Song, Bing, Mutual Independence of Loci in databases of Multi-locus Genotypes: Application in Human Identification and Population Genetics. Doctor of Philosophy (Biomedical Science), November 2020, 118 pp., 4 tables, 12 illustrations, reference, 63 titles.

Multi-locus genotype data are widely used in population genetics and disease studies. In evaluating the utility of multi-locus data, the independence of markers is commonly considered in many genomic assessments. Generally, pairwise non-random associations are tested for linkage disequilibrium; however, the dependence of one panel might be triplet, quartet, or other. Therefore, a compatible and user-friendly software is necessary for testing and assessing the global linkage disequilibrium among mixed genetic data.

This study describes a software package for testing the mutual independence of mixed genetic datasets. The new R package "*mixIndependR*" calculates basic genetic parameters like allele frequency, genotype frequency, heterozygosity, and Hardy-Weinberg equilibrium by mutual independence from population data, regardless of the type of markers, such as simple nucleotide polymorphisms, short tandem repeats, insertions and deletions, and any other genetic markers. A novel method of assessing the dependence of mixed genetic panels is developed in this study and functionally analyzed in the software package. By comparing the observed distribution of two common summary statistics (the number of heterozygous loci [K] and the number of share alleles [X]) with their expected distributions under the assumption of mutual independence, the overall independence is tested.

The package "*mixIndependR*" is compatible to all categories of genetic markers and detects the overall non-random associations. Compared to pairwise disequilibrium, the approach described herein tends to have higher power, especially when the numbers of markers are large. With this package, more multi-functional genetic panels can be developed, like mixed panels with different kinds of markers. In population genetics, the package "*mixIndependR*" makes it possible to discover more about admixture, natural selection, genetic drift, and population demographics, as a more powerful method of detecting LD. Moreover, this new approach can optimize variants selection in disease studies and contribute to panel combination for treatments in multimorbidity. Application of this approach in real data is expected in the future, and this might bring a leap in the field of genetic technology.

The R package "*mixIndependR*", is available on the Comprehensive R Archive Network (CRAN) at: https://cran.r-project.org/web/packages/mixIndependR/index.html

MUTUAL INDEPENDENCE OF LOCI IN DATABASES

OF MULTI-LOCUS GENOTYPES: APPLICATION

IN HUMAN IDENTIFICATION AND

POPULATION GENETICS

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MUTUAL INDEPENDENCE OF LOCI IN DATABASES OF MULTI-LOCUS GENOTYPES: APPLICATON IN HUMAN IDENTIFICATION AND POPULATION GENETICS

DISSERTATION

Presented to the Graduate Council of the

Graduate School of Biomedical Sciences

University of North Texas

Health Science Center at Fort Worth

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For the Degree of

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By

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Table 1. Difference of Variable Number of Tandem Repeat and Short Tandem Repeat [1-3]

Tandem Repeats	Minisatellites (VNTRs usually)	Microsatellites (STRs usually)
Repeat Unit	10~100bp	2~9bp
Repeats	200~several hundreds	5~200, usually less than 100

Minisatellites have longer repeat unit and higher number of repeats. Variable Number Tandem Repeat (VNTR) is the most common minisatellites. Microsatellites have shorter repeat unit and usually less than 100 times of repeat, in which short tandem repeat (STR) is the most popular.

Table 2. Example of Dataset to Import for *mixIndependR*

Sample ID	STR1	STR1_1	SNP1	SNP1_1
1	12	12	A	A
2	13	14	T	T
3	13	13	A	T
4	14	15	A	T
5	15	13	T	A
6	13	14	A	T
7	14	13	A	A
8	12	12	T	A
9	14	14	T	T
10	15	15	A	T

Each row denotes each individual sample; each column denotes each locus. Alleles on the same loci need to be side by side. Names of markers are not required to be identical, but the names of 1st,3rd,5th, …, (2i-1)-th loci will be read into the results of relative functions like "*AlleleFreq*".

X.1	Panel Size	NO_SNP	NO_STR	NO_Ln	SNP_Ln	STR_Ln	Linkage	*Bias*	*K*	*X*
1	10	5	5	0	0	0	Unlinked	Both	0.047	0.039
2	20	10	10	0	0	0	Unlinked	Both	0.050	0.036
3	30	15	15	0	0	0	Unlinked	Both	0.051	0.048
4	40	20	20	0	0	0	Unlinked	Both	0.055	0.038
5	50	25	25	0	0	0	Unlinked	Both	0.045	0.053
6	100	50	50	0	0	0	Unlinked	Both	0.047	0.051
7	10	5	5	2	2	0	OnePair-Linked	SNP	0.126	0.060
8	20	10	10	2	2	0	OnePair-Linked	SNP	0.066	0.055
9	30	15	15	2	2	0	OnePair-Linked	SNP	0.072	0.050
10	40	20	20	2	2	0	OnePair-Linked	SNP	0.064	0.040
11	50	25	25	2	2	0	OnePair-Linked	SNP	0.054	0.046
12	100	50	50	2	2	0	OnePair-Linked	SNP	0.042	0.046
13	10	5	5	2	0	2	OnePair-Linked	STR	0.040	0.042

14	20	10	10	2	0	2	OneP air-Linke d	STR	0.051	0.040
15	30	15	15	2	0	2	OneP air-Linke d	STR	0.053	0.044
16	40	20	20	2	0	2	OneP air-Linke d	STR	0.058	0.049
17	50	25	25	2	0	2	OneP air-Linke d	STR	0.045	0.045
18	100	50	50	2	0	2	OneP air-Linke d	STR	0.064	0.060
19	16	8	8	2	2	0	HalfQ uarter-Linke d	SNP	0.094	0.063
20	32	16	16	4	4	0	HalfQ uarter-Linke d	SNP	0.145	0.092
21	48	24	24	6	6	0	HalfQ uarter-Linke d	SNP	0.230	0.122
22	64	32	32	8	8	0	HalfQ uarter-Linke d	SNP	0.280	0.138
23	80	40	40	10	10	0	HalfQ uarter-Linke d	SNP	0.329	0.168
24	96	48	48	12	12	0	HalfQ uarter	SNP	0.400	0.178

							- Linked			
25	16	8	8	2	0	2	HalfQuarter - Linked	STR	0.063	0.032
26	32	16	16	4	0	4	HalfQuarter - Linked	STR	0.055	0.057
27	48	24	24	6	0	6	HalfQuarter - Linked	STR	0.047	0.051
28	64	32	32	8	0	8	HalfQuarter - Linked	STR	0.058	0.042

Table 3. Proportion of p-values<0.05 in 1000 times for different levels of linkage using summary statistics

X.1	Panel Size	NO_SNP	NO_STR	NO_Ln	SNP_Ln	STR_Ln	Linkage	*Bias*	*K*	*X*
29	80	40	40	10	0	10	HalfQuarter-Linked	STR	0.052	0.051
30	96	48	48	12	0	12	HalfQuarter-Linked	STR	0.049	0.037
31	16	8	8	2	1	1	HalfQuarter-Linked	Both	0.045	0.044
32	32	16	16	4	2	2	HalfQuarter-Linked	Both	0.069	0.041
33	48	24	24	6	3	3	HalfQuarter-Linked	Both	0.072	0.063
34	64	32	32	8	4	4	HalfQuarter-Linked	Both	0.082	0.065

35	80	40	40	10	5	5	HalfQuarter-Linked	Both	0.094	0.068
36	96	48	48	12	6	6	HalfQuarter-Linked	Both	0.109	0.069
37	8	4	4	2	2	0	Quarter-Linked	SNP	0.171	0.087
38	16	8	8	4	4	0	Quarter-Linked	SNP	0.263	0.133
39	24	12	12	6	6	0	Quarter-Linked	SNP	0.384	0.206
40	32	16	16	8	8	0	Quarter-Linked	SNP	0.485	0.238
41	40	20	20	10	10	0	Quarter-Linked	SNP	0.595	0.348
42	64	32	32	16	16	0	Quarter-Linked	SNP	0.802	0.530
43	80	40	40	20	20	0	Quarter-Linked	SNP	0.919	0.652
44	96	48	48	24	24	0	Quarter-Linked	SNP	0.960	0.748
45	8	4	4	2	0	2	Quarter-Linked	STR	0.044	0.037
46	16	8	8	4	0	4	Quarter-Linked	STR	0.042	0.049
47	24	12	12	6	0	6	Quarter-Linked	STR	0.058	0.035
48	32	16	16	8	0	8	Quarter-Linked	STR	0.051	0.056
49	40	20	20	10	0	10	Quarter-Linked	STR	0.050	0.045
50	64	32	32	16	0	16	Quarter-Linked	STR	0.057	0.040
51	80	40	40	20	0	20	Quarter-Linked	STR	0.045	0.055
52	96	48	48	24	0	24	Quarter-Linked	STR	0.048	0.051
53	8	4	4	2	1	1	Quarter-Linked	Both	0.015	0.047
54	16	8	8	4	2	2	Quarter-Linked	Both	0.03	0.058
55	24	12	12	6	3	3	Quarter-Linked	Both	0.057	0.074
56	32	16	16	8	4	4	Quarter-Linked	Both	0.052	0.094
57	40	20	20	10	5	5	Quarter-Linked	Both	0.186	0.09
58	64	32	32	16	8	8	Quarter-Linked	Both	0.303	0.137

Table 3. Proportion of p-values<0.05 in 1000 times for different levels of linkage using summary statistics (cont.)

Table 3. Proportion of p-values<0.05 in 1000 times for different levels of linkage using summary statistics (cont.)

X.1	**PanelSize**	**NO_SNP**	**NO_STR**	**NO_Ln**	**SNP_Ln**	**STR_Ln**	**Linkage**	***Bias***	***K***	***X***
59	80	40	40	20	10	10	Quarter-Linked	Both	0.382	0.154
60	96	48	48	24	12	12	Quarter-Linked	Both	0.421	0.209
61	8	4	4	4	4	0	Half-Linked	SNP	0.495	0.333
62	12	6	6	6	6	0	Half-Linked	SNP	0.603	0.405
63	16	8	8	8	8	0	Half-Linked	SNP	0.705	0.513
64	20	10	10	10	10	0	Half-Linked	SNP	0.807	0.595

65	24	12	12	12	12	0	Half-Linked	SNP	0.870	0.683
66	32	16	16	16	16	0	Half-Linked	SNP	0.940	0.831
67	40	20	20	20	20	0	Half-Linked	SNP	0.980	0.889
68	60	30	30	30	30	0	Half-Linked	SNP	0.999	0.989
69	80	40	40	40	40	0	Half-Linked	SNP	1.000	0.999
70	100	50	50	50	50	0	Half-Linked	SNP	1.000	1.000
71	8	4	4	4	0	4	Half-Linked	STR	0.036	0.037
72	12	6	6	6	0	6	Half-Linked	STR	0.036	0.043
73	16	8	8	8	0	8	Half-Linked	STR	0.051	0.039
74	20	10	10	10	0	10	Half-Linked	STR	0.053	0.041
75	24	12	12	12	0	12	Half-Linked	STR	0.041	0.045
76	32	16	16	16	0	16	Half-Linked	STR	0.042	0.048
77	40	20	20	20	0	20	Half-Linked	STR	0.048	0.045
78	60	30	30	30	0	30	Half-Linked	STR	0.055	0.044
79	80	40	40	40	0	40	Half-Linked	STR	0.052	0.064
80	100	50	50	50	0	50	Half-Linked	STR	0.035	0.057
81	8	4	4	4	2	2	Half-Linked	Both	0.011	0.116
82	12	6	6	6	3	3	Half-Linked	Both	0.290	0.150
83	16	8	8	8	4	4	Half-Linked	Both	0.326	0.171
84	20	10	10	10	5	5	Half-Linked	Both	0.388	0.221
85	24	12	12	12	6	6	Half-Linked	Both	0.419	0.242
86	32	16	16	16	8	8	Half-Linked	Both	0.513	0.297
87	40	20	20	20	10	10	Half-Linked	Both	0.638	0.374
88	60	30	30	30	15	15	Half-Linked	Both	0.830	0.516
89	80	40	40	40	20	20	Half-Linked	Both	0.934	0.687
90	100	50	50	50	25	25	Half-Linked	Both	0.982	0.819
91	16	8	8	12	8	4	ThreeQuarter-Linked	SNP	0.742	0.547
92	24	12	12	18	12	6	ThreeQuarter-Linked	SNP	0.875	0.712
93	32	16	16	24	16	8	ThreeQuarter-Linked	SNP	0.945	0.829

Table 3. Proportion of p-values<0.05 in 1000 times for different levels of linkage using summary statistics (cont.)

X.1	PanelSize	NO_SNP	NO_STR	NO_Ln	SNP_Ln	STR_Ln	Linkage	*Bias*	*K*	*X*
93	32	16	16	24	16	8	ThreeQuarter-Linked	SNP	0.945	0.829
94	40	20	20	30	20	10	ThreeQuarter-Linked	SNP	0.982	0.923
95	64	32	32	48	32	16	ThreeQuarter-Linked	SNP	0.999	0.992

96	80	40	40	60	40	20	ThreeQuarter-Linked	SNP	1	0.999
97	96	48	48	72	48	24	ThreeQuarter-Linked	SNP	1	1
98	16	8	8	12	4	8	ThreeQuarter-Linked	STR	0.378	0.207
99	24	12	12	18	6	12	ThreeQuarter-Linked	STR	0.462	0.271
100	32	16	16	24	8	16	ThreeQuarter-Linked	STR	0.614	0.339
101	40	20	20	30	10	20	ThreeQuarter-Linked	STR	0.692	0.441
102	64	32	32	48	16	32	ThreeQuarter-Linked	STR	0.897	0.667
103	80	40	40	60	20	40	ThreeQuarter-Linked	STR	0.95	0.778
104	96	48	48	72	24	48	ThreeQuarter-Linked	STR	0.976	0.846
105	16	8	8	12	6	6	ThreeQuarter-Linked	Both	0.582	0.372
106	24	12	12	18	9	9	ThreeQuarter-Linked	Both	0.738	0.499
107	32	16	16	24	12	12	ThreeQuarter-Linked	Both	0.845	0.635
108	40	20	20	30	15	15	ThreeQuarter-Linked	Both	0.914	0.719
109	64	32	32	48	24	24	ThreeQuarter-Linked	Both	0.986	0.943
110	80	40	40	60	30	30	ThreeQuarter-Linked	Both	0.997	0.974
111	96	48	48	72	36	36	ThreeQuarter-Linked	Both	0.999	0.995

Table 3. Proportion of p-values<0.05 in 1000 times for different levels of linkage using summary statistics (cont.)

X.1	**PanelSize**	**NO_SNP**	**NO_STR**	**NO_Ln**	**SNP_Ln**	**STR_Ln**	**Linkage**	***Bias***	***K***	***X***
112	10	5	5	8	5	3	Almost-Linked	SNP	0.583	0.352
113	20	10	10	18	10	8	Almost-Linked	SNP	0.82	0.682
114	30	15	15	28	15	13	Almost-Linked	SNP	0.958	0.85
115	40	20	20	38	20	18	Almost-Linked	SNP	0.99	0.928
116	50	25	25	48	25	23	Almost-Linked	SNP	0.998	0.97

117	100	50	50	98	50	48	Almost-Linked	SNP	1	1
118	10	5	5	8	3	5	Almost-Linked	STR	0.278	0.18
119	20	10	10	18	8	10	Almost-Linked	STR	0.726	0.52
120	30	15	15	28	13	15	Almost-Linked	STR	0.928	0.731
121	40	20	20	38	18	20	Almost-Linked	STR	0.976	0.894
122	50	25	25	48	23	25	Almost-Linked	STR	0.997	0.959
123	100	50	50	98	48	50	Almost-Linked	STR	1	1
124	10	5	5	10	5	5	Fully-Linked	Both	0.604	0.404
125	20	10	10	20	10	10	Fully-Linked	Both	0.835	0.691
126	30	15	15	30	15	15	Fully-Linked	Both	0.957	0.849
127	40	20	20	40	20	20	Fully-Linked	Both	0.989	0.936
128	50	25	25	50	25	25	Fully-Linked	Both	0.997	0.973
129	100	50	50	100	50	50	Fully-Linked	Both	1	1
117	100	50	50	98	50	48	Almost-Linked	SNP	1	1
118	10	5	5	8	3	5	Almost-Linked	STR	0.278	0.18
119	20	10	10	18	8	10	Almost-Linked	STR	0.726	0.52
120	30	15	15	28	13	15	Almost-Linked	STR	0.928	0.731
121	40	20	20	38	18	20	Almost-Linked	STR	0.976	0.894
122	50	25	25	48	23	25	Almost-Linked	STR	0.997	0.959
123	100	50	50	98	48	50	Almost-Linked	STR	1	1
124	10	5	5	10	5	5	Fully-Linked	Both	0.604	0.404
125	20	10	10	20	10	10	Fully-Linked	Both	0.835	0.691
126	30	15	15	30	15	15	Fully-Linked	Both	0.957	0.849
127	40	20	20	40	20	20	Fully-Linked	Both	0.989	0.936
128	50	25	25	50	25	25	Fully-Linked	Both	0.997	0.973
129	100	50	50	100	50	50	Fully-Linked	Both	1	1

'*PanelSize*': the number of markers in each panel

'NO_SNP': the number of SNPs in each panel

'NO_STR': the number of STRs in each panel

'NO_Ln': the number of linked markers in each panel

'SNP_Ln': the number of linked SNPs in each panel

'STR_Ln': the number of linked STRs in each panel

'Linkage': the level of Linkage/ the percentage of linked markers among the total number of markers.

'Bias': the distribution of linkage, In the linked markers, if the number of linked SNPs is larger than the number of linked STRs, then the variable '*Bias*' = 'SNP'; if the number of linked SNPs is smaller than the number of linked STRs, then the variable '*Bias*' = 'STR'; if the number of linked SNPs and STRs are equal, the '*Bias*'= 'Both'.

'K': the percentage which p-value <0.05 for the statistic- total number of heterozygous loci

'X': the percentage which p-value <0.05 for the statistic- total number of shared alleles

Table 4. List of 151 selected markers from the reference haplotype panel of Gymrek Lab.

MARKER ID	MARKER ID	MARKER ID	MARKER ID
4:15024:G:A	rs145035138	rs60075201	rs6824180
4:15027:A:T	rs147159831	rs60400620	rs6829346
rs10001263	rs148270126	rs60616698	rs6837818
rs10004179	rs149293287	rs60994255	rs6841277
rs10006358	rs150033822	rs61447907	rs6841415
rs10009670	rs17745701	rs61792225	rs6841571
rs10027065	rs200264340	rs61792227	rs6842197
rs10030553	rs200325555	rs61792228	rs6854023
rs10030871	rs200582289	rs61792230	rs73073891
rs111372941	rs2006748	rs61792232	rs73075705
rs111733658	rs201472453	rs61792238	rs73075709
rs112310878	rs201501054	rs61792240	rs73213566
rs11248005	rs201999055	rs61792256	rs73213573
rs113650514	rs202215695	rs61792257	rs73213577
rs113792592	rs2097491	rs61792258	rs75433628
rs116471062	rs2187874	rs61794960	rs76125013
rs11721745	rs2353623	rs61794965	rs7660115
rs11724335	rs28522661	rs61794967	rs7664056
rs11725979	rs28605783	rs61794968	rs7665922
rs11727678	rs28637238	rs61794969	rs7667153
rs11728864	rs28641663	rs61794991	rs7667654
rs11730821	rs28716751	rs61794993	rs7678326
rs11731927	rs28752145	rs61794994	rs7678633
rs11732336	rs2883236	rs6599293	rs7692530
rs11733385	rs28851238	rs6599306	rs76966599
rs11733927	rs3747693	rs6599313	rs7697467
rs11736321	rs375557453	rs6599368	rs7699689
rs11932337	rs3829	rs6599371	rs77249521
rs12509346	rs4315728	rs66492268	rs77815676
rs12511220	rs4522818	rs66526558	rs9884834
rs13114862	rs4541451	rs66830343	rs9996597
rs13119939	rs4565026	rs66898918	
rs13125667	rs4582104	rs67183375	
rs13125929	rs4627799	rs67576438	
rs13130581	rs4634177	rs6812799	
rs13145153	rs56036594	rs6814287	
rs13147163	rs57013142	rs6815089	
rs13148549	rs58344931	rs6815339	
rs13434621	rs59464888	rs6816881	
rs140113772	rs59603164	rs6817633	

The table is the list of selected markers from the STR-SNP haplotype reference created by Gymrek Lab, among which 2 markers are STRs and 149 are SNPs.

The rules for selection are as below:

Region: 10k bp to 200k bp on chromosome

Missing data: exclude the variants with $\geq 10\%$ missing genotypes

Allele Frequency: MAF (minor allele frequency) >= 0.05

Genotype missing rate per locus: genotyping rate$\geq 90\%$

Hardy Weinberg Equilibrium: $p \geq 0.001$

LD: $r^2 \geq 0.9$

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Figure 11. Power of significance level on different level of linkage for pure SNP panels…… liv

Figure 12. Power and significance level comparison between summary statistics and traditional LD test…….lvi

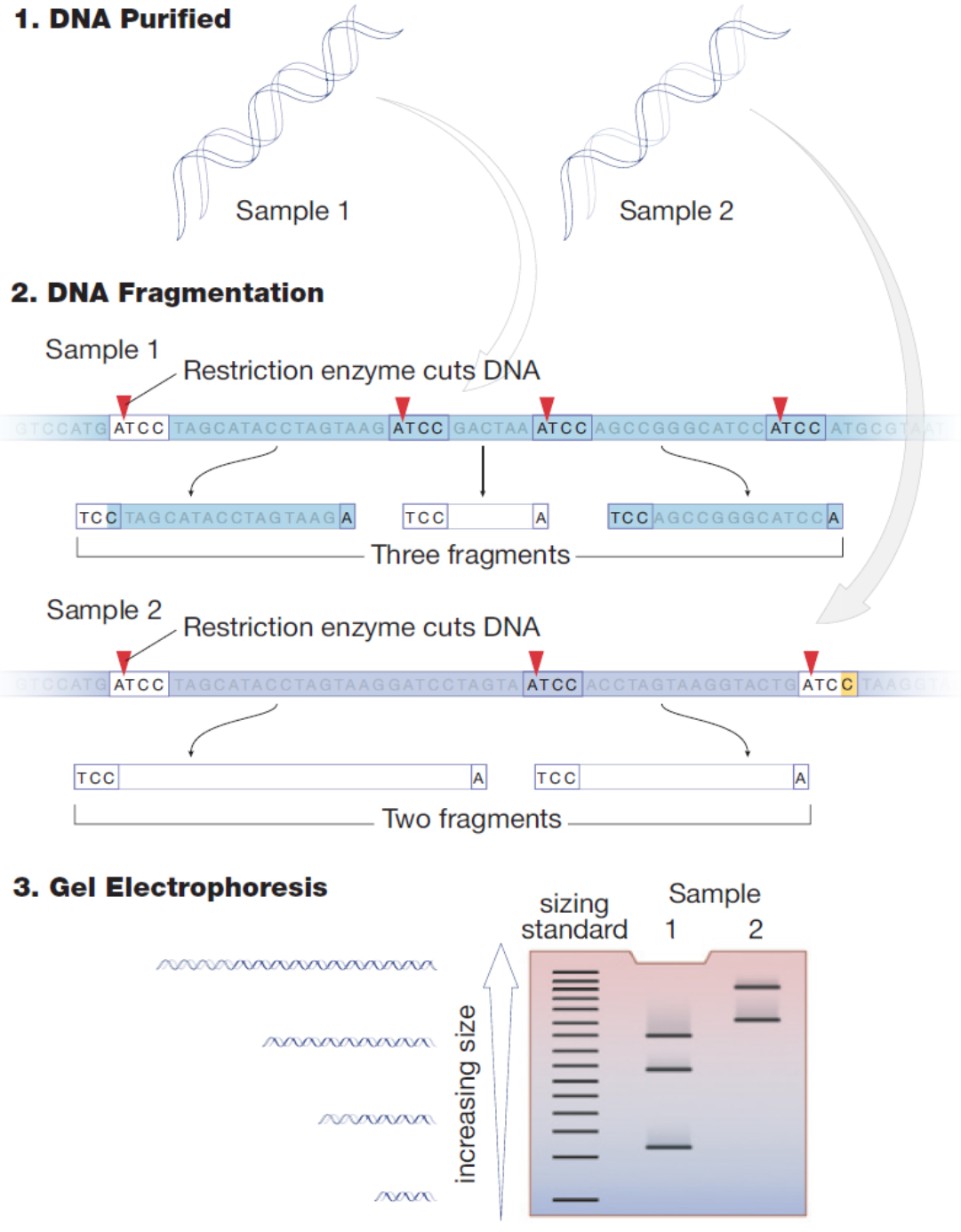

1. DNA Purified
Sample 1
Sample 2
2. DNA Fragmentation
Sample 1
Restriction enzyme cuts DNA
ATCC
TCC
A
Three fragments
Sample 2
Restriction enzyme cuts DNA
Two fragments
3. Gel Electrophoresis
sizing standard
Sample
1
2
increasing size

Figure 1

Figure 1. Restriction Fragment Length Polymorphisms[4]

1. Deoxyribonucleic acid (DNA) is extracted and purified from different samples; 2. Restriction enzyme cuts DNA at specific recognition sites. Due to the different base pair coding caused by mutations, samples are cut into different length of fragments. 3. Longer fragments run slower and closer while short fragments run farther in the gel electrophoresis. By reading the result of electrophoresis, samples are distinguished by RFLP.

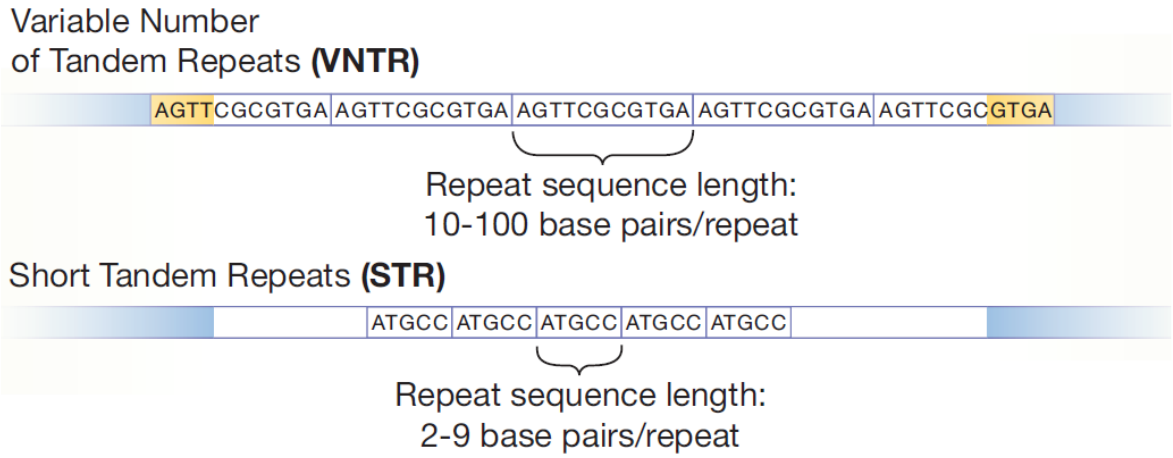

Variable Number
of Tandem Repeats (VNTR)
AGTTCGCGTGA AGTTCGCGTGA AGTTCGCGTGA AGTTCGCGTGA AGTTCGCGTGA
Repeat sequence length:
10-100 base pairs/repeat
Short Tandem Repeats (STR)
ATGCC ATGCC ATGCC ATGCC ATGCC
Repeat sequence length:
2-9 base pairs/repeat

Figure 2

Figure 2. A Comparison of Variable Number of Tandem Repeat (VNTR) and Short Tandem Repeat (STR) in structure [1]

Length of the repeat unit of VNTR is over 10 base pairs while STR have usually only 2-9 base pairs in each one repeat.

