random forest (RF), and regularized multinomial logistic regression (RMLR)) were used.; dashed lines represent the average predictive accuracy due to random chance (39.9% for pathway model and 23.8% for *CYP2D6* model; 10%-trimmed mean). Note the cube root scale in panel B with standard error shown in grey shading along the length of each robust linear regression.

Predicting T:M1

Supervised machine learning was performed on the T:M1 outcome variable in the same manner as t-MP except that the LR classifier was used instead of RMLR. The average difference between actual and predicted T:M1 (ΔT:M1) using 8,546 phased SNVs from *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* was -1.54 ± 17.6, indicating overall underestimation of T:M1. The 1NN classifier underestimated T:M1 with significantly greater magnitude than the RF and LR classifiers ($p < 1 \times 10^{-20}$) with mean ΔT:M1 of -5.89 ± 18.9 (1NN), 0.191 ± 19.0 (LR), and -0.581 ± 18.8 (RF).

The same five feature inclusion thresholds were evaluated for the T:M1 variable (Figure 4). Overall, T:M1 was modestly predicted regardless of feature-inclusion stringency or supervised machine learning algorithm used. The average correlation coefficients between actual and predicted T:M1 were not significantly different regardless of feature-inclusion stringency; however, the correlation coefficients from the LR classifier ($r^2 = 0.113 \pm 0.0212$) were significantly lower than those of the 1NN ($r^2 = 0.277 \pm 0.0520$) and RF ($r^2 = 0.284 \pm 0.0307$) classifiers. The maximum observed correlation coefficient was 0.383 with the 1NN classifier.

T:M1 predictions with *CYP2D6* alone and the pathway-driven model were evaluated. For 44 samples and the full set of genotype data without feature selection ($N_{SNVs} = 10\ 421$), the pathway-driven model (mean ΔT:M1 -1.35 ± 12.8) yielded a significantly lower ΔT:M1 than the *CYP2D6* model (mean ΔT:M1 = -6.79 ± 34.9; p = 0.0293). This observation was especially true for the LR classifier ($\Delta T{:}M1_{pathway} = -0.101 \pm 12.3$ and $\Delta T{:}M1_{CYP2D6} = -20.1 \pm 56.2$) which had a significantly decreased ΔT:M1 with the pathway-driven model ($p < 0.01$). Note that the 1NN classifier performed less well with pathway-driven data (ΔT:M1 = -4.40 ±

13.6) relative to the *CYP2D6* data (ΔT:M1 = -1.10 ± 14.3). This observation holds true for the LR classifier using the >12%, >25%, >50%, and >75% feature inclusion thresholds with significant improvements of the pathway-driven models relative to the equivalent feature-inclusion model using *CYP2D6* alone ($p < 0.00330$).

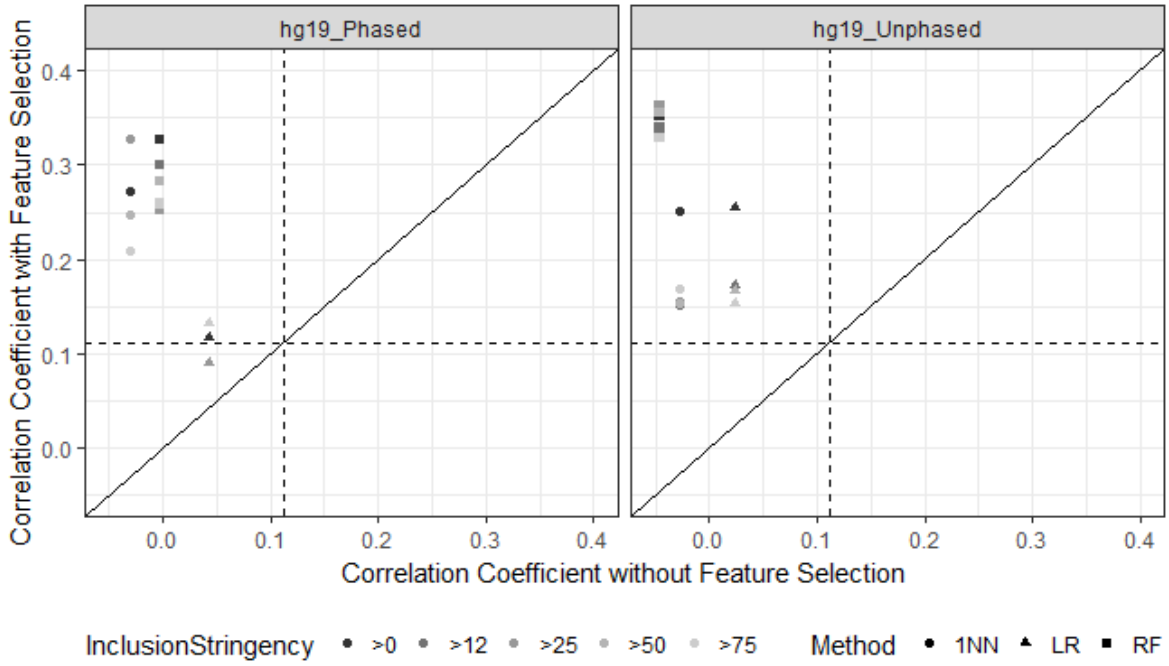

Figure 4. Summary of tramadol O-demethylation (T:M1 ratio) predictions using three supervised machine learning algorithms (1-nearest neighbor [1NN], linear regression [LR], and random forest [RF]) and five feature-inclusion criteria (i.e., features included in > 0%, > 12%, > 25%, > 50%, and > 75% of cross-validation folds) relative to the prediction using genotype data from 8,546 loci in *UGT2B7*, *OPRM1*, *ABCB1*, and *COMT* for phased and unphased hg19/GRCh37 data. The dashed lines represent the average predictive accuracy due to random chance (0.112; 10%-trimmed mean). The individual data points contributing to these correlation coefficients are shown in Figure S1.

Discussion

This study evaluated a combinatorial, pathway-driven pharmacogenetic model of tramadol O-demethylation using a custom TSCA Low Input library preparation panel targeting the exons of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*, which are responsible for various stages of tramadol ADME-R. Note that while exons were targeted for panel design, optimization of amplicon size involved capturing some intronic loci. While not specifically interrogated here, there are intronic, promoter, enhancer, and/or silencer SNVs that have been implicated in variable gene expression, splicing, and/or post-translational modifications that need to be explored further to develop fully pathway-driven models of drug-specific and drug-class ADME-R.

Fourteen SNVs were significantly associated with T:M1; however, only one of these (NC_000007.13:g.87178819C>T) was predicted to alter protein function by causing a valine to isoleucine amino acid change adjacent to the ATP-binding cassette signature sequence, between the signature and Q-loop. This locus was observed with an allele frequency of 0.000200 in the 1kGP (South Asian super-population only) but was not present in the Sequencing Initiative Suomi (SISu; Finnish population only; see Sequencing Initiative Suomi project (SISu), Institute for Molecular Medicine Finland, University of Helsinki, Finland. URL: http://sisuproject.fi [SISu v4.1, May, 2018]). Combined Annotation Dependent Depletion (CADD) indicates this locus as one of the top 0.1-1% most deleterious substitutions in the human genome with SIFT and PolyPhen-v2 providing agreeable predictions (33-35). Its position within the binding pocket of ABCB1 is quite close to cross linked regions of the domain; though charge is not disrupted by the change of valine to isoleucine, the extra methyl

group of isoleucine may sterically hinder appropriate cross-linking between nucleotide binding domains 1 and 2 (refs. 36-38).

The t-MP variable was relatively poorly explained by the genetic data from *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* (10 421 SNVs) with restricted maximum likelihood analysis for all combinations of genes (i.e., singlets, pairs, trios, etc.). Interestingly, T:M1 was highly explained by genetic variation at *UGT2B7* and the combination of *UGT2B7-CYP2D6*, which was likely an artifactual inflation of the poor explanation of T:M1 by *CYP2D6* relative to *UGT2B7*. This is an interesting observation since *CYP2D6* data alone are routinely relied upon for predicting drug response. *CYP2D6* information is typically used as a predictor for the ratio of drug concentration to active metabolite concentration (1,4,5,39,40), thereby guiding safer first-pass drug doses in place of solely trial-and-error. While CYP2D6 is considered a front-end indicator of drug to metabolite ratio, UGT2B7 is responsible for efficient glucuronidation of the metabolite, facilitating its biliary excretion. Increased or decreased activity of UGT2B7 may be associated with fast or slow excretion of a metabolite, respectively, influencing patient outcomes (i.e. slow glucuronidation of morphine via UGT2B7 may result in accumulation of morphine and its associated toxicity). The data herein suggest that *UGT2B7* may serve as an equally, or more, informative back-end indicator of the same phenotype predicted frequently by *CYP2D6*.

Three supervised machine learning algorithms were used to predict t-MP and T:M1. In general, t-MP was predicted well using the combination of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* genotype information. Classification accuracies were especially high for the t-NM-F and t-NM-S categories, demonstrating reliable detection of normal versus non-normal metabolizers. Predicting the direction of non-normality was less successful; however, the

highest feature inclusion stringency increased classification accuracies of the t-UM, t-IM, and t-PM categories. Overall, t-PM was poorly predicted with these SNVs using all three models. It is important to note that this MP is regularly characterized by a variety of structural aberrations and while SNV predictions may have been poor, large cohorts of known PMs may enable SNV models in the absence of structural information. T:M1 was poorly predicted using the three selected algorithms; however, predicting this outcome variable was noticeable, and significantly, algorithm dependent. While using multiple machine learning algorithms and feature inclusion criteria may be seen as biased, this approach may be beneficial for future application and possible best practices for clinical implementation of predictive models based on genotyping approaches. The data presented using a pathway-driven predictive model of tramadol ADME-R demonstrated clear algorithm differences with the RF and 1NN classifiers exhibiting the highest correlation coefficients between predicted and actual T:M1. While the RF classifier produced some of the highest t-MP prediction accuracies, it failed to reliably predict the extreme categories (i.e., t-PM, t-IM, and t-UM); on the other hand, the RMLR classifier predicted t-MP quite well across a range of categories.

A subset of samples were assayed in a truly combinatorial fashion, with full genotype data for *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*. By applying the RMLR, 1NN, RF, and LR classifiers to this subset of samples, it was demonstrated that a pathway-driven model of tramadol ADME-R more accurately predicts outcome than a *CYP2D6*-driven model. The predictive models presented here for T:M1 and t-MP achieved high accuracies depending on category and algorithm used; however, the power of this approach is represented by the number of loci used to predict either outcome variable. Relative to a model using 10,421 SNVs (maximum accuracy of 68.8%), t-MP can be predicted with up to 93.8% accuracy using 16

SNVs (651-fold reduction in SNVs) and T:M1 can be predicted with a correlation coefficient up to 0.329 with 33 SNVs (316-fold reduction in SNVs; Table 4).

A pathway-driven predictive model was applied to tramadol ADME-R in this study and similar approaches can be applied to other opioids or the general opioid analgesic drug class. It is likely that a more broadly applicable predictive model will employ supplementary DNA elements (i.e., introns, promoters, enhancers, silencers, distant regulatory elements, etc.), and the data described here demonstrate feasibility of pathway-driven models such that additional DNA elements may be explored and exploited for development of relatively small, accurate, and easily implemented MPS library preparation kits for clinical application of drug response models.

Table 4. Relevant locus information for 16 and 33 loci used to predict the tramadol to O-desmethyl tramadol ratio (T:M1) and the toxicologically-inferred metabolizer phenotype (t-MP) at the most stringent feature inclusion threshold (i.e., all listed single nucleotide variants were used in >75% of supervised machine learning cross-validation folds).

Gene	Position	Coding DNA Position	rs Number	Base Change	Amino Acid Change	CADD	SIFT	PolyPhen-v2	Used to Predict
UGT2B7	NC_000004.11:g.69962282	NM_001074.2:c.44	-	G>A	-	0.135	Tolerated (0.110)	Benign (0.0310)	T:M1
UGT2B7	NC_000004.11:g.69962349	NM_001074.2:c.111	rs1255338508	G>T	Met>Ile	0.004	Tolerated (1.00)	Benign (0.0750)	T:M1
UGT2B7	NC_000004.11:g.69962583	NM_001074.2:c.345	rs1453130551	C>T	-	7.24	-	-	T:M1
UGT2B7	NC_000004.11:g.69962586	NM_001074.2:c.348	rs772560918	G>C	Met>Ile	0.121	Tolerated (0.385)	Benign (0.00300)	T:M1
UGT2B7	NC_000004.11:g.69962610	NM_001074.2:c.372	rs28365063	A>G	Arg>Ser	0.009	-	-	t-MP
UGT2B7	NC_000004.11:g.69964232	NM_001074.2:c.722-726	-	A>C	-	2.37	-	-	T:M1
UGT2B7	NC_000004.11:g.69978319	NM_001074.2:c.1455	-	G>A	Trp>Stop	36	-	-	T:M1
UGT2B7	NC_000004.11:g.69978334	NM_001074.2:c.1470	-	T>C	Ser>Ser	0.005	-	-	T:M1
OPRM1	NC_000006.11:g.154360666	NM_001145279.2:c.266	rs199648369	C>T	Pro>Leu	21.4	Deleterious (0)	Benign (0)	t-MP
OPRM1	NC_000006.11:g.154407705	NM_001145279.2:c.570-3256	rs101840062	insT	-	1.25	-	-	t-MP
OPRM1	NC_000006.11:g.154408673	NM_001145279.2:c.570-2288	-	C>T	-	5.66	-	-	T:M1
OPRM1	NC_000006.11:g.154412242	NM_001145279.2:c.1078	-	delT	Leu>New ReadingFrame	34	-	-	T:M1
OPRM1	NC_000006.11:g.154412881	NM_001145279.2:c.1443+274	-	A>C	-	4.67	-	-	T:M1
OPRM1	NC_000006.11:g.154414312	NM_001145279.2:c.1443+1705	-	T>C	-	4.57	-	-	t-MP
OPRM1	NC_000006.11:g.154414459	NM_001145279.2:c.1443+1852	-	G>A	Val>Met	3.27	Deleterious (0.0400)	Benign (0.00300)	t-MP
OPRM1	NC_000006.11:g.154414611	NM_001145279.2:c.1443+2004	rs200646591	G>A	-	5.17	-	-	T:M1
OPRM1	NC_000006.11:g.154414678	NM_001145279.2:c.1443+2071	-	G>A	-	14.8	-	-	t-MP
OPRM1	NC_000006.11:g.154428905	NM_001145279.2:c.1444-10913	rs1357614491	C>A, C>T	Ala>Asp	2.99	Deleterious (0)	Benign (0.00900)	t-MP
OPRM1	NC_000006.11:g.154429085	NM_001145279.2:c.1444-10733	rs1319935018	insT	-	0.796	-	-	T:M1
OPRM1	NC_000006.11:g.154430035	NM_001145279.2:c.1444-9783	-	A>T	-	0.162	-	-	T:M1
OPRM1	NC_000006.11:g.154439693	NM_001145279.2:c.1444-125	-	G>A	-	1.01	-	-	t-MP
OPRM1	NC_000006.11:g.154439699	NM_001145279.2:c.1444-119	-	C>T	-	2.38	-	-	T:M1
OPRM1	NC_000006.11:g.154439986	NM_001145279.2:c.*130	-	delTT	-	9	-	-	T:M1
OPRM1	NC_000006.11:g.154440143	NM_001145279.2:c.*287	-	delA	-	9.15	-	-	T:M1
OPRM1	NC_000006.11:g.154440379	NM_001145279.2:c.*523	rs1252162127	T>A	-	9.57	-	-	T:M1
OPRM1	NC_000006.11:g.154567680	NM_001130699.1:c.246+45	rs766006523	C>G	-	6.36	-	-	T:M1
ABCB1	NC_000007.13:g.87138569	NM_000927.4:c.3489+22	-	G>A, G>C, G>T	-	1.84	-	-	t-MP
ABCB1	NC_000007.13:g.87144642	NM_000927.4:c.3187	rs761914266	C>A	Gly>Cys	35	Deleterious (0)	Probably Damaging (0.996)	t-MP
ABCB1	NC_000007.13:g.87144644	NM_000927.4:c.3185	-	T>C	Lys>Arg	17.5	Tolerated (0.185)	Benign (0.0250)	T:M1
ABCB1	NC_000007.13:g.87165761	NM_000927.4:c.2481+13	-	A>C	-	2.39	-	-	t-MP
ABCB1	NC_000007.13:g.87175444	NM_000927.4:c.1726-104	-	C>T	-	9.3	-	-	T:M1
ABCB1	NC_000007.13:g.87178819	NM_000927.4:c.1570	-	C>T	Val>Ile	28.3	Deleterious (0)	Probably Damaging (0.818)	T:M1
ABCB1	NC_000007.13:g.87179086	NM_000927.4:c.1554+81	rs2235035	G>A	-	0.167	-	-	t-MP
ABCB1	NC_000007.13:g.87179342	NM_000927.4:c.1379	-	G>T	Thr>Asn	18.8	Tolerated (0.0900)	Benign (0.0165)	T:M1
ABCB1	NC_000007.13:g.87179361	NM_000927.4:c.1360	-	C>T	Asp>Asn	32	Deleterious (0.0100)	Probably Damaging (0.782)	T:M1
ABCB1	NC_000007.13:g.87179532	NM_000927.4:c.1305	-	T>C	Thr>Thr	0.033	-	-	T:M1
ABCB1	NC_000007.13:g.87183652	NM_000927.4:c.828-404	rs5885589	insA, insAA, insAAA, insAAAAA	-	3.26	-	-	t-MP
ABCB1	NC_000007.13:g.87214505	NM_000927.4:c.286+323	-	A>C, A>T	-	1.04	-	-	t-MP
ABCB1	NC_000007.13:g.87214740	NM_000927.4:c.286+88	-	G>T	-	4.11	-	-	T:M1
ABCB1	NC_000007.13:g.87214994	NM_000927.4:c.120	-	A>G	Phe>Phe	15.7	-	-	T:M1
ABCB1	NC_000007.13:g.87229912	NM_000927.4:c.7+159	-	C>T	-	11.4	-	-	T:M1
ABCB1	NC_000007.13:g.87230159	NM_000927.4:c-95	-	C>A	-	13.1	-	-	T:M1
COMT	NC_000022.10:g.19929314	NM_006440.3:c.13	-	C>T	Ala>Thr	12.2	Deleterious (0.0600)	Benign (0.0618)	T:M1
COMT	NC_000022.10:g.19951173	NM_000754.3:c.374	rs759305975	G>A	Arg>His	25.2	Deleterious (0.0100)	Probably Damaging (1.00)	t-MP
COMT	NC_000022.10:g.19951174	NM_000754.3:c.375	rs1223964672	C>T	Arg>Arg	23.6	-	-	T:M1
COMT	NC_000022.10:g.19957537	NM_000754.3:c.*1278	-	G>A	-	10.1	-	-	T:M1
CYP2D6	NC_000022.10:g.42522312	NM_000106.5:c.*264	rs116390392	G>A	-	2.19	-	-	T:M1 & t-MP
CYP2D6	NC_000022.10:g.42528224	NM_000106.5:c.-1431	rs28588594	C>T	-	1.33	-	-	t-MP