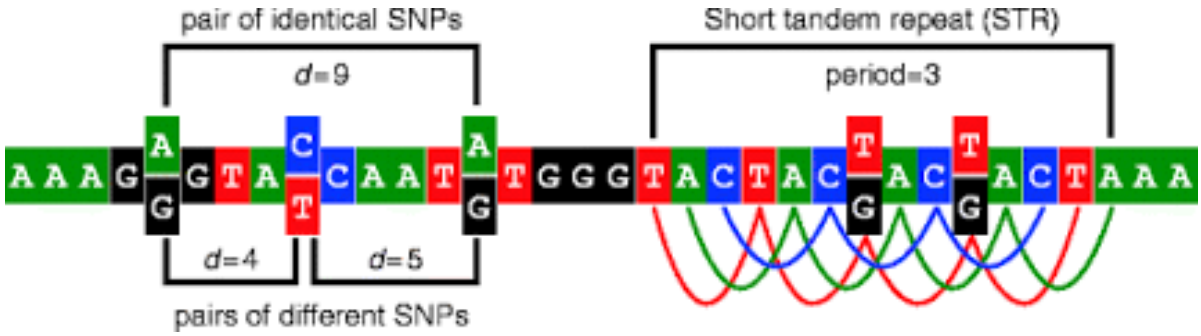

pair of identical SNPs
d=9
Short tandem repeat (STR)
period=3
AAAG
A
G
GTA
C
T
CAAT
A
G
TGGG
TACTAC
T
G
AC
T
G
ACTAAA
d=4
d=5
pairs of different SNPs

Figure 3. Single Nucleotide Polymorphism vs Short Tandem Repeats [1]

Single Nucleotide Polymorphism is a substitution of one single nucleotide at a specific position in a region of genes.

Short Tandem repeats are a pattern of nucleotides which repeat as a unit for several times, usually in different number of times between individuals. The repeat unit can be as short of 2 base pairs or as long as 100 base pairs. Tandem repeats are mostly located at non-coding region of DNA, or non-reading code region of genes.

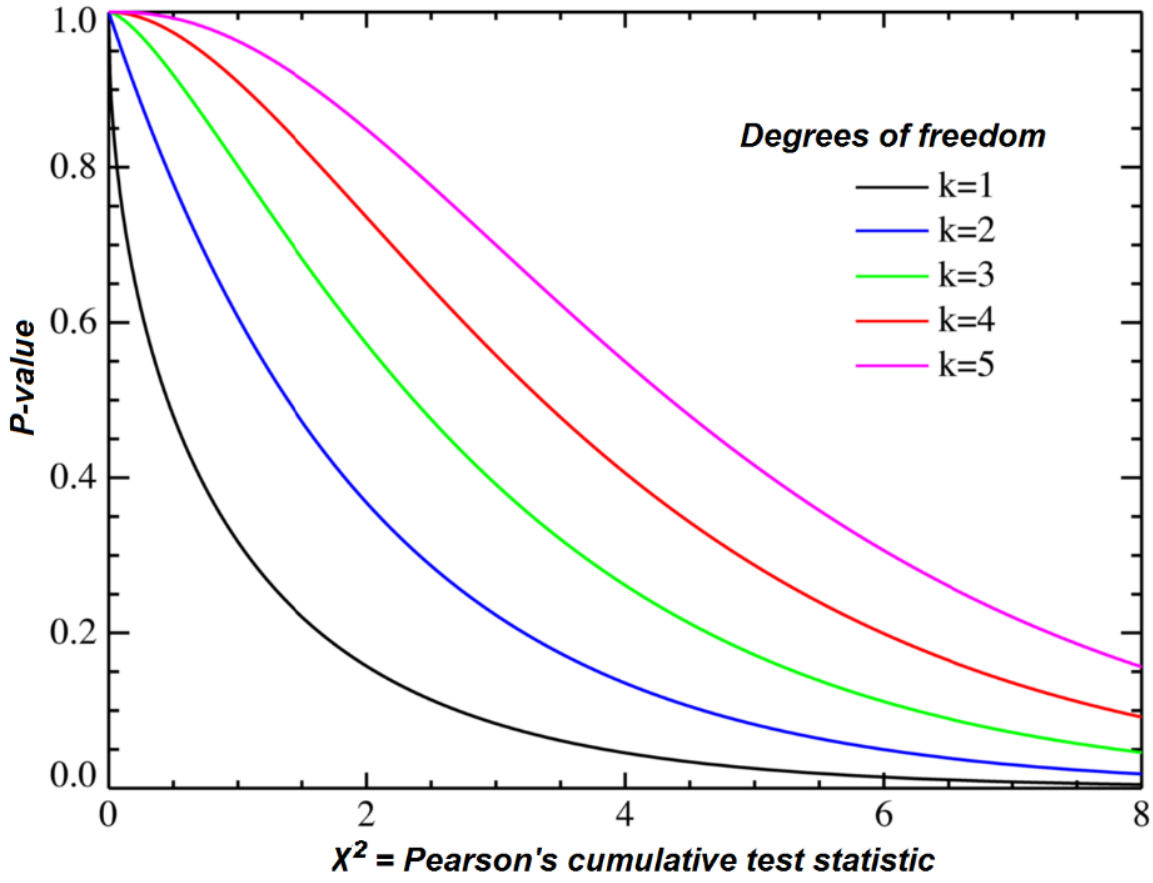

1.0
0.8
0.6
0.4
0.2
0.0
P-value
0
2
4
6
8
X² = Pearson's cumulative test statistic
Degrees of freedom
k=1
k=2
k=3
k=4
k=5

Figure 4

Figure 4. Distribution of χ^2 with different degree of freedom [5]

X-axis is the value of test statistic- χ^2; Y-axis is the p-value of χ^2 with different degree of freedom.

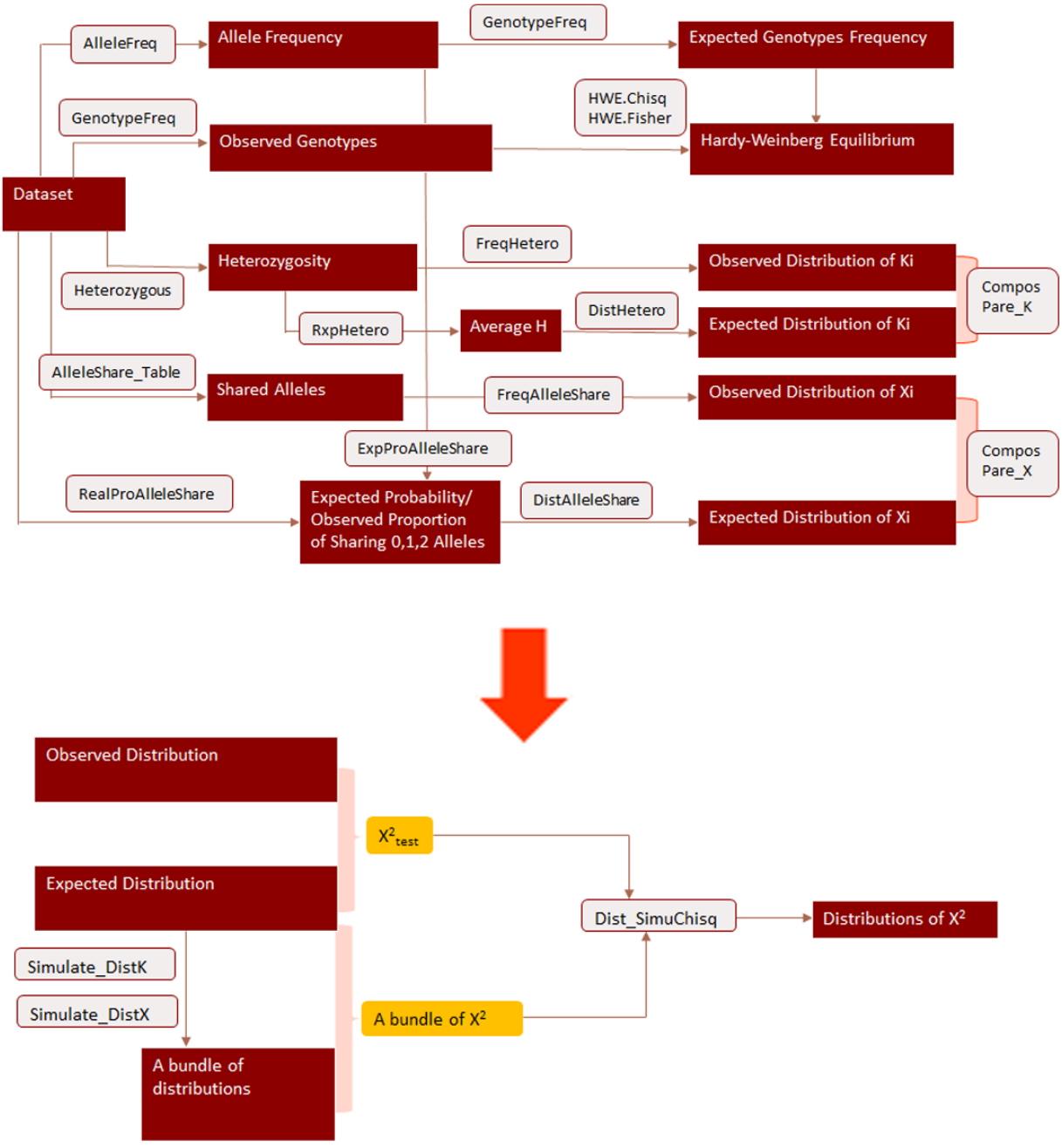

AlleleFreq
Allele Frequency
GenotypeFreq
Expected Genotypes Frequency
HWE.Chisq
HWE.Fisher
GenotypeFreq
Observed Genotypes
Hardy-Weinberg Equilibrium
Dataset
FreqHetero
Heterozygosity
Observed Distribution of Ki
Heterozygous
Compos Pare_K
RxpHetero
Average H
DistHetero
Expected Distribution of Ki
AlleleShare_Table
Shared Alleles
FreqAlleleShare
Observed Distribution of Xi
ExpProAlleleShare
Compos Pare_X
RealProAlleleShare
Expected Probability/ Observed Proportion of Sharing 0,1,2 Alleles
DistAlleleShare
Expected Distribution of Xi
Observed Distribution
X^2_{test}
Expected Distribution
Dist_SimuChisq
Distributions of X^2
Simulate_DistK
Simulate_DistX
A bundle of X^2
A bundle of distributions

Figure 5

Figure 5. Pipeline of *mixIndependR*

Functions are presented in the grey boxes, and the results are in dark red boxes. The same function in different paths use different logic parameters. Crossed paths share input parameters.

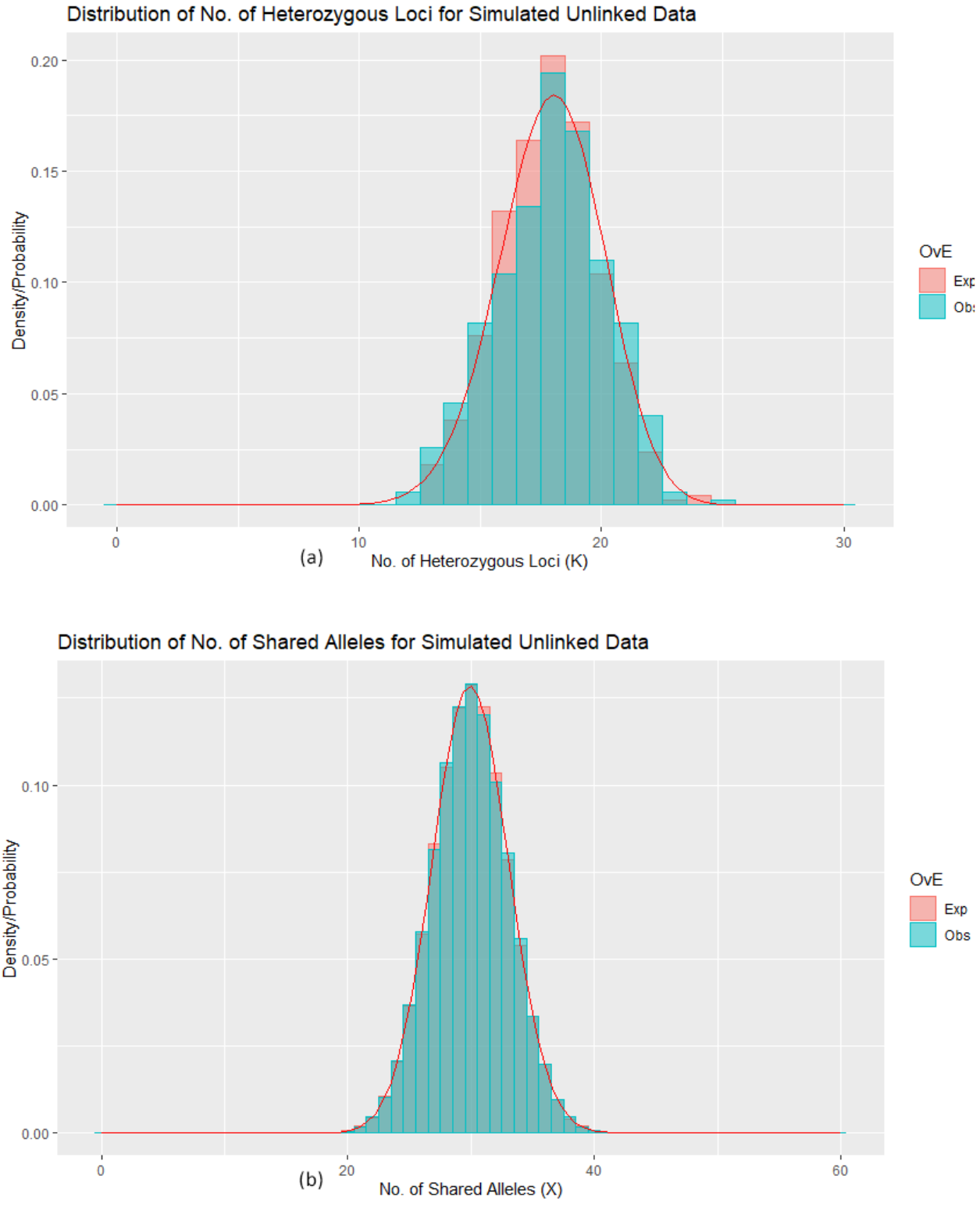
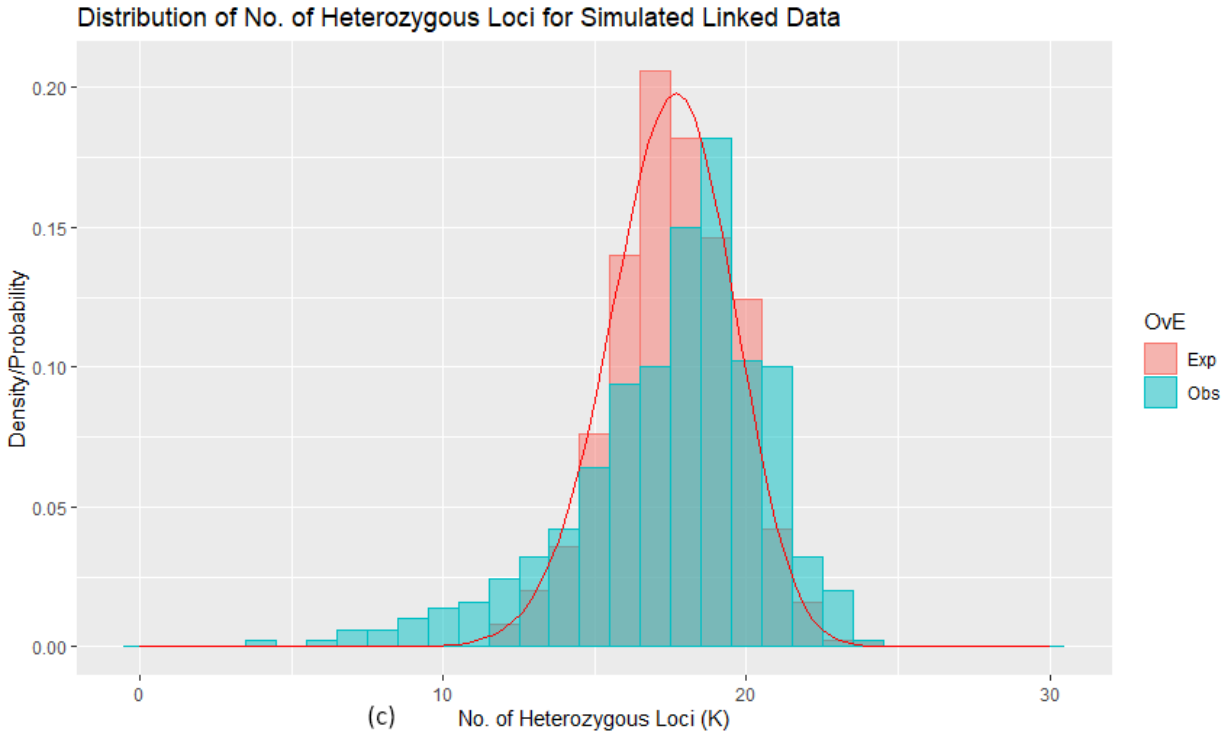

Distribution of No. of Heterozygous Loci for Simulated Unlinked Data
Density/Probability
0.20
0.15
0.10
0.05
0.00
0
10
20
30
(a)
No. of Heterozygous Loci (K)
OvE
Exp
Obs
Distribution of No. of Shared Alleles for Simulated Unlinked Data
Density/Probability
0.10
0.05
0.00
0
20
40
60
(b)
No. of Shared Alleles (X)
OvE
Exp
Obs

Figure 6



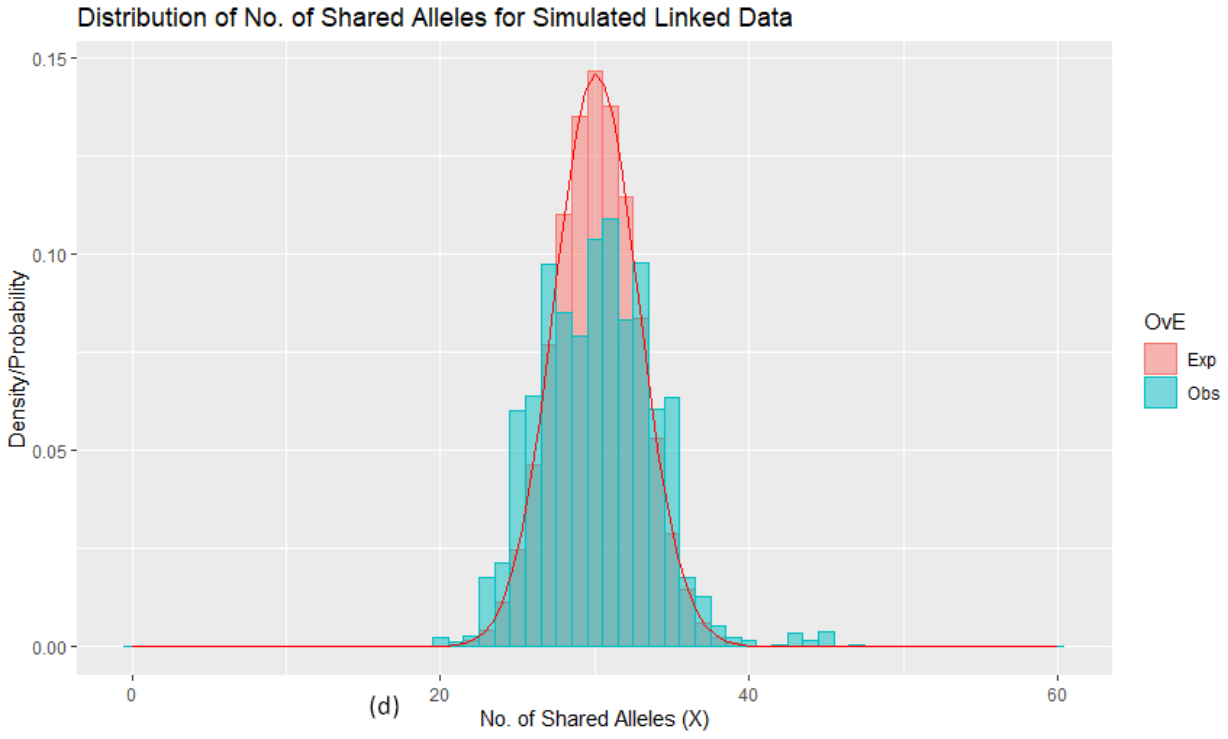
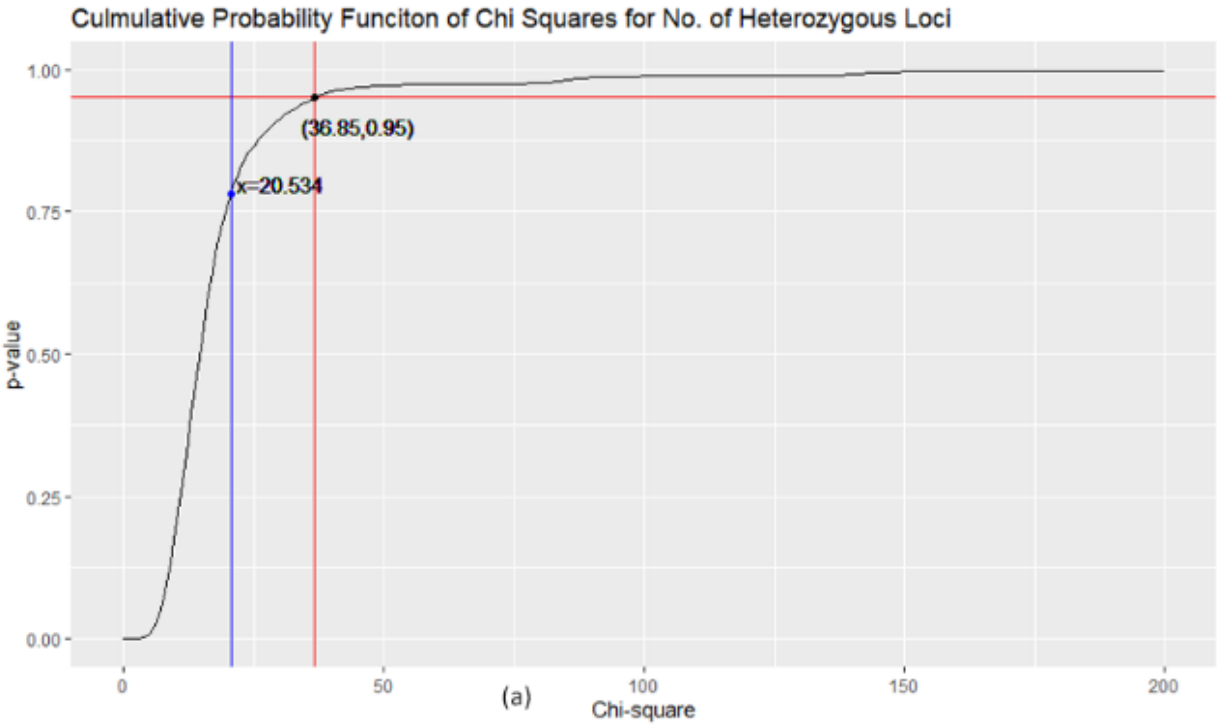


Figure 6 (Cont.)

Figure 6. Distribution of number of heterozygous loci and shared alleles for unlinked vs fully linked data

The simulated dataset is a mixed genetic panel with 20 STRs and 10 SNPs for 500 random individuals. (a) and (b) are the distribution comparisons of number of heterozygous loci and Shared Alleles (non-overlapped pairs) for unlinked data. All STRs and SNPs were generated from different chromosomes randomly. (c) and (d) are distribution comparisons of number of heterozygous loci and Shared Alleles (non-overlapped pairs) for linked data. All STRs were from the same chromosome, and all SNPs were from the same chromosome. However, STRs and SNPs were randomly grouped. Red line in plots are curves of expected probabilities.


Culmulative Probability Funciton of Chi Squares for No. of Heterozygous Loci
1.00
0.75
0.50
0.25
0.00
p-value
(36.85,0.95)
x=20.534
0
50
100
150
200
(a)
Chi-square

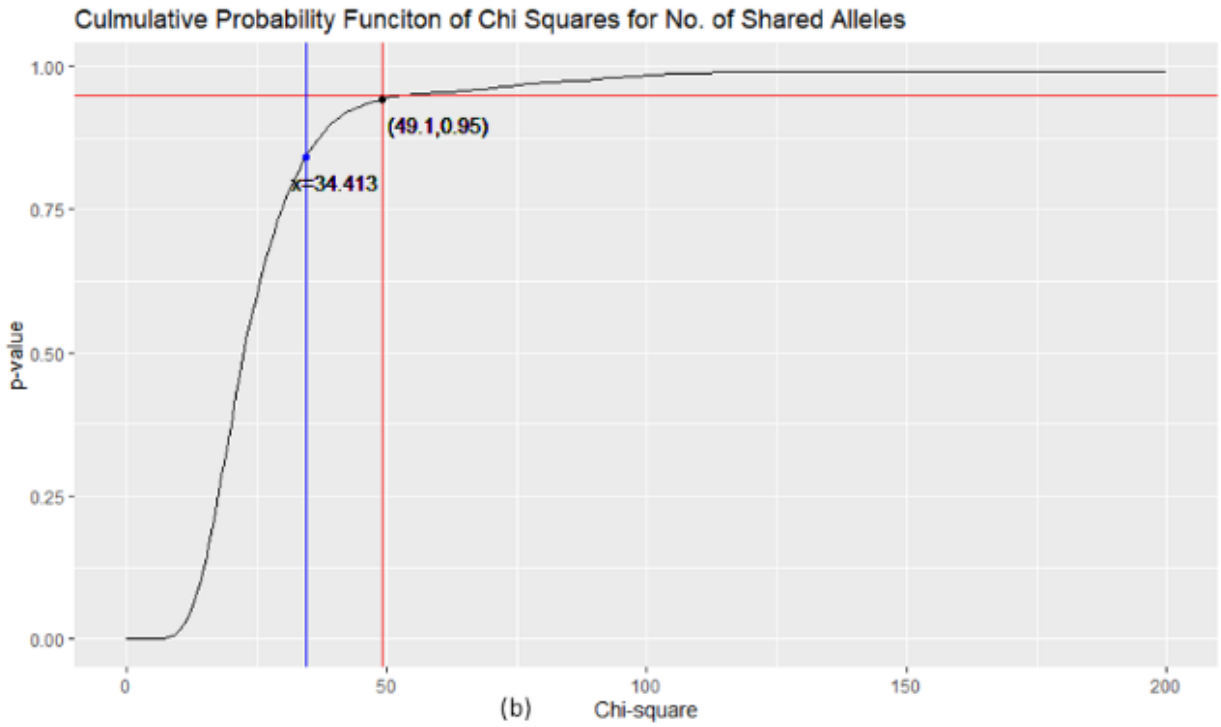
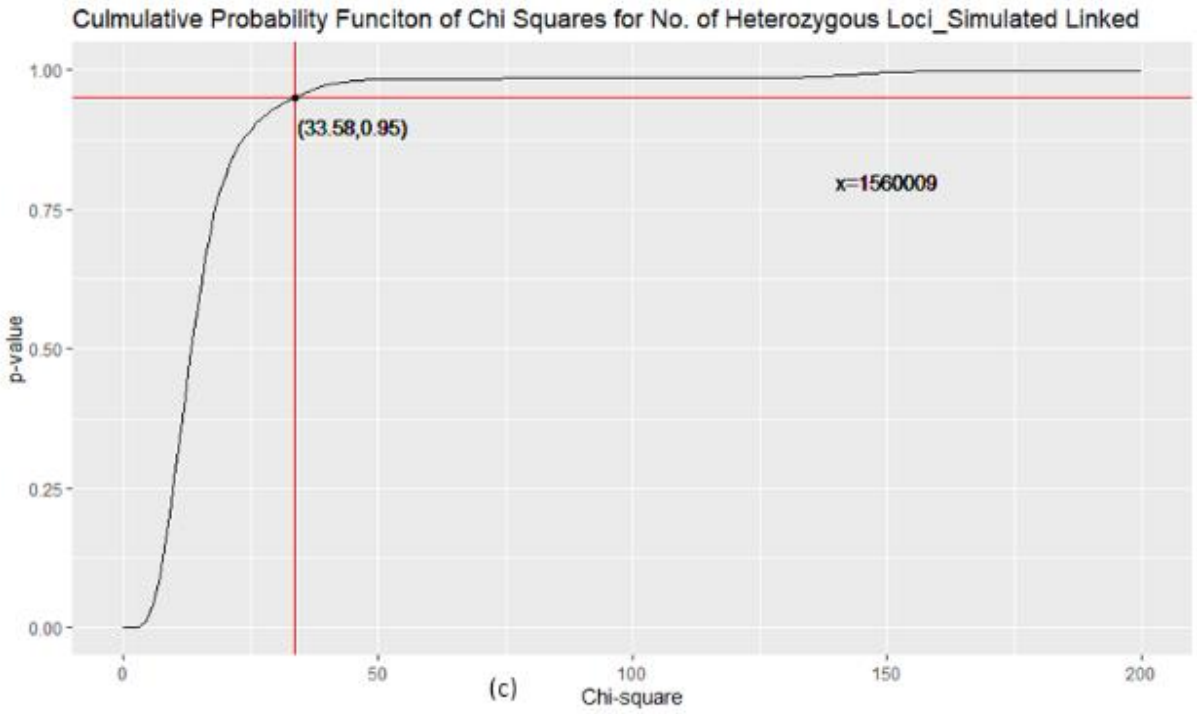

Culmulative Probability Funciton of Chi Squares for No. of Shared Alleles
1.00
0.75
0.50
0.25
0.00
p-value
(49.1,0.95)
x=34.413
0
50
100
150
200
(b)
Chi-square

Figure 7



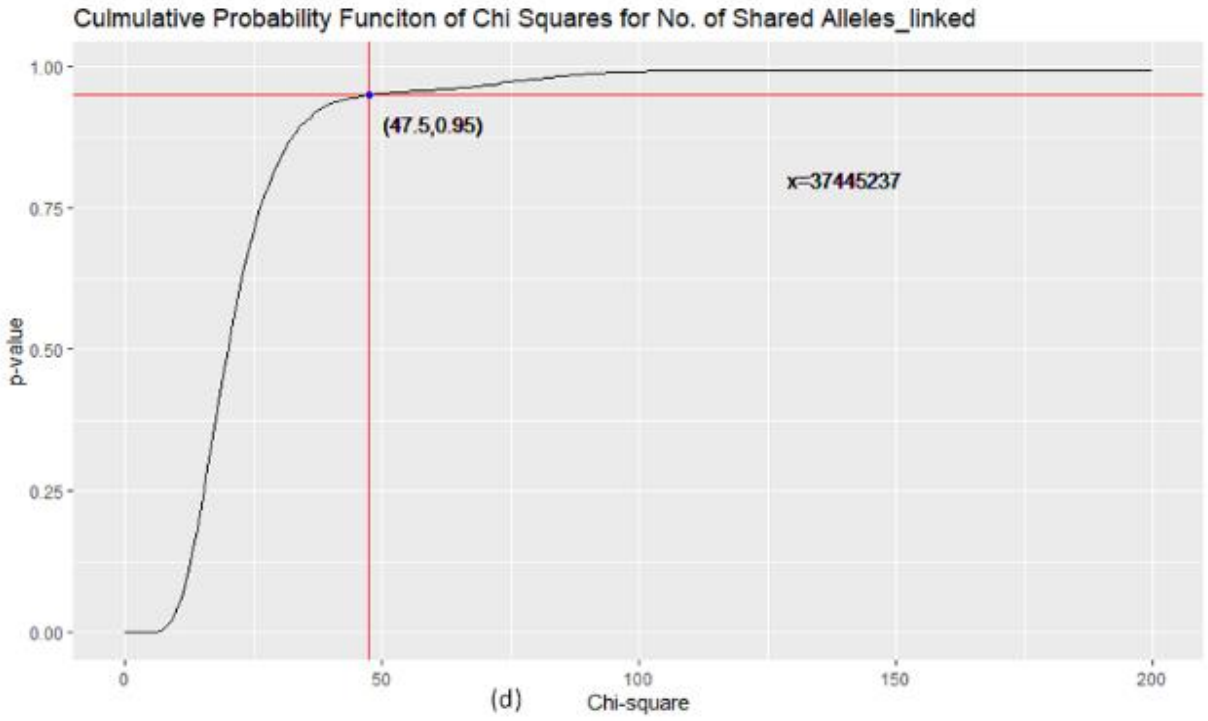
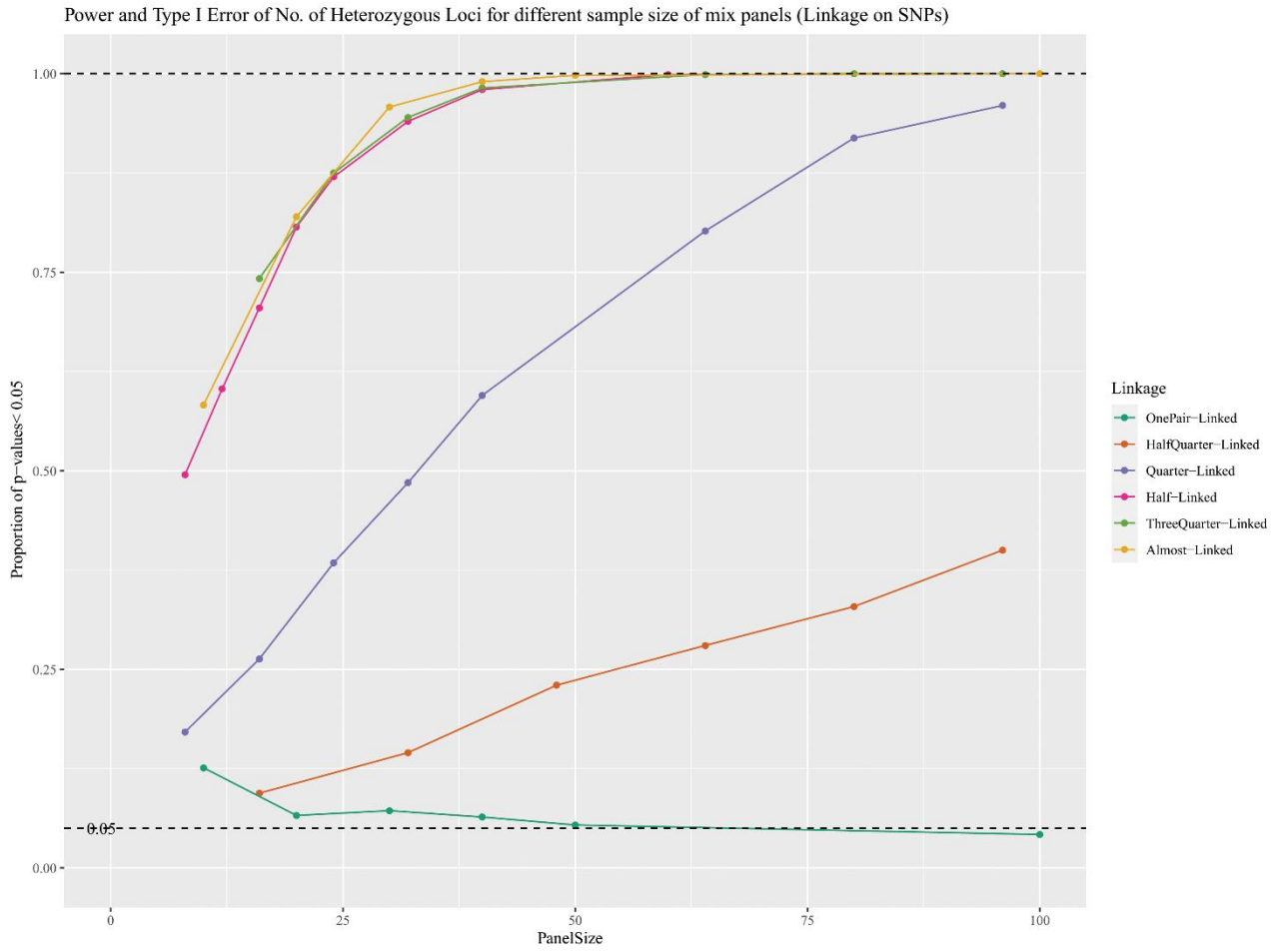


Figure 7 (Cont.)

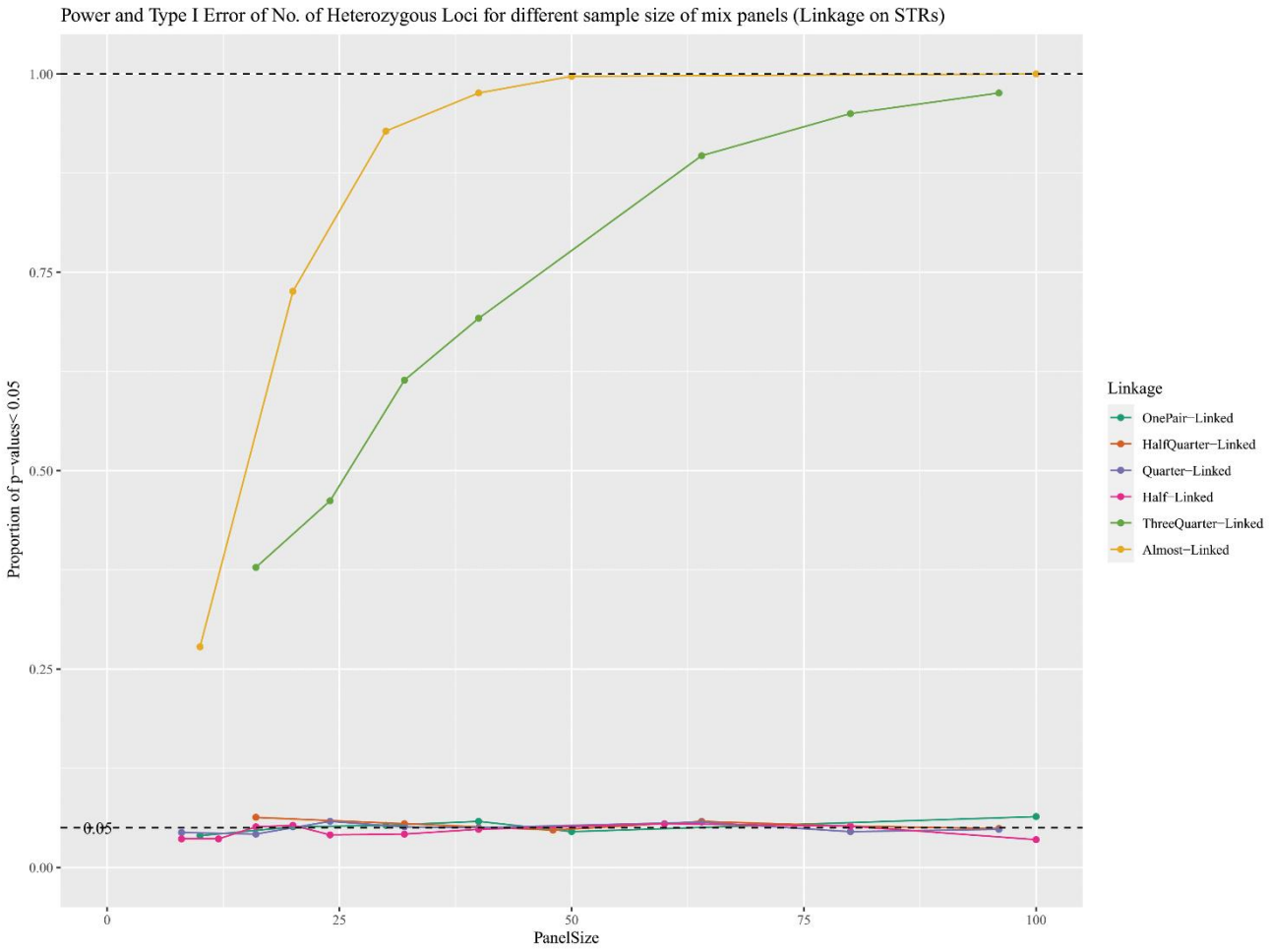
Figure 7. Curve of cumulative probability of chi-square values for number of heterozygous loci or shared alleles.

Red line is where the critical value lies for the confidence level of 95%; while the blue one is the test statistic. (a) and (b) are figures for unlinked data; (c) and (d) are figures for fully linked data. In (c) and (d), the test statistic is far larger than the critical value, and beyond the limit of x-axis.


Power and Type I Error of No. of Heterozygous Loci for different sample size of mix panels (Linkage on SNPs)
Proportion of p−values< 0.05
1.00
0.75
0.50
0.25
0.05
0.00
0
25
50
75
100
PanelSize
Linkage
OnePair−Linked
HalfQuarter−Linked
Quarter−Linked
Half−Linked
ThreeQuarter−Linked
Almost−Linked

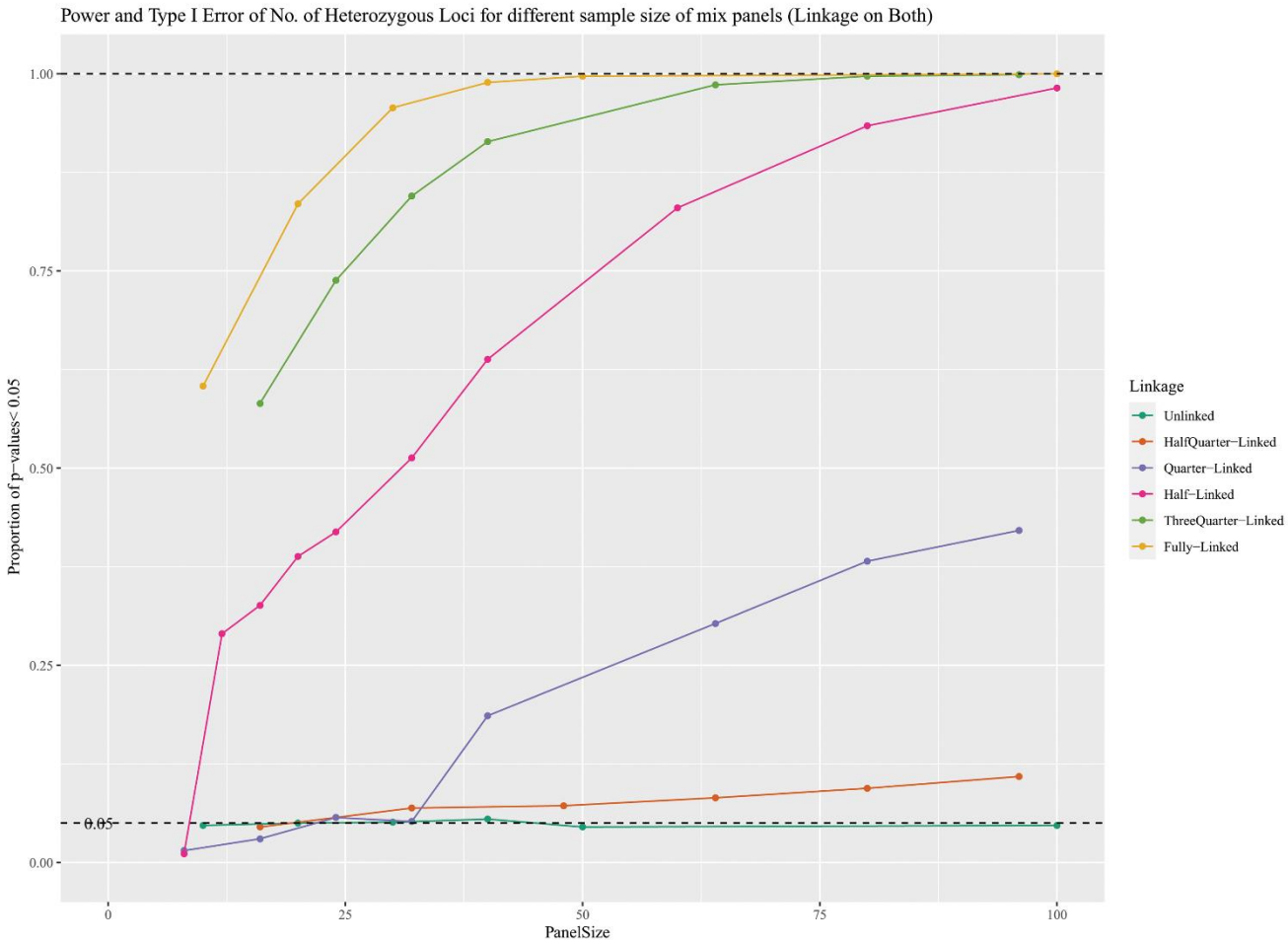
a.

Figure 8



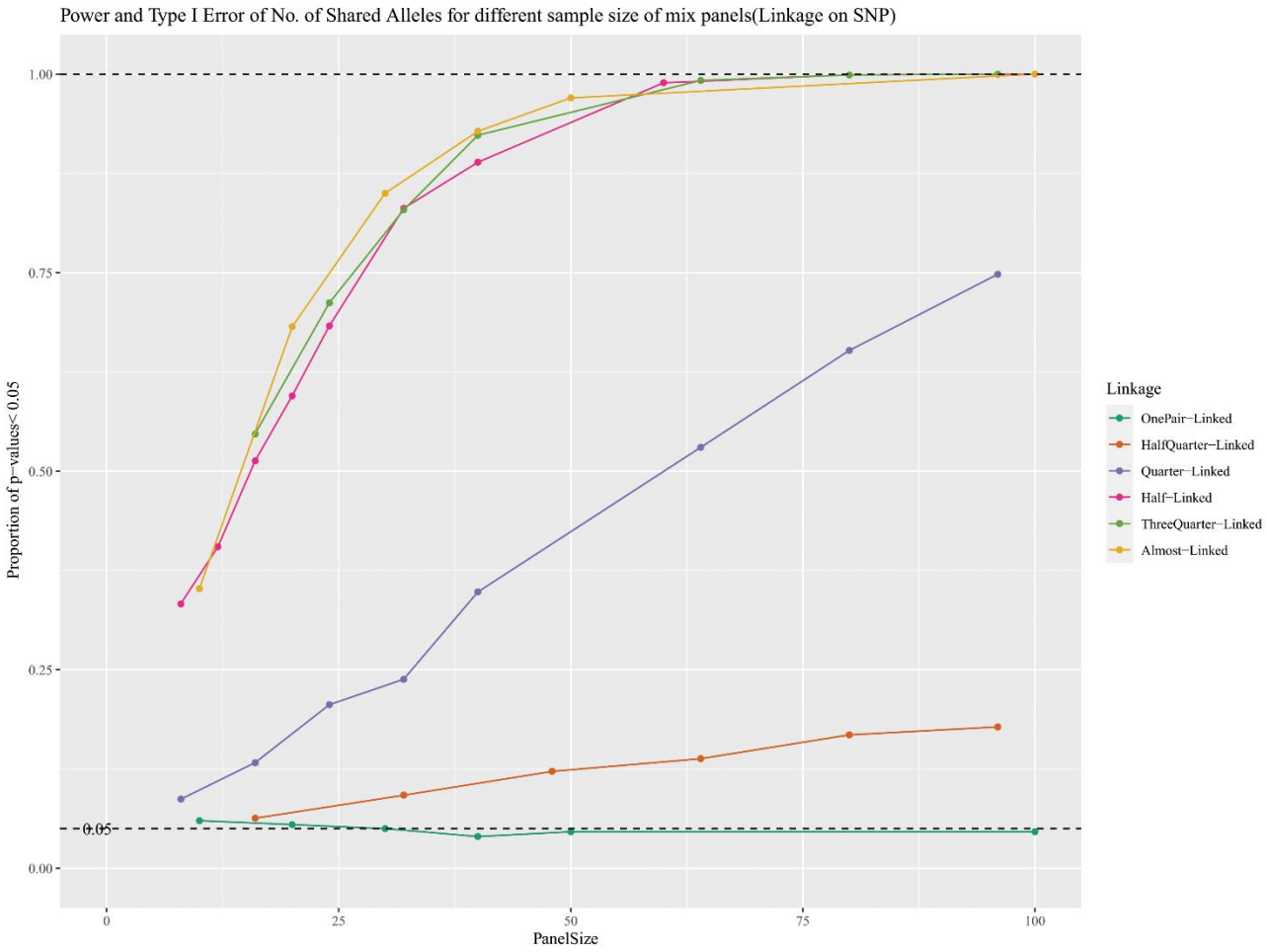
b.

Figure 8 (Cont.)



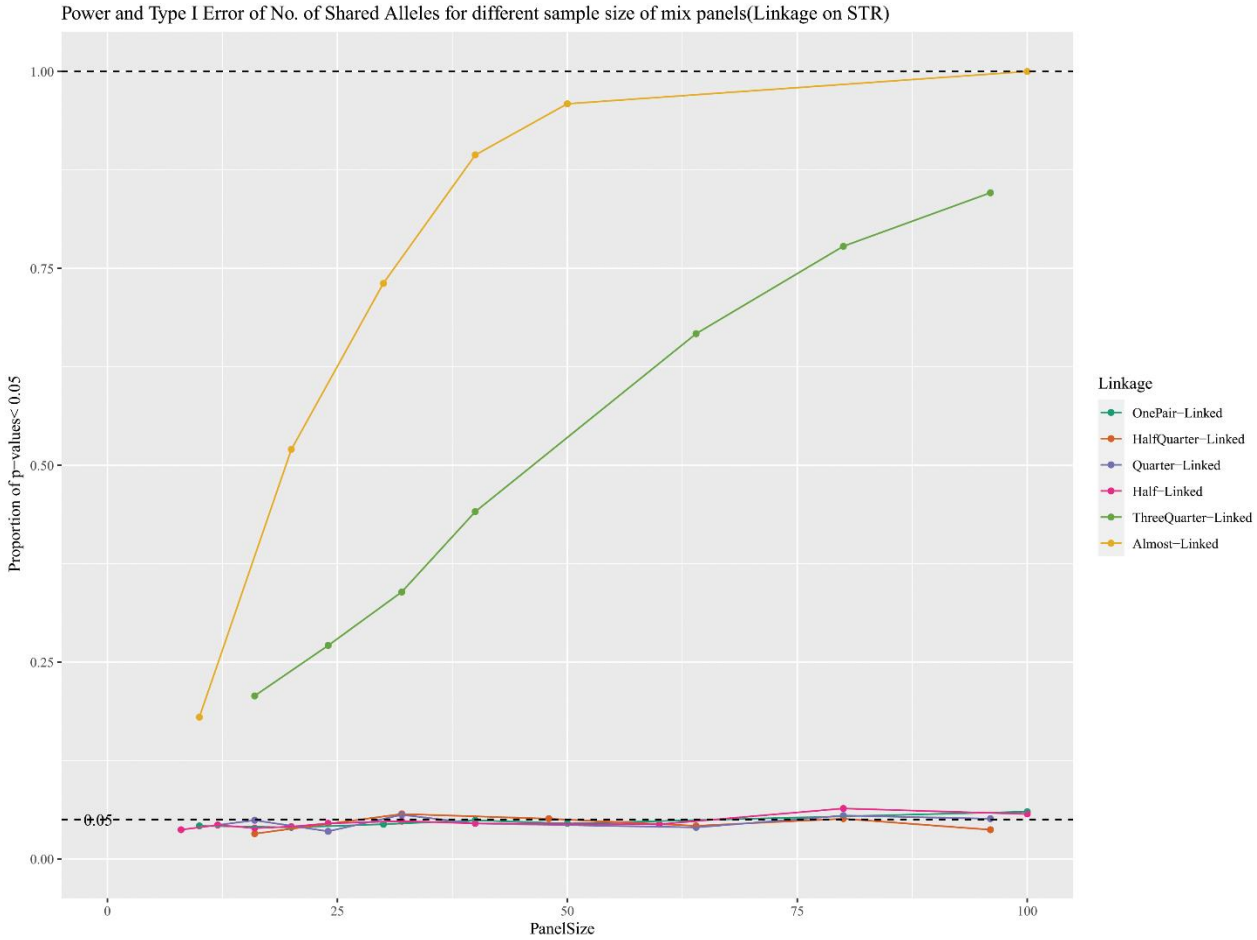
c.

Figure 8 (Cont.)



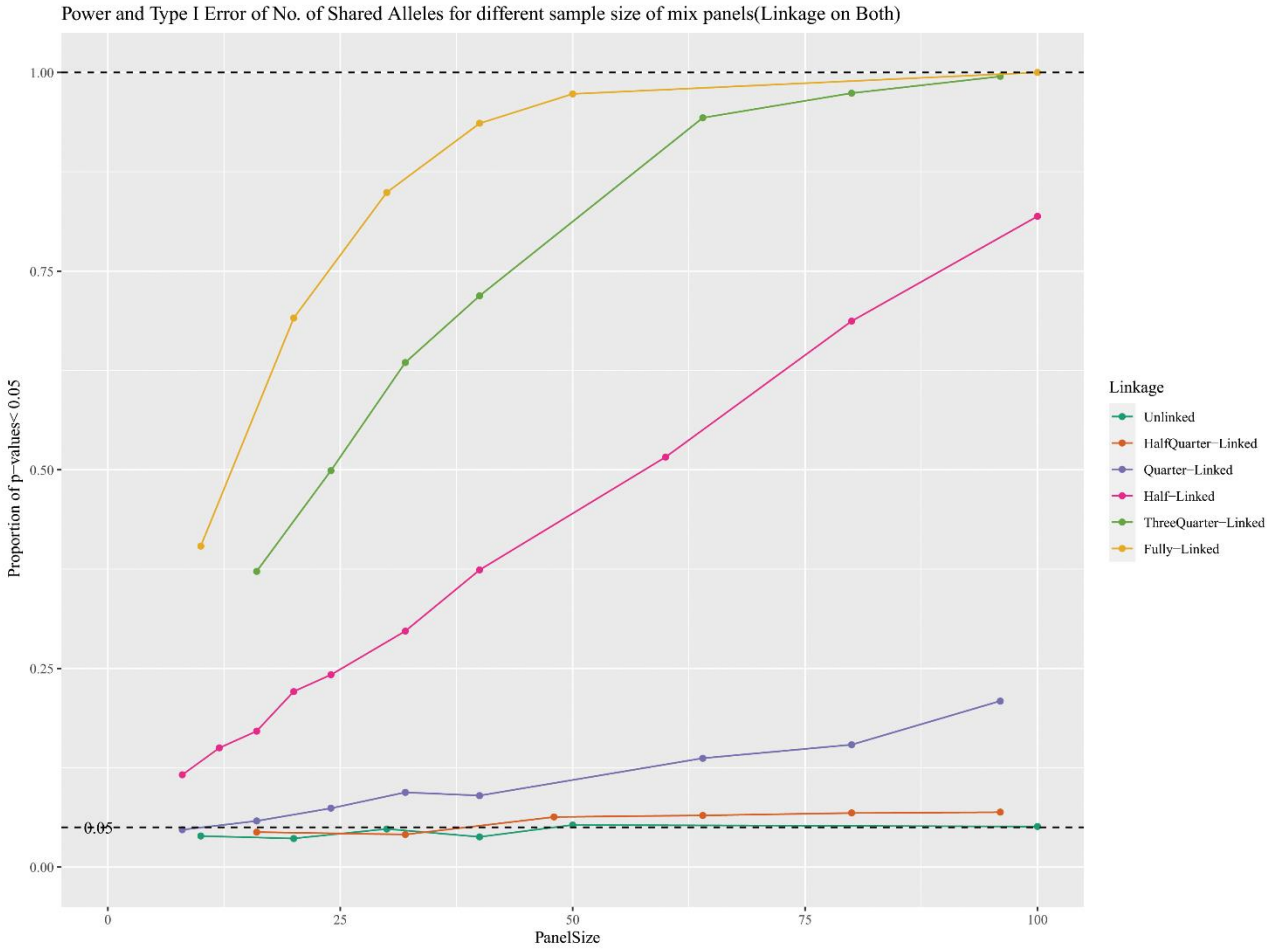
d.