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Supplementary Information

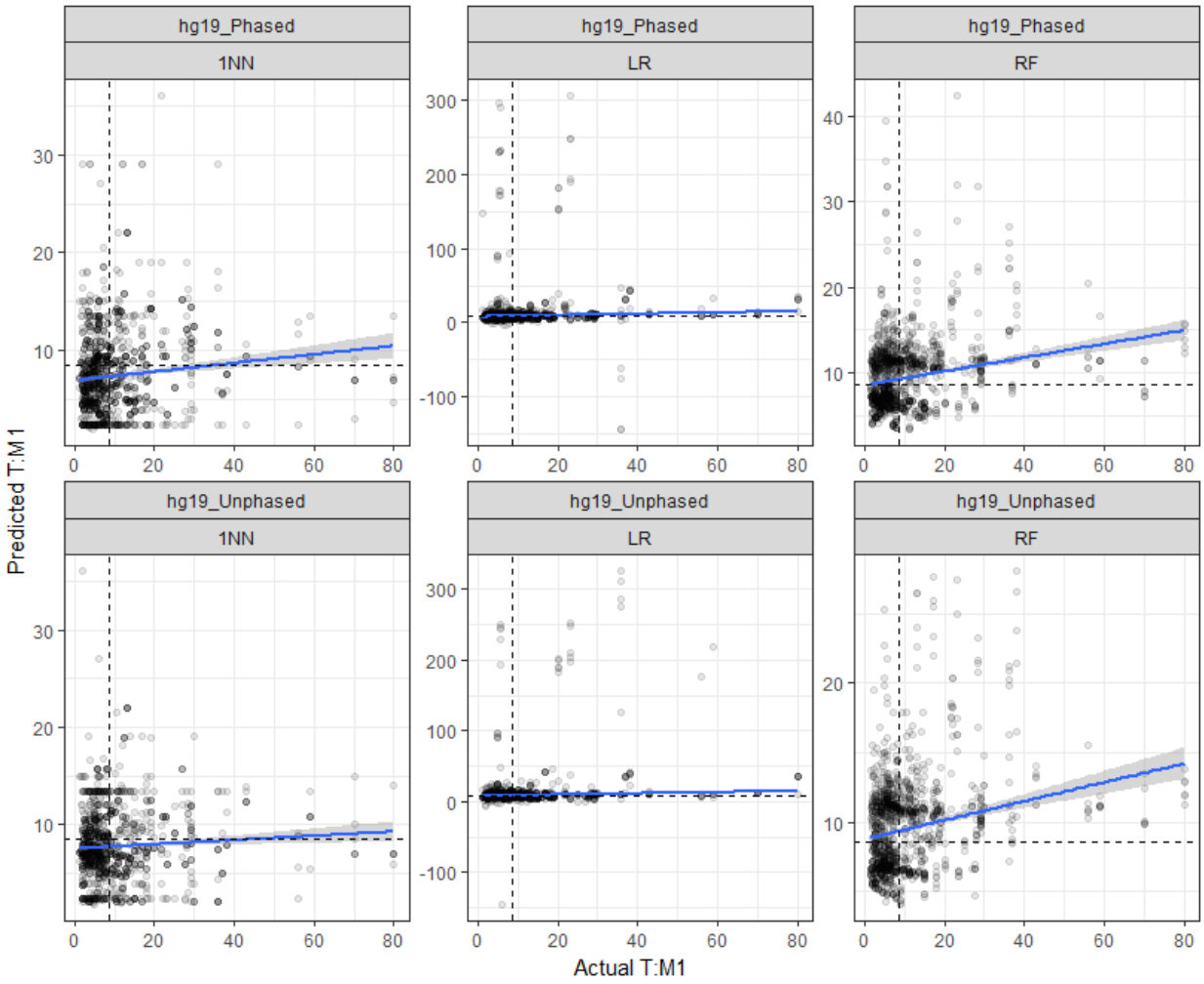

Figure S1. Summary of machine learning predicted tramadol:O-desmethyltramadol (T:M1) ratios using phased and unphased genotype data from *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* aligned to the hg19/GRCh37 reference genome for varying feature selection stringencies compared to the observed toxicologically determined T:M1 using three supervised machine learning algorithms (1-nearest neighbor [1NN], linear regression [LR], and random forest [RF]). The shading of data points is scaled to represent the relative abundance of data points; dashed horizontal and vertical lines represent the average prediction accuracy due to random chance (5.59; 10%-trimmed mean); solid diagonal lines represent the robust linear regression between the predicted and actual T:M1 with standard error represented by the grey shaded region surrounding each diagonal line.

Table S1. Amplicons Export file from Illumina TruSeq Custom Amplicon Design Studio. Each amplicon is given a unique identifier; amplicon information, including chromosome (Chr), start and stop positions relative to the hg19/GRCh37 reference genome, forward (F) or reverse (R) strand orientation, and total length, are listed; note that the "Avoid SNP" option was used for panel design.

Amplicon	Chr	Start Coordinate	Stop Coordinate	Length	Strand	Amplicon	Chr	Start Coordinate	Stop Coordinate	Length	Strand	Amplicon	Chr	Start Coordinate	Stop Coordinate	Length	Strand
190848108	4	69962058	69962227	170	R	190848131	6	154428795	154428966	172	F	190848157	7	87183606	87183780	175	R
190848104	4	69962168	69962338	171	F	190848139	6	154428903	154429072	170	R	190848156	7	87183726	87183898	173	F
190848109	4	69962256	69962425	170	R	190848132	6	154429009	154429181	173	F	190848123	7	87183968	87184157	190	R
190848105	4	69962342	69962511	170	F	190848140	6	154429121	154429291	171	R	190848124	7	87189779	87189963	185	R
190848110	4	69962448	69962618	171	R	190848133	6	154429229	154429400	172	F	190848020	7	87190524	87190693	170	R
190848106	4	69962560	69962729	170	F	190848141	6	154429341	154429511	171	R	190848019	7	87190636	87190816	181	F
190848111	4	69962656	69962825	170	R	190848134	6	154429455	154429627	173	F	190848125	7	87191641	87191811	171	R
190848107	4	69962772	69962942	171	F	190848142	6	154429569	154429738	170	R	190848126	7	87194992	87195174	183	R
190848112	4	69962888	69963061	174	R	190848135	6	154429681	154429851	171	F	190848042	7	87195353	87195535	183	R
190848120	4	69963142	69963320	179	R	190848143	6	154429791	154429973	183	R	190848041	7	87195481	87195655	175	F
190848146	4	69964025	69964208	184	R	190848136	6	154429921	154430109	189	F	190848158	7	87195822	87195993	172	R
190848145	4	69964153	69964329	177	F	190848144	6	154430053	154430229	177	R	190848049	7	87196064	87196245	182	R
190848147	4	69964275	69964444	170	R	190848189	6	154431353	154431528	176	R	190848048	7	87196188	87196366	179	F
190848101	4	69968490	69968675	186	R	190848188	6	154431463	154431649	187	F	190848127	7	87196567	87196737	171	R
190848100	4	69968620	69968803	184	F	190848095	6	154439687	154439856	170	R	190848161	7	87199148	87199331	184	R
190848114	4	69972838	69973008	171	R	190848091	6	154439805	154439974	170	F	190848159	7	87199272	87199442	171	F
190848113	4	69972954	69973130	177	F	190848096	6	154439891	154440060	170	R	190848162	7	87199382	87199556	175	R
190848103	4	69973784	69973970	187	R	190848092	6	154439979	154440148	170	F	190848160	7	87199502	87199678	177	F
190848102	4	69973914	69974084	171	F	190848097	6	154440073	154440242	170	R	190848167	7	87214141	87214311	171	R
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190848115	4	69978268	69978440	173	F	190848098	6	154440271	154440445	175	R	190848168	7	87214323	87214492	170	R
190848118	4	69978384	69978556	173	R	190848094	6	154440389	154440559	171	F	190848164	7	87214407	87214576	170	F
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190848119	4	69978624	69978810	187	R	190848191	6	154567638	154567812	175	R	190848165	7	87214607	87214777	171	F
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190847980	6	154331716	154331892	177	F	190848192	6	154567890	154568064	175	R	190848166	7	87214855	87215041	187	F
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190847981	6	154331958	154332132	175	F	190848043	7	87133242	87133423	182	F	190848173	7	87224402	87224578	177	R
190847984	6	154332078	154332250	173	R	190848046	7	87133368	87133557	190	R	190848172	7	87224520	87224690	171	F
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190848078	6	154408459	154408628	170	F	190848022	7	87170628	87170802	175	R	190848053	22	19938425	19938597	173	R
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190848130	6	154428571	154428742	172	F	190848153	7	87183162	87183337	176	F	190848069	22	19957334	19957522	189	R
190848138	6	154428685	154428854	170	R	190848155	7	87183282	87183466	185	R	190848062	22	19957464	19957633	170	F

Table S2. TruSeq Custom Amplicon Low Input manifest file for probes designed to target the exonic regions of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*. Table S2 is available at the publisher's website: https://www.nature.com/ejhg/.

PART 4

CONCLUSIONS

CHAPTER 7

A Genome-Wide Association Study of Tramadol Metabolism from Post-Mortem Samples

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Abstract

Tramadol is commonly prescribed to relieve moderate-to-severe pain. Phase I tramadol metabolism depends on cytochrome p450 family 2, subfamily D, polypeptide 6 (CYP2D6) to form O-desmethyltramadol (M1). CYP2D6 is an extensively studied pharmacogene, and clinically genetic variants may be used to infer patient metabolizer phenotype. However, drug ADME (absorption, distribution, metabolism, and excretion) depends on many functional and structural proteins in a pathway(s), not just a single protein. Though CYP2D6 function is well characterized, there is a paucity of data regarding whether trans-acting metabolic enzymes, if any, also may contribute to idiosyncratic phenotypes following drug exposure. A genome-wide association study was performed scanning ~2.6 million single nucleotide polymorphisms (SNPs) to identify loci associated with the rate of tramadol to M1 metabolism (M1:T). Five markers (rs79983226/kgp11274252, rs9384825, rs62435418/kgp10370907, rs72732317/kgp3743668 and rs184199168/exm1592932) were highly significantly associated with M1:T with the presence of the alternate allele resulting in decreased M1:T. Replication of these relationships was performed with targeted massively parallel sequencing and supported the relative trends observed in the genome-wide scan. These SNPs reside within five genes (RFPL4B/RNF211, KHDRBS3, HCN1, ICA1, and RGL4) previously implicated with adverse reactions. Analysis of toxicological meta-data accompanying each sample revealed a significant positive linear correlation between M1:T and sample polypharmacy, with M1:T increases in samples carrying the rs79983226/kgp11274252 alternate allele. Taken together, these data indicate five candidate loci for potential clinical inferences/predictions of metabolizer phenotype following exposure

to tramadol and possibly other opiates and highlight sample polypharmacy as a possible diagnostic covariate in post-mortem genetic studies.

Introduction

Tramadol is an opioid agonist, structurally and metabolically similar to codeine [1, 2], commonly prescribed to treat moderate to severe post-operative, dental, and/or musculoskeletal pain [1]. Typically administered orally as a racemic mixture of (+) and (-) tramadol, it is rapidly and almost completely absorbed and transported to the liver where it is converted to O-desmethyltramadol (M1) by the cytochrome p450 family 2 subfamily D, polypeptide 6 (CYP2D6). M1 is the most pharmacologically active metabolite of the parent drug, has significantly higher affinity for opioid receptors, and is a more potent analgesic [3, 4].

Genetic variants of CYP2D6 are routinely used to predict metabolizer phenotype (MP) of patients and have demonstrated value in autopsy-negative post-mortem investigations [5-8]. This gene has been extensively studied in many global, regional, and isolated populations [9-17]. These population genetic characterizations and predictive assessments of selected single nucleotide polymorphisms (SNPs) have enabled refinement of prescription doses. However, CYP2D6 is only part of the full ADME (absorption, distribution, metabolism, and excretion) process and therefore may inaccurately or incompletely predict metabolic state of some individuals [18, 19].

It has been demonstrated that a combined (i.e., multigene) and/or comprehensive (i.e., full-gene) approach to predicting MP may lead to more efficacious patient outcomes than a targeted monogenic approach [20-22]. Altar, *et al.* [20, 21] described a combinatorial predictive model for antidepressant response in the clinic and demonstrated increased patient outcomes over a single-gene model. It is reasonable to hypothesize that increased efficacy may be achieved with multigenic models of other drug response pathways. While tramadol is a

commonly prescribed opioid analgesic, which depends on the activity of CYP2D6, there is little understanding of which additional enzymes play a role in idiosyncratic responses following tramadol exposure and how polymorphisms in genes encoding trans-acting metabolism and/or response enzymes may associate or interact with those of CYP2D6.

Herein, an exploratory genome-wide association study was performed to identify additional, potentially predictive, biomarkers for inferring the rate of tramadol metabolism in Finns, a valuable medical genetic cohort. Correlations were made between genetic variations and the rate of tramadol to M1 metabolism (M1:T) in deceased Finns. Patient polypharmacy was explored as an additional covariate in post-mortem genetic testing. These results indicate potentially informative targets for refining clinical and post-mortem predictions of metabolic activity and thus patient responses to tramadol and/or ancillary data for inferring cause and/or manner of death in medico-legal investigations. They also demonstrate that, while difficult to control in such studies, patient polypharmacy may be another factor to consider when attempting to elucidate the complex genotype-environment-phenotype interactions that may impact cause and manner of death.

Materials and Methods

Subjects

Whole blood preserved on FTA® cards was obtained from a total of 37 deceased Finns (13 females and 24 males) between the ages of 13 and 91 (mean 52.3 ± 19.0) years of age with concentrations of tramadol and M1 in their blood and an associated autopsy-determined under the International Statistical Classification of Diseases (ICD) and Health Related Problems, 10th Revision code [23]. All subjects and associated toxicology data were collected according

to the ethical handling of human subject practices of the University of Helsinki. Anonymized DNA samples from each subject were transferred to University of North Texas Health Science Center (UNTHSC) and handled according to the UNTHSC Institutional Review Board Protocol Number 2016-051.

DNA Extraction and Quantitation

DNA was extracted from FTA cards using the QIAamp® DNA Investigator Kit and quantitated using the Quantifiler™ Trio DNA Quantification Kit according to their respective manufacturers' recommendations [24, 25]

Genome-Wide Genotyping and Image Acquisition

Genotyping was performed using the Illumina Infinium® LCG Assay [26] and Infinium® Omni2.5Exome-8 v1.3 BeadChip according to the manufacturer's recommended protocol. Template DNA input ranged from 200 ng to 1 ng genomic DNA. Image acquisition was performed on the Illumina HiScan™ System using the iScan Control Software.

Image Processing and Statistical Considerations

BeadChip images (.idat files) were analyzed in GenomeStudio® Genotyping Module v2.0.2, following the manufacturer's recommended quality control procedures [27, 28] including a Genotype Call (GenCall) Score cutoff of 0.15. Clustering was performed using the manufacturer's cluster (InfiniumOmni2-5-8v1-3_A1_ClusterFile.egt) and hg19 manifest (InfiniumOmni2-5-8v1-3_A1.bpm) files [29, 30]. Sensitivity study data were analyzed as an independent GenomeStudio project, providing insight into downstream genome-wide

association study sample preparation and analysis. In general, GenomeStudio® output files were analyzed further using the ggplot2 package in RStudio® version 3.3.1 [31, 32] and Microsoft Excel®.

System Sensitivity

The capability of the Infinium LCG assay to analyze input DNA quantities substantially less than the manufacturer's recommended 200 ng was tested. Three samples were prepared at eight input DNA quantities: 200, 150, 100, 50, 25, 10, 5, and 1 ng. Comparisons of sensitivity data among different input DNA preparations were processed under the assumption that the 200 ng preparations produced the highest quality data and the genotype calls were accurate and correct. Under this assumption, high quality SNP-array data were obtained down to 25 ng of input DNA, a minimum threshold used for association study sample inclusion. Additional information for evaluating SNP-array sensitivity can be found in the Supplemental Materials and Methods.

Association Study Pre-Processing

Post-hoc power considerations indicated that a sample size of 37 was sufficient for detecting a relatively large effect size ($|\rho| = 0.5$) with a power of 0.927 ($\alpha = 0.05$; two tails). Pre-processing followed the recommendations described by Turner, et al. [33] using PLINK version 1.90beta4.6 [34, 35] and involved analysis of marker quality, sample quality, and potential batch effects. After pruning, 1,499,150 autosomal loci (total of 1,537,230 loci) and all individuals remained for subsequent association studies [33]. A comprehensive description of marker and sample pre-processing can be found in the Supplemental Materials and Methods.

This study aimed to identify loci associated with M1:T in Finns. Image data processing involved robust linear regression and Pearson correlation in RStudio® using all pre-processed loci and toxicology information. The resulting p-values were corrected using the Benjamini-Hochberg post-hoc correction for false discovery [36]. Manhattan plots of all p-values were generated using the qqman library in RStudio® [37]. All significantly associated loci were analyzed for apparent genotype clustering abnormalities in the iScan Control Software v3.4.8 [38] and pairwise linkage disequilibria (LD). Self-reported healthy cohort population data for significantly associated loci were extracted from the 1000 Genomes Project using the University of California at Santa Cruz (UCSC) Table Browser [39, 40] and compared to tramadol-exposed Finns.

Gene-ontology (GO) terms were searched using the Protein ANalysis THrough Evolutionary Relationships (PANTHER™) Classification System Version 12.0 [41, 42]. PANTHER overrepresentation test (release 20170413) using client textbox input was used to evaluate over- or under-enrichment of "GO biological process complete" terms relative to the GO Ontology Homo sapiens database (release 2017-09-26).

Targeted Massively Parallel Sequencing

Independent replication of genotype-phenotype associations was performed for an additional 99 deceased tramadol-exposed Finns using in-house designed primers for the highly significant SNPs (rs79983326F-ATGCCACCACATCAGGCTAT; rs79983326R-ATGCTGGACCACAGGATTTC; rs984825F-TAGCTGCCATCTTTCTTATCCTG; rs984825R-CACTGCTGAAACCTAATCACCTC; rs62435418F-CATATCCCAAAGCTACACAAGTCA; rs62435418R-

TTTGTTCATTTTCCAAACTGCTTA; rs72732317F-ATTCTAGGTTATGGGCACAGC; rs72732317R-TGGTCATGATCTGTCCTCTCA; rs184199168F-CTACTCCATCACCAGCACCAT; rs184199168R-ATTTCCTGATGGTCCTCCAAG. Multiplexed PCRs were performed using the Qiagen® Multiplex PCR Kit with 1 ng input DNA and the standard multiplex PCR recommendations. Temperature cycling on a Eppendorf Mastercycler pro S (Eppendorf, Hamburg, Germany) was programmed as follows: 95°C for 15 minutes, 42 cycles of 94°C for 30 seconds, 60°C for 90 seconds, and 57°C for 90 seconds, and 72°C for 10 minutes [43]. Note that all PCR primers in the multiplex had melting temperatures below 60°C so an annealing temperature of 57°C was used. PCR products were size-separated on the Agilent 2200 TapeStation using the D1000 screentape [44] and quantified using the Qubit® dsDNA Broad Range assay [45] on the Qubit 2.0 fluorometer. Qubit quantification values were used to normalize each sample to 0.2 ng/µl, which was used as input for Nextera XT library preparation [46]. Massively parallel sequencing (MPS) was performed on the Illumina MiSeq™ using the MiSeq Reagent Kit v2 (2 x 250 bp read length) chemistry and v3 (2 x 300 bp read length). The resulting .fastq files were locally aligned to the hg38 reference genome using Burrows-Wheeler Aligner (bwa) mem command and the Sequence Alignment/Map Tools (SAMtools) view, sort, and index commands [51-53] The resulting sorted batch alignment/map (.sorted.bam) files were standard input for the Genome Analysis Toolkit (GATK) [54].

Results

Genotype Phenotype Association

Samples prepared for this association study had average template DNA inputs of 103 ± 48.5 ng with a range of 200 to 58.0 ng. The average concentration of tramadol and M1, and the average M1:T ratio, were 3.87 mg/l ± 6.27, 0.410 mg/l ± 0.576, and 0.183 ± 0.171, respectively. Pearson's correlation was used to determine associations between M1:T and the genotypes of 1,499,150 autosomal loci. A total of 3,033 loci, none of which deviated from HWE expectations, across all 22 autosomes (representing 888 genes) were significantly correlated with the M1:T phenotype (padj < 3.34 x 10-8; Figure 1). 91.1% of the genes were associated with a GO term (Figure 2). After Bonferroni correction for multiple testing, three GO biological processes exhibited nearly two-fold enrichment relative to the GO database: (1) cell-cell adhesion (GO:0098609; 2.28 fold enrichment; p = 0.0240), (2) neuron development (GO:0048666; 1.93 fold enrichment; p = 0.0214), and (3) circulatory system development (GO:0072359; 1.89 fold enrichment; p = 0.0283).

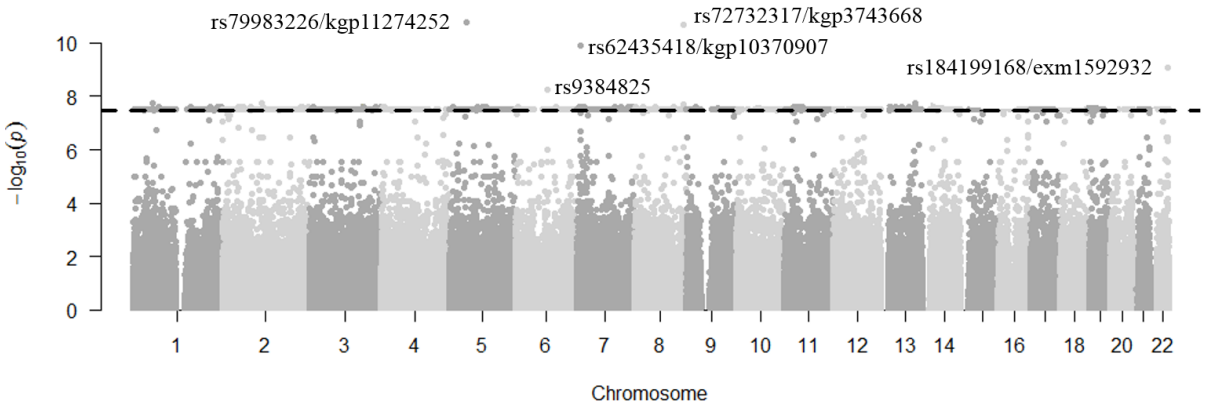

Fig. 1 Manhattan plot of –log10(p-value) for correlation between 1,499,150 autosomal loci and the O-desmethyltramadol:tramadol ratio (M1:T). The dashed horizontal line indicates genome-wide significance after correction for multiple testing (p = 3.34 x 10-8); the locus with the lowest p-value on each chromosome is annotated with either an rs number or Illumina's 1000 Genomes Project (kgp) indicator [30].

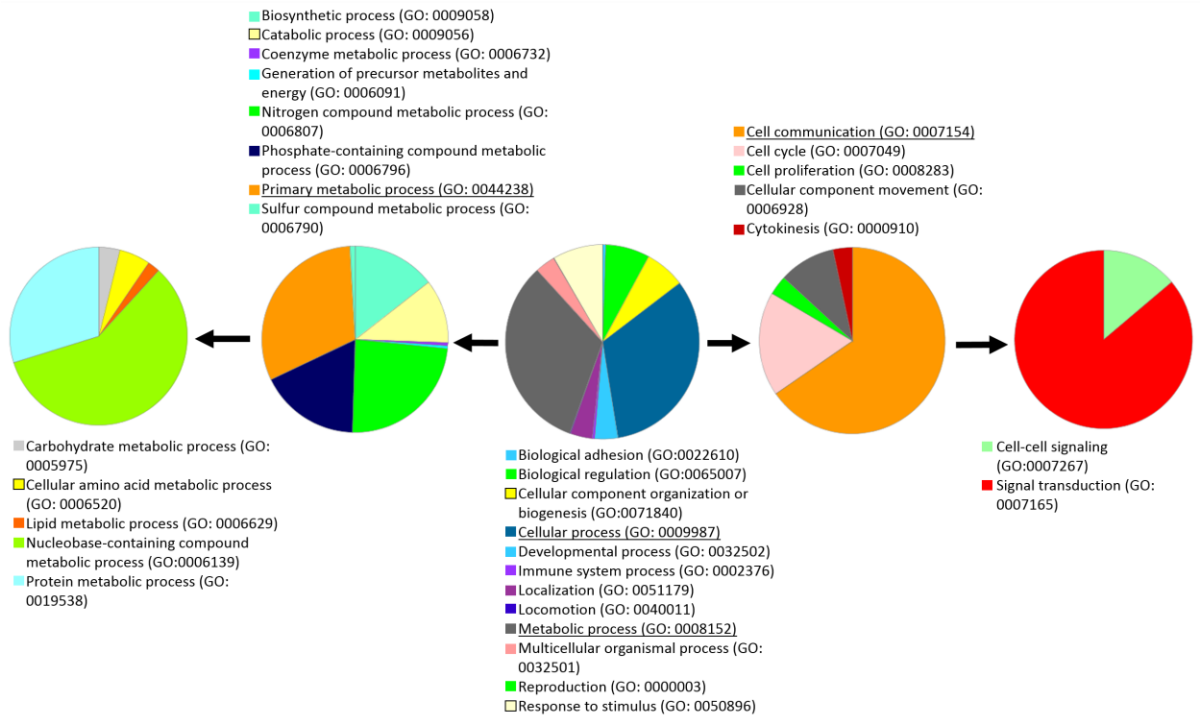

Fig. 2 Summary of gene ontology (GO) terms associated with genes of suggestive significance with the M1:T phenotype. GO terms reported by PANTHER™ Version 12.0 (released 2017-07-10) for 888 genes associated with 3,033 loci meeting the suggestive significance threshold for assiciation with the rate of conversion for tramadol to M1 relative to the Homo sapiens all genes database using the client text box input.

Five loci had p-values lower than the Benjamini-Hochberg corrected value (Table 1): rs79983226/kgp11274252 (r2 = 0.762; chromosome 5), rs9384825 (r2 = 0.615; chromosome 6), rs62435418/kgp10370907 (r2 = 0.615; chromosome 7), rs72732317/kgp3743668 (r2 = 0.749; chromosome 8), and rs184199168/exm1592932 (r2 = 0.610; chromosome 22). The average alternate allele frequencies in the deceased Finn cohort were 0.0143, 0.0571, 0.0286, 0.0441, and 0.0286 for rs184199168/exm1592932, rs72732317/kgp3743668, rs62435418/kgp10370907, rs79983226/kgp11274252, and rs9384825, respectively. There were no significant differences in allele frequencies between the affected cohort and the 1000 Genomes Project FIN self-reported healthy population. Note that in a large cohort of mixed phenotype Finns housed in the Sequencing Initiative Suomi (SISu v4.1),

rs184199168/exm1592932 has a minor allele frequency of 0.00310. Due to the exome-targeted nature of the project, the remaining four loci are not reported in SISu [47]. After Bonferroni correction (p_{adj} = 0.00192), significant pairwise LDs were observed for 8/10 pairs. Additionally, the multi-locus (all five markers together) LD was significant ($p < 0.00192$). These LDs may indicate some association at the SNP level, or in combination, with various features of these four samples (i.e., in this sampling of 74 chromosomes, a maximum of five haplotypes were observed with four of them occurring only once). According to their death certificates, these four individuals died as a result of poisoning by, adverse effect of, and under-dosing of systemic antibiotics (ICD-T36; N = 2), closed fracture to vault of skull (ICD10-S02.0; N = 1), and other specified chronic pulmonary disease (ICD10-J44.8; N = 1) [23]. It may also be postulated that this observation be attributed to allele dropout and/or the relatively small sample size and the presence of low frequency alleles/genotypes in the same four individuals (Table S1; samples 26, 27, 31, and 37). This situation may lead to a significant LD pattern by chance while a true interaction on the population level may not be significant. While the LDs observed in the test population are not significant in the 1000 Genomes Project FIN cohort [48], sensitivity data (Figure S2) demonstrate that there were no significant differences between allele dropout at 50 ng versus 200 ng input DNA.

Table 1 Summary of loci with strong significance to the O-desmethyltramadol:tramadol ratio in autopsied Finns. Omni2.5exome8 v1.3 locus names were cross referenced to their corresponding rs numbers and general locus information is provided, including chromosome (Chr), forward (F) or reverse (R) strand, reference genome positions and alleles (relative to the F strand), global minor allele frequency (gMAF), p-value for Pearson's r correlation, and relevant genes.