Figure 8 (Cont.)



e.

Figure 8 (Cont.)



f.

Figure 8 (Cont.)

Figure 8. Power and significance level (proportion of p-values < 0.05) for different levels of linkage.

X-axis denotes the number of markers in one panel; Y-axis denotes the proportion of cases when p-values < 0.05 out of 1000 cases. For the completely unlinked panels, this proportion means significance level (Type I error) in null hypothesis; for other panels with linkages, this proportion means power (1- Type II error) of these two methods.

Figure 8a are panels with all linked markers are SNPs for *K*.

Figure 8b are panels with all linked markers on STRs for *K*.

Figure 8c are panels with equal number of linked SNPs and STRs for *K*.

Figure 8d are panels with all linked markers are SNPs of *X*.

Figure 8b are panels with all linked markers on STRs for *X*.

Figure 8c are panels with equal number of linked SNPs and STRs for *X*.

In condition, power increases with panel size extends; linkage on SNPs contributes more power than STRs; and *K* shows more power than *X*. For SNP-biased (linkage on SNPs) panels, dependency can be detected when linkage is quarter-linked or more; but for STR-biased panels, only three-quarter-linked and almost -linked panels can be tested as dependent panels. In unbiased panels, half-quarter-linkage are also hardly to be detected.

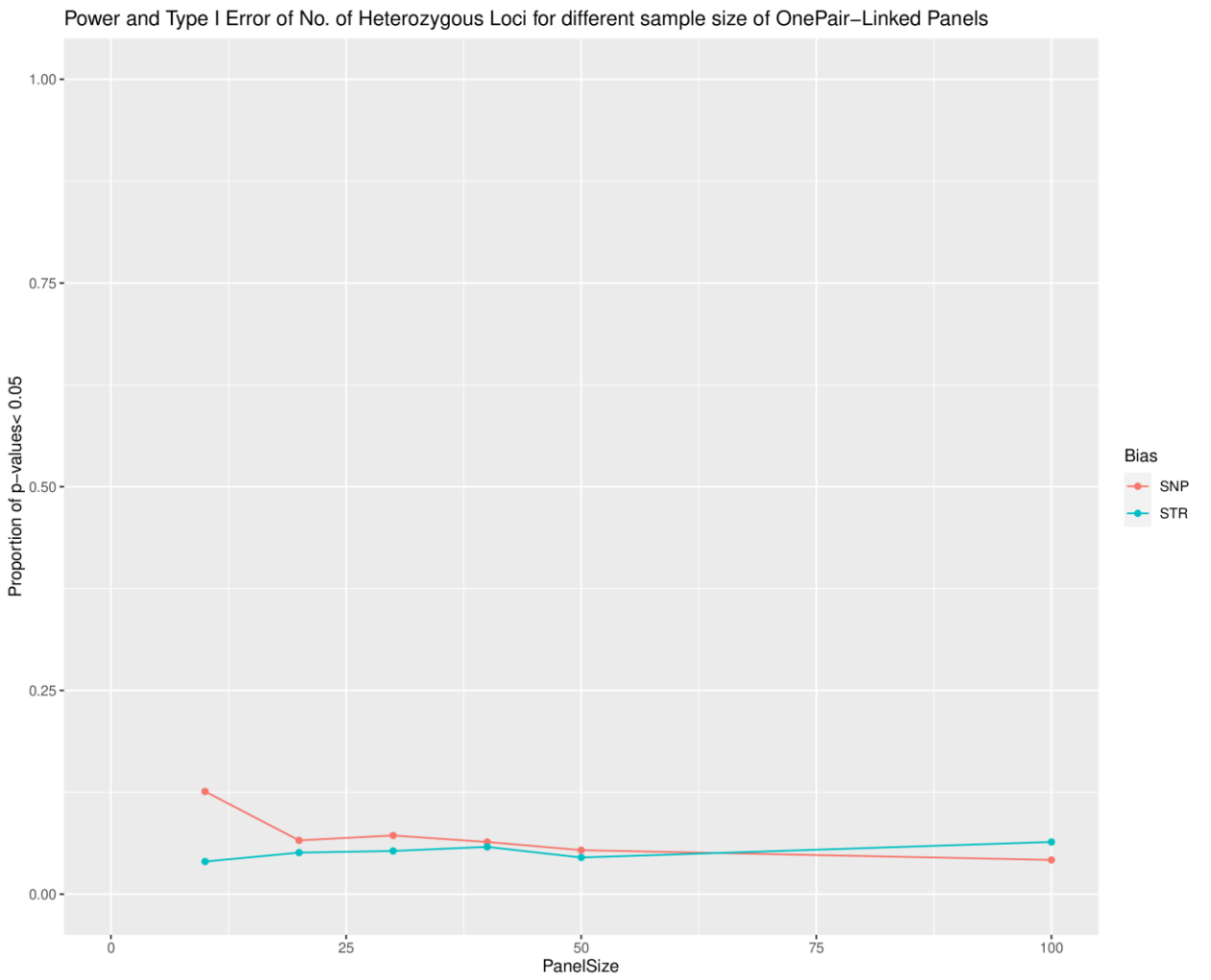

Power and Type I Error of No. of Heterozygous Loci for different sample size of OnePair−Linked Panels
Proportion of p−values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PanelSize
Bias
SNP
STR

Figure 9a

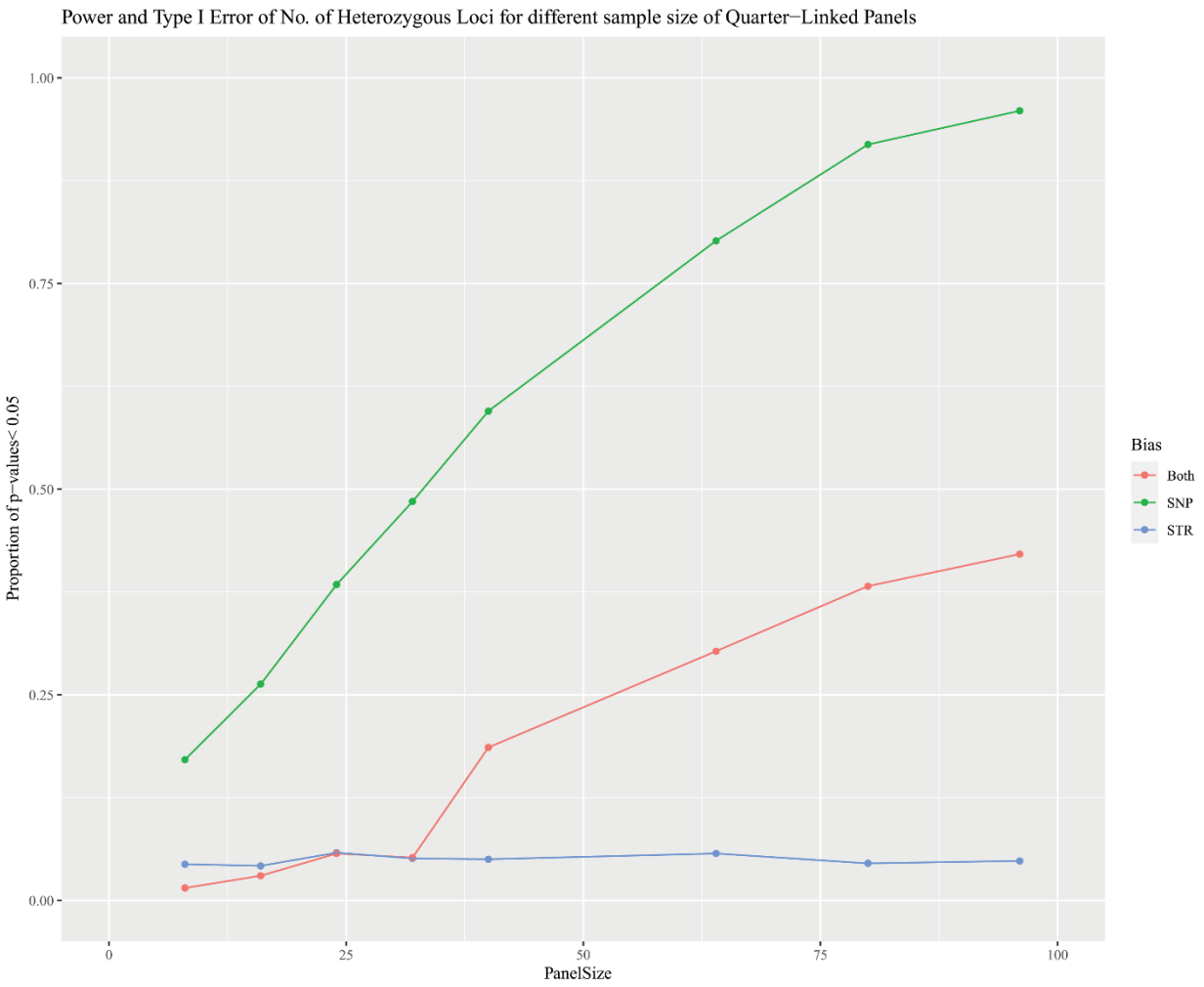

Power and Type I Error of No. of Heterozygous Loci for different sample size of Quarter−Linked Panels
Proportion of p−values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PanelSize
Bias
Both
SNP
STR

Figure 9b

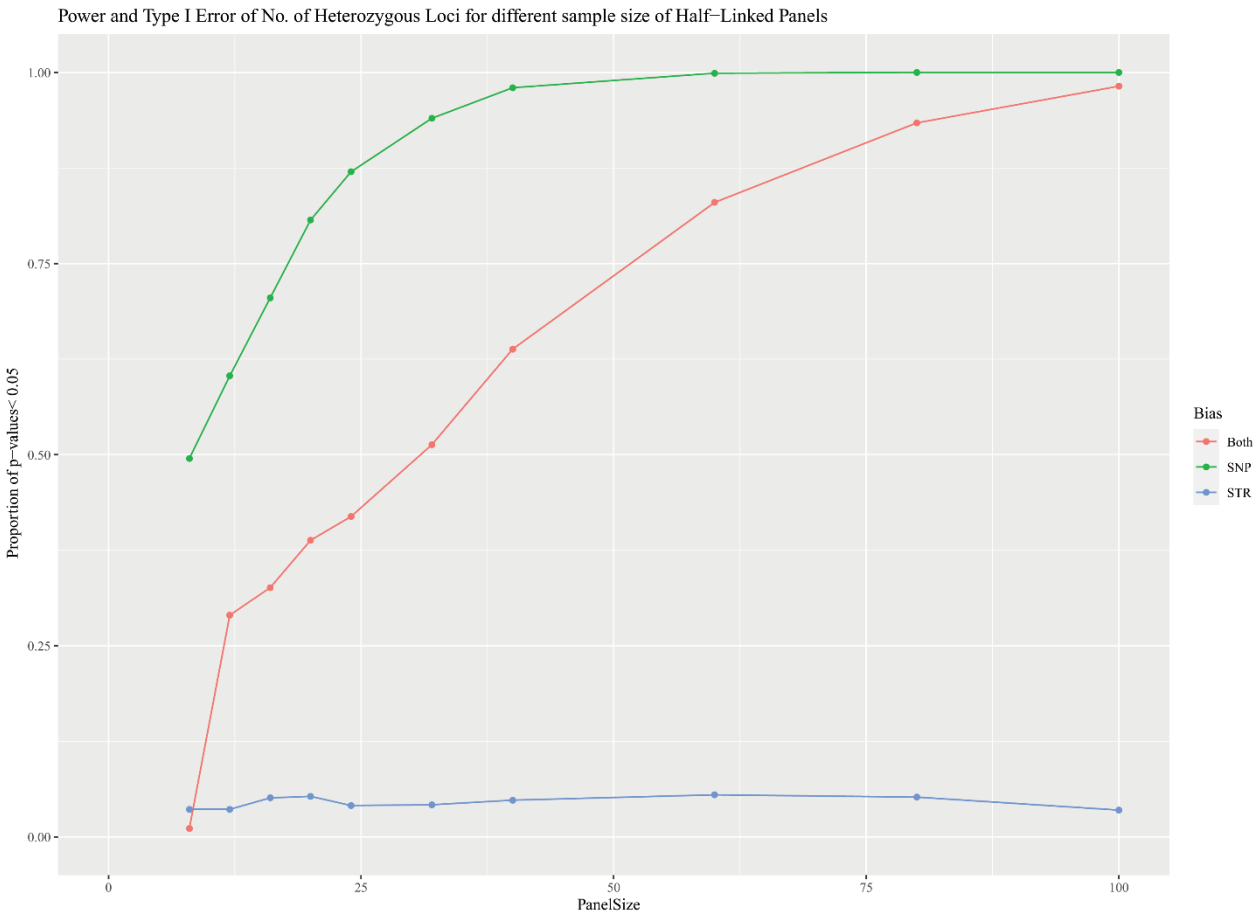

Power and Type I Error of No. of Heterozygous Loci for different sample size of Half−Linked Panels
Proportion of p−values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PanelSize
Bias
Both
SNP
STR

Figure 9c

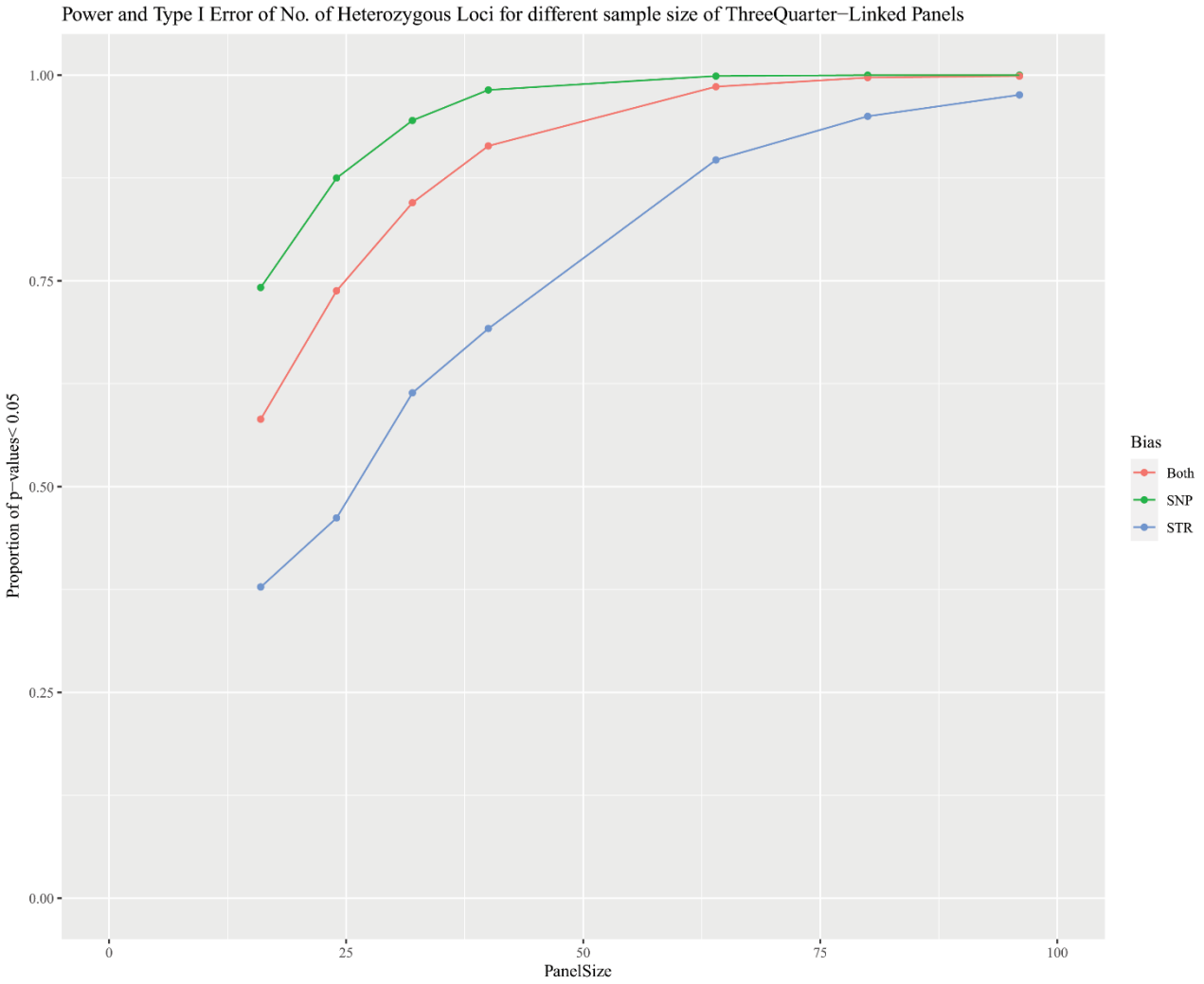

Power and Type I Error of No. of Heterozygous Loci for different sample size of ThreeQuarter−Linked Panels
Proportion of p−values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PanelSize
Bias
Both
SNP
STR

Figure 9d

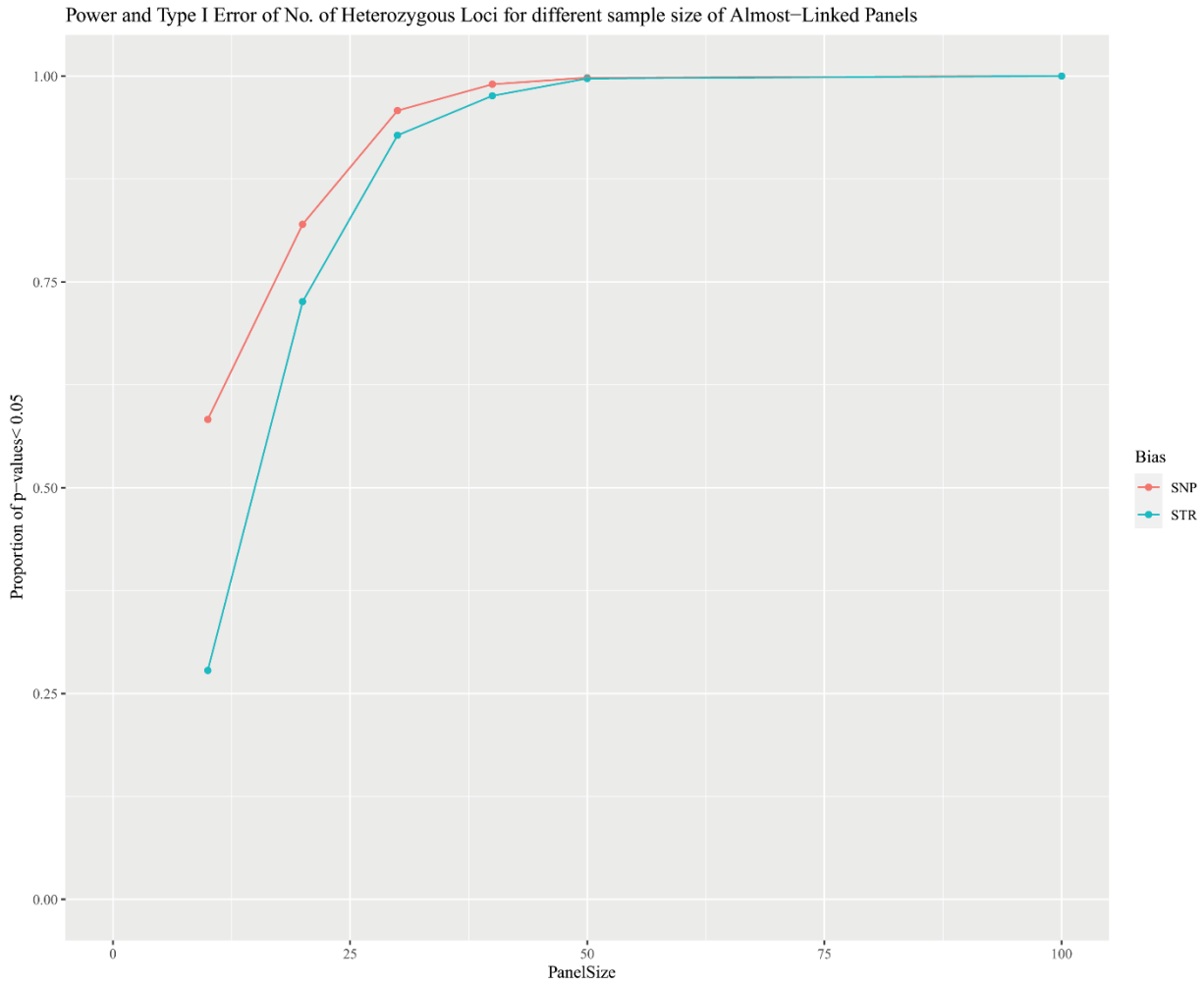

Power and Type I Error of No. of Heterozygous Loci for different sample size of Almost−Linked Panels
Proportion of p−values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PanelSize
Bias
SNP
STR

Figure 9e

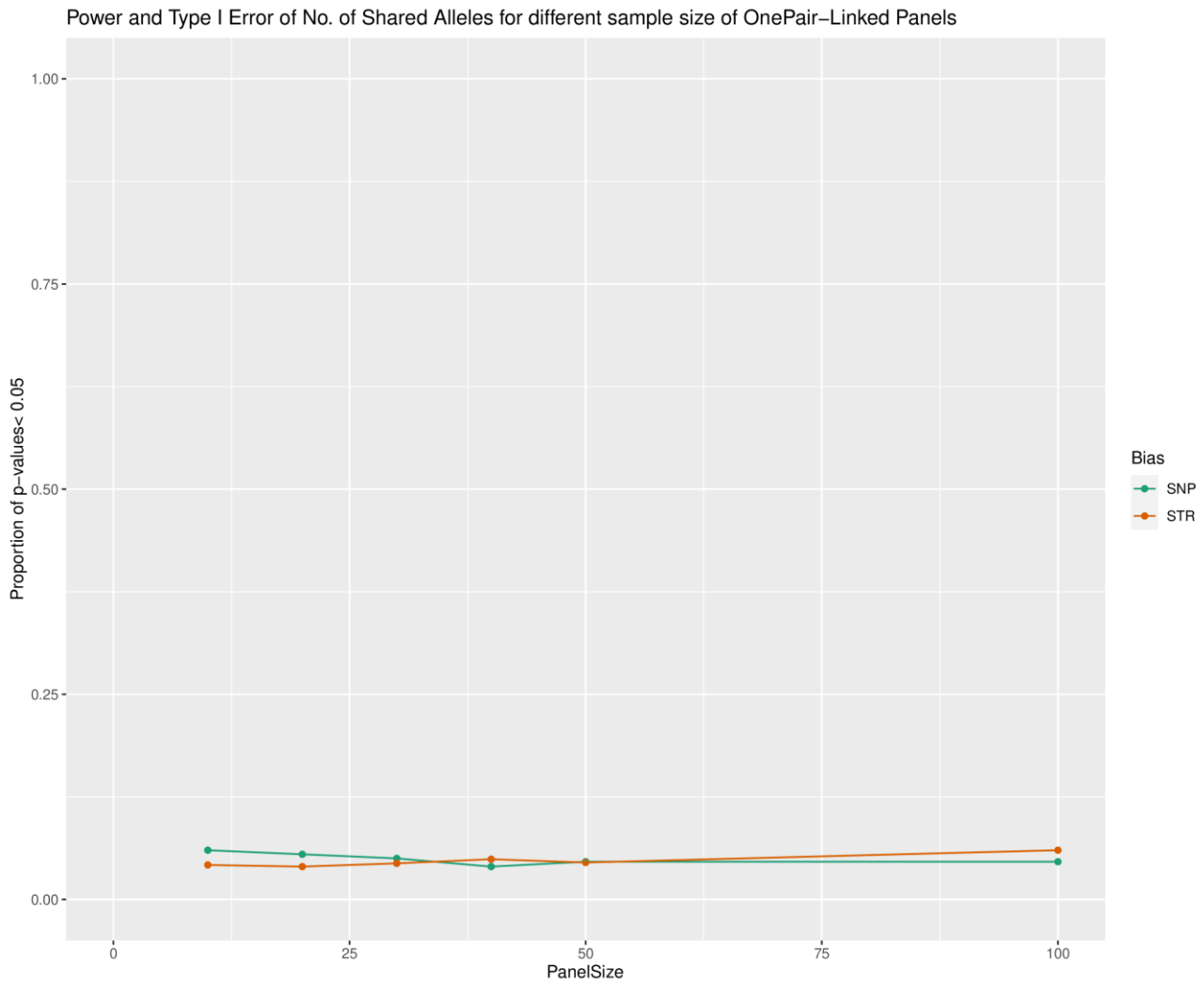

Power and Type I Error of No. of Shared Alleles for different sample size of OnePair−Linked Panels
Proportion of p−values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PanelSize
Bias
SNP
STR

Figure 9f

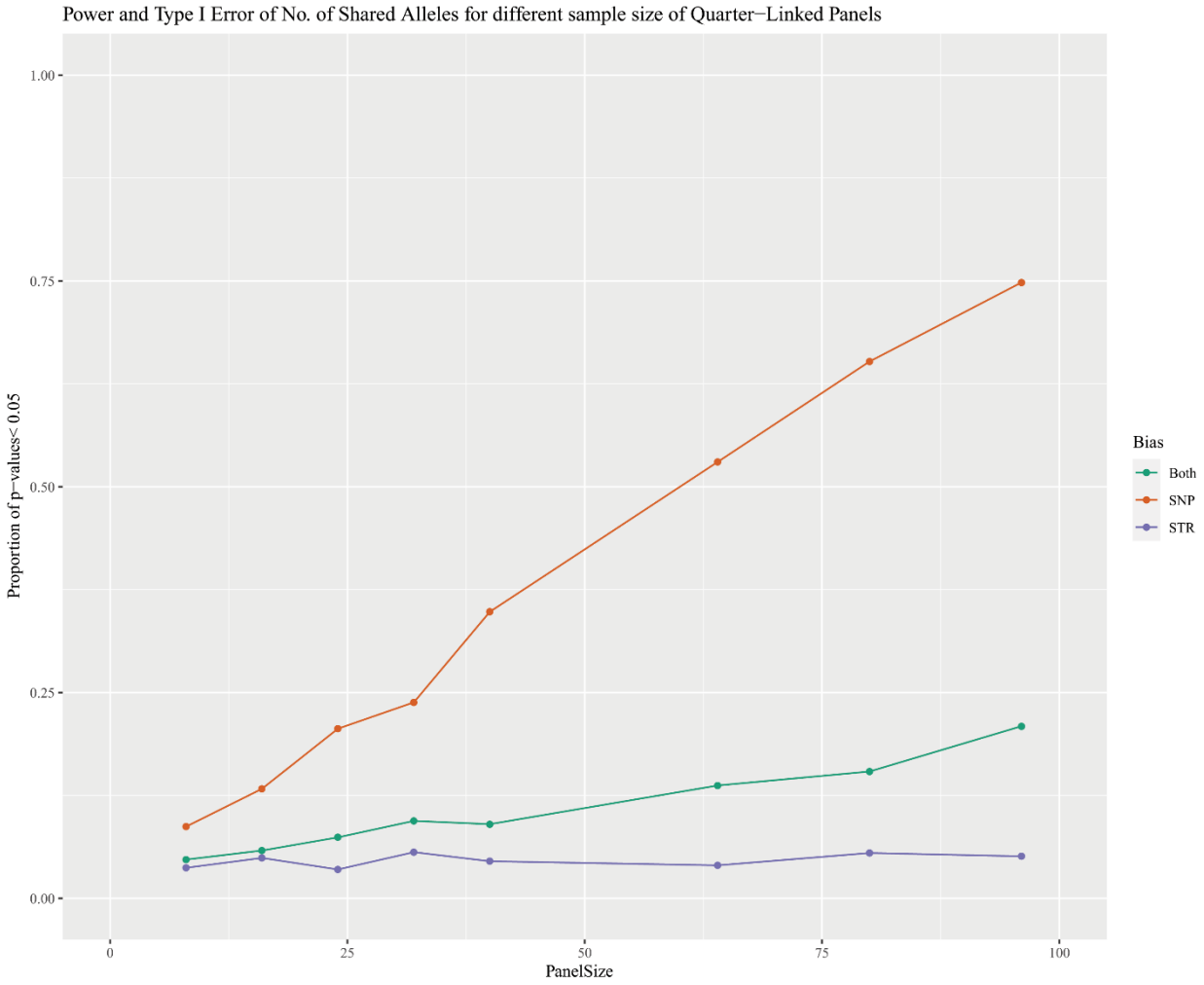

Power and Type I Error of No. of Shared Alleles for different sample size of Quarter−Linked Panels
1.00
0.75
0.50
0.25
0.00
Proportion of p−values< 0.05
0
25
50
75
100
PanelSize
Bias
Both
SNP
STR