Locus rs Number	Omni2.5exome-8 v1.3 Locus	Chr	Strand	Hg19 Position	Hg38 Position	Reference Allele	gMAF	p	Gene(s)
rs79983226	kgp11274252	5	R	45595655	45595553	G	0.0066	1.703×10^{-11}	*HCN1*
rs9384825	rs9384825	6	F	112668193	112346991	C	0.1983	2.537×10^{-8}	*RFPL4B/RNF211*[a]
rs62435418	kgp10370907	7	F	8187646	8148016	G	0.0044	2.537×10^{-8}	*ICA1*
rs72732317	kgp3743668	8	F	136425579	135413336	G	0.0116	1.987×10^{-11}	*KHDRBS3*[a]
rs184199168	exm1592932	22	F	24034611	23692424	T	0.0002	3.043×10^{-8}	*GUSBP11*[b] and *RGL4*

[a]SNP is located in an intergenic region. The nearest gene(s) are listed.
[b]Pseudogene

the five variants detected, these include: Sort Intolerant from Tolerant (SIFT) [49, 50, 52-54], Polymorphism Phenotyping v2 (PolyPhen-v2) [55, 56], Protein Variant Effect Analyzer (PROVEAN) [58, 61], Human Splicing Finder (HSF) [60], Regulome Database (RegulomeDB) [62], and Combined Annotation Dependent Depletion (CADD) [63]. One SNP, rs184199168/exm1592932, is a missense mutation at position 90 of ral guanine nucleotide association stimulator like 4 (RGL4), causing a leucine to glutamine amino acid change (CADD: 22.7; SIFT: 0.001; PROVEAN: -2.84; PolyPhen-v2: 0.999). Note that the CADD score for rs184199168/exm1592932 identifies it within the top 1% of damaging polymorphisms relative to all possible genomic substitutions. Two loci are found within the intronic regions of potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1 (HCN1; rs79983226/kgp11274252) and islet cell autoantigen 1 (ICA1; rs62435418/kgp10370907); however, these loci are located too far from an exon (> 1000 bases) to perform HSF splice site predictions. Using RegulomeDB, rs79983226/kgp11274252 (score: 6) and rs62435418/kgp10370907 (score: 3a) were scored as having minimal impact on gene regulation and likely to affect transcription factor binding (though expression quantitative trait locus observations have not been reported), respectively. Lastly, two loci are located just

upstream of exon 1 of Ret Finger Protein-like 4B (RFPL4B/RNF211; rs9384825/kgp10370907) and KH domain-containing, RNA-binding, signal transduction-associated protein 3 (KHDRBS3; rs72732317/kgp3743668) and are not searchable in SIFT [49, 51-54, 57], PolyPhen-v2 [55-57], PROVEAN [58, 61], or HSF [60]. However, they are predicted to have little impact on protein function or regulation rs9384825/kgp10370907 and rs72732317/kgp3743668, with CADD scores of 0.460 and 0.149, respectively, and RegulomeDB scores of 6 and 5, respectively. In general, these five genes have been associated with epilepsy (including sudden unexpected death in epilepsy; HCN1 [64, 65]), asthma and allergic reactions, specifically in Europeans (RFPL4B [66, 67]), neurotransmitter transport (ICA1 [68-70]), expression of synapse function regulators in brain neuron populations (KHDRBS3 [71, 72]), and chemosensitivity in breast cancer treatment (RGL4 [73]), adding weight to their detection as tramadol ADME-relevant loci.

Independent Replication

Although the sample size is small, these five SNPs were highly significantly associated with metabolism rate. Given the samples size, the empirically determined associations between these five loci and the M1:T phenotype were tested in two phases: first, genotype-M1:T relationships were identified in the 37 genome-wide association samples; second, the conclusions were assessed in an additional set of samples by targeted PCR and sequencing by MPS. The empirical associations between these five loci and the M1:T phenotype were tested using a Student's t-test (Figure 3 and Table S1). Note that to account for sample size, genotypes are analyzed in terms of homozygous reference versus alternate allele carriers. Generally, the presence of the alternate allele in all five loci was connected to a decreased conversion of

tramadol to its primary metabolite; however, the significance of these differences was only evaluated for rs9384825, rs62435418/kgp10370907, rs72732317/kgp3743668, and rs79983226/kgp11274252 due to multiple observations of the heterozygous genotype at each locus. For these loci, the heterozygous condition resulted in significantly decreased M1:T ratio ($p < 0.05$). Though no mean M1:T ratio was present in this dataset for the rs184199168/exm1592932 heterozygous and homozygous-alternate genotypes (one observation of each), the trend of decreased M1:T ratio was observed but not statistically evaluated.

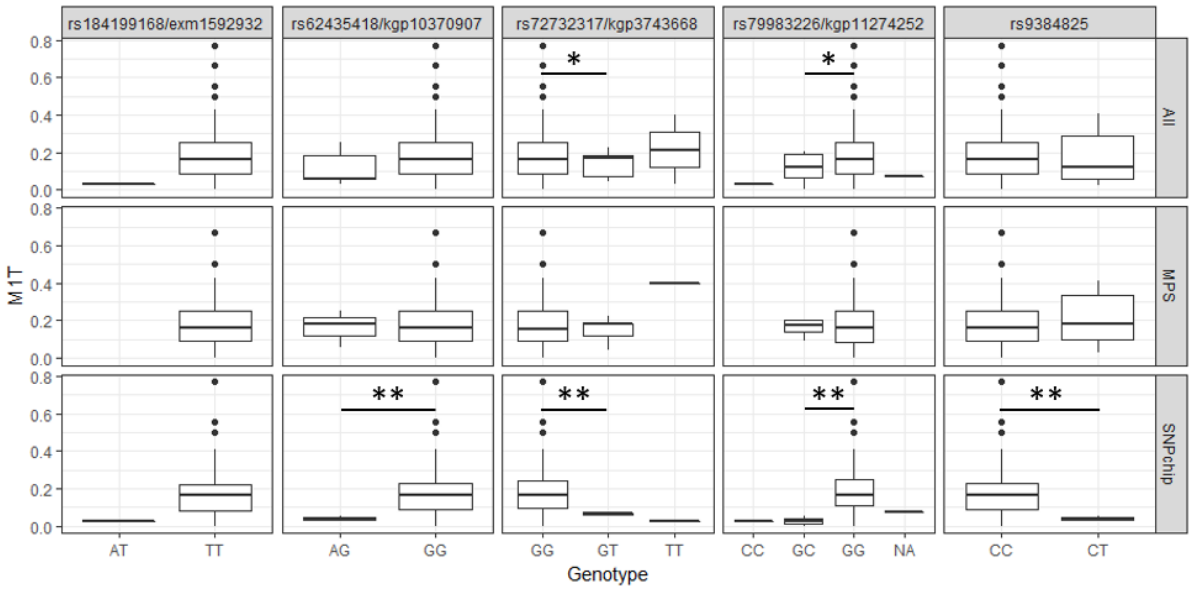

Fig. 3 Association between genotype at five genome-wide significant loci and the ratio of M1 to tramadol (T) for N = 37 (Omni2.5exome8 v1.3; "SNPchip"), N = 99 (NexteraXT; "MPS"), and N = 136 ("All") individuals. Each boxplot represents a single genotype relative to the forward DNA strand of the indicated single nucleotide polymorphism locus; the center horizontal line represents the median, the lower and upper boundaries of each box represent the first and third quartiles, respectively; the top and bottom vertical lines indicate plus and minus three times in the interquartile range, respectively; boxplot outliers are indicated by black data points. A student's t-test was used to compare the mean M1:T ratio ("M1T") between the homozygous-reference genotype at each locus and all other genotypes observed more than once with asterisks indicating $p < 0.05$ (**) and 0.1 (*); "NA" indicates absence of genotype call. Note that the heterozygous "SNPchip" genotypes were observed in the same four individuals.

To further support the association output from PLINK, which uses independent genotypes (e.g., AA, AB, and BB), individuals were pooled into groups of homozygous reference and alternate allele carriers for rs72732317/kgp3743668 (N = 3/37) and rs79983226/kgp11274252 (N = 3/37). Both loci exhibited significantly decreased M1:T in the presence of the alternate allele relative to the homozygous reference condition ($p = 0.000202$ and 0.0278 for rs72732317/kgp3743668 and rs79983226/kgp11274252, respectively).

A pentaplex PCR and subsequent targeted MPS were used to independently replicate the genotype-phenotype associations observed in an additional 99 Finns plus the four rare SNP array haplotypes. The average read depth for each locus was 102X ± 40.4 (rs79983226/kgp11274252), 113 ± 45.9 (rs9384825/kgp10370907), 93.5 ± 39.9 (rs62435418/kgp10370907), 91.4X ± 38.8 (rs72732317/kgp3743668), and 125 ± 58.2 (rs184199168/exm1592932). All four rare haplotypes detected with the SNP array data were concordant with the associated targeted sequencing data. Considering just the replicate population, there were no significant differences between pairwise comparisons of the homozygous reference, heterozygous, and homozygous alternate genotypes (Figure 3). To maximize the sample size for overall representation of tramadol to M1 conversion in Finns, all 136 samples were pooled. The alternate allele frequencies in this cohort were 0.0294 for rs79983226/kgp11274252, 0.0331 for rs9384825, 0.0184 for rs62435418/kgp10370907, 0.0478 for rs72732317/kgp3743668, and 0.00368 for rs184199168/exm1592932. As observed in the association study cohort, there are relatively decreased M1:T ratios for Finns carrying the alternate allele at rs62435418/kgp10370907 and rs9384825 but these relationships are not significant. The presence of the heterozygous condition at the SNPs rs79983226/kgp11274252 and rs72732317/kgp3743668 resulted in relatively decreased M1:T ratios ($p < 0.1$).

Interestingly, it appears that the homozygous alternate genotype at rs72732317/kgp3743668 may be associated with the reverse effect of that of the heterozygous condition while at rs79983226/kgp11274252 the heterozygous effect is exacerbated. In the total population of 136 Finns, there were no deviations from HWE after Bonferroni correction. The combined impact of all five loci on M1:T was investigated using multifactorial analysis of variants (ANOVA). There were significant relationships between rs79983226/kgp11274252 ($p = 0.00952$) and the combination of rs9384825 and rs72732317/kgp3743668 ($p = 0.00242$); however, specific pairwise genotype combinations were not significant (Tukey Honest Significant Difference test).

Interestingly, the LD structure observed with the SNP-array data only also was observed in the total dataset (padj < 0.002). Significant LD for the group of five loci may indicate real relationships rather than spurious observation of all five alternate alleles in the same individual(s) as the larger dataset includes greater distribution of allele combinations across individuals. Considering the dataset as a whole (N = 136), there were no significant relationships between the five-locus haplotype and M1:T with or without inclusion of outliers (one-way ANOVA; $p = 0.966$ and 0.412, respectively). Nevertheless, functional/mechanistic consequences of this LD need to be validated in controlled studies.

Covariate Considerations

The samples analyzed above represent a non-random sampling of deceased individuals with an exhaustive list of additional compounds detected during routine autopsy toxicology screening. These data were explored in the context of the genotype-phenotype relationships described above. There were no detectable significant relationships between the M1:T and age,

sex, or specific compounds in the toxicology data; however, the combined impact of the number of additional compounds plus the rs79983226/kgp11274252 genotype plus the MoD significantly impacted M1:T (multiple linear regression; $p = 0.00673$). The number of additional compounds in a sample's toxicology screen was positively correlated with the M1:T ratio in the trauma MoD cohort (Pearson's $r = 0.344$; $p = 0.0258$; Figure 4) and the same relative observation is seen with the disease (Pearson's $r = 0.0235$), suicide (Pearson's $r = 0.0159$), and merged MoD (Pearson's $r = 0.0900$) cohorts. Though the sample size is small, the slope of the linear regression describing the relationship between the number additional compounds and M1:T is significantly greater for the disease, suicides, and trauma MoDs carrying the alternate allele at rs79983226/kgp11274252 ($p < 0.05$); however, the suicide cohort demonstrated an inverse relationship between the two variables. These observations suggest that M1:T is generally higher in individuals with more compounds in their blood.

The number of additional compounds detected in sample toxicology screens was evaluated for all alternate allele carriers (heterozygotes plus homozygous alternate samples) versus homozygous reference samples at each locus individually. The number of additional compounds detected was significantly greater in the rs72732317/kgp3743668 alternate allele carriers (6.8 compounds ± 3.66; $N = 11$) relative to the homozygous reference samples (4.57 compounds ± 2.59; Student's t-test; $p = 0.0419$). While not significant, there was a general increase in the number of additional compounds in the blood of alternate allele carriers when all five loci of interest are pooled (5.56 compounds ± 3.19) relative to those with the homozygous reference condition (4.95 compounds ± 3.36).

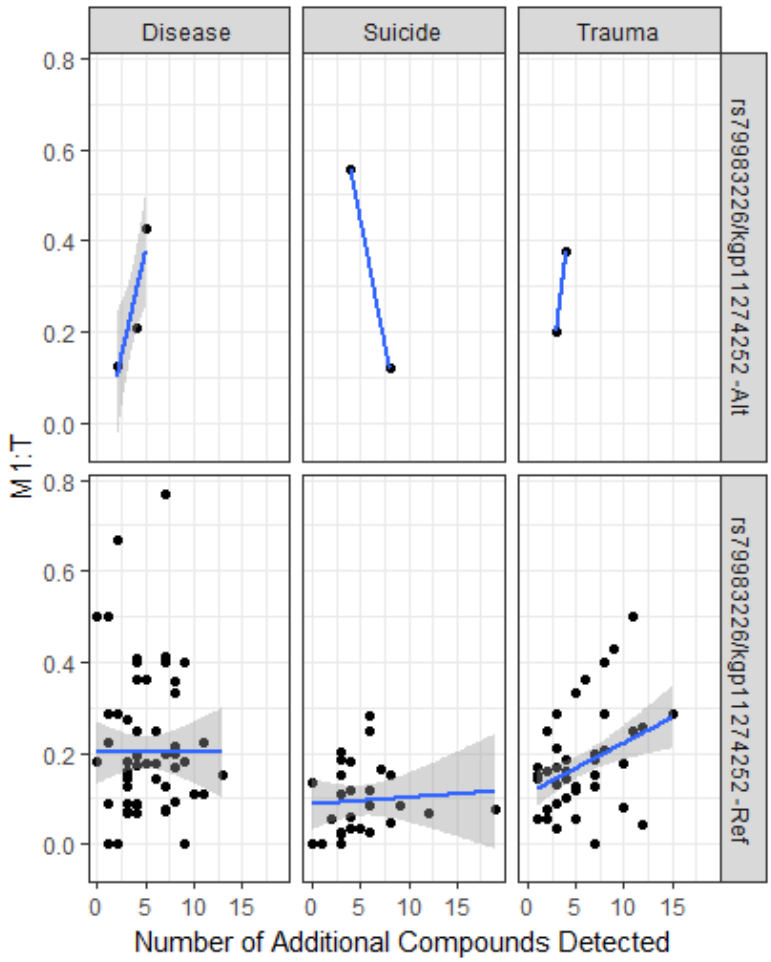

Fig. 4 Robust linear regression between the number of additional compounds in each sample toxicology screen and the ratio of O-desmethyltramadol to tramadol for homozygous reference ("Ref") and alternate ("Alt") allele carriers at the rs79983226/kgp11274252 locus for disease, suicide, and trauma manners of death. Note that standard error is shown in grey surrounding each blue regression line.

These observations suggest that the M1:T values in Figure 3 possibly may be inflated compared to those in the absence of additional compounds, particularly for samples carrying an alternate allele at rs72732317/kgp3743668 and rs79983226/kgp11274252 and samples of the disease and trauma MoD classes (29.2% and 64.0% of the 25 total alternate allele carriers, respectively). The inflated M1:T measurements may have contributed to alternate allele carriers appearing more similar to the homozygous reference samples, leading to lack of

detection of significance between the mean M1:T at each genotype in the larger MPS and combined cohorts.