Figure 9g

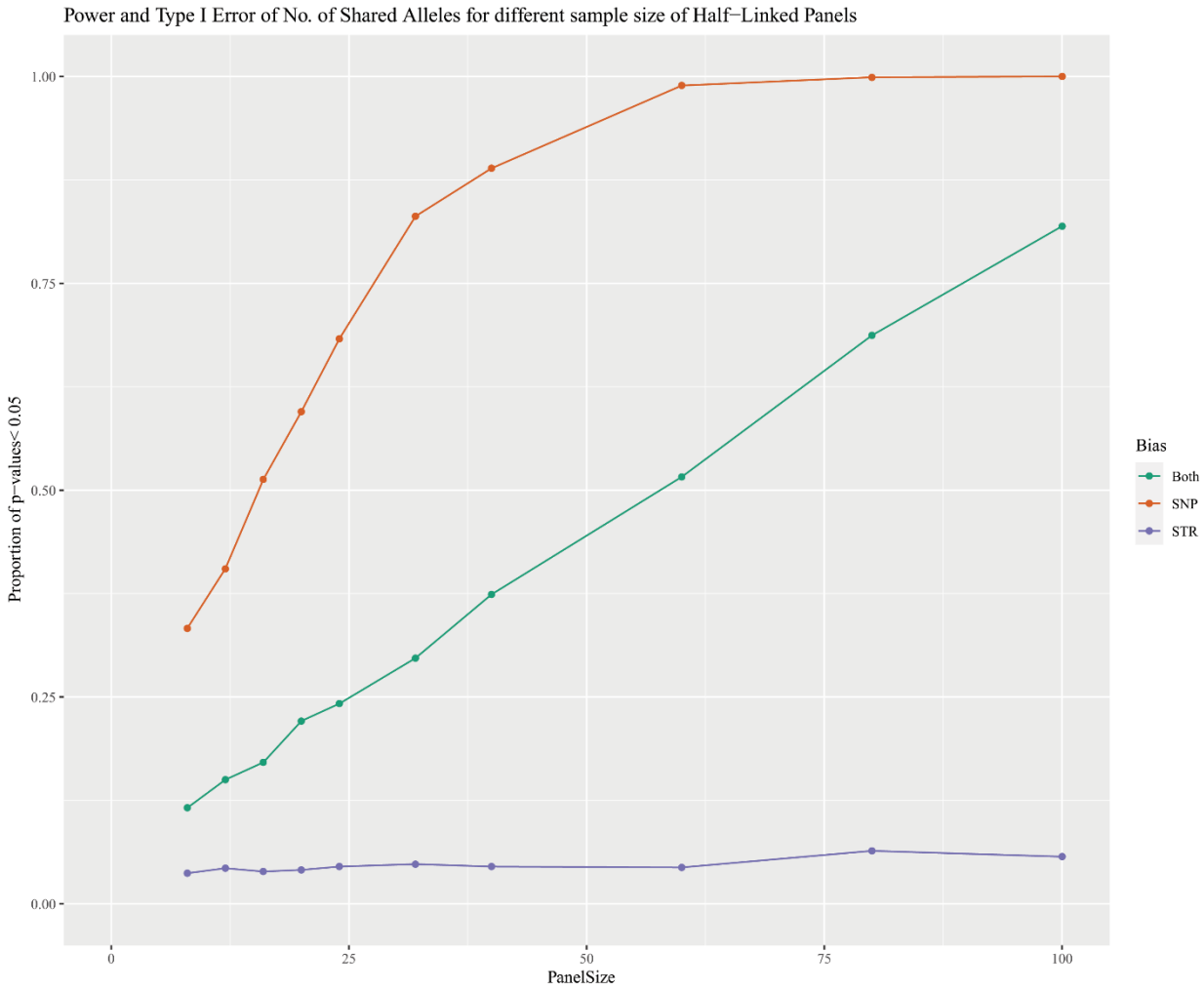

Power and Type I Error of No. of Shared Alleles for different sample size of Half−Linked Panels
Proportion of p−values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PanelSize
Bias
Both
SNP
STR

Figure 9h

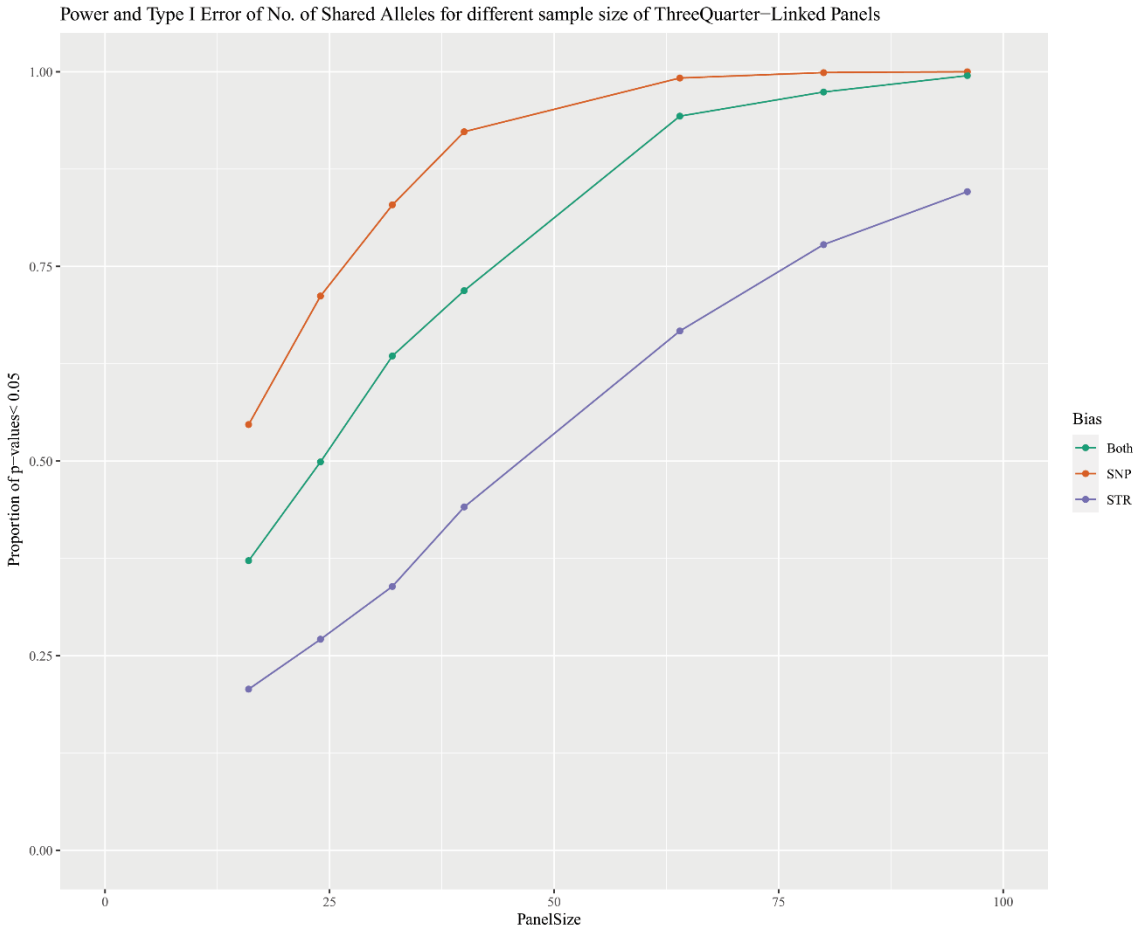

Power and Type I Error of No. of Shared Alleles for different sample size of ThreeQuarter−Linked Panels
Proportion of p−values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PanelSize
Bias
Both
SNP
STR

Figure 9i

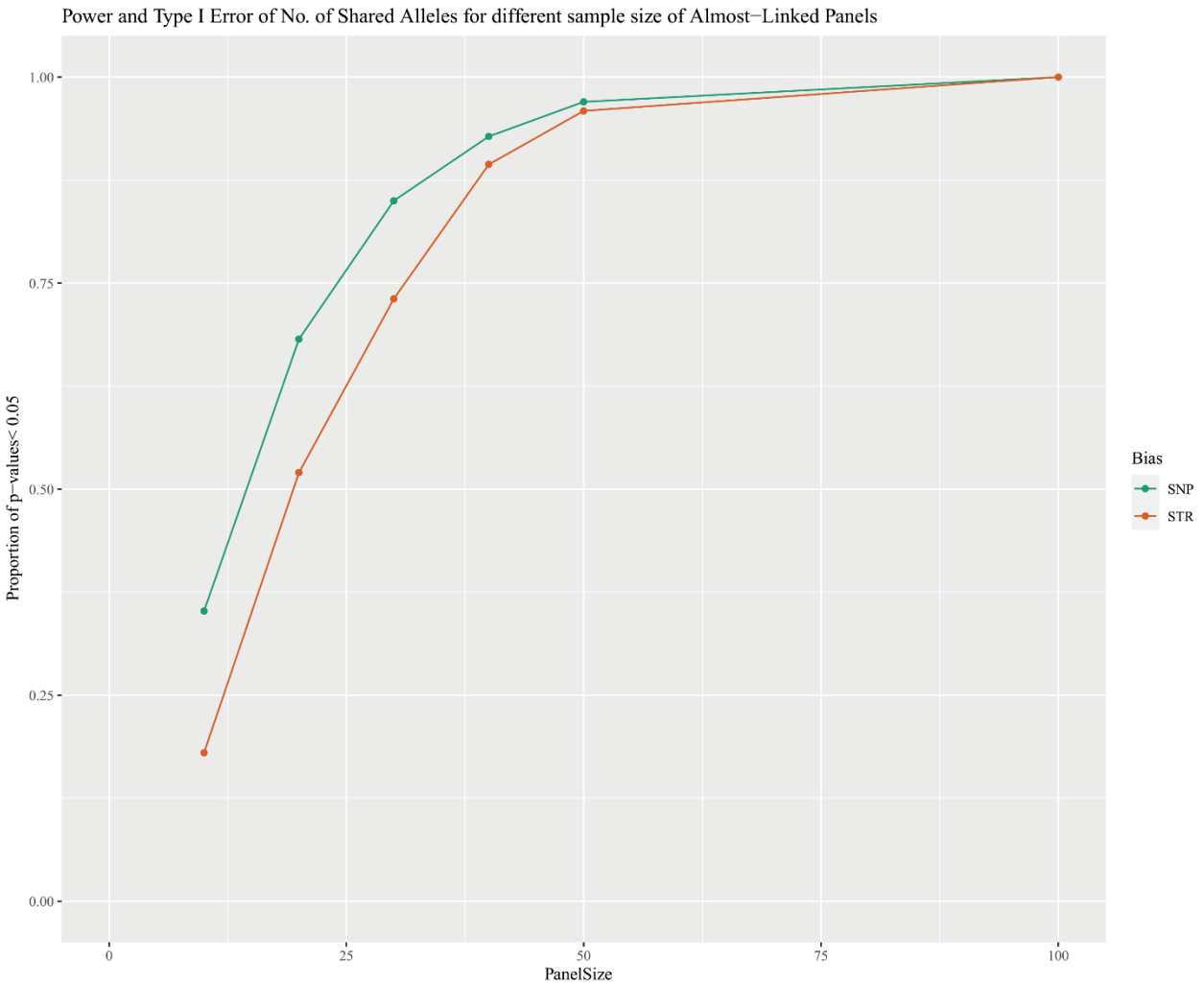

Power and Type I Error of No. of Shared Alleles for different sample size of Almost−Linked Panels
Proportion of p−values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PanelSize
Bias
SNP
STR

Figure 9j

Figure 9. Power on different levels of linkage from different markers

X-axis denotes the number of markers in one panel; Y-axis denotes the proportion of cases when p-values < 0.05 out of 1000 trials. '*Bias*' is defined as the types of linked markers, for example, if "*Bias*= SNP", all the linked markers are SNPs; if "*Bias*= STR", all the linked markers are STRs; if "*Bias*= Both", half of linked markers are SNPs and the other half are STRs. In each sub-figure, the red line presents the power trend of panels with linkage on both SNP and STR equally (*Bias* = Both); the green line is that of linkage on only SNPs (*Bias*= SNP); and the blue means that of linkage on only STRs (*Bias* = STR).

Figure 9a: The power of *K* for "one-pair-linked" panels among different '*Bias*'.

Figure 9b: The power of *K* for "quarter-linked" panels among different '*Bias*'.

Figure 9b: The power of *K* for "half-linked" panels among different '*Bias*'.

Figure 9b: The power of *K* for "three-quarter-linked" panels among different '*Bias*'.

Figure 9b: The power of *K* for "almost-linked" (one-pair-unlinked) panels among different '*Bias*'.

Figure 9f: The power of *X* for "one-pair-linked" panels among different '*Bias*'.

Figure 9g: The power of *X* for "quarter-linked" panels among different '*Bias*'.

Figure 9h: The power of *X* for "half-linked" panels among different '*Bias*'.

Figure 9i: The power of *X* for "three-quarter-linked" panels among different '*Bias*'.

Figure 9j: The power of *X* for “almost-linked” (one-pair-unlinked) panels among different ‘*Bias*’.

It needs to be noticed that in “One-Pair-Linked” or “Almost-Linked” groups, there are only one pair of markers are linked or only one pair of markers are unlinked among each size of the panel, so no “both” linkage group exists. In conclusion, the power of linkage on only SNPs is larger than both, and larger than only STRs.

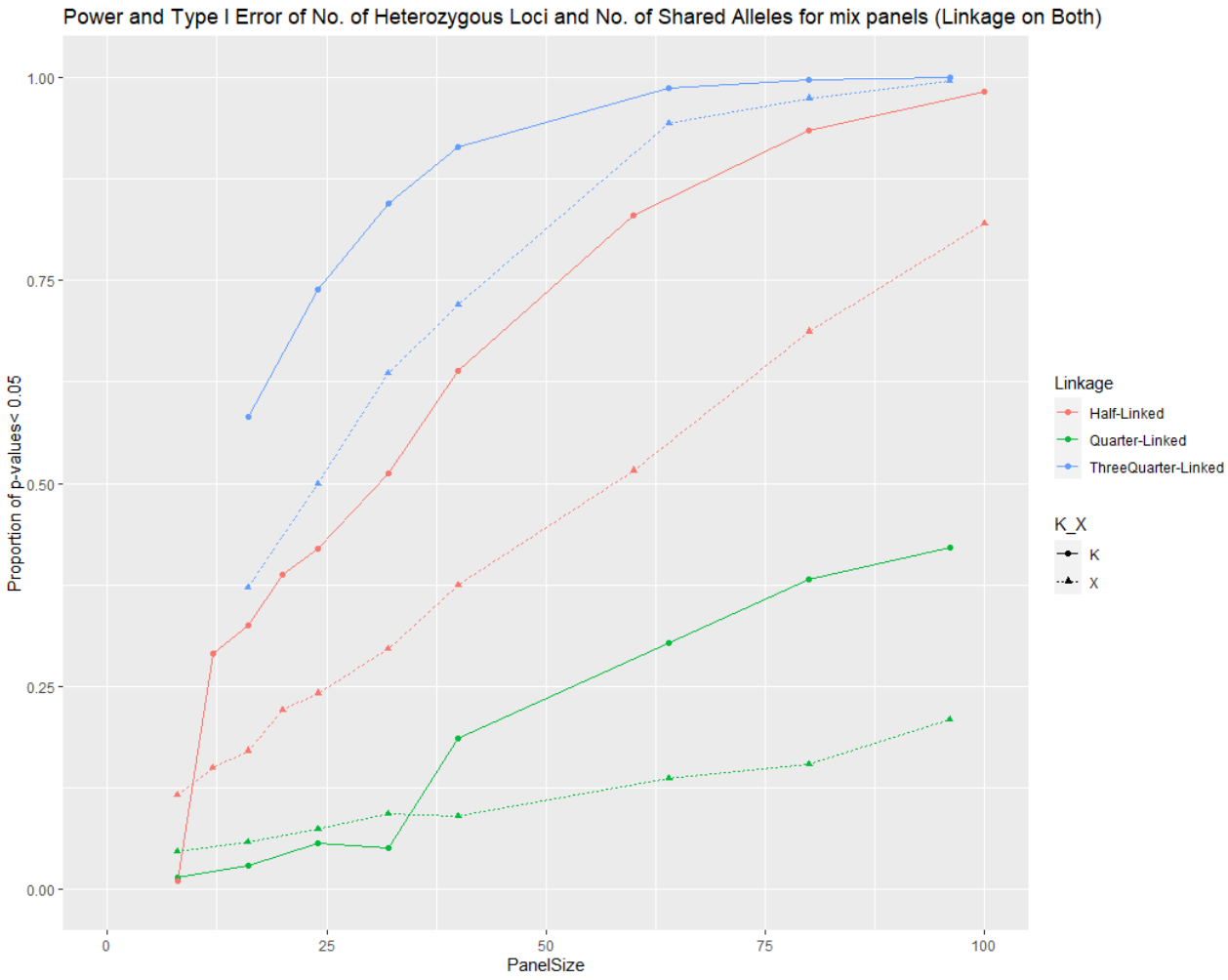

Power and Type I Error of No. of Heterozygous Loci and No. of Shared Alleles for mix panels (Linkage on Both)
Proportion of p-values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PanelSize
Linkage
Half-Linked
Quarter-Linked
ThreeQuarter-Linked
K_X
K
X

Figure 10

Figure 10. Power of *K* and *X* for mix Panels (Linkage on Both)

Power of *K* and *X* is compared among different levels of linkage. The red line presents the trend of half-linked panels; the green line denotes the quarter-linked panels; and the blue one is the power trend of three-quarter-linked panels. Controlling the *Bias* denoting linkage on which type of markers as “both”, at each level of linkage, the solid line presents the values of *K*, and the dotted line denotes the values of *X* in contrast. As a conclusion, the power of *K* is stronger than *X* on each level of linkage.

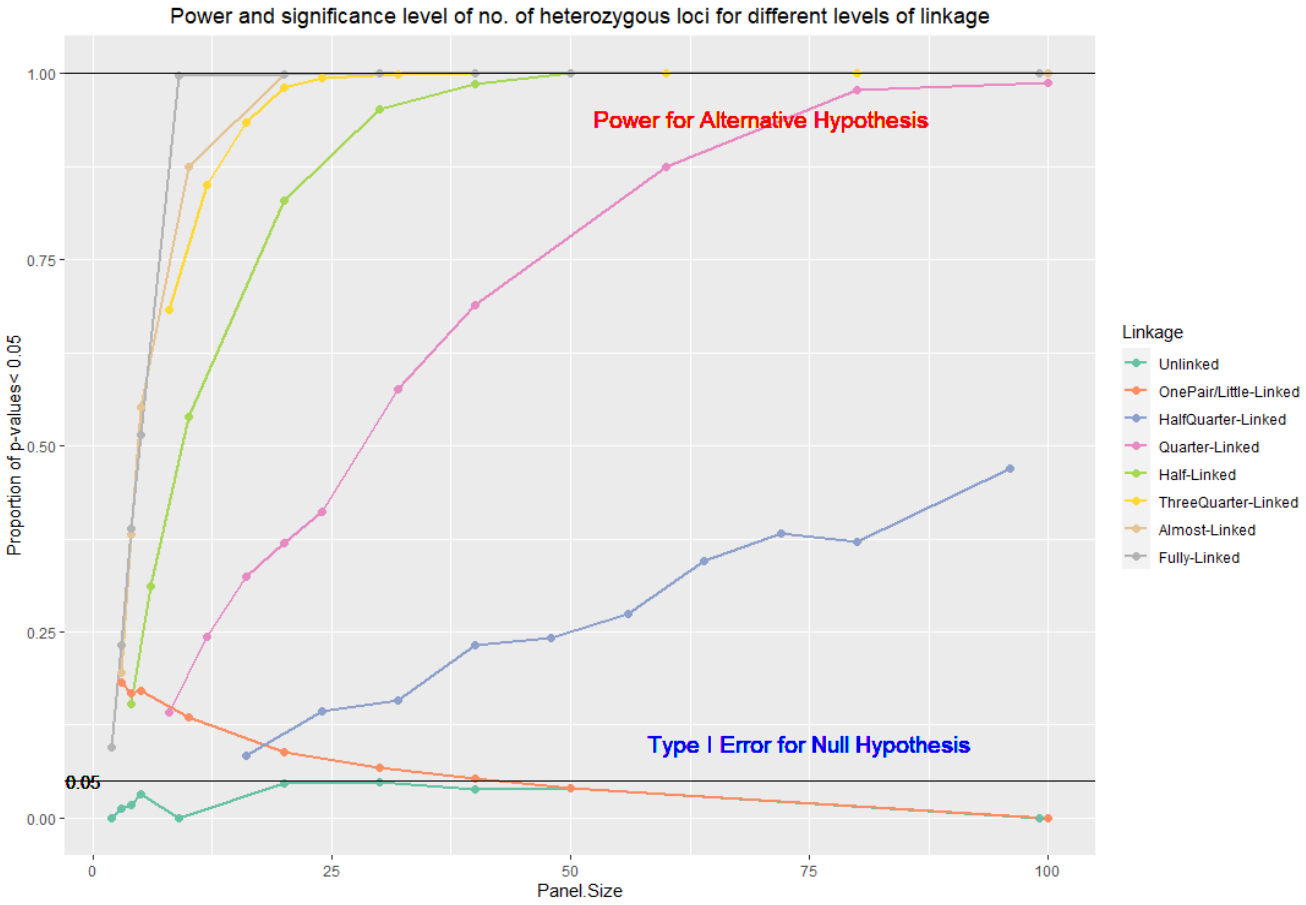

Power and significance level of no. of heterozygous loci for different levels of linkage
Power for Alternative Hypothesis
Type I Error for Null Hypothesis
0.05
Proportion of p-values< 0.05
Panel.Size
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
Linkage
Unlinked
OnePair/Little-Linked
HalfQuarter-Linked
Quarter-Linked
Half-Linked
ThreeQuarter-Linked
Almost-Linked
Fully-Linked

Figure 11a

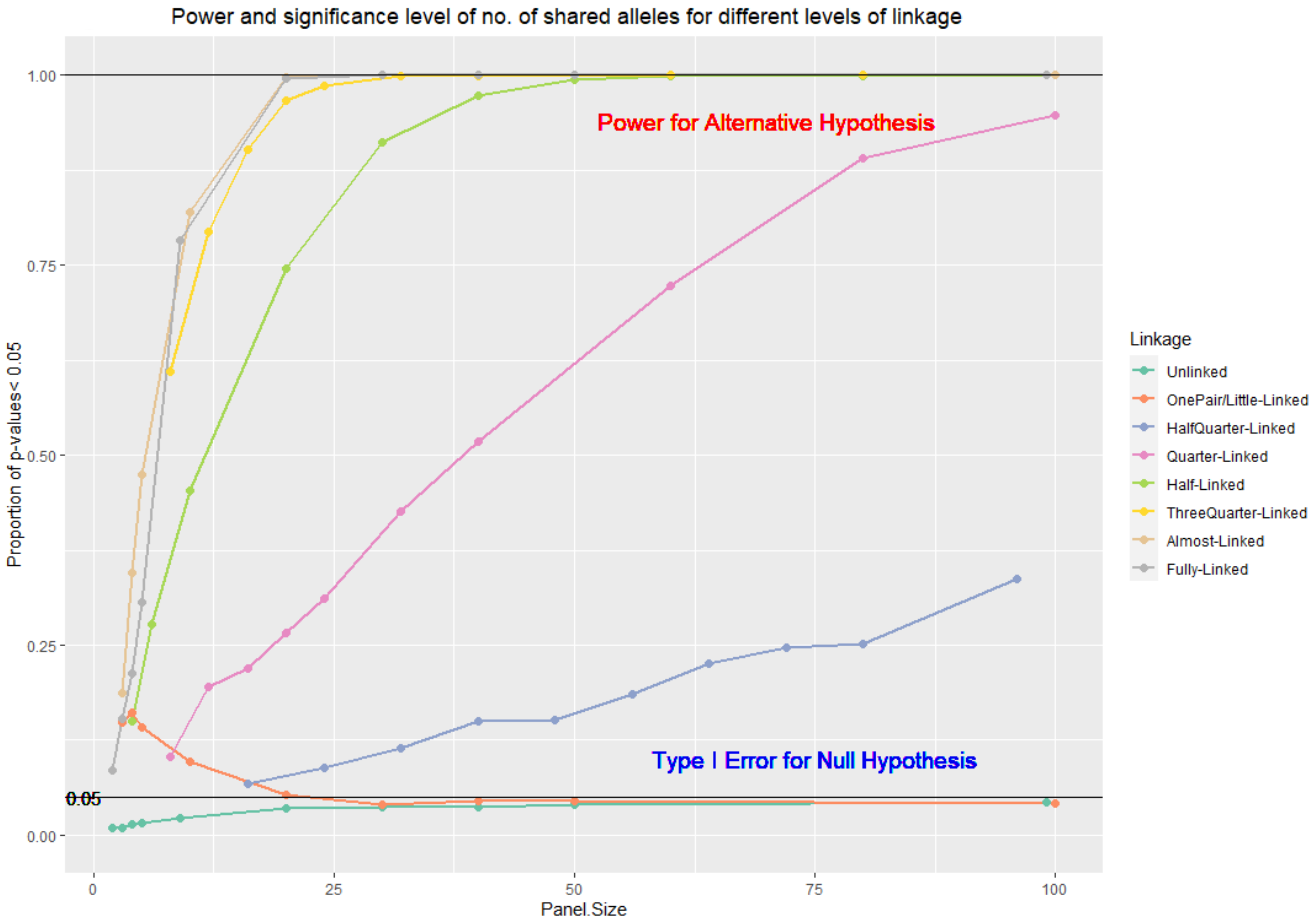

Power and significance level of no. of shared alleles for different levels of linkage
Power for Alternative Hypothesis
Type I Error for Null Hypothesis
0.05
Proportion of p-values< 0.05
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
Panel.Size
Linkage
Unlinked
OnePair/Little-Linked
HalfQuarter-Linked
Quarter-Linked
Half-Linked
ThreeQuarter-Linked
Almost-Linked
Fully-Linked

Figure 11b

Figure 11. Power of significance level on different level of linkage for pure SNP panels

Figure 11a: The power and significance level of *K* for different level of linkage.

Figure 11b: The power and significance level of *X* for different level of linkage

For unlinked SNP panels, the significance level is smaller than 0.05 for both *K* and *X*, the power of linked SNPs panels increase with the panel size increasing, expect the "one-pair-linked" group in which the percent of linkage decrease when the panel size increase.

With the linkage levels come up, the power of *K* or *X* increases for pure SNP panels.

For half-quarter-linked panels, the power of *K* and *X* are lower than 50% when the panel size is smaller than 100, but the power of *K* in the 100-SNP panel is close to 50%.

When the panel size is larger than 30, the power of both *K* and *X* in quarter-linked panels are larger than 50% approximately.

When the linkage percentage is larger than 50%, the power of *K* and *X* is higher than 90% when the panel size is over 30.

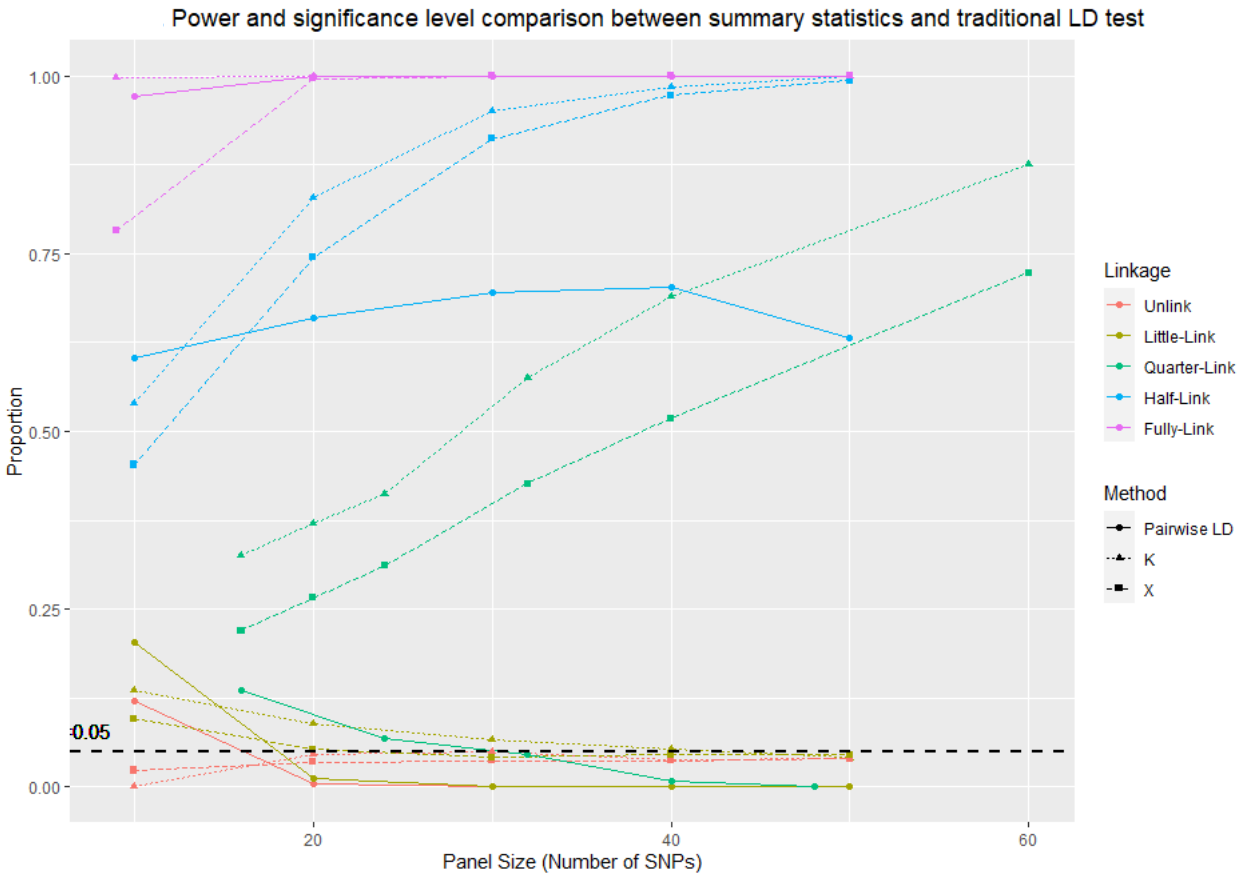

Power and significance level comparison between summary statistics and traditional LD test
Proportion
1.00
0.75
0.50
0.25
0.05
0.00
20
40
60
Panel Size (Number of SNPs)
Linkage
Unlink
Little-Link
Quarter-Link
Half-Link
Fully-Link
Method
Pairwise LD
K
X

Figure 12

Figure 12. Power and significance level comparison between summary statistics and traditional LD test.

Comparison among *K*, *X*, and pairwise LD calculated by R package *genetics*. *K* denotes number of heterozygous loci; *X* denotes number of shared alleles; Pairwise LD denotes the results from the function *LD* of package *genetics*

The solid lines with round dots present the power trends of pairwise LD on different level of linkage; the dotted lines with triangles present the power trends of *K*; the dashed lines with squares present the power trends of *X*.

Different levels of linkage are shown in different colors: the red lines are for unlinked panels; the yellow for little-linked (one-pair-linked) panels; the green ones are for quarter-linked panels; blue for half-linked panels; and purple for fully-linked panels.

For the unlined panels, the significance levels for *K* and *X* are smaller than pairwise LD, even when the panel size is smaller than 20 where the pairwise LD presents a high proportion for Type I error.

For little-linked panels, pairwise LD has higher power when the panel size is smaller than twenty than summary statistics; but as the panel size increasing, the power of LD decreases drastically and lower than summary statistics after 10 or 15.

For other groups where the percentage of linkage is constant, the power of all three statistics increase when the panel size increases, but the slopes of increasing of *K* and *X* is larger than pairwise LD. When sample size becomes larger, the advantage of summary statistics is more significant over pairwise LD. Between *K* and *X*, *K* is more powerful than *X*, which agrees with Figure 10.

CHAPTER I

INTRODUCTION

Multi-locus genotype data are widely used in population genetics and disease studies. In the evaluating the utility of multi-locus data, the independence of the single nucleotide polymorphism (SNP), insertions and deletions (INDEL) or short tandem repeats (STR) markers is an inevitable factor that needs to be considered. Due to the disparate characteristics of these different kinds of markers, most software is not compatible for mixed genetic data, but focus on one specific type of markers instead, such as *adegenet* which deal with SNPs and STRs separately, *SAMTools* and *SNPrelate* which focus on SNPs, and *Genetic Data Analysis(GDA)* which targets STRs specially. With more and more loci discovered and added to databases and panels, the incompatibility between most software and data with multiple types of markers is restricting developing of panels with mixed kinds of genetic markers. The design of one single type of marker limited the capacity of information that one panel is possible to hold. Even if mixed panels have been produced, a separate data-tidy spent more time on data analyzing. Therefore, the combination of different markers is an evitable trend, in which scenario, a software compatible with multi-type loci and testing independence between different type of data is urgently necessary.

This study is aimed at developing a software package for testing the mutual independence of mixed genetic datasets. The new R package "*mixIndependR*" can calculate basic genetic parameters, such as allele frequency, genotype frequency, heterozygosity, and Hardy-Weinberg equilibrium, from population data, regardless of the

type of markers, e.g. SNPs, STRs, InDels, Variable Number Tandem Repeats (VNTRs)), and then test for mutual independence between mixed genetic panels based on these genetic calculations.

I hypothesize that the basic genetic calculations could be obtained by genetic definitions, via easy transformation of format; and the mutual independence of the SNP, INDEL or STR markers could be tested using summary statistics when multi-locus genotype data are interrogated.

I hypothesize that the observed distribution of the total number of heterozygous loci (K)[6, 7] or total number of shared alleles (X)[8] is not significantly different from the expected one under the assumption of mutual independence. Therefore, the independence of mixed dataset can be tested by comparing the observed and expected distributions of K and X, and the expected distributions can be built by mathematics under the assumption of independence, ignoring the type of markers.

CHAPTER II

BACKGROUND

a. Multi-locus genotype data application

Genetic markers are utilized broadly in both revealing disease phenotypes and human identification. In either field, the application of genetic markers has a long history and is developing rapidly along with the technology innovation.

In the field of forensic genetics, DNA evidence was introduced in the courts for an immigration case in 1985, and since then, technology of DNA fingerprinting, defined as the technology comparing the DNA from one person with sample collected in crime scene or another person [6] has been advancing for decades [9, 10]. In 1987, genetic fingerprinting was first used in a forensic application, in which case the criminal who raped and murdered two teenage girls was captured when his DNA sample was matched with that from semen of the crime scenes. After the polymerase chain reaction(PCR) was developed to synthesize DNA much faster, the fluorescent labels was discovered to read DNA visually, and the capillary electrophoresis was applied to detecting DNA, the application of DNA profiling enters forensic labs all over the world [10]. Over the course of time, more and more polymorphisms are discovered and applied as genetic markers in different fields.

Early in 1980s, restriction fragment length polymorphism (RFLP), the polymorphism detected by different restriction enzyme sites, was described by Botstein in 1980 [11], and the “DNA fingerprint” was invented in 1984 by Alec Jeffreys [12]. The

RFLP method is a technique to identify DNA profiles using the different numbers and lengths of DNA fragments when cut by restriction enzyme specifically (Figure 1). Due to the specificity of restriction enzyme and the diversity of DNA, DNA regions will be "cut" into fragments which differ from individual to individual [13], RFLP markers become the first "DNA fingerprint". Not only as a tool of human identification and paternity [14], RFLP markers are also applied in disease diagnosis [15].

As one of the main sources of RFLP, variable number tandem repeats (VNTR) are described and applied into forensics and medical sciences spread as well. In 1985, minisatellites were named as one of the DNA polymorphisms which describe a variable region containing tandem repeats of short sequences [12]. Later, VNTR was discovered as one of the most common minisatellites when the repeating times of sequences were found vary between individuals,. VNTR is characterized as the repeat unit is 10-100 base pairs and the number of repeating is range between 5~50 times. Both as the tandem repeats, VTNR is much longer compared to Short Tandem Repeats (STR) whose repeat unit is usually 2~9 base pairs (Table 1; Figure 2), discovered more recently.

As mentioned, the tandem repeats are a short of DNA region where a motif is repeated in variable times (Figure 3), with high variability and high mutation rates between individuals. With different length of repeat unit, tandem repeats are categorized into minisatellites (length from 10-100 base pairs and repeated 200 to several hundred times) and microsatellites (2-9 base pairs and repeated 5-200 times, usually less than 100) (Details in Table 1) [16]. In 1991, Dr. Caskey's team succeeded in discovering the distribution and frequency of STR in human genome and proved their highly variability. With a method developed to localize STR locus, they achieved in identifying the

polymorphism of STRs and then brought the stably-heritable genetic markers into application of DNA typing [17]. In forensics, STR become the new popular DNA fingerprint for its speed and high discrimination.

As the technology developed, the “short”, “high variable” STRs came to the main stage. Because multiple STRs can be tested at one-time, and are amenable to degraded or fragmental DNA [13], which is more common in crime scene, STRs replaced RFLPs as the most popular genetic markers in forensics.

In 1990s, DNA database in Europe and US were established [13, 18, 19]. In the US, the Federal Bureau of Investigation (FBI) defined 13 STRs in 1997, and stop running RFLPs in 2000; in the same year, the combined DNA Index System (CODIS) STRs were first amplified in a multiplex way [13, 20]. With these 13 STRs, a 1 in 1 billion probability when two individuals are found identical randomly can be given [10]. In 2015, seven new loci were added to CODIS [21] and the completed expanded system got improved by 10~13 orders of magnitude for total probability of identity, tested using the NIST 1036 dataset, refer to the presentation of Becky Hill in Washington DC in 2013 [22].

Besides genetic markers on autosomes, Y-STR and mitochondrial DNA (mtDNA) are also very helpful in criminal science, anthropology, and disease studies, especially when the samples contains low level of DNA. Differing from autosomal STR, Y-STR and mtDNA are linkage markers, which have unusual non-recombination mode [10]. This character made them efficient in maternity or paternity analysis, and that is why they are so widely applied into sex criminals [23] and the studies of human migration [24] . However, at the same time, the profile of Y-STR or mtDNA must be utilized separately

with autosomal markers. In my project, only autosomal markers are studied for this moment.

There is another DNA polymorphism widely used in genetics which should not be overlooked- the single nucleotide polymorphism (SNP). SNPs are variations of a single nucleotide at specific position (Figure 3). Unlike STRs, SNPs are more utilized in population genetics and disease studies, compared to forensic genetics (but see [21]). Even though, SNP is attracting more interest in the field of forensic these years [25]. Five different categories of SNPs have been studied- individual identifying SNPs, ancestry informative SNPs, phenotype informative SNPs, Y-SNPs, and mitochondria SNPs. Because the mutation rate of SNP is low relatively, SNPs are more likely to be passed down to the next generation, thus SNPs on the autosomes and the Y chromosomes are used for ancestry information [26]. With distinct allele frequencies among different populations, millions of SNPs are selected as ancestry informative markers (AIMs) [27]. There is almost no doubt on SNPs being outstanding for analyzing structure and admixture of populations [28, 29]. In addition, SNPs also contribute on individual identification. In 2006, Dr. Kidd and his team developed a panel of 19 SNPs for human identification[30]. Those SNPs have stable allele frequency due to little variation among different populations and provide an average of match probability of less than 10(-7) in about forty populations [30]. By 2010, Dr. Kidd has developed a set of 92 SNPs for individual identification [31]. Another advantage is that SNP is one-base pair polymorphism, which will resolve the problems of fragmental and broken DNA.

Not only in the field of forensic science, are genetic markers widely applied in disease studies-both diagnostic and therapy. In principle, mutations lead to malfunctional

expression or regulation. Taking SNP as an example, the mutation of nucleotides in non-coding region may influence gene expression, while the mutation in coding region might result in synonymous or missense or nonsense substitutions. Nonsense and missense substitution change the product of gene expression, which might be an enzyme, structural protein, transportation protein or other functional proteins; and the synonymous substitution is likely to have influence in other ways, like in the multidrug resistance gene [32]. Therefore, disease researchers pay a lot of attention on genetic markers.

The 1000 Genome project was a project aiming at finding most genetic variants with frequencies of more than 1% in population. From 2008 to 2015, over 88 million genetic variants have been found and filed in 1000 genome including 84.7 million Single Nucleotide polymorphisms, 2.6 million short insertions and deletions and 60,000 structural variants [33],, which provide a template for localizing disease-associated variants[34]. It is expected that these variants in pool will contribute to selection of disease-related variants, human identification markers, phenotype related variants and ancestry informative markers [35].

b. Multi-type of genetic markers and compatibility

Genetic polymorphisms are commonly classified into different classes, such as RFLP, SNPs, and STRs. Different characteristics, such as mutation rates and heterozygosity, may make these markers incompatible with each other. However, for the their specific advantages, such as higher power of discrimination of STRs, and important roles of SNPs in application of AIMs, prediction of physical traits[36] and disease diagnostic [37], multiplex assay or panels are considered in applications of molecular genetics [38-40]. However, though the association between different markers exists and

are may be assessed, most of the software are designed specific for one of those markers. For example, the popular R package "*adegenet*" deals with STRs and SNPs separately, *SNPrelate* [41] is used for SNPs, and the widely-used *plink* treats with InDels and STRs as bi-allele genetic data as 0, 1, and 2 to agree with the format of SNPs, and overlooks the difference of specific allele status such as: "15,16" and "15,17". Taking a simple example, for as STR marker with at least three alleles- 15,16, and 17, if the genotypes of the first and the second sample are "15,16" and "16,17", the results read out in *plink* are "1" and "1" respectively, because both of the samples are heterozygous. In this way, the variability is "missing" during the analysis.

c. Mutual Independence

Hardy and Weinberg demonstrated an equilibrium to define an "ideal" population, which is a population with no effects of natural selection, no mutation, no gene flow, whose population size is infinite and where the individuals mate randomly. In the "ideal" population, loci which are far enough from each other (on the same or different chromosomes) are independent, and the genotype frequencies follow the equation:

$$(p+q)^2 = p^2 + 2pq + q^2 \quad (1)$$

$$where\ assumming\ the\ allele\ frequency\ of\ A = p, and\ a = q, on\ a\ bi-allelic\ locus;$$

$$then, the\ frequency\ of\ genotype\ AA = p^2; Aa = 2pq; aa = q^2; due\ to\ the\ gametes\ unite\ at\ random.$$

Under the ideal circumstances, all associations are randomly generated. However, in a natural population, “inbreeding” and “interbreeding” (which results in mating not randomly), geographic segregation (rivers and mountains segregate a population and isolate mating), migration and island effects (allele frequencies are effected, and even some alleles disappears with migration), mutations (DNA mutates along the time and change the allele frequency even without mating), and various factors affect the linkage equilibrium, resulting in non-random associations, and they are described as linkage disequilibrium (LD).

In fields of populations genetics, LD plays an important role on ancestry studies, like the ancestry informative markers (AIMs). The AIMs are single-nucleotide polymorphisms that are selected to estimate the proportion of ancestry of an individual. The allele frequencies of AIMs are expected to be significantly distinct in different ancestry populations. Thus, the markers selected as AIMs would be in high linkage disequilibrium.

In forensics, a panel with independent markers are preferred so that the combined power of identity can be calculated by timing up the probabilities on each marker, which process assumes of independence. Therefore, non-random associations are controlled at a low level as possible.

Linkage disequilibrium, which has been a complex term since it was created, is the non-random association of alleles at different loci. LD is defined in mathematical way: if allele A occurs with frequency p_A at one locus, allele B at another locus with frequency p_B, and the frequency of one gamete carries both A and B is p_{AB}, then LD is defined as the difference between the frequency of gametes with both allele A and allele

B and the product of frequencies of carrying each, implying the nonrandom association of alleles at two loci. It is denoted in equation (2):

$$D = p_{AB} - p_A p_B \qquad (2)$$

where p_{AB} is the frequency/proportion of chromosome with both allele A on one locus and allele B on the second locus; $p_{A/B}$ is the frequency/proportion of allele A or B in the whole population.

The statistical test, like the chi-square or Fisher's exact test can be used to indicate the statistical significance or lack of significance on association[42] and in statistics, lack of significance on associations are independence- the situation where the probability of event A and event B happens at the same time equals to the product of the probability of event A and event B happen independently.. Since there can be more alleles at each locus, the value of D is in a set of values. Then D', as the ratio of D to its largest possible value is defined.

$$D' = \frac{D}{D_{max}} \qquad (3)$$

where D_{max} is the smaller of $p_A(1 - p_B)$ and $p_B(1 - p_A)$ [43]. Similarly, r is also a widely used way to qualify LD:

$$r = \frac{D}{\sqrt{(p_A(1-p_A)p_B(1-p_B))}} \qquad (4)$$

known as the correlation coefficient of LD. When there are more than two loci to test, a practical method is to plot the LDs between all possible pairs and find out the significant pairwise LD from a heat map. A heat map can illustrate the distribution of pairwise LDs clearly. Dealing with multiple pairwise LDs, the Bonferroni correction is

typically the chosen method to simplify the calculation of significance level for multiple hypothesis tests.

For multiple hypothesis testing, like in the situation of multiple pairs of loci are tested for linkage equilibrium in multi-locus genotype data, the Type I error here is the probability of making one or more false discoveries when the null hypothesis is true, also named as family-wise error rate(FWER).

If the total number of null hypotheses is m, and the number of true null hypotheses is m_0 (unknown), V is the number of cases of type I error (the null hypothesis is true but the test statistic is declared significant), the $FWER = Pr_{(V\geq 1)} = 1 - Pr_{(V=0)}$. In hypothesis testing, we control FWER at level of alpha: FWER ≤ α.

The Bonferroni correction is a widely used method to control the level of FWER, by testing each individual null hypothesis at a significance level of α/m. For example, if we are testing the LE of 10 loci at α=0.05, where we have 45 pairs of loci to test (m=45), then the Bonferroni correction will test each pair at α=0.05/45=0.00011.

However, Bonferroni correction is precise if all individual hypotheses are mutually exclusive; for example, "locus 1 and locus 2 are independent" and "locus 1 and locus 3 are independent" Cannot occur simultaneously. In mathematics, this assumption ensures that:

$$\text{FWER}=P[\bigcup_{i=1}^{m_0}(p_i \leq \alpha/m)]=\sum_{i=1}^{m_0}[P(p_i \leq \alpha/m)\}]=m_0*\alpha/m$$

But usually the individual hypotheses are not mutually exclusive, so FWER= $P[\bigcup_{i=1}^{m_0}(p_i \leq \alpha/m)] \leq \sum_{i=1}^{m_0}[P\left(p_i \leq \frac{\alpha}{m}\right)] = m0 * \alpha/m$; and m0 ≤ m, thus FWER ≤ α.

When m is large, FWER may be much smaller then designated value of α. Bonferroni correction is conservative to ensure a small type I error, but the probability of type II error is much increased. With a higher probability of type II error (false negative), we lose the power of detecting the dependence, especially when panel size is large.

For multi-locus genotype data, linkage is a key factor in revealing the evolutionary history and population structures. As the combination of heterogeneous type of genetic markers is more and more expected, the linkage between different types of markers needs to be assessed. For human identification, an increasing number of SNPforID have been discovered, which can join the STR for human identification [31]; in the ancestry studies, panels of Indels for ancestry information have been designed, which are prepared to combine with SNPs as AIMs [44]; in the disease studies, STR panels are regarded as the option to explain the complicated disease, which has been imputed and mixed with SNPs in panels [45].

Therefore, in considering mutual independence include not only pairwise associations, but also triplet, quartet and higher associations, a method more comprehensive and compatible for mixed data of different kinds of markers is needed to be developed in order to assess the associations beyond pairwise markers among the mix panel.

d. History of Summary Statistics in Independence Testing

In descriptive statistics, summary statistics are summary of a set of observations. In this project, the mutual independence including a large quantity of subsets. If test for each of the subsets, huge calculation and consumed time will be a difficult problem. With

summary statistics, information is communicated in a simple way so that time and calculation are spared.

Summary statistics treat the set of markers as a whole and avoid the conflicts between characteristics for different genetic markers. Early in 1984, it was observed that variance of number of heterozygous loci, which was denoted by s_k^2 , is efficient for detecting the non-random association [6]. On the other aspect, the deviation of observed and expected genotype frequencies which can be calculated by allele frequencies directly contributes to the definition of linkage disequilibrium, so two summary statistics - the total number of heterozygous loci (*K*) and the total number of shared alleles (*X*) are chosen.

Assuming the loci are independent,

$$K = K_1 + K_2 + \cdots + K_n \quad (5)$$

$$where\ K_i\ is\ the\ status\ of\ heterozygozygosity\ \ on\ the\ i-th\ locus,$$

$$n\ is\ the\ number\ of\ loci\ of\ interest$$

$$X = X_1 + X_2 + \cdots + X_n \quad (6)$$

$$where\ X_i\ is\ the\ number\ of\ shared\ alleles\ for\ each\ pair\ of\ individuals\ on\ the\ i$$

$$-th\ locus, n\ is\ the\ number\ of\ loci\ interested$$

and *K* and *X* are multi-nominal distributed (0 or 1 for *K*; 0,1, or 2 for *X*) with different probability for each trial. Under independence, a recurrence formula to calculate the expected distribution for the number of heterozygous loci was given [7]. Similarly, the formula for expected distribution of number of shared alleles also can be built [8].

$$P_{x=r}^{m} = P_{x=r}^{m-1} * (1 - h_m) + P_{x=r-1}^{m} * h_m \quad (7)$$

$$P_{x=r}^{m} = P_{x=r}^{m-1} * p_0^m + P_{x=r-1}^{m-1} * p_1^m + P_{x=r-2}^{m-1} * p_2^m \quad (8)$$

$P_{x=r}^{m}$ *means when the first m loci are counted, the probability that the test statistic x equals to r.*

h_m *means the probability that the* $m-th$ *locus is heterozyous.*

p_0^m *means the probabiltiy that there are* 0 *shared alleles on the* $m-th$ *locus;*

p_1^m *means the probabiltiy that there are* 1 *shared alleles on the* $m-th$ *locus;*

p_2^m *means the probabiltiy that there are* 0 *shared alleles on the* $m-th$ *locus;*

The principles of the recurrence formulas are simple, if taking *K* as an example, among the first m loci under observation, the case of *K*=r (there are r heterozygous loci on the first m loci) is possible to occur in two different scenarios: 1) there are r heterozygous loci on the first (m-1) loci and the last locus is homozygous. 2) there are (r-1) heterozygous loci on the first (m-1) loci and the last locus is heterozygous. These two phenomena are mutually exclusive, so the total probability is calculated by summing their values.

Similarly, the case of *X*=r (there are r shared alleles in total) along the first m loci only happens in three ways: 1) On the first (m-1) loci, there are r shared alleles and on the last locus there is 0 shared alleles; 2) on the first (m-1) loci, there are (r-1) shared alleles and on the last locus there is 1 allele shared; 3) on the first (m-1) loci, there are (r-2) shared alleles and on the last locus there are 2 sharing alleles. The three cases cannot appear at the same time, therefore, the final probability of observing r shared alleles on the first m loci equals to the summation of probabilities of the three scenarios.

Thus, a test for independence can be developed based on comparing the observed distribution and the expected distribution of selected summary statistics. Under the assumption of mutual independence, the distribution of K or X follows a restricted multinomial distribution. This expected distribution can be built under the assumption of mutual independence[8], and by comparing the observed and expected distribution, the hypothesis for mutual independence can be tested.

e. Significance and Chi-square Test

In statistics, a test of goodness of fit assesses whether a model fits the observed data. In this research, the expected multinomial distribution under the independence hypothesis is the model I built, while the observed distribution is compared to it. For categorical variables (the genetic markers are treated as categorical variables in this study), the Pearson chi-square test is most commonly employed . Alternately, the Hosmer-Lemeshow test can be used for logistic linear regression models; Kolmogorov-Smirnov test and Anderson-Darling test are for non-parameter statistics. In this study, chi-square test has been selected because it works for discrete distributions like binominal or multi-nominal distribution. K-S and A-D test are restricted to continuous distribution.

The chi-square test is a widely used hypothesis test when the test statistic is distributed in chi-square distribution. For a series of independent, standard normal random variables, the sum of their squares is distributed according to chi-square distribution with the number of variables as the degrees of freedom (Figure 4).

$$Q = \sum_{i=1}^{k} Z_i^2 \sim \chi_k^2 \quad (9)$$

$$if\ Z_1, Z_2, \dots, Z_k\ are\ independent, standard\ normal\ distributed.$$

The chi-square test can be used for evaluating the goodness of fit of observed data to expected distributions for categorical data. For categorical data, the chi-square value is the summation of the squared errors.

$$\chi^2 = \sum \frac{(\text{Observed}-\text{Expected})^2}{Expected} \qquad (10)$$

With the assumption that all categories are mutually exclusive. the categories are merged to make sure the expected count in each category is no less than five.

In this project, the numbers of heterozygous loci or shared alleles are grouped into categories, and categories are merged to ensure all the expected counts are no less than five. The degrees of freedom are determined by the difference of observed and expected number of free parameters (a variable in the model which cannot be predicted precisely). In terms of independence, for numbers of the shared alleles, un-replaceable trials are used to pair those individuals, instead of replaceable trials to get all possible pairs.

To define the critical value, the question whether the test statistic χ^2 follows a chi-square distribution needs to answer. According to the basic statistical definition of Chi-square distribution- the distribution of a sum of the squares of *k* independent standard normal random variables, where *k* is the degrees of freedom. It is widely used in testing goodness of fit for binomial distributions, but the distribution of *K* or *X* is not standard binominal or multi-nominal distribution. With the probability of each trial is not constant or even the distribution of probability varies in different panels, it is complicated to judge whether the distribution of our test statistic χ^2follows the chi-square distribution or not. Though, the distribution of test statistic can be drawn by simulation, which I expect resembles the distribution of chi-square values (Figure 4). Under the distribution of test

statistics, a critical value can be defined by the cumulative probability function; and if the tested χ^2 is larger than the critical value, the null hypothesis will be rejected.

f. R Platform

R is a free environment for statistical computing and graphics, and a popular programming tool in the field of statistical genetics. There are already a lot of packages in the field of genetics developed on the platform of R. To organize the resources, Dr. Kamvar, et. Developed a resources website for population genetics [46]. The organization of this education resources is tidy and clear, but the separation also triggered me in the development of the package "*mixIndependR*".

On the other hand, R is a good tool for data tidy and visualization. With the package "*dplyr*", cleaning data is convenient and efficient. The package "ggplot2" can make customized and delicate figures. In the meantime, data tidy and visualization are both important and evitable in the study of statistical genetics.