Discussion

This study aimed to identify potential pharmacogenes associated with tramadol metabolism using genome-wide genotyping of a convenient cohort of deceased, tramadol-exposed Finns. 3,033 suggestive trait-associated loci were identified in the study group, five of which demonstrated genome-wide significance. In general, the presence of the alternate allele at rs9384825, rs62435418/kgp10370907, rs72732317/kgp3743668, and rs79983226/kgp11274252 correlated with decreased conversion of tramadol to its primary metabolite M1. Two genes identified here, *ICA1* and *HCN1*, have been implicated in idiosyncratic drug reactions and death by potentiating hyperalgesia [68-70] and epilepsy-associated sudden unexpected death [64, 65], respectively. Two general themes of the five associated genes (*RFPL4B/RNF211*, *KHDRBS3*, *HCN1*, *ICA1*, and *RGL4*) are relatively high brain abundance and involvement in synaptic signal transduction. It may be reasonable to hypothesize that targeted assays involving a combination of liver (e.g. CYP2D6) and brain (e.g. HCN1) enzymatic variation may provide increased MP inferences and further improve patient efficacy. It should be noted that significant relationships between genotype and the M1:T phenotype were not detected when samples were pooled into a larger dataset. However, the number of additional compounds detected in the sample's toxicology screen (i.e. severity of patient polypharmacy) may significantly inflate the associated M1:T value, especially in trauma and disease MoDs. Though the sample size is relatively small, the alternate allele condition, most notably at rs72732317/kgp3743668 and rs79983226/kgp11274252, may

impact this observation, thereby contributing to lack of detection of significant genotype-phenotype association in the combined dataset.

The data presented are limited by three main factors. (1) The sample size (N = 136) may be relatively small for a study of this nature, decreasing the overall relative effect size that can be detected with confidence. An increased sample size may lead to identification of more rare loci, or loci with relatively small effects, that could contribute to the M1:T ratio [74]; however, the size of this quite unique cohort is not uncommon in genome-wide studies [75-77] and indeed, several targets of interest with relatively large effect sizes were detected. The Finnish population has a relatively small effect size and has been through at least one evolutionarily recent ancestral bottleneck, potentially enriching certain polymorphisms in the Finns which are rare in the general population and/or non-Finnish Europeans [78]. Conversely, certain globally common variants may not exist currently in the Finns; however, the sample size with which the general archive of variants can be detected is likely smaller than that of non-Finnish Europeans [79]. (2) The individuals used for this study were selected based on two criteria: a) died and had exposure to tramadol and b) sufficient DNA (between 50 and 200 ng) for SNP array typing. Population substructure was not indicated by PCA and IBS testing; however, there may be inherent substructure in the cohort if considering MP selection based on *CYP2D6* diplotype (i.e., the specific value of M1:T is associated with different CYP2D6 MP but was not considered an inclusion criterion for sample selection) [14, 80, 81]. The population used here represents a heterogeneous cohort of individuals who expired due to a variety of causes/manners of death. The data herein demonstrated that variation may exist in these categories individually that warrants their investigation as unique cohorts. Consequently, the associations identified here may need to be explored in larger studies focusing on *CYP2D6*

extreme MPs (poor and ultra-rapid) and/or MoD cohorts individually. Additionally, while typically considered relatively homogeneous, a fine level of east-west duality has been identified in the Finnish population [82, 83], which may need to be considered for subsampling individuals from these parts of the country. (3) Polypharmacy may be defined as the use of a) multiple, b) five or more, or c) multiple contraindicated drugs recreationally or to treat one or more medical conditions [86]. Multi-drug use, especially drugs which act as substrates for the same enzymes or enzymatic pathways, has the potential to confound association study results as the measured M1:T is contingent upon availability of CYP2D6 to metabolize tramadol. The presence of even minor non-tramadol CYP2D6 substrates may compete with tramadol for hepatic CYP2D6 binding sites, thereby artificially altering the M1:T phenotype, or any pharmacological measurement, being used to infer general MP. The deceased Finns in this study demonstrate polypharmacy as a confounding covariate for validating the genotype-phenotype associations detected with the SNP-array data. Note that specific confounding compound/drug combinations were not discovered here, however the observed phenomenon is quite complex and will require additional controlled studies to fully elucidate the consequences of pairwise combinations of commonly co-administered drugs/medications.

The ancillary relationships identified here between sample degradation and inhibition and overall SNP array performance indicate that the relatively high recommended sample DNA input may not be a limiting factor for retrospective genome-wide interrogation of autopsied, blood-bank, and/or forensic-type samples, particularly those stored on FTA cards. Thus, large repositories of autopsy samples and data may be useful for comprehensive pharmacogenetic studies of phenotypes common to those individuals. These studies have the potential to provide meaningful insight into potential markers to target for clinical trials or clinical applications.

Additional targeted genotyping studies of the polymorphic nature of each gene reported here may be required to further explain specific SNP and/or gene interactions generating the M1:T phenotype. The BeadChip used in this study types primarily gene-associated loci. Cis- and/or trans-non-coding polymorphic sites may not be immediately informative but may demonstrate deleterious or advantageous effects in relation to phenotype of interest by altering splice junctions, regulating translational stability, and/or influencing gene promoter/enhancer sequences [84]. It is likely that through advances of continuous-read DNA sequencing and/or targeted genotyping assays, the functional relevance of these polymorphisms can be elucidated [85, 86].

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Supplemental Information

System Sensitivity

The capability of the Infinium LCG assay to analyze input DNA quantities substantially less than the manufacturer's recommended 200 ng was tested. Three samples were prepared at eight input DNA quantities: 200, 150, 100, 50, 25, 10, 5, and 1 ng. Comparisons of sensitivity data between different input DNA preparations were processed under the assumption that the 200 ng preparations produced the highest quality data and the genotype calls are accurate. Using this assumption, high quality SNP-array data were obtained down to 25 ng of input DNA. Samples included for association study testing had at

The assay contains four sample independent and four sample dependent controls housed on 15-30 beads of the BeadChip [1] which are used to evaluate workflow and between-sample performance, respectively. Sample-dependent and sample-independent controls performed as expected (Figure S1A). However, many of the metrics vary between BeadChips with the same preparation in a sample-independent manner and thus it was not possible to determine the limit of detection of the assay from these controls. Regardless, the mean sample call rate for all DNA template quantities was > 90%, i.e., approximately 2.3 million out of 2.6 million loci typed at all input DNA quantities tested (Figure S1B). The overall quality of genotype calls decreased slightly as template DNA decreased. Considering the tenth (p10 GC) and fiftieth (p50 GC) percentile GenCall scores, respectively, the 200, 150, 100, 50, and 25 ng template preparations performed similarly with average p10 GC and p50 GC > 0.49 and 0.86, respectively. The average call rates and p10 GC values for the 10, 5, and 1 ng preparations (call rates: 0.993 ± 3.19 x 10-3, 0.989 ± 4.43 x 10-3, and 0.913 ± 4.40 x 10-2, respectively; p10 GC: 0.498 ± 1.10 x 10-3, 0.497 ± 1.56 x 10-3, and 0.443 ± 3.51 x 10-2, respectively)

significantly deviated from those of the 200 ng preparations (call rate: 0.998 ± 6.69 x 10-4; p10 GC: 0.500 ± 2.11 x 10-4; $p < 0.04$). This decrease in overall quality of genotype calls is correlated with an increased number of no call (NC) genotypes (Figure S1C); thus, the accuracy of some allele calls at individual loci may be impacted with lower amounts of template input.

Comparisons of sensitivity data between different input DNA preparations were processed under the assumption that the 200 ng preparations produced the highest quality data and the genotype calls are accurate. For comparisons to the 200 ng preparation the following operational definitions were used: locus dropout was any locus successfully typed in the 200 ng sample but assigned no call (NC) in a lower quantity sample; locus recovery was any locus assigned NC in the 200 ng sample but successfully typed in a lower quantity sample; allele dropout was any heterozygous locus in the 200 ng sample that was typed as a homozygous locus in a lower quantity sample; allele dropin was any homozygous locus in the 200 ng sample that was typed as a heterozygous locus in a lower quantity sample. Overall sample performance was quite high regardless of template DNA quantity; however, the decreased quality of genotype calls is more evident on the locus-level. Figure S2A shows the density distribution of p10 GC scores for eight template DNA quantities. The 200, 150, 100, 50, 25, 10, and 5 ng preparations show considerable overlap in distribution of the p10 GC scores while the 1 ng preparation had decreased abundance of high-quality loci, as demonstrated by the substantial decrease in density of p10 GC scores between 0.75 and 1.0. The p10 GC scores for the 200 ng preparations were compared to those of seven lower template DNA quantities in a pairwise manner (Figure S2B). When differences were observed, loci typically performed worse in the lower DNA quantity preparation; however, a relatively small set of loci performed better in

DNA template preparations less than the recommended 200 ng (data not shown). While interesting, this observation was nominal and may be attributed to stochastic sampling and/or unequal bead representation per locus per sample. In general, all sample preparations, with the exception of the 1 ng samples, the genotype calls for all template DNA preparations were similar to those of the 200 ng preparations even though genotype call scores decreased. The individual genotypes assigned to each locus also were compared to the genotype assigned to the 200 ng preparation (Figure S2C) using a $\chi 2$-goodness-of-fit test, considering each sample as a population of generic AA, AB, and BB genotypes representing homozygous allele 1, heterozygous, and homozygous allele 2 genotypes, respectively. Significant differences were observed only with the genotype distributions of the 10, 5, and 1 ng preparations relative to the 200 ng preparations ($p < 0.001$). While not significant, the three 25 ng preparations did have a prominently broad range of p-values relative to the 200 ng preparations, suggesting inconsistent performance with this template DNA quantity.

A key locus performance metric of interest is the loss of information at individual loci as a consequence of template DNA available for genome-wide amplification. Figure S2D compares the 150, 100, 50, 25, 10, 5, and 1 ng preparations to the 200 ng preparations to identify and characterize instances of locus dropout, locus recovery, allele dropout, and allele dropin as template DNA decreased. With the exception of locus recovery, there is an obvious relationship between DNA quantity and the occurrence of the remaining metrics. Locus and allele dropout (mean range of 1,140 ± 119 loci to 66,530 ± 36,670 loci and 64.7 ± 7.64 loci to 19,030 ± 18,580 loci for the 150 and 1 ng preparations, respectively) are tolerable and expected as template DNA decreases and stochastic effects during genome-wide amplification increase. Locus recovery and allele dropin (mean range of 1,230 ± 322 loci to 1,190 ± 266 loci and 70.3

± 23.1 loci to 41,770 ± 20,950 loci for the 150 and 1 ng preparations, respectively) may be the result of contamination and/or some cross hybridization, though not evident by the criterion of total heterozygosity across the loci in the samples tested (data not shown). It also should be noted that there may be very small levels of dropout and contamination on the locus and allele levels which may go undetected. Studies attempt to correct for these events during sample pre-processing by eliminating loci with a specified genotype call threshold and GC score but may not be readily apparent if the second allele of a heterozygote is consistently not typed.

Association Study Pre-Processing

Marker quality assessments involved establishing appropriate genotype call rate and minor allele frequency (MAF) cutoffs, and evaluation of possible genotyping errors. All X- and Y-chromosomal and mitochondrial loci, and any autosomal locus with MAF = 0 were removed from the HWE analysis procedure resulting in family-wise testing of 1,499,150 loci for deviations from HWE expectations. There were 2,579 significant deviations from HWE expectations after Bonferroni correction (padj < 3.34 x 10-8) and a Manhattan plot indicates little-to-no pattern or clustering of HWE deviating loci (Figure S4). This value is substantially less than that due to chance alone (~74,958) and thus these loci were not removed from the dataset.

Sample quality was checked at multiple levels, including biological sex prediction accuracy, cryptic sample relatedness, sample profile call rate, and population substructure. Principal component analysis (PCA; mean-centered and normalized) and identity-by-state (IBS; autosomal loci only) were used to detect population substructure [2]; outliers (individual samples) were identified based on a sample's z-score converted distance to its nearest three

neighbors [3]. Sample call rates and p10 GC scores reflect high quality sample performance (Figure S5) with average call rates and p10 GC scores of 0.999 ± 0.00191 and 0.738 ± 0.0218, respectively. Biological sex predictions from PLINK were compared to those contained within the autopsy information for each sample. One sample was recorded as female but was predicted as a male from the genetic data. The sample also was determined to be of male origin based on quantitative PCR assay (see methods; data not shown). Additionally, the genome-wide heterozygosity of the sample is lower than the cohort mean (0.695 ± 0.00223) suggesting that the sample is not a mixture. Based on these observations, this sample was treated as being derived from a male. The underlying pairwise cryptic relatedness of samples was tested using PLINK (Figure S5A). All 666 pairwise comparisons have high Z0 (0.958 to 1; the proportion of loci where sample pairs share zero alleles) and low Z1 values (0 to 0.0421; the proportion of loci where sample pairs share one allele), respectively, indicating no cryptic relationships among the individuals (i.e., first, second, third degree relatives were not detected). The presence of population substructure has the potential to alter underlying allele frequency data and may affect the false positive rate. One potential outlier was detected visually using PCA (Figure S5B). This sample had low performing p10 GC score (0.619) and call rate (0.988) relative to other samples; however, its pairwise IBS z-scores are within two standard deviations of the cohort mean so it would not be considered an outlier in this study. Quantile-quantile plots of the z-score-converted first, second, and third nearest neighbor distances for each sample also indicated a lack of detectable population substructure as each observed z-score-converted distance was relatively close to the expected (Figure S5C). After pruning, all 37 samples (13 females and 24 males) were used for the association study.

Samples were processed in three batches of three (sensitivity samples), four, and one BeadChips. Batch effects (i.e., genotype-phenotype associations confounded by samples being processed in batches) were explored by comparing the MAFs and average call rates within and between BeadChip batches. No significant differences were detected between pairwise comparisons of sample call rate, p10 GC score, or MAFs with batch- or BeadChip-specific attributes.

Though not conventional quality metrics or considerations for sample inclusion, the age and storage conditions of post-mortem samples (i.e., sample degradation index and inhibition [inferred by internal PCR control cycle threshold (IPC Ct) values]) were considered additional factors influencing sample performance [4]. The degradation index (Figure 3) was significantly associated with sample call rate ($p = 3.30 \times 10\text{-}9$; $r = -0.814$) and p10 GC scores ($p = 2.53 \times 10\text{-}10$; $r = -0.851$) but IPC Ct was not ($p > 0.05$; $r = 0.129$ and 0.192 for sample call rate and p10 GC score, respectively). Rahikainen, et al. [4] showed that DNA can degrade in aged blood samples stored in FTA paper, which might suggest that such archived samples may not be ideal for genomic studies. However, herein there was no relationship between collection year (2002 through 2012) and sample DI, IPC Ct, call rate, or p10GC (data not shown). These results support that post-mortem blood samples stored on FTA paper can provide sufficient quality template DNA for large-scale genomic studies.

This study aimed to identify loci associated with M1:T in Finns. Image data processing involved robust linear regression and Pearson correlation in RStudio® using all pre-processed loci and toxicology information. The resulting p-values were corrected using the Benjamini-Hochberg post-hoc correction for false discovery [5]. Manhattan plots of all p-values were generated using the "qqman" library in RStudio® [6]. All significantly associated loci were

analyzed for apparent genotype clustering abnormalities in the iScan Control Software v3.4.8 [7] and pairwise linkage disequilibria (LD). Self-reported healthy cohort population data for significantly associated loci were extracted from the 1000 Genomes Project using the University of California at Santa Cruz (UCSC) Table Browser [8, 9] and compared to tramadol-exposed Finns.

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Supplemental Figures

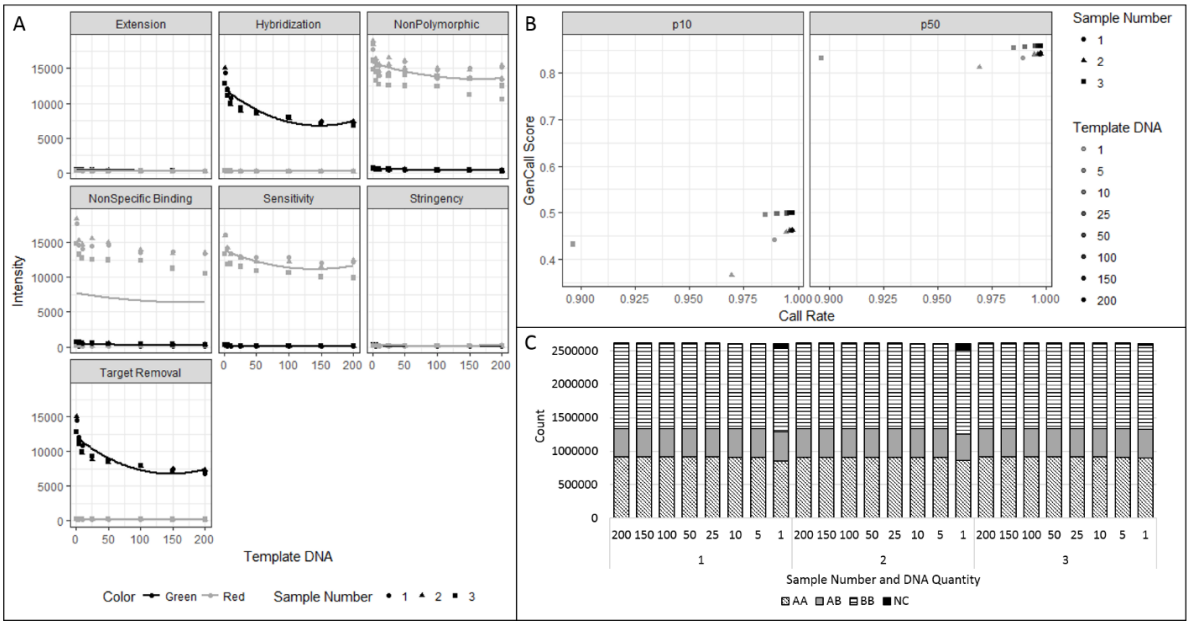

Fig. S1 Sample performance summary (N = 3 individuals per template quantity [in nanograms]). A) Sample-dependent and sample-independent control signal intensities by template DNA quantity. B) Call rate versus genotype call (GenCall) score for each sample at each template DNA quantity. C) Sample profile composition at each DNA quantity using the generic abbreviations AA, AB, BB, and NC for homozygous allele 1, heterozygous, homozygous allele 2, and no call genotypes, respectively

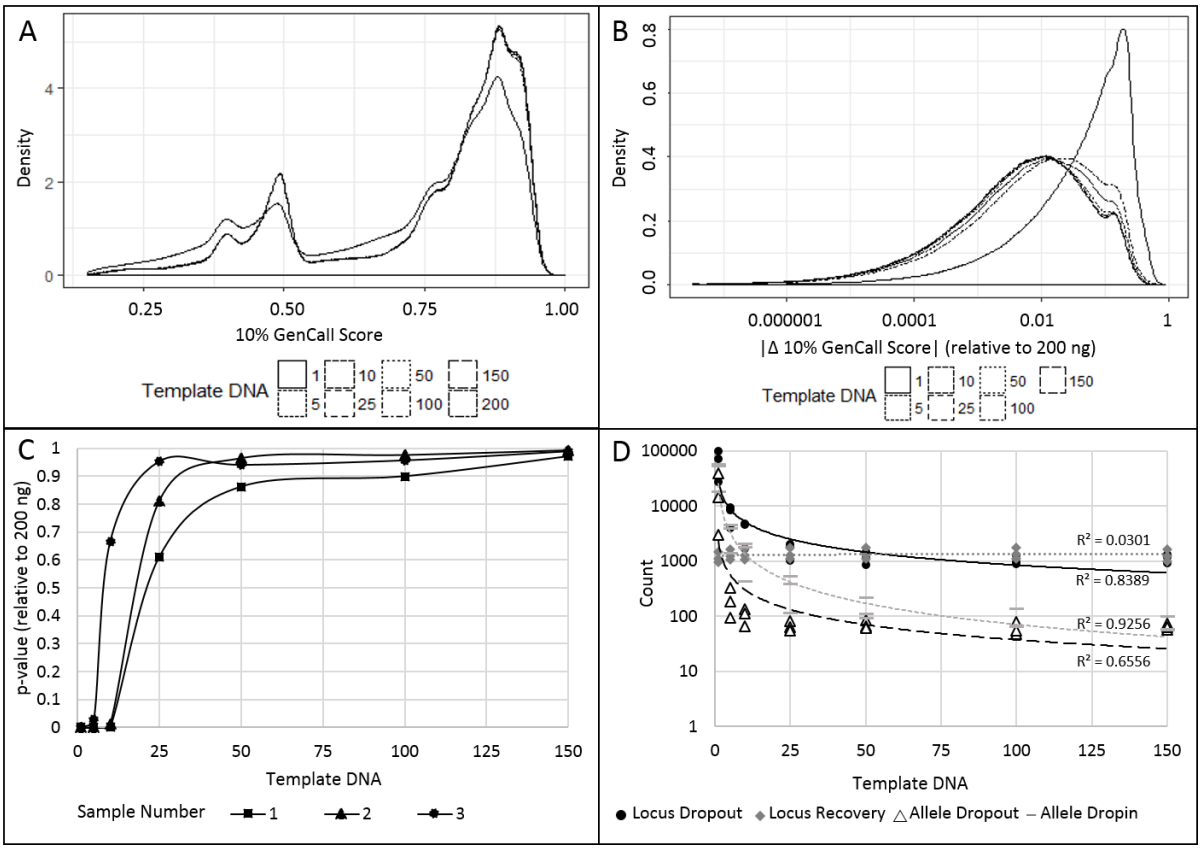

Fig. S2 Locus performance summary (N = 3 individuals per template DNA quantity [in nanograms]) for approximately 2.6 million loci on the Infinuium Omni2.5Exome-8 v1.3 BeadChip. A) Density plot of the mean 10th percentile genotype call (GenCall) scores by template DNA in each sample preparation. It should be noted that there is considerable overlap between all DNA quantities except the 1 ng preparation. B) Density plot of the absolute value of the change (|Δ|) in 10th percentile GenCall Score distribution compared to a 200 ng sample. C) Chi-squared p-value distribution for genotype distributions using pairwise comparisons of the 200 ng sample with all other template DNA quantities. D) Distribution of locus dropout, locus recovery, allele dropout, and allele dropin counts for each template DNA quantity relative to the 200 ng sample profile. Locus dropout was defined as any locus successfully typed in the 200 ng sample but assigned no call (NC) in a lower quantity sample; locus recovery was defined as any locus assigned NC in the 200 ng sample but successfully typed in a lower quantity sample; allele dropout was defined as any heterozygous locus in the 200 ng sample that was successfully typed as a homozygous locus in a lower quantity sample; allele dropin was defined as any homozygous locus in the 200 ng sample that was successfully typed as a heterozygous locus in a lower quantity sample; power trend lines and R2 values are shown.

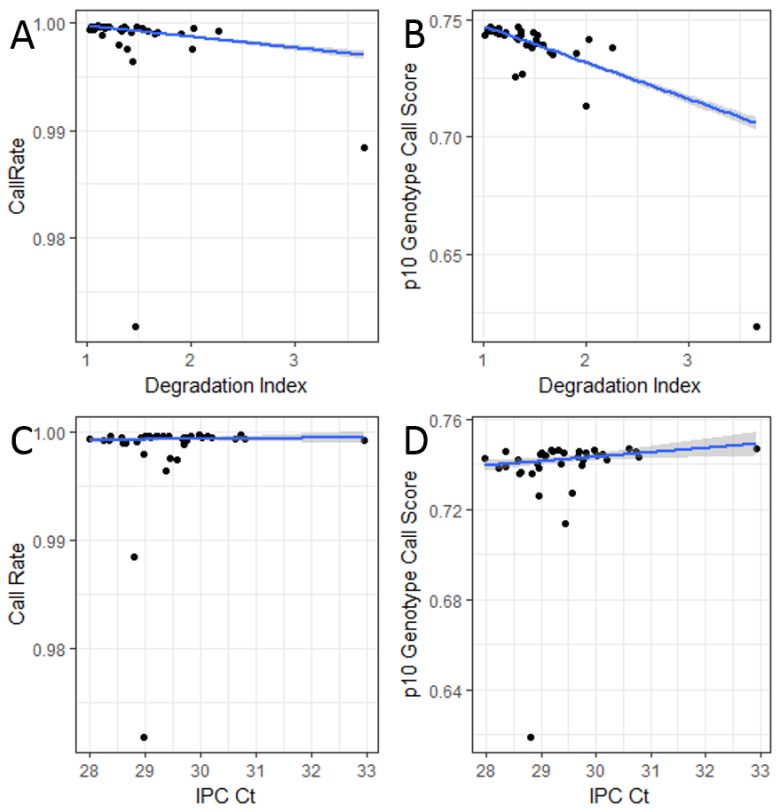

Fig. S3 Additional attributes influencing sample performance. Scatterplots, robust linear regression (solid lines), and 95% confidence intervals (shaded region) for the covariance of sample call rate and 10th percentile (p10) Genotype Call and DNA degradation index (DI) and internal PCR control cycle threshold (IPC Ct) values (data not shown). Pearson's r-values indicated generally negative and positive relationships between the DI or IPC Ct values of the input DNA, respectively, and the sample call rate and p10 GenCall Scores, though only DI was significant ($p = 3.30 \times 10\text{-}9$ and $2.53 \times 10\text{-}10$).

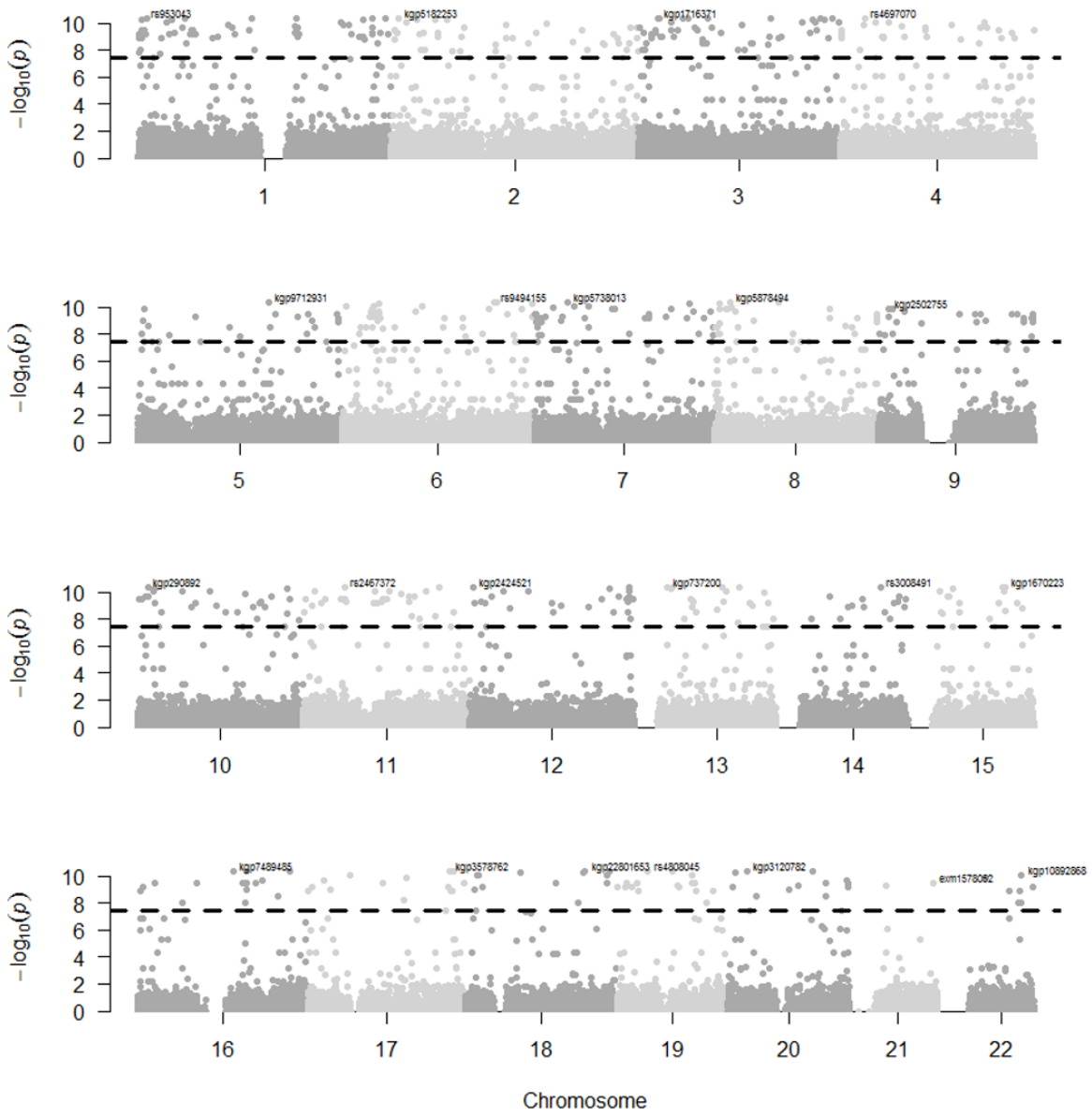

Fig. S4 Hardy-Weinberg Equilibrium p-values for 1,499,150 loci on chromosomes 1-22. The dashed horizontal lines indicate significance after Bonferroni correction (p = 3.34 x 10-8); the locus with the lowest p-value on each chromosome is annotated either with an rs number or Illumina's 1000 Genomes Project (kgp) indicator [10].

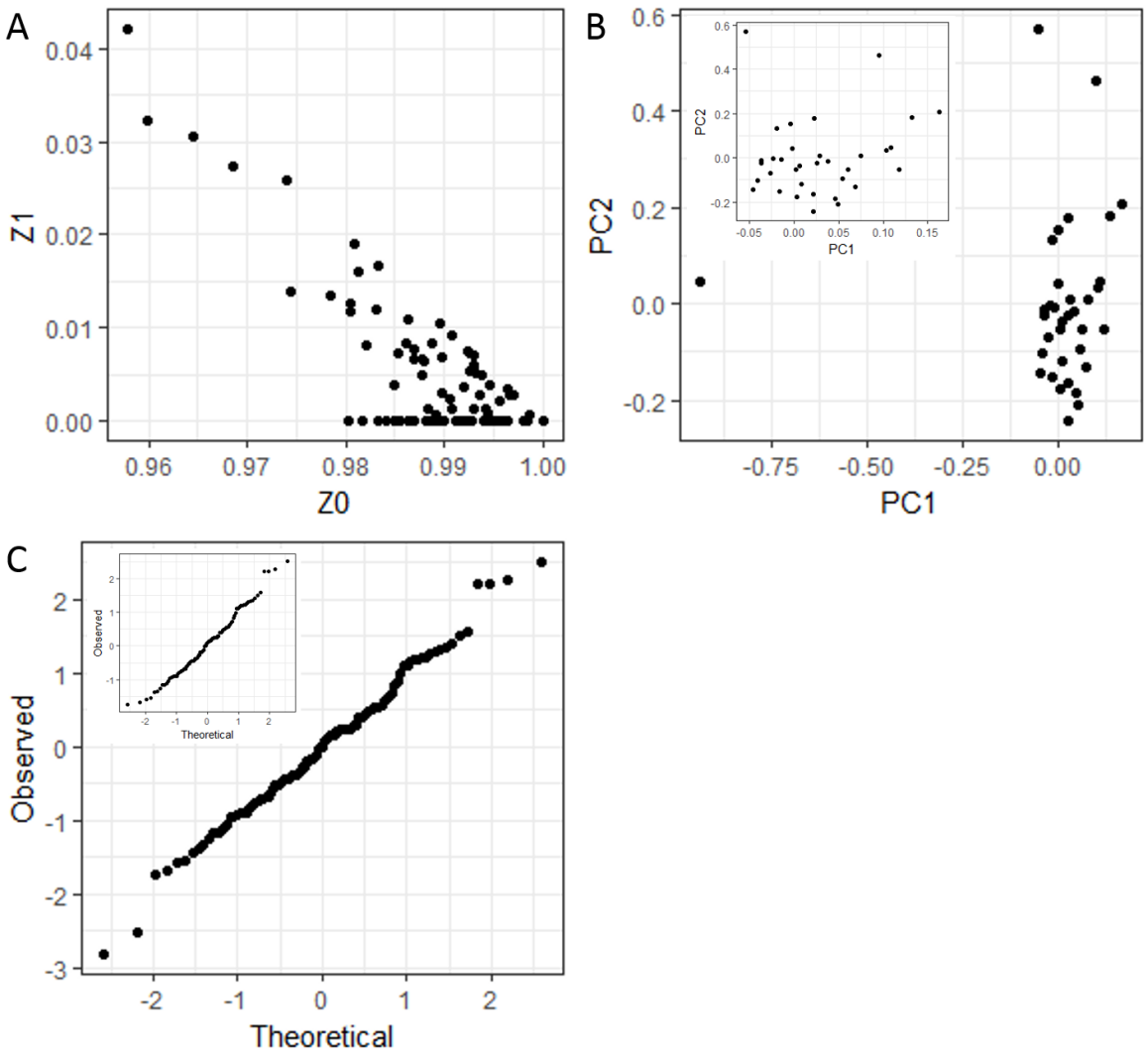

Fig. S5 Summary of sample pre-processing results. A) Scatterplot of identity-by-descent to determine cryptic relatedness within the sample cohort; Z0 and Z1 are the probabilities of pairwise sample comparisons sharing zero and one allele(s), respectively. B) Principal component (PC) analysis of 37 Finns using PC1 and PC2, identified using autosomal loci. The inset depicts the same information with the visual outlier removed. C) Quantile-quantile plot of the z-score-converted observed and theoretical distances between each sample and its first, second, and third nearest neighbors. The inset depicts the same information with the visual outlier from B removed.