CHAPTER III

ALGORITHM AND FUNCTION BUILDING

The package *mixIndependR* is made up of two main components—basic genetic calculations and mutual independence testing. Calculations obtained in the first part can be used in the second section. The software pipeline presented a structure of all the functions (Figure 5).

a. Format of Data Import

The basic dataset imported into genetic software is usually bi-allele data of a panel of markers, transformed from the vcf file format, Gen, or other genotype data files. In *mixIndpendR*, datasets to import needs to be an excel or csv file, with the marker names in the first row, and sample ID in the first column. For genotype data where two alleles are in one cell, conversion after importing is required. The function "split_Genotype" can make this conversion. Besides, there are similar functions in other available packages, like the function "*makeGenotypes*" in *genetics* [47, 48].

As the example in Table 2, the converted dataset fitting later calculations should be in the format of alleles with each row denoting each individual and each column denoting each marker. As genetic data of human beings are diploid (autosome-DNA), two neighbor columns should hold the same marker, as in "marker 1, marker 1, marker 2, marker 2.". To distinguish the two alleles, usually the second one will be tagged as "marker 1*" or "marker 1_1". However, the rule for naming is not strict. Only if the alleles from the same loci are side by side are any different names the user likes accepted.

b. Basic Genetic Calculations

The first part of this package was developed to calculate the basic genetic parameters of a mixed or non-mixed panel, including the allele frequencies *(AlleleFreq),* the genotype frequencies or expected genotype probabilities *(GenotypeFreq),* and the Hardy-Weinberg equilibrium *(HWE.Chisq, HWE.Fisher)* [49, 50]. Unlike other packages or software, the functions for basic genetic parameters can ignore the types of genetic markers and do not need to input the list of marker names. The markers' names can be grabbed from the original dataset, so users must make sure that the names in the odd numbers of columns are correct.

Below is a brief description how these functions are designed and used with example data. The dataset used in this part is a mix panel with 20 STRs and 10 SNPs, which is attached in Appendix 1.

1. Allele Frequency (*@AlleleFreq*)

This function is simply designed to calculate the allele frequency for each marker in the dataset. Different from other software or packages, there is no need to input the name of markers or alleles before obtaining the frequency with this function. This function itself will first grab the list of markers and alleles and input them as the column and row name respectively, regardless of the type of markers. Note: all alleles in this dataset should be listed in the row names. For those markers which does not have that allele, zero will be in assigned in the cell of frequency.

Example: *p <- AlleleFreq(x)*

An example of the result can be found in Appendix 1.

2. Genotype Frequency and Expected Probability (*@GenotypeFreq*)

This function is to calculate the observed or expected genotype frequencies or probabilities. With the dataset imported *(x)* and the allele frequency *(p)* table which is calculated by *AllelFreq*, and a logic parameter *(expect, if TRUE, calculate the expected probability; if FALSE, calculate the observed frequency)* to define, this function will export a matrix of genotype frequency, observed or expected, in which each row denotes each genotype according to the row names and each column denotes each marker. Usually the homozygous genotypes come first, and the heterozygous genotypes follow.

Example: *G0 <- GenotypeFreq(x, p, expect = T)*

3. Hardy-Weinberg Equilibrium Test (*@HWE.chisq*; *@HWE.Fisher*)

This function is designed to test the Hardy-Weinberg Equilibrium for the target dataset. When the sample size is large, with the dataset imported*(x)*, the allele frequency *(p)*, and an integer assigned as the times of bootstrapping, the Hardy- Weinberg equilibrium can be tested by Pearson chi-square test.

For small size sample, with the allele frequency*(p)*, number of heterozygotes*(H)* and the observed genotype frequency *(g)*, HWE can be checked by Fisher's Exact test.

Example: *HWE,chisq(x, p, rescale.p=F, simulate.p.value=F,B)*

HWE.Fisher(p, H, g)

To be noticed, in the chi-square test, there is a correction that the expected frequency in each cell must be over five. This correction has been included in the code of

this function. The probability of Fisher's exact test is corrected with the permutation version given by Guo and Thompson[49, 50].

c. Summary Statistics

In genetics, independence of two loci is defined as the allele frequency of locus A is not influenced by locus B- locus A is not associated with locus B or locus A and locus B are linkage equilibrium. When extended to multiple loci, the mutual independence of the whole panel is defined as all independence among any of these loci is met. As mentioned above, in this study, two summary statistics- the total number of heterozygous loci and the total number of shared alleles are chosen as the test statistics. The process below is calculating the required parameters to distribute the two summary statistics- *K* and *X*.

1. Total Number of Heterozygous Loci (*K*)

The total number of heterozygous loci in this sample is the sum of the number of heterozygous loci of each individual, which are defined with function (5) (See Chapter II Section d).

With the raw data *(x),* a table for heterozygosity can be built by *@Heterozygous*. This function will export a table of 0 and 1 where 0 denotes homozygous and 1 denotes heterozygous, with each row for each individual and each column for each marker.

Example: *h <-Heterozygous(x)*

The number of heterozygous loci each person has can be easily obtained by summing up this heterozygosity table in rows, and then the observed distribution of *K* can be drawn. This process is written in the function *@FreqHetero.*

Example: *ObsDist_K<-FreqHetero(h)*

For the expected distribution, the heterozygosity for each locus needs to be calculated by the function *@RxpHetero*. The observed average heterozygosity is the summation of column divided by the sample size and the expected heterozygosity under Hardy-Weinberg equilibrium is calculated by $1 - \sum p_i^2$. If the heterozygosity of this panel is saved into a vector *(H)* in order of loci; the expected distribution of *K* can be built by *@DistHetero:*

Example: *H <-RxpHetero(h, p, HWE = F) (when HWE=F, H is the average heterozygosity of each locus by observation)*

ExpDist_K<- DistHetero(H)

The expected distribution is built according to a recurrence formula with a specially assigned "Start" and "End" [7]. This recurrence formula was built based on the function (7) (See Chapter II Section d).

2. Total Number of Shared Alleles(*X*)

The total number of shared alleles(*X*) is just like *K*, which is the summation of number of shared alleles on each locus by comparing each two individuals (See Function 5 in Chapter II Section d).

By the function *@AlleleShare_Table*, a table of X_{i} can be built only if the dataset is imported(x) and a logic parameter is defined for how to "pick up pairs", which is "replicate" (for TRUE) or not (FALSE).

For example: *AS<-AlleleShare_Table(x, replicate=T)*

If replicate =TRUE, the "pairs of individuals" are chosen with replacement, and the number of pairs can be n(n-1)/2 if n is the sample size; If false, the pairs of individuals are chosen without replacement and the number of pairs is n/2.

The observed distribution of *X* can be found by summing up *AS* in rows, which process is done with the function *@FreqAlleleShare.*

Example: *ObsDist_X<-FreqAlleleShare(AS)*

Similarly, an expected distribution for *X* (total number of shared alleles) is needed to be built and compare with the observed one. The average proportion of sharing 0,1, and 2 is easy to calculate from the observed table for number of shared alleles *AS.*

Example: *e <-RealProAlleleShare(AS)*

However, the expected probability for sharing 0, 1 or 2 alleles on each locus needs to be calculated. According to Weir [51], two unrelated individuals have the probability of share 0, 1 or 2 alleles as follows:

$$\Pr(X_{\mathrm{i}} = 0) = 1 - 4\sum(\mathrm{p}_{\mathrm{i}}^2) + 4\sum\mathrm{p}_{\mathrm{i}}^3 + 2(\sum p_i^2)^2 - 3\sum p_i^4$$

$$\Pr(X_{\mathrm{i}} = 1) = 4\sum\mathrm{p}_{\mathrm{i}}^2 - 4\sum p_i^3 - 4(\sum p_i^2)^2 + 4\sum p_i^4$$

$$\Pr(X_{\mathrm{i}} = 2) = 2(\sum\mathrm{p}_{\mathrm{i}}^2)^2 - \sum(p_i^4)$$

$$Assuming\ \theta = 0 \qquad where\ \theta\ is\ the\ population\ substructure\ parameter \quad (11)$$

In the function *@ExpProAlleleShare*, this calculation can be completed with a known table of allele frequencies.

For example: *e0 <- ExpProAlleleShare(p)*

Using the observed or expected probability of sharing 0, 1, and 2 alleles, the expected distribution of *X* is built by *@DistAlleleShare* referring to the function (8) (See Chapter II Section d).

Example: *ExpDist_X<-DistAlleleShare(e)*

To this point, both observed and expected distributions are built as *ObsDist* and *ExpDist.* Before comparing them statistically, a visual comparison helps the user to estimate the results intuitively. The functions *ComposPare_K* and *ComposPare_X* are used to convert the distributions into a format suitable for visualization. With the "*trans=TRUE*", the observed frequencies and the expected density would be in separate columns. If it is "*False"*, two variables would be "*OvE*" (denoting the status of "observed or expected") and "*frequencies"*. With this dataset, figures of comparison will be created.

df_K <- ComposPare_K(h, ExpDist_K, trans = F)

df_X <- ComposPare_X(AS, ExpDist_X, trans = F)

d. Definition of Test Statistics and Critical Value

The null hypothesis is all those markers, regardless of types, is independent from each other. Under this assumption, the summary statistics follow a specified or restricted multinomial distribution. Generally, a multinomial distribution has a fixed probability for

each trial, as if the heterozygosity for each locus is equal; or at least follow a uniform distribution. However, in populations, the distribution of the heterozygosity or probability of sharing alleles cannot be predicted in an unknown panel. Thus, there is not a perfect statistical method designed for this special problem.

Despite the lack of fitted existing models a, it is not difficult to find the distribution of a test statistic by simulation, and then clarify the critical value from this distribution.

After the mean and variance which obtained, the chi-square value is chosen as a statistic to check the significance. For categorical data, the chi-square test statistic is in the format as Function (10) (See Chapter II Section e).

In this project, if the numbers of heterozygous loci or shared alleles are grouped into categories, the degrees of freedom which should be determined by the difference of free parameters between the null and alternative hypotheses will become zero, so the null distribution will need to be simulated.

The function *@Simulate_DistK* and *@Simulate_DistX* can build the simulation for *K* and *X*, respectively.

Example: *Simu_K<-Simulate_DistK(H, s, t)* *where s is sample size; t is the number of samples to simulate*

Simu_X<-Simulate_DistX(e, s, t) *where s is sample size; t is the number of samples to simulate.*

Since each panel has a fixed H or e (H is the table of average or expected heterozygosity and e is the table of average proportion or expected probability of shared alleles, for each locus), one distribution of *K* or *X* under independence will be simulated specifically for one interested panel.

After simulation of the distributions under null hypothesis, a set of chi-square values would be obtained by comparing the observed one to them. In this set of chi-square values, the critical value can be found after distributing them. *@Dist_SimuChisq*

Example: *x2_K<-Dist_SimuChisq(Simu_K,ExpDist_K$Density,2000)*

x2_X<-Dist_SimuChisq(Simu_X,ExpDist_X$Density,2000) #where 2000 is the times of bootstrapping; A set of chi-square values and p-values is returned

With the set of chi-square values, a plot of cumulative distribution of χ^2 will be drawn, and from the cumulative probability function of χ^2, the critical value will be specified.

This R package "*mixIndependR*" is available on the Comprehensive R Archive Network (CRAN): https://cran.r-project.org/web/packages/mixIndependR/index.html. Use *browseVignettes("mixIndependR")* to access to the manual.

e. A Complete Example

This section presents a complete example how a multi-locus genotype panel with mixed genetic markers (SNPs and STR) can be tested for its mutual independence using *mixIndependR*. In the following example, a simulated sample with 20 STRs and 10 SNPs (Table 3a) was imported as *x*.

First, basic genetic parameters were calculated for the data x, and generated tables of allele frequencies and heterozygous status.

p <- AlleleFreq(x) ##Calculate the allele frequency (Table 3b)

h<-Heterozygous(x) ##Calculate the heterozygosity (Table 3c)

H <-RxpHetero(h, p, HWE = F) ## Calculate the average heterozygosity at each locus.

AS<-AlleleShare_Table(x) ##Calculate the table of number of shared alleles. (Table 3d)

e0<-ExpProAlleleShare(p) ##Calculate the expected probability of sharing 0,1 and 2 alleles at each locus.

e <-RealProAlleleShare(AS) ##Calculate the average proportion of sharing 0,1 and 2 alleles at each locus.

All required parameters, such as average heterozygosity and proportion of sharing 0,1 and 2 alleles for each marker, were calculated in terms of HWE (or disequilibrium). With those parameters, the observed and expected distributions were built separately.

ObsDist_K<-FreqHetero(h) ## Observed distribution of number of heterozygous loci (K).

ExpDist_K<- DistHetero(H) ## Expected distribution of number of heterozygous loci (K)

ObsDist_X<-FreqAlleleShare(AS) ## Observed distribution of number of shared alleles (X)

ExpDist_X<-DistAlleleShare(e) ## Expected distribution of number of shared alleles (X).

Before comparing the observed and expected distributions, *ComposPare* was used to convert the distributions into a format suitable for visualization. With the "*trans=TRUE*", the observed frequencies and the expected density would be in separate columns. If *False*, two variables would be "*OvE*" (denoting the status of "observed or expected") and "*frequencies"*. With this dataset, figures of comparison were created (Figure 6).

df_K <- ComposPare_K(h, ExpDist_K, trans = F)

df_X <- ComposPare_X(AS, ExpDist_X, trans = F)

After visualization, *Simulate_Dist* was used to simulate a set of "observed" distributions, and then compare them to the expected ones to obtain a set of chi-square values. After that, a cumulative probability function was generated and saved into *P*.

Simu_K <- Simulate_DistK(H,50,500) ## Simulated bundles of number of heterozygous loci (K) (Table 3e)

Simu_X <- Simulate_DistX(e,25,500) ## Simulated bundles of number of shared alleles (X) (Table 3f)

x2_K<-Dist_SimuChisq(Simu_K,ExpDist_K$Density,2000) ## Obtain the simulated bundle of chi-square values for number of heterozygous loci (K)

x2_X<-Dist_SimuChisq(Simu_X,ExpDist_X$Density,2000) ##Obtain the simulated bundle of chi-square values for number of shared alleles (X)

P<-ecdf(x2_K) ## build the Cumulative Probability Function of K

P2 <- ecdf(x2_X) ## build the Cumulative Probability Function of X

Using the probability function, it is easy to calculate the probability of the observed Chi-square value and compare it with 95% (Figure 7).

The example script, the example data, and the example of outputs in this section are all available in Appendix 1.

CHAPTER IV

DATA REPRESENTATION

I simulated unlinked and linked data under the Wright-Fisher neutral model using the software *ms* [52]; the microsatellite data were converted by *microsat* [53] from *ms* format. For data simulation, we chose the average mutation rate (μ) 1.3x 10^{-3} [54] and an effective population (N) size of 3100, that latter of which was estimated from linkage disequilibrium [55]. Thus, to simulate the unlinked STR data the mutation parameter θ ($\theta = 4N\mu$) is equal to 16.12. In contrast, to simulate SNPs a fixed number of segregating sites was simulated for both unlinked data and linked data.

Real data was downloaded and filtered from the reference panel of Gymrek lab using *vcftools 0.1.17* [56] and *plink 1.90* [57, 58]. To select close-linked markers and include both types, range 10k bp to 200k bp on chromosome 4 are targeted. To ensure the quality of selected data or to reduce the size of output files, filtered out of the total 27,185,239 SNP and 445,725 STR markers [45, 59] were the variants with the missing data ($\geq 10\%$ missing genotypes), the variants with low allele frequency (MAF (minor allele frequency) ≤ 0.05), the variants with high genotype missing rate per locus (genotyping rate missing $\geq 10\%$), the variants of low Hardy Weinberg equilibrium ($p \leq 0.001$) , and the variants with low LD ($r^2 < 0.2$). After the filtering, 386 variants were selected. To make a close linked panel, variants with LD r2 <0.9 were filtered out, and finally 151 variants remained, among which there were 2 STRs (Table 4). All the panels simulated or designed can be accessed in Appendix 2.

CHAPTER V

RESULTS

a. One-Run Result

In the simulated examples, and consistent with expectations, the unlinked STR - SNP panel shows significant LD both for *K* (Figure 6a) and *X* (Figure 6b). At the same time, significant LD was detected with the fully linked STR-SNP panel (Figure 6c and Figure 6d). In contrast, for the simulated unlinked panel, the observed distribution of *K* and *X* matched the expected distribution visually under the assumption of mutual independence while, for the fully-linked panel, there is significant offset between the observed and expected distributions.

Not only were the visual comparisons made, but statistical tests were also conducted using this package. Considering the expected distributions under assumption of mutual independence follow restricted multinomial distributions with fixed probabilities on each trial, no traditional statistical tests can be applied (e.g. traditional chi-square test for multinomial distribution). Instead, simulations were conducted to obtain null distributions of chi-square values and cumulative probability functions were built to find an accurate critical value. If the significant level is 0.05, the critical value of the chi-square value for each specific expected distribution is the value when cumulative probability equals 95%. In Figure 7, the cross points of vertical and horizontal line represent the critical values. For the unlinked panel, the test statistic of *K* is 20.534 and

that of *X* is 34.413, both smaller than the critical value 36.85 and 49.10, respectively (Figure 7a and Figure 7b). However, the test values (1560009 and 37445237 for *K* and *X*, respectively) for the fully linked panel are much larger than the critical values (33.58, 47.50 for *K* and *X*, respectively) (Figure 7c and Figure 7d). The results agree with my hypothesis that the mutual independence can be tested by comparing the observed and expected distribution of *K* or *X* under the independence assumption. Not only the visualization gave an expected offset for linked panels, resulted the test statistics in the same conclusion with significant residuals. In the contrast, the simulated unlinked panels are proved "no significant different" between the observed and expected. Both the null and alternative hypotheses presented the output as expected, and this approach has been proved works by simulation.

b. Power Test

Simulated data with different levels of linkage were tested to determine the Type I error and power of the method. Figure 6 and Figure 7 present the results for completely unlinked and fully linked panels (20 STRs and 10 SNPs). To test different extents of LD more adequately, different numbers of randomly selected genetically unlinked and fully linked markers were imported into the package and tested for mutual independence. A P-value, which equal to one minus the cumulative probability was chosen as the critical value. Among the 1000 *in silico* replicates, the percentages of significant cases were recorded in Table 5 for different levels of linkage. The level of linkage is defined as the variable "*Linkage*", which has 7 levels: "Unlinked (all markers are unlinked are linked in each panel)", "OnePair-Linked (only one pair of markers are linked in each panel)", "HalfQuarter-Linked (12.5% of markers are linked in each panel)", "Quarter-Linked

(25% of markers are linked in each panel)", "Half-Linked" (50% of markers are linked in each panel), "ThreeQuarter-Linked (75% of markers are linked in each panel)", "Almost-Linked (only one pair of markers are unlinked in each panel)" and "Fully-Linked (all markers are linked in each panel)". In this process, mixed panels with equal numbers of SNPs and STRs were simulated, and each level of linkage was set up in three ways which is defined with a variable "*Bias*": biased to SNPs (*Bias*= SNP), biased to STRs, (*Bias*= STR) and unbiased (*Bias*= Both)-. If the "*Bias* = SNP" or "STR", the linked markers in each panel are only SNPs or only STRs; while if the "*Bias*= Both", the linked markers are made up by SNPs and STRs half to half. For example, in a panel of 20 markers, 10 SNPs and 10 STRs were selected; if the linkage is set as half-linked in the SNP-biased panel, there would be 10 linked SNPs and 10 unlinked STRs. In contrast, if the panel is STR-biased, 10 linked STRs and 10 unlinked SNPs would be chosen. In the unbiased group, the linked STRs and linked SNPs are always of the same number, which is 5 linked SNPs, 5 linked STRs, 5 unlinked SNPs, and 5 unlinked STRs in the unbiased half-linked panels of 20 markers (Details in Table 5).

For the unlinked panels, the proportion of p-values smaller than 0.05 was approximately 50 out of 1000 trials. As the number of markers increased, the proportions of significant results became closer to 0.05 (Table 5). In a fully linked dataset, the power of this test was over 50% when one panel had more than 20 markers, and as the sizes of panels increase, the power of *K* and *X* is stronger and stronger.

As the visualization of the results in Table 5, a comparison of different levels of linked data are presented in Figure 8. Additionally, three linkage *Bias* scenarios were also

compared at each level of linkage (Figure 9), and the comparisons of *K* and *X* are shown in Figure 10.

In conclusion, the power of *mixIndependR* appears to follow three basic trends: 1. when the number of markers increases, the power of testing increases (Figure 8); 2. compared to STRs, linkage in SNPs gives more power for linkage tests (Figure 9); 3. between the two summary statistics, the number of heterozygous loci (*K*) can detect dependency more powerful than the number of shared alleles (*X*) for the same panel (Figure 10).

When there is only one pair of genetic markers linked, neither of the two summary statistics detected the dependency effectively (Figure 8, Figure 9a and Figure 9f). In half-quarter-linked (12.5% of total markers are linked in one panel) panels, the SNP-biased group has a little higher power than STR-biased group - approximately 10% to 40% on *K* (Figure 8a and Figure 8b) and 6% to 18% on *X* (Figure 8d and Figure 8e); besides, power of the unbiased group is weaker than that of SNP-biased and stronger than that of STR-biased groups, but none of the three groups ("*Bias*= SNP, STR, or Both") present a strong enough power in half-quarter-linked panels. However, for quarter-linked (25% of markers are linked) or higher-levels of linkage (more than 50% of markers are linked including 50%), both *K* and *X* yield power greater than 50% when the number of markers is no less than 60 in SNP-biased group (Figure 8a and Figure 8d). In contrast, only the three-quarter of linkage (75% markers are linked) and almost-linkage (only one pair of markers are not linked) can be detected in the STR-biased group (Figure 8b and Figure 8e). Moreover, at these two levels of linkage, only when the panel sizes exceed 40 markers can the power of STR-biased groups reach 50% and more (Figure 8b and Figure

8e). In the unbiased group where the number of linked SNPs and linked STRs are equal, *K* presented more than 50% power when panel sizes were greater than 32 in half-linked panels and greater than 16 in three-quarter-linked panels (Figure 8c); the power of *X* is not as strong as *K*, only greater than 50% when panel sizes are over 60 in half-linked panels and over 32 in three-quarter-linked panels (Figure 8f).

The comparisons between different groups of *Bias* are presented in Figure 9. For each of the two summary statistics, the results for five levels of linkage are shown in order: "OnePair-Linked" (1 pair of markers are linked), “Quarter-Linked” (25% markers are linked), “Half-Linked” (50% markers are linked), “ThreeQuarter-Linked” (75% markers are linked) and “Almost-Linked” (1 pair of markers are unlinked). In the level of “OnePair-Linked”, none of SNP or STR groups is powerful. But for all other levels of linkage, the power of SNP group is larger than the unbiased group (*Bias*= Both), and larger than the STR group, with no exceptions.

In another direction, the number of shared alleles (*X*) has a lower power than the number of heterozygous loci (*K*), but the Type-I error is larger for *K* when the panel size is small (Figure 10).

Panels containing only SNP panels were selected to compare summary statistics with other methods. When the panels have more than 10 SNPs the power of both *K* and *X* are larger than 50%, even in quarter-linked scenarios. For “OnePair/Little-Linked” panels where only one pair of SNPs in linkage, summary statistics can detect with power of about 10%~ 20% when panel size are smaller than twenty SNPs, which is much more powerful than pairwise LD. For quarter and half-linked panels, summary statistics presented their advantage with distinguished power for larger panels. In half-linked

panels, summary statistics can detect linkage disequilibrium with power of approximately 75%~80% when the sample size is larger than 20 and more than 40%~50% in quarter-linked panels when the panel sizes are not smaller than 30. For panels with more than 30 SNPs, the power of summary statistics is larger than 40% and increases with the panel size. When there are more than 20 SNPs, the power is estimated to be 100% for fully linked loci, more than 50% for quarter-linked panels, and nearly 90% for half-linked panels (Figure 11).

Furthermore, having been used in the tests on simulated panels, *mixIndependR* was applied to panels in the real world. Based on the SNP+STR reference haplotype panel created by Gymrek Lab on 2018 [45, 59], a mix panel of 151 variants (Table 4) was designed, including 2 STRs and 149 SNPs. In the study of Dr. Gymrek group, a SNP+STR reference haplotype panel was created, in which the STRs imputed are highly polymorphic with high heterozygosity and significant LD with tag the SNPs in the same panel. The panel of 151 markers are designed as a closely linked panel with high LD ($r^2 \geq 0.9$) according to the results of *plink 1.9*. (Codes See Appendix 6)

With a sample size of 2504, p-values of mutual independence test were calculated by *K* and *X*. In the 1000 trials, 100% of p-values equal to 0, which indicates that the markers of this panel are closely linked. In the reference panel designed with high concordance, the LD between STRs and nearby SNPs are significant (length r^2 $p < 0.05$) [45]. In comparison, the pairwise LDs between these markers gave a result of $r^2 > 0.9$. Our new approach with summary statistics agree with the traditional method-pairwise LD in real data.

CHATER VI

DISCUSSION

a. Comparison within the Package

According to the Chapter V Results, the trends of power for *K* and *X* were described in three dimensions: with panel size, with level of linkage, with distribution of linkage (*Bias*). In addition, the comparison between *K* and *X* was also presented. In this section, causations will be discussed in each aspect.

Power equals one minus the probability of Type II error and means the probability of rejecting the alternative hypothesis. In this project, the power is the probability of finding significant difference between observed and expected distributions for a panel with linkage disequilibrium.

Usually, with the sample size (panel size here) increasing, the chance of failing to reject the false hypothesis decreases, so the power of test increases. In this approach, the variable is the sum of number of heterozygous loci or shared alleles. If the number of loci (panel size) is N, the range of *K* is from 0 to N and the range of *X* is from 0 to 2N. The distribution for *K* and *X* is an approximate multi-nominal distribution. Controlling the number of individuals for testing, the range of *K* or *X* determines the sample size. Therefore, the positive relationship between power and panel size is the easiest to understand.

The level of linkage is defined with the percentage of linked markers among the total number of loci in this project. Due to the definition of hypothesis, *K* and *X* only

check the “existence” of dependency, but not the “degree” of dependency. However, similarly to the p-values of chi-square test, the smaller p-values are, the larger difference are. In the hypothesis of this project, the difference between the observed and the expected distribution of *K* or *X* means the degree of linkage disequilibrium. In other words, the deviation from mutual independence indicates the level of linkage. Consequently, the p-values tends to be smaller with a higher linkage level; and the proportion of “small (≤ 0.05)” p-values is larger.

The characteristics of SNPs and STRs contribute to the difference between linkage distribution (linkage on SNPs or linkage on STRs). It is well-recognized that the mutation rate of STRs is much higher and the recurrent mutation is more probable to occur compared to SNPs [60]. Accordingly, the LD among STRs or between STRs and SNPs is weaker, which also matched the results of the real data from Dr. Saini et al. [45]. Theoretically on the design of the summary statistics, the diversity of STRs with more allele status makes it worse impaired than SNPs which is bi-allelic by summarizing. Simply for example, the summary statistics cannot differentiate “17,17”, “16,16” and “15,15” since all of them collapsed to “homozygous”. Instead, a SNP usually have one alternative genotype vs one referential genotype, to be homozygous or heterozygous. The diversity explains the power offset between SNPs and STRs.

Finally, with in this method, *K* presented higher power than *X* controlling other variables. The reason also lies in the definitions of the two statistics. Similarly, during the process of calculating X_i, some variance was reduced by merging scenarios. Taken instance with SNPs, “A/T” and “A/T” share 2 alleles, while “A/A” and “A/A” share 2 alleles, too. In contrast, for SNP with a reference genotype “A/A”, it is less likely to have

an additional alternative genotype “T/T”, besides the heterozygous alternative genotype “A/T”. That should be the reason why *K* has a higher power.

b. Comparison with Other Approaches

To evaluate the package “*mixIndependR*” as a new approach for testing independence, the comparison between it and traditional methods is evitable to make. In this study, I compared the power of my method with pairwise LD calculated by another R package “*genetics*” using the simulated panels.

To be noticed, due to the fact that pairwise LD test conducted by “*genetics*” limited to only bi-allelic genetic markers and the mixed panels with STRs and SNPs are difficult to be tested with traditional approach, the panels with only SNPs were chosen to be experimented in this section.