Supplemental Table

Table S1 Genotype data for five loci meeting genome-wide significance in relation to the ratio of O-desmethyltramadol to tramadol (M1:T) phenotype of 136 autopsied Finns. Genotypes are indicated in the forward strand; "NA" indicates missing genotype assignment; general sample information including biological sex, M1:T phenotype measurement, age, and genotyping method are provided.

Sample Number	rs184199168/ exm1592932	rs72732317/ kgp3743668	rs62435418/ kgp10370907	rs79983226/ kgp11274252	rs9384825	Sex	M1:T	Age	Method
1	TT	GG	GG	GG	CC	Male	0.1875	28	SNPchip
2	TT	GG	GG	GG	CC	Male	0.25	68	SNPchip
3	TT	GG	GG	GG	CC	Male	0.161	47	SNPchip
4	TT	GG	GG	GG	CC	Male	0	55	SNPchip
5	TT	GG	GG	GG	CC	Female	0.25	91	SNPchip
6	TT	GG	GG	GG	CC	Male	0.0833	48	SNPchip
7	TT	GG	GG	GG	CC	Female	0.2	86	SNPchip
8	TT	GG	GG	GG	CC	Female	0.167	78	SNPchip
9	TT	GG	GG	GG	CC	Male	0.154	40	SNPchip
10	TT	GG	GG	GG	CC	Male	0.556	32	SNPchip
11	TT	GG	GG	GG	CC	Male	0.208	37	SNPchip
12	TT	GG	GG	GG	CC	Male	0.13	26	SNPchip
13	TT	GG	GG	GG	CC	Male	0	45	SNPchip
14	TT	GG	GG	GG	CC	Female	0.208	40	SNPchip
15	TT	GG	GG	GG	CC	Male	0.364	76	SNPchip
16	TT	GG	GG	GG	CC	Female	0	42	SNPchip
17	TT	GG	GG	GG	CC	Female	0.182	78	SNPchip
18	TT	GG	GG	GG	CC	Female	0.77	59	SNPchip
19	TT	GG	GG	GG	CC	Male	0.11	33	SNPchip
20	TT	GG	GG	GG	CC	Male	0	67	SNPchip
21	TT	GG	GG	GG	CC	Male	0.167	41	SNPchip
22	TT	GG	GG	GG	CC	Male	0.125	38	SNPchip
23	TT	GG	GG	GG	CC	Female	0.2	83	SNPchip
24	TT	GG	GG	GG	CC	Male	0.0882	44	SNPchip
25	TT	GG	GG	GG	CC	Male	0.5	68	SNPchip
26	AT	TT	AG	CC	CT	Male	0.0278	57	SNPchip
27	TT	TG	AG	GC	CT	Male	0.0556	39	SNPchip
28	TT	GG	GG	GG	CC	Female	0.111	63	SNPchip
29	TT	GG	GG	GG	CC	Female*	0.412	55	SNPchip
30	TT	GG	GG	GG	CC	Male	0.152	36	SNPchip
31	TT	TG	GG	NA	CC	Male	0.0741	78	SNPchip
32	TT	GG	GG	GG	CC	Female	0.333	13	SNPchip
33	TT	GG	GG	GG	CC	Female	0	39	SNPchip
34	TT	GG	GG	GG	CC	Male	0.171	33	SNPchip
35	TT	GG	GG	GG	CC	Female	0	66	SNPchip
36	TT	GG	GG	GG	CC	Female	0.255	60	SNPchip
37	TT	GG	GG	GC	CC	Male	0	28	SNPchip
38	TT	GG	GG	GG	CC	Male	0.10952	47	MPS
39	TT	GG	GG	GG	CC	Male	0.1579	57	MPS
40	TT	GG	GG	GG	CC	Female	0	52	MPS
41	TT	GG	GG	GG	CC	Female	0.1	89	MPS
42	TT	GG	GG	GG	CT	Male	0.40909	60	MPS
43	TT	GG	GG	GG	CC	Male	0.28571	38	MPS
44	TT	GG	GG	GG	CC	Male	0.14286	49	MPS
45	TT	GG	GG	GG	CC	Female	0.66667	69	MPS
46	TT	GG	GG	GG	CT	Female	0.38	61	MPS
47	TT	GG	GG	GG	CC	Male	0.03421	33	MPS
48	TT	GG	GG	GG	CC	Female	0.14286	57	MPS
49	TT	GG	GG	GC	CC	Female	0.2	86	MPS
50	TT	GG	GG	GG	CC	Female	0.22222	59	MPS
51	TT	GG	GG	GG	CC	Male	0.16129	23	MPS
52	TT	GG	GG	GG	CC	Female	0.12727	66	MPS
53	TT	GT	GG	GG	CC	Male	0.06923	55	MPS
54	TT	GG	GG	GG	CC	Male	0.03333	17	MPS
55	TT	GG	GG	GG	CC	Male	0.14286	75	MPS
56	TT	GG	GG	GG	CC	Male	0.42857	65	MPS
57	TT	GT	GG	GG	CT	Male	0.18421	23	MPS
58	TT	GG	GG	GG	CT	Female	0.02619	67	MPS
59	TT	GG	GG	GG	CC	Male	0.03448	50	MPS
60	TT	GG	GG	GG	CC	Female	0.04546	49	MPS
61	TT	GG	GG	GG	CC	Male	0.152	55	MPS
62	TT	GG	GG	GG	CC	Male	0.09375	84	MPS
63	TT	GG	GG	GG	CC	Male	0.25	62	MPS
64	TT	GG	GG	GG	CC	Male	0.35714	28	MPS

Table S1 (continued) Genotype data for five loci meeting genome-wide significance in relation to the ratio of O-desmethyltramadol to tramadol (M1:T) phenotype of 136 autopsied Finns. Genotypes are indicated in the forward strand; "NA" indicates missing genotype assignment; general sample information including biological sex, M1:T phenotype measurement, age, and genotyping method are provided.

Sample Number	rs184199168/exm1592932	rs72732317/kgp3743668	rs62435418/kgp10370907	rs79983226/kgp11274252	rs9384825	Sex	M1:T	Age	Method
65	TT	GG	GG	GG	CC	Female	0.11864	59	MPS
66	TT	GG	GG	GG	CC	Male	0.08333	31	MPS
67	TT	GG	GG	GG	CC	Female	0.13333	76	MPS
68	TT	GG	GG	GC	CC	Male	0.2037	21	MPS
69	TT	GG	GG	GG	CC	Female	0.12069	22	MPS
70	TT	GG	GG	GG	CC	Female	0.125	83	MPS
71	TT	GG	GG	GG	CC	Female	0.28571	63	MPS
72	TT	GT	GG	GG	CC	Male	0.18182	65	MPS
73	TT	GG	GG	GG	CC	Male	0.375	76	MPS
74	TT	GG	GG	GG	CC	Male	0.4	64	MPS
75	TT	GG	GG	GG	CC	Female	0.06667	65	MPS
76	TT	GG	GG	GG	CC	Male	0.17647	69	MPS
77	TT	GG	GG	GG	CC	Male	0.25	23	MPS
78	TT	GG	GG	GG	CC	Male	0.125	NA	MPS
79	TT	GG	GG	GG	CC	Male	0.14286	35	MPS
80	TT	GG	GG	GG	CC	Female	0.08889	89	MPS
81	TT	GT	GG	GG	CC	Male	0.04286	48	MPS
82	TT	GG	GG	GG	CC	Male	0.28571	69	MPS
83	TT	GG	GG	GG	CC	Male	0.28261	32	MPS
84	TT	GG	GG	GG	CC	Male	0.42857	54	MPS
85	TT	GG	GG	GG	CC	Male	0.2	42	MPS
86	TT	GT	GG	GG	CC	Male	0.18367	50	MPS
87	TT	GG	GG	GG	CT	Male	0.12	54	MPS
88	TT	GG	GG	GG	CC	Male	0.02326	41	MPS
89	TT	GG	GG	GG	CC	Male	0.21429	70	MPS
90	TT	GG	GG	GG	CC	Male	0.17143	77	MPS
91	TT	GG	GG	GG	CT	Female	0.08	86	MPS
92	TT	GG	GG	GG	CC	Male	0.07692	40	MPS
93	TT	GG	AG	GG	CC	Male	0.05882	46	MPS
94	TT	GG	GG	GG	CC	Male	0.27273	57	MPS
95	TT	GT	GG	GG	CC	Female	0.16667	21	MPS
96	TT	GG	GG	GG	CC	Male	0.05405	32	MPS
97	TT	GG	GG	GG	CC	Female	0.04	45	MPS
98	TT	GG	GG	GG	CC	Male	0.01429	56	MPS
99	TT	GG	GG	GG	CC	Male	0.25	63	MPS
100	TT	GG	GG	GG	CC	Male	0.18182	61	MPS
101	TT	TT	GG	GG	CC	Male	0.4	89	MPS
102	TT	GG	GG	GG	CC	Male	0.4	26	MPS
103	TT	GG	GG	GG	CC	Female	0.05556	46	MPS
104	TT	GG	GG	GG	CC	Female	0.17647	64	MPS
105	TT	GG	GG	GG	CC	Male	0.14286	55	MPS
106	TT	GG	GG	GG	CC	Male	0.28571	39	MPS
107	TT	GG	GG	GG	CC	Female	0.07813	62	MPS
108	TT	GG	GG	GG	CC	Female	0.07692	82	MPS
109	TT	GG	GG	GG	CC	Female	0.08462	36	MPS
110	TT	GG	GG	GG	CC	Male	0.4	70	MPS
111	TT	GG	AG	GG	CC	Male	0.25	94	MPS
112	TT	GG	GG	GC	CC	Female	0.08889	81	MPS
113	TT	GG	AG	GG	CC	Female	0.18182	54	MPS
114	TT	GG	GG	GG	CC	Female	0.125	92	MPS
115	TT	GG	GG	GG	CC	Male	0.21053	30	MPS
116	TT	GG	GG	GG	CC	Male	0.33333	57	MPS
117	TT	GG	GG	GG	CC	Female	0.16154	70	MPS
118	TT	GG	GG	GG	CC	Male	0.05517	55	MPS
119	TT	GG	GG	GG	CC	Female	0.07143	47	MPS
120	TT	GG	GG	GG	CC	Female	0.17647	67	MPS
121	TT	GG	GG	GG	CC	Female	0.09091	49	MPS
122	TT	GG	GG	GG	CC	Male	0.19355	50	MPS
123	TT	GG	GG	GG	CC	Male	0.18	52	MPS
124	TT	GG	GG	GG	CC	Male	0.36145	29	MPS
125	TT	GG	GG	GG	CC	Male	0.06667	31	MPS
126	TT	GG	GG	GG	CC	Male	0.20833	68	MPS
127	TT	GT	GG	GG	CC	Male	0.22222	66	MPS
128	TT	GG	GG	GC	CC	Female	0.15385	63	MPS
129	TT	GG	GG	GG	CC	Male	0.11111	82	MPS
130	TT	GG	GG	GG	CC	Male	0.15385	43	MPS
131	TT	GG	GG	GG	CT	Male	0.28571	89	MPS

Table S1 (continued) Genotype data for five loci meeting genome-wide significance in relation to the ratio of O-desmethyltramadol to tramadol (M1:T) phenotype of 136 autopsied Finns. Genotypes are indicated in the forward strand; "NA" indicates missing genotype assignment; general sample information including biological sex, M1:T phenotype measurement, age, and genotyping method are provided.

Sample Number	rs184199168/ exm1592932	rs72732317/ kgp3743668	rs62435418/ kgp10370907	rs79983226/ kgp11274252	rs9384825	Sex	M1:T	Age	Method
132	TT	GG	GG	GG	CC	Female	0.36364	33	MPS
133	TT	GG	GG	GG	CC	Male	0.12	22	MPS
134	TT	GG	GG	GG	CC	Male	0.5	71	MPS
135	TT	GG	GG	GG	CC	Female	0.5	62	MPS
136	TT	GG	GG	GG	CC	Male	0.2	40	MPS

[a]Sample death certificate indicates female biological sex but sample is treated as male (see Supplemental Materials and Methods *Association Study Pre-Processing*).

Chapter 8

Concluding Remarks on the Future Direction and Application of Comprehensive Pharmacogenetic Data

Summary

This dissertation evaluated a comprehensive (full-gene) and combinatorial (multiple genes) predictive model of tramadol MP using information from five key pharmacogenes (*CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*) under the **hypothesis that comprehensive (full-gene) and combinatorial (multi-gene) pharmacogenetic profiles of select genes in the opiate metabolism and response pathways can be used to better predict MP of an individual**. The overall strategy and approach to address this hypothesis involved two specific aims: (1) define a comprehensive list of opiate-metabolism-gene polymorphisms in unexposed populations and/or populations of exposed indivudlas with no adverse side effects and (2) evaluate the predictive capability of polymorphisms on deceased tramadol-exposed Finns.

In Specific Aim 1, three levels of analysis were performed using the publicly available 1000 Genomes Project self-reported healthy individuals: (1) assess global genetic diversity of opiate metabolism genes in healthy cohorts, (2) define *CYP2D6* full-gene * alleles/haplotypes, and (3) perform haplotype analyses of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*. This Aim was divided into three chapters (Chapter 2 through 4) addressing genetic diversity in self-reported healthy individuals. **Chapter 2** characterized the population genetic diversity of approximately 15,000 single nucleotide polymorphisms (SNPs) and insertion/deletion polymorphisms (INDELs) within five genes involved in the opiate ADME (absorption, distribution, metabolism, excretion) and response processes and identified some degree of association between individual markers within different genes. **Chapter 3** used data from Chapter 2 to characterize numerous polymorphisms in the *CYP2D6* region that are not currently considered for * allele definitions. When included, the average CYP2D6 activity score decreased significantly, indicating that the inclusion of these loci is likely critical for clinical

implementation of *CYP2D6* data. Additionally, the haplotype diversity of *CYP2D6* is likely substantially higher than what is reported with existing targeted genotype approaches. Finally, **Chapter 4** established full-gene haplotypes of *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* and identified associations between the predicted activity of these trans-acting ADME and response proteins and the *CYP2D6*-predicted activity score.

Specific Aim 2 elaborated on the studies performed in Aim 1. This aim involved the design and empirical evaluation of a pathway-driven predictive model of MP in three phases. (1) **Chapter 5** analyzed the full gene region of *CYP2D6* and demonstrated the ability to predict normal versus non-normal MP with relatively high accuracy using supervised machine learning. These data demonstrated that *CYP2D6* is generally sufficient for differentiating EM/NM from all other phenotypes with high accuracy. Using phased genotype data, however, offered only slightly increased prediction accuracy for those samples in the non-EM/NM categories (i.e. PM, IM, and UM). Ultimately, the heritability of T:M1 was quite low, suggesting that the full variation in phenotype is yet to be explained, or is not fully explained, by *CYP2D6* information. (2) **Chapter 6** utilized supervised machine learning and combinatorial genetic data from *UGT2B7, ABCB1, OPRM1*, and *COMT* to predict MP in the same cohort of tramadol-exposed Finns. This phase identified a subset of fourteen loci significantly associated with the T:M1 phenotype and identified *UGT2B7* as a pharmacogene maximally explaining phenotypic variance. (3) **Chapter 6** also evaluated a fully combinatorial model (i.e., *CYP2D6*, *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT* together) of tramadol metabolism. Using all five genes together produced significantly higher MP classification accuracies than the models using *CYP2D6* alone. Overall, these data shed light on the association between various opiate ADME-R gene polymorphisms and the conversion of

tramadol to its primary metabolite M1. Additionally, associations between specific polymorphisms in all five target genes were observed. The combinatorial, pathway-driven model far exceeded the accuracy of the monogenic approach, and accuracy was maintained after an over 300-fold reduction in loci required to make the prediction. Taken together, this finding demonstrated support of a comprehensive and combinatorial multigenic approach to tramadol pharmacogenetics.

To conclude this dissertation, in **Chapter 7** the results of a genome-wide association study are described that identify potential additional genetic targets that may be relevant for future optimization of a combinatorial/pathway-driven approach to tramadol (and likely other opioids) pharmacogenetics of ante- and/or post-mortem patients. These data elucidated kgp11274252/rs79983226 (*HCN1*), rs9384825 (*RFPL4B/RNF211*), kgp10370907/rs62435418 (*ICA1/ICA69/ICAp69*), kgp3743668/rs72732317 (*KHDRBS3/T-STAR/SLM2/SALP*), and exm1592932/rs184199168 (*RGL4*) as potential genes to include in future studies due to their significant association with the rate of T to M1 conversion. Further analysis of the meta-data accompanying each sample identified patient polypharmacy as a significant confounding variable contributing to the T:M1 measurement in post-mortem tramadol-exposed Finns.

Limitations

The presented dissertation is limited by four factors. First is the selection of the 1000 Genomes Project database as a starting point to investigate the five selected genes offers some bias in the loci that could reasonably be observed. While freely available and user-friendly, the read depth requirement for submission of sequence information to the 1000 Genomes Project

is quite low (~4X) (1000 Genomes Project Consortium, *et al.* 2015). Read depth this low produces an inherent level of error and/or allele drop out possibly resulting in missing data. Additionally, the relatively large sample size of the whole database (N = 2,504) is divided into 26 smaller populations of approximately 100 individuals each. Combined with the self-reported healthy status of each sample, these features mean that some rare causal alleles will not be captured in the sample (1000 Genomes Project Consortium, *et al.* 2015). Finally, tests for departures from HWE and pairwise LD are sensitive to rare alleles as the homozygous-alternate condition is presumably infrequent in healthy/unexposed populations (Teo, *et al.* 2007). A phenotype-positive population (i.e., drug-exposed) may select for individuals of the homozygous-alternate condition via sampling bias. While likely altering HWE of the population, this is a critical feature of identifying many causal loci by enriching for the causal variant(s) via selective sampling. Additionally, the 1000 Genomes Project is limited by sequence read depth. The low read depth of the 1000 Genomes Project (minimum of 4X) may inflate the pseudohomozygote frequency (i.e., heterozygotes that appear homozygous due to drop-out of one allele). As evidenced by the data generated to date in Phase 1 of Specific Aim 1, a large number of polymorphisms in the five selected genes are observed once in various super-populations. While possibly the result of population substructure, sampling variance, and/or natural selection of an allele in those populations, rare variants observed in the homozygous-alternate condition may skew the presented HWE and pairwise LD results and downstream application of these data to population pharmacogenetics.

The second limitation to this body of research is use of the Finnish population for Specific Aim 2. While valuable for medical genetic studies due to at least one relatively recent bottleneck event and resulting population homogeneity (Palo, *et al.* 2009), the population has

a relatively small effect size, meaning that certain causal polymorphisms will not be identified that may be quite frequent in the global population. However, the data obtained from using this population will serve as the first assessment of all five selected genes in the same homogeneous population, enabling characterization of common variants, stable genetic regions, and highly evolving regions and identify loci of importance for common disease/phenotypes with relatively diverse genetic etiologies. While the assumption of population homogeneity is typically made for medical genetic studies based on this population, there is real substructure effects between the eastern and western sides of the country (Hannelius, *et al.* 2008; Palo, *et al.* 2009). Though still lower relative to other populations, the degree of substructure is significant and may impact underlying genotype-phenotype associations depending on the specific geographic origin of samples collected for this dissertation and indeed future studies of the Finnish population.

Next, this dissertation used gene-targeted MPS of critical regions and computationally inferred genotype phase (the assignment of alleles to the paternal and maternal chromosomes). As described in Chapter 1, computational phase is a limiting factor for application of pharmacogenes, specifically *CYP2D6*, due to potentially inaccurate prediction of certain * alleles. The presented data somewhat overcome this limitation by using overlapping amplicons where appropriate (i.e., within an exon) in an effort to identify which polymorphic state can be assigned to each parental chromosome. While using phased * allele information is routine in the scientific community, the data from this dissertation demonstrate that phasing may not be necessary in routine diagnostic applications of the data, especially due to the poor amplification and interrogation of the Alu regions upstream of *CYP2D6*. It may be sufficient to type and identify the presence of only those polymorphisms with potential damaging consequences or

those showing maximal impact on the phenotype of interest, such as those described in Chapters 5 and 6 of this dissertation.

Lastly, the potential for drug-drug, drug-protein, and/or protein-protein interactions is a confounding factor in Specific Aim 2 (see Chapter 7). However, it is possible, and has been eluded to herein, that drugs in the toxicology reports of this Finnish population set have uncharacterized relationships with one or more of the five proteins of interest or other trans-acting opiate ADME and response proteins that confound these toxicological data and downstream association with genetic data. It may also be possible that there are protein-protein interactions unique to either extreme of the MP spectrum. These possibilities require additional controlled experiments to systemically assess the impact of specific drug combinations on the ability to predict MP using genetic information.

Topic-specific Future Directions

A combinatorial, pathway-driven predictive model of ADME and response was generated to predict MP in a deceased tramadol-exposed Finnish population sample. The classifier accuracy relative to the *CYP2D6*-inferred MP is quite high (up to 96% depending on MP and classifier used); however, the features underlying the model rely on presence/absence of certain loci that may or may not be present in non-Finnish Europeans, other global/isolated populations, or individuals with a specific disease phenotype. Because of this population-specific allele frequency variation, the features used for Finns may be different than those necessary to classify individuals from the Brazilian, Ashkenazi Jewish, or current cosmopolitan populations, for example. Studies have demonstrated that genotype-phenotype findings from a Finnish cohort are likely more applicable to other populations than those made

from non-Finnish Europeans, for example. The Finns have at least one relatively recent evolutionary bottleneck resulting in increased genetic homogeneity and potential enrichment of globally rare loci. Studies involving the applicability of Finnish population data to other populations are still required to identify relevant markers tha may be population specific and make the defined marker set relevant to a broad community. Additionally, the selected genes are key components of the tramadol ADME and response pathways but other opioid analgesics may not rely solely on these proteins of interest for their primary activation. Oxycodone, for example, is not an agonist of the OPRM1 receptor so the associated gene may not be appropriate for predicting phenotype following exposure to oxycodone using the model developed in this dissertation. Feasibility testing in groups exposed to different types of opiate-based medications would provide classifier accuracy and better describe the potential broad impact of this panel.

As listed above and overcome in Chapters 5 and 6, phasing of genotype data only is only as good as the bioinformatic pipeline and reference population(s) used to infer chromosomal association of SNPs. There are instruments available, such as nanopore technologies, to enable sequencing of single-stranded DNA and RNA of notable length (Feng, *et al.* 2015). The resulting data contain polymorphisms on the same read, eliminating ambiguity from computational phasing. Such devices are readily available for testing. Unfortunately, they are largely still in development stages with large error rates, and small alterations to their chemistry may have impeded the studies described herein or impacted the feasibility of study findings. The base calling accuracies and quality scores have improved but remain too low (approximately 67.4-85%) for the interests of this project (Jain, *et al.* 2016; Jain, *et al.* 2016; Lindberg, *et al.* 2016; Lu, *et al.* 2016). As these chemistries become more

robust, utilizing the single molecule approaches may be vastly beneficial for combinatorial pharmacogenomic screening, especially for *CYP2D6*, which already aims to employ a more comprehensive genotyping strategy.

The word "comprehensive" has been used loosely throughout the presentation of these data to describe inclusion of *CYP2D6* intron, exon, 5' and 3' untranslated regions, and promoter targets in the MP prediction. While substantially increasing the genetic data included in the tramadol MP prediction, there are a variety of additional regulatory elements and/or alternative gene selections that may or may not directly contribute to ADME and response for the broad opiate drug class or specific drugs in this class, such as tramadol. Wang, *et al.* (2014) characterized two polymorphisms (rs133333 and rs5758550) over 10,000 bases from *CYP2D6* in the WW Binding Protein 2 N-terminal Like (*WWBP2NL*) locus that are associated with at least a two-fold increase in transcription of *CYP2D6*. The same group also characterized *CYP2D6* distant enhancer polymorphisms that are significantly associated with variable expression of CYP2D6, which may ultimately influence rate of phase I drug metabolism (Wang, *et al.* 2015). Inclusion of gene expression regulators is still an underexplored area for pharmacogenomic studies involving *UGT2B7*, *ABCB1*, *OPRM1*, and *COMT*; however, some studies have found interactions between polymorphisms in the target gene and its associated promoter and/or enhancer(s) resulting in varied gene expression (Wang, *et al.* 2013). It may be necessary to include additional elements (i.e., enhancers, micro RNA [miRNA] coding sites, and/or other genes) in the predictive model to improve accuracy.

The question of epigenetic modulation of drug metabolism has been proposed more recently as studies of miRNA activity and histone and DNA methylation studies discover disease and/or phenotype associated methylation signatures. Zeng, *et al.* (2017) identified a

miRNA (hsa-miR-370-3p) that participates in the degradation of CYP2D6, thereby modulating the efficacy of its substrates and contributing to potential idiosyncratic responses following drug administration. There are no studies suggesting that *UGT2B7*, *ABCB1*, or *OPRM1* have epigenetic regulation as a contributing factor to gene expression or enzyme activity. Conversely, *COMT* promoter hypomethylation has been correlated with positive selection of the Val158Met polymorphism that is commonly implicated in schizophrenia and bipolar disorder studies (Abdolmaleky, *et al* 2006). In addition, Park, *et al.* (2015) described differential expression of hepatic CYPs during fetal and adult stages of life. It is reasonable to hypothesize that similar regulatory patterns may exist within normal, rapid, and poor drug metabolizers either at the target gene itself or its associated regulatory elements.

Patient polypharmacy is a considerable limitation of clinical implementation of pharmacogenetic data because so few studies 1) recognize and include polypharmacy in their data analysis or 2) study the specific impact of multiple drug use on the phenotype of interest. Given the relatively broad activity of CYP2D6, it is reasonable to consider multiple drugs competing for active sites of the finite quantity of enzyme available in the body. Understanding the interplay between specific drug combinations commonly encountered (such as opioids plus benzodiazepines) will provide better support for implementing pharmacogenetic testing and ultimately provide more efficacious patient outcomes.

Conclusions

In this dissertation, a novel pathway-driven model of tramadol pharmacogenetics was evaluated using supervised machine learning algorithms and a cohort of individuals from the Finnish population. The combined predictive power of a pathway driven model was superior

to that of the single gene model currently employed in many clinical applications. The future directions of this project should focus on evaluation of the model using other populations, cohorts exposed to non-tramadol opioids, and controlled combinations of opioids and additional compounds. The resulting model could be developed into a broadly-applicable and easily clinically implemented massively parallel sequencing library preparation panel for prediction of opioid response and guidance for prescription medication practices to ultimately reduce drug administration and/or dependence.

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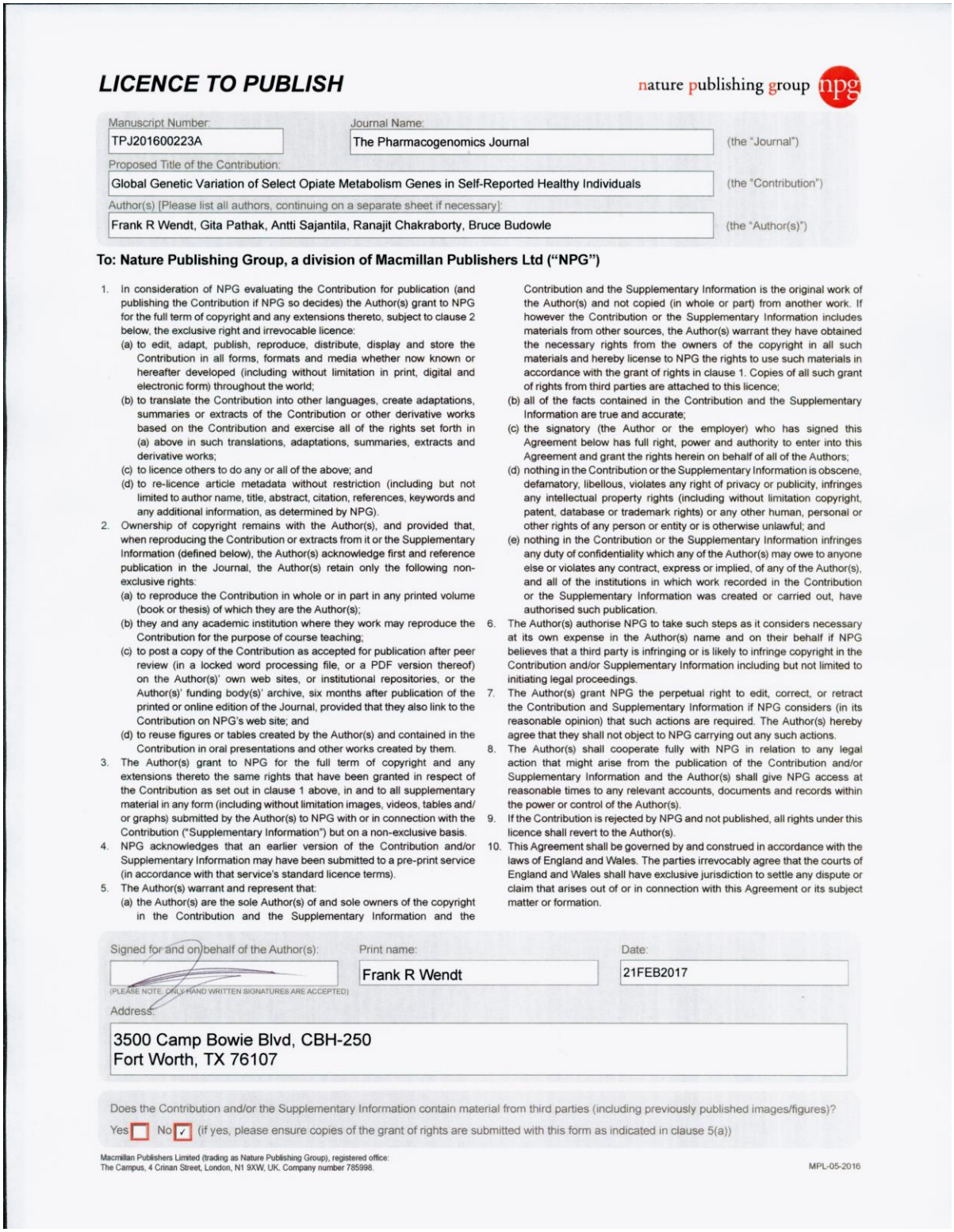

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Woerner AE, Ambers A, **Wendt FR**, King JL, Budowle B. Complete mitochondrial genome sequencing with the Precision ID Whole mtDNA Genome Panel on the MiSeq. Forensic Science International: Genetics. In Review.

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