The R package *genetics* provides a function *LD* to test the linkage disequilibrium for all possible pairs of loci in one panel. This function can output D, D’, Pearson’s correlation coefficient, chi-square statistic for linkage equilibrium (D=D’=0) and the p-value of chi-square test for independence [48]. Using the unlinked data and linked data simulated above, a distribution of the proportion of p-values smaller than significance level after Bonferroni correction can be obtained. The null hypothesis is that there is no significant LD among all the pairs for unlinked panel [61], which is $\Pr\left(P-values<\frac{0.05}{number\ of\ pairs}\right)=0$. Even though the markers were simulated on different chromosomes in the circumstances of null hypothesis and there should be no association between any pair of them, some random associations may still be generated by chance. Ideally under null hypothesis of mutual independence, no more than 5% random associations among

the 1000 runs was allowed. In other words, if the percentage of significant p-values is larger than 0.05, the null hypothesis would be rejected.

Compared to traditional LD tests (e.g., D′), the approaches presented herein appear to become more powerful as the size of the panel increases. Figure 12 presented the comparisons of power between summary statistics and pairwise LD on pure SNP panels with different levels of linkage. For little-linked panels where there is only one pair SNPs in linkage, none of these methods are powerful, but summary statistics are able to detect with power of about 10%~ 20% when panel size are smaller than twenty SNPs. Summary statistics showed ten more percentage points of power than pairwise LD in half-linked panels and holds a stronger advantage in quarter-linked panels, where pairwise LD loss its power. In half-linked panels, summary statistics can detect linkage disequilibrium with power of approximately 75%~80% and more. In contrast, the pairwise LD only has power around 60%~70%. The summary statistics are holding a stronger advantage in quarter linked panels, for which pairwise LD loses its power. For more than 30 SNPs, the power of summary statistics is larger than 40%, and increases with the panel size using the package *mixIndependR*. When there are more than 20 SNPs, the power is estimated to be 100% for fully linked loci, more than 50% for quarter-linked panels, and nearly 90% for half-linked panels (Figure 11, Figure 12). According to the results above, it is concluded that the new approach- summary statistics has a lower probability of Type I error when the null hypothesis is true, and on the other hand, has a higher power when the null hypothesis is false, compared to the conventional method- pairwise LD. More excitingly, with the sample size increasing, the power of K or X

increases, opposite to pairwise LD which decreases. This property makes it more advantageous in the future where more and more variants are discovered and imputed.

CHAPTER VII

CONCLUSIONS

The R package *mixIndependR* is available on the Comprehensive R Archive Network (CRAN) at: https://cran.r-project.org/web/packages/mixIndependR/index.html [62] and contributes to the LD test of mixed panels with different types of genetic markers. It permits several new approaches to estimating LD, with the described method permitting LD estimation between heterogeneous marker types (e.g., SNPs and STRs). Instead of pairwise LD, the method tests mutual independence across all the markers of one panel. With new test statistics, this approach improved the power of dependency testing, and succeeded in testing the overall linkage disequilibrium across all sites simultaneously.

First, *mixIndependR* solved the incompatibility of heterogeneous marker types and open a door to mix panel analysis systematically. Without the restriction of marker types, the unexplained heritability of many complex traits by current SNPs can be studied in correlation with other polymorphism like STRs. Majority of panels in application now is SNP panels. Even there are some mixed reference panel created recently, the number of mixed panels are much fewer than SNP panels due to the complication of analysis. This package broke the barrier of separation analysis-"SNP to SNP", "STR to STR", and "STR to SNP", but integrated all scenarios in one calculation and analysis. With only one test, the association of the whole panel can be described and assessed. The improvement of time-consuming and convenience will accelerate the research of developing panels with heterogeneous type of genetic markers.

Secondly, this approach increases the power of detecting associations over a whole panel in a wide margin. It is not neglectable of a forty (for half-linked panels) to eighty (for quarter-linked panels) percentage of progress in power of testing. The improvement of power is possible to change results of variants selection and panel design.

Furthermore, with the characteristic of prevalence in larger panel size, the method of summary statistics will play a more important role with the database expanding. There is no doubt that more and more variants will be identified and added into different databases, to explain more and more traits. No matter the development of naïve panels or expansion of existing panels, associations between different loci is evitable to test. This approach is prepared for big data in principle and will also be kept updated to follow the latest improvement in the future.

A thorough evaluation of a new method expecting more tests and applications in real data. In future studies, larger worldwide samples will be included in testing to achieve a better understanding of the power and sensitivity of this approach. With large worldwide samples collected from real population, the effect of substructure is also be able to introduce to this method. In the situation of Hardy-Weinberg equilibrium, probability of sharing 0,1, and 2 alleles on each locus is calculated using function (11) (See Chapter III Section c). However, considering substructure of populations, a θ correction needs to be introduced into the formula [63]. When an admixed population data is tested, the effects of subpopulation to the test of mutual independence can be studied.

APPENDIX

Appendix 1. Example Data, script, and outputs

1a. The example dataset with 20 STRs and 10 SNPs Simulated by *ms*

1b. The output table of allele frequency

1c. The output table of heterozygosity

1d. The output table of number of shared alleles

1e. The output table of Simulated *K*

1f. The output table of Simulated *X*

1g. The example script of R file.

Appendix 2. Panels Simulated or Designed.

2a. Simulated Linked 100 SNPs of 500 Individuals

2b. Simulated Unlinked 100 SNPs of 500 Individuals

2c. Simulated Linked 100 STRs of 500 Individuals

2d. Simulated Unlinked 100 STRs of 500 Individuals

2e. Real Data of 151 Markers (149 SNPs and 2 STRs) of 2504 Individuals

Appendix 3. Manual of '*mixIndependR*'

Appendix 4. R Functions

Appendix 5. *ms* command lines

Appendix 6. *plink 1.9* command lines

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Appendix 1a. The example dataset with 20 STRs and 10 SNPs Simulated by ms

Sample ID	STR1	STR1	STR2	STR2	STR3	STR3	STR4	STR4	STR5	STR5	STR6	STR6
Sample1	12	12	14	14	15	14	15	14	13	13	15	19
Sample2	12	12	18	12	19	14	14	16	15	13	13	17
Sample3	18	12	17	17	15	18	12	12	13	18	11	13
Sample4	11	12	13	18	16	18	11	14	13	13	20	14
Sample5	17	19	15	15	16	17	11	12	14	14	18	21
Sample6	11	12	14	13	15	14	11	14	13	13	11	14
Sample7	11	12	16	14	15	16	12	14	13	13	14	14
Sample8	18	11	15	17	16	16	10	14	15	13	20	11
Sample9	10	17	18	18	15	16	14	12	18	18	9	11
Sample10	18	12	18	17	15	18	15	16	17	12	14	13
Sample11	20	17	13	18	16	14	14	12	13	13	13	17
Sample12	12	11	18	12	19	13	11	12	13	18	11	11
Sample13	11	18	13	13	15	14	11	14	16	12	11	18
Sample14	12	12	18	18	14	15	16	12	14	18	21	11
Sample15	11	11	15	17	18	15	15	10	14	13	14	14
Sample16	12	12	15	15	19	16	13	12	13	13	11	18
Sample17	19	12	12	15	16	15	10	11	15	13	11	13
Sample18	12	17	13	15	16	15	11	11	13	18	11	14
Sample19	19	12	13	12	16	18	16	14	13	14	10	18
Sample20	20	12	13	13	18	18	16	12	15	18	17	17
Sample21	17	11	18	17	16	16	16	16	13	14	14	13
Sample22	12	11	13	11	18	18	10	12	15	13	11	13
Sample23	12	10	13	15	14	14	16	14	12	13	16	15
Sample24	12	11	15	15	16	14	12	12	13	18	13	18
Sample25	17	19	17	14	16	15	11	14	15	15	13	14
Sample26	12	10	15	17	14	15	14	11	18	18	13	13
Sample27	12	11	17	13	15	15	14	12	13	18	13	17
Sample28	11	12	15	15	18	16	10	11	13	12	14	11
Sample29	11	12	14	17	14	15	12	11	18	13	18	21
Sample30	12	11	13	15	18	15	12	14	14	13	11	21
Sample31	12	19	16	17	15	14	11	11	18	13	14	13
Sample32	11	19	15	17	18	15	15	14	15	12	13	13
Sample33	12	17	17	15	18	15	12	14	14	13	12	11
Sample34	12	17	15	17	17	18	14	16	13	14	13	12
Sample35	12	19	15	20	16	16	14	12	18	12	14	11
Sample36	12	17	12	18	18	15	16	12	18	16	14	14
Sample37	10	20	18	13	14	16	11	16	18	15	13	14
Sample38	12	20	18	17	15	16	14	11	18	12	11	13
Sample39	11	12	15	17	16	14	13	16	18	13	14	11
Sample40	12	12	15	13	16	14	14	10	14	18	13	17
Sample41	11	11	13	12	16	14	15	10	18	15	14	20
Sample42	12	12	15	15	14	15	14	14	18	18	13	13
Sample43	12	17	15	15	13	16	12	12	13	18	16	13
Sample44	11	12	15	13	15	15	12	16	18	13	13	11
Sample45	12	11	13	18	16	14	15	11	13	13	14	17
Sample46	12	19	12	12	14	16	11	12	12	13	13	18
Sample47	11	12	18	15	16	15	14	11	13	14	14	14

Sample48	11	11	14	15	16	15	12	14	18	16	18	17
Sample49	10	17	15	13	14	15	12	15	18	13	11	14
Sample50	12	11	13	18	14	14	12	14	14	16	17	14

STR7	STR7	STR8	STR8	STR9	STR9	STR10	STR10	STR11	STR11	STR12	STR12	STR13
15	14	17	18	22	19	11	15	15	14	11	11	15
13	15	17	16	21	21	16	16	14	10	13	11	15
14	13	13	17	20	17	14	15	14	16	12	13	16
15	12	16	17	13	19	15	16	14	16	11	12	15
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15	15	17	14	19	19	11	14	10	17	13	11	17
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13	15	17	18	21	21	17	16	14	16	10	15	17
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15	15	13	16	21	21	11	14	16	14	11	13	18
15	15	16	16	20	18	16	16	16	14	11	10	19

15	13	18	17	19	15	15	15	14	14	13	11	19
15	15	16	18	18	20	14	12	13	16	11	11	17
15	15	18	17	20	20	15	15	13	14	12	10	17

STR13	STR14	STR14	STR15	STR15	STR16	STR16	STR17	STR17	STR18	STR18	STR19
19	18	19	17	15	13	13	11	17	15	13	15
21	18	19	18	18	17	17	14	15	13	13	17
15	19	16	12	18	18	18	13	18	13	14	16
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13	20	19	15	18	18	17	14	18	15	13	16
14	14	18	18	18	14	12	17	18	13	16	18
15	17	17	17	18	14	18	14	14	16	13	16
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17	18	19	18	17	13	17	14	18	15	14	15
21	14	14	18	19	18	18	18	18	13	15	15
19	19	18	15	18	15	12	14	17	15	15	15
19	19	20	18	15	18	12	14	14	15	15	14
19	18	13	12	17	18	12	14	15	14	15	17
17	19	19	15	15	13	12	15	14	13	15	14
17	17	18	16	18	15	13	18	11	16	15	15
15	14	18	18	18	18	13	14	18	13	14	18
14	19	18	16	18	13	13	18	15	15	16	16
17	18	18	18	11	14	13	14	14	15	15	18
14	18	14	16	18	19	12	14	15	16	14	15
21	20	18	13	18	12	19	17	14	15	13	16
16	21	19	18	18	14	18	18	14	12	13	16
17	19	20	18	18	12	18	14	15	13	15	16
16	18	18	18	18	14	13	14	11	16	16	18
17	14	14	18	16	14	12	15	14	15	13	14
16	18	18	16	15	14	14	14	14	15	15	17
18	19	18	17	18	17	12	14	14	13	14	15
15	19	17	18	15	13	18	18	14	15	12	15
18	18	17	18	17	13	13	18	15	15	11	14
17	18	14	19	18	16	13	18	18	13	16	15
17	14	14	18	16	13	12	15	15	13	15	16
15	16	20	19	12	14	12	18	15	11	15	16
19	18	19	17	19	12	18	14	18	13	15	16
18	17	18	15	12	18	14	11	14	13	13	15
17	18	18	16	17	13	15	15	15	15	13	15
21	19	18	18	15	16	12	18	18	16	16	14
18	19	19	18	18	13	13	11	15	15	15	17
19	17	14	15	19	13	13	13	14	16	15	16
16	18	19	15	15	12	14	14	18	15	13	16
17	17	19	18	15	12	17	14	14	13	16	17
17	18	14	12	16	15	18	15	18	14	16	13
15	14	18	11	18	18	18	14	18	16	15	14

16	18	14	18	16	14	18	11	14	15	11	15
17	18	19	18	18	18	12	13	15	13	15	16
17	17	17	16	15	14	14	13	18	16	15	16

STR19	STR20	STR20	SNP1	SNP1	SNP2	SNP2	SNP3	SNP3	SNP4	SNP4	SNP5	SNP5
14	18	17	0	0	0	1	1	0	0	0	0	0
16	17	19	0	0	1	0	0	0	0	0	0	0
16	17	13	0	0	0	1	0	0	1	0	0	0
18	19	19	0	0	1	0	0	0	0	0	1	0
17	15	17	0	0	0	1	0	0	0	1	0	0
15	19	18	0	0	1	1	0	0	0	0	0	0
15	19	19	0	0	0	1	0	0	1	0	0	0
15	17	17	0	0	0	0	0	0	0	0	0	0
16	17	15	1	0	1	1	0	0	1	0	0	0
16	16	19	0	0	1	1	0	0	0	1	0	0
17	14	19	0	0	0	0	0	0	0	1	0	0
15	17	17	0	0	1	1	0	0	0	1	0	0
14	17	19	0	0	0	1	0	0	0	0	0	0
15	13	17	0	0	1	1	0	0	0	0	0	0
15	19	15	1	0	0	1	0	0	1	0	0	0
17	17	18	0	0	1	1	0	1	0	0	0	0
16	17	17	0	0	1	1	0	0	0	1	0	0
15	17	19	0	0	1	1	0	0	1	0	0	0
14	13	14	0	0	1	1	0	0	0	0	0	0
15	17	17	0	0	1	1	0	0	1	1	0	0
17	19	17	0	0	1	0	0	0	0	0	0	0
16	19	19	0	0	1	0	0	0	0	0	1	0
18	13	19	0	0	0	0	0	0	0	1	0	0
15	19	14	0	0	1	0	0	0	0	0	0	0
15	19	18	0	0	1	0	0	0	1	1	0	0
18	16	17	0	0	0	0	0	0	1	0	0	0
18	17	17	0	0	0	1	0	0	0	1	0	0
16	18	18	0	0	0	1	0	0	0	1	0	1
15	19	17	0	0	1	1	0	0	1	1	0	0
14	14	17	0	0	0	1	0	0	0	0	1	0
15	14	19	0	0	0	0	0	0	1	1	1	0
16	17	16	0	0	1	1	0	0	0	0	0	1
16	15	15	0	0	1	1	0	0	0	0	1	0
17	18	14	0	0	1	0	0	0	0	1	0	1
18	16	19	0	0	1	0	0	0	0	0	0	0
18	13	15	0	0	1	1	0	1	0	0	0	0
15	19	19	0	0	1	1	0	0	0	1	0	0
15	19	17	0	0	1	1	0	0	0	0	0	0
18	13	19	0	0	1	1	0	0	0	0	0	0
16	17	13	0	0	1	1	0	0	1	0	1	0
16	19	16	0	0	1	1	0	0	0	1	0	0
15	19	19	0	0	1	0	0	0	0	0	0	0
16	19	16	0	0	1	1	0	0	0	1	0	0
16	19	16	0	0	0	1	0	0	0	0	0	0
15	17	18	0	0	1	1	0	0	0	1	0	0
15	19	19	0	0	1	1	0	0	0	0	1	0
16	17	17	0	0	1	1	0	0	1	0	0	0

15	17	14	0	0	1	1	1	0	0	0	0	0
17	12	19	0	0	0	1	0	0	0	0	1	0
16	19	19	0	0	1	0	0	0	1	1	0	0

SNP6	SNP6	SNP7	SNP7	SNP8	SNP8	SNP9	SNP9	SNP10	SNP10
0	0	1	1	1	0	1	1	0	0
0	0	1	1	1	0	0	1	0	0
0	0	1	1	0	0	1	0	0	0
0	0	0	1	1	0	0	0	0	0
0	0	1	1	0	0	0	0	0	1
0	0	1	1	1	0	1	0	0	0
0	0	1	1	0	1	0	0	1	0
0	0	0	1	0	1	0	1	0	0
0	0	1	1	0	0	0	1	0	0
0	0	1	0	1	1	1	0	0	0
0	0	0	1	0	0	1	1	0	0
0	0	1	1	0	0	0	0	0	0
0	0	1	1	0	0	1	0	0	0
0	0	1	1	1	0	0	1	0	0
0	0	1	1	1	1	1	1	1	0
0	0	1	1	0	1	0	1	0	0
0	0	1	0	0	0	1	1	0	0
0	0	1	1	0	1	1	0	0	0
0	0	1	0	1	1	1	0	0	0
0	0	1	1	1	1	0	0	0	0
0	0	1	0	0	0	1	1	0	0
0	0	0	1	0	0	1	0	0	0
1	0	1	0	0	0	1	0	1	0
0	0	1	1	0	1	1	0	1	0
0	0	1	1	0	0	1	1	1	0
0	0	0	1	0	0	0	0	0	0
0	0	1	1	1	0	0	1	0	0
0	0	1	1	0	0	1	1	1	0
0	0	1	1	0	1	0	1	0	0
0	0	1	1	0	1	0	0	0	1
0	0	1	1	0	1	0	1	0	0
0	0	1	1	1	0	1	1	1	0
0	0	1	1	0	0	1	0	0	0
0	0	1	0	0	0	0	0	0	1
0	0	0	1	0	0	0	1	0	0
0	0	1	1	1	0	1	0	0	1
0	0	0	1	0	0	0	0	0	0
0	0	1	1	0	0	0	1	1	0
0	0	0	0	0	0	1	1	1	1
0	0	1	1	1	1	1	1	0	0
0	0	1	0	0	0	1	0	0	1
0	0	1	1	0	0	1	0	0	0
0	0	1	0	0	1	1	1	0	0
0	0	1	1	0	0	1	1	0	0
0	0	1	0	0	1	1	1	0	0
0	0	0	1	0	0	1	1	0	1
0	0	1	1	0	0	1	1	1	0

0	0	1	0	0	0	1	1	0	1
0	0	1	1	0	0	1	1	0	0
0	0	1	1	0	0	1	0	0	0

Appendix 1b. The output table of allele frequency

Alleles	STR1	STR2	STR3	STR4	STR5	STR6	STR7	STR8
0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0.01	0	0
10	0.05	0	0	0.07	0	0.01	0	0
11	0.25	0.01	0	0.19	0	0.2	0	0
12	0.43	0.08	0	0.26	0.08	0.02	0.05	0.01
13	0	0.2	0.02	0.02	0.39	0.24	0.24	0.15
14	0	0.07	0.22	0.26	0.12	0.23	0.19	0.05
15	0	0.29	0.28	0.07	0.1	0.02	0.5	0.01
16	0	0.02	0.28	0.13	0.04	0.02	0.02	0.24
17	0.11	0.16	0.02	0	0.01	0.09	0	0.36
18	0.04	0.16	0.15	0	0.26	0.08	0	0.11
19	0.08	0	0.03	0	0	0.01	0	0.07
20	0.04	0.01	0	0	0	0.03	0	0
21	0	0	0	0	0	0.04	0	0
22	0	0	0	0	0	0	0	0

STR9	STR10	STR11	STR12	STR13	STR14	STR15	STR16	STR17
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0.04	0.13	0	0	0	0	0
0	0.04	0	0.4	0	0	0.03	0	0.06
0	0.06	0.06	0.22	0	0	0.06	0.19	0
0.06	0.02	0.21	0.19	0.01	0.01	0.01	0.23	0.05
0	0.21	0.32	0.01	0.09	0.17	0	0.15	0.41
0.05	0.24	0.05	0.05	0.1	0	0.17	0.06	0.19
0	0.28	0.31	0	0.14	0.02	0.13	0.03	0
0.02	0.15	0.01	0	0.37	0.11	0.12	0.07	0.04
0.13	0	0	0	0.08	0.37	0.42	0.25	0.25
0.1	0	0	0	0.12	0.25	0.06	0.02	0
0.21	0	0	0	0.03	0.06	0	0	0
0.41	0	0	0	0.06	0.01	0	0	0
0.02	0	0	0	0	0	0	0	0

STR18	STR19	STR20	SNP1	SNP2	SNP3	SNP4	SNP5	SNP6
0	0	0	0.98	0.31	0.96	0.69	0.89	0.99
0	0	0	0.02	0.69	0.04	0.31	0.11	0.01
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0.03	0	0	0	0	0	0	0	0
0.03	0	0.01	0	0	0	0	0	0
0.28	0.01	0.07	0	0	0	0	0	0
0.11	0.13	0.07	0	0	0	0	0	0
0.39	0.33	0.06	0	0	0	0	0	0
0.16	0.3	0.07	0	0	0	0	0	0
0	0.12	0.3	0	0	0	0	0	0
0	0.11	0.08	0	0	0	0	0	0
0	0	0.34	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0

SNP7	SNP8	SNP9	SNP10
0.2	0.72	0.42	0.82
0.8	0.28	0.58	0.18
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0
0	0	0	0

Appendix 1c. The output table of heterozygosity

Sample ID	STR1	STR2	STR3	STR4	STR5	STR6	STR7	STR8
Sample1	0	0	1	1	0	1	1	1
Sample2	0	1	1	1	1	1	1	1
Sample3	1	0	1	0	1	1	1	1
Sample4	1	1	1	1	0	1	1	1
Sample5	1	0	1	1	0	1	1	1
Sample6	1	1	1	1	0	1	1	1
Sample7	1	1	1	1	0	0	1	1
Sample8	1	1	0	1	1	1	0	1
Sample9	1	0	1	1	0	1	1	1
Sample10	1	1	1	1	1	1	1	1
Sample11	1	1	1	1	0	1	1	1
Sample12	1	1	1	1	1	0	1	0
Sample13	1	0	1	1	1	1	1	1
Sample14	0	0	1	1	1	1	1	1
Sample15	0	1	1	1	1	0	0	1
Sample16	0	0	1	1	0	1	1	1
Sample17	1	1	1	1	1	1	0	1
Sample18	1	1	1	0	1	1	1	1
Sample19	1	1	1	1	1	1	1	1
Sample20	1	0	0	1	1	0	0	0
Sample21	1	1	0	0	1	1	1	1
Sample22	1	1	0	1	1	1	1	1
Sample23	1	1	0	1	1	1	0	1
Sample24	1	0	1	0	1	1	1	0
Sample25	1	1	1	1	0	1	1	1
Sample26	1	1	1	1	0	0	1	1
Sample27	1	1	0	1	1	1	0	1
Sample28	1	0	1	1	1	1	0	1
Sample29	1	1	1	1	1	1	0	1
Sample30	1	1	1	1	1	1	1	0
Sample31	1	1	1	0	1	1	1	1
Sample32	1	1	1	1	1	0	1	0
Sample33	1	1	1	1	1	1	0	1
Sample34	1	1	1	1	1	1	1	1
Sample35	1	1	0	1	1	1	1	0
Sample36	1	1	1	1	1	0	0	1
Sample37	1	1	1	1	1	1	1	1
Sample38	1	1	1	1	1	1	1	0
Sample39	1	1	1	1	1	1	1	1
Sample40	0	1	1	1	1	1	1	1
Sample41	0	1	1	1	1	1	0	0
Sample42	0	0	1	0	0	0	1	1
Sample43	1	0	1	0	1	1	1	1
Sample44	1	1	0	1	1	1	1	1
Sample45	1	1	1	1	0	1	1	1
Sample46	1	0	1	1	1	1	0	1
Sample47	1	1	1	1	1	0	0	0

Sample48	0	1	1	1	1	1	1	1
Sample49	1	1	1	1	1	1	0	1
Sample50	1	1	0	1	1	1	0	1

STR9	STR10	STR11	STR12	STR13	STR14	STR15	STR16	STR17
1	1	1	0	1	1	1	0	1
0	0	1	1	1	1	0	0	1
1	1	1	1	1	1	1	0	1
1	1	1	1	1	1	1	1	0
1	1	1	1	0	1	1	1	0
1	1	1	1	1	1	1	1	1
0	0	0	1	1	1	1	0	1
1	1	1	1	1	1	1	1	1
1	1	0	1	1	1	0	1	1
1	1	1	0	1	0	1	1	0
1	0	1	1	1	1	1	1	1
1	1	0	0	1	1	1	1	1
1	1	1	1	1	1	1	1	1
0	1	1	1	1	1	0	1	1
1	1	0	1	0	1	1	1	1
1	1	1	0	1	0	1	0	0
1	1	0	1	1	1	1	1	1
1	1	1	1	0	1	1	1	0
0	1	1	1	1	1	1	1	1
1	1	0	1	1	0	0	1	1
1	1	1	1	1	1	1	1	1
1	0	1	0	1	1	0	1	1
1	1	1	1	1	1	1	0	1
0	0	1	1	0	0	1	1	0
1	0	0	1	1	1	1	1	1
1	0	1	0	1	1	1	1	1
1	1	1	0	1	1	0	1	1
0	1	1	1	0	1	0	1	1
1	0	1	1	0	0	0	1	1
1	0	1	1	1	0	1	1	1
0	0	1	1	0	0	1	0	0
0	1	1	1	1	1	1	1	0
0	1	1	1	1	1	1	1	1
1	0	0	0	1	1	1	0	1
1	0	1	0	0	1	1	1	0
1	0	1	1	0	0	1	1	0
1	0	0	1	1	1	1	1	1
0	1	1	1	1	1	1	1	1
0	1	1	1	1	1	1	1	1
1	1	1	1	0	0	1	1	0
1	0	1	1	1	1	1	1	0
1	1	1	1	1	0	0	0	1
1	1	0	1	1	1	1	0	1
0	1	1	0	1	1	0	1	1
1	1	1	1	1	1	1	1	0
0	1	1	1	1	1	1	1	1
1	0	1	1	1	1	1	0	1

1	0	0	1	1	1	1	1	1
1	1	1	0	0	1	0	1	1
0	0	1	1	0	0	1	0	1

STR18	STR19	STR20	SNP1	SNP2	SNP3	SNP4	SNP5	SNP6
1	1	1	0	1	1	0	0	0
0	1	1	0	1	0	0	0	0
1	0	1	0	1	0	1	0	0
0	1	0	0	1	0	0	1	0
1	1	1	0	1	0	1	0	0
1	0	1	0	0	0	0	0	0
1	0	0	0	1	0	1	0	0
1	1	0	0	0	0	0	0	0
1	1	1	1	0	0	1	0	0
1	0	1	0	0	0	1	0	0
0	1	1	0	0	0	1	0	0
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1	1	1	0	1	0	0	0	0
1	1	1	0	0	0	0	0	0
1	0	1	1	1	0	1	0	0
1	1	1	0	0	1	0	0	0
0	1	0	0	0	0	1	0	0
0	1	1	0	0	0	1	0	0
1	1	1	0	0	0	0	0	0
1	1	0	0	0	0	0	0	0
1	1	1	0	1	0	0	0	0
1	1	0	0	1	0	0	1	0
1	1	1	0	0	0	1	0	1
0	1	1	0	1	0	0	0	0
1	0	1	0	1	0	0	0	0
1	1	1	0	0	0	1	0	0
1	1	0	0	1	0	1	0	0
1	0	0	0	1	0	1	1	0
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1	0	1	0	1	0	0	1	0
0	1	1	0	0	0	0	1	0
1	1	1	0	0	0	0	1	0
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1	1	1	0	1	0	1	1	0
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1	1	1	0	0	1	0	0	0
1	1	0	0	0	0	1	0	0
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0	1	1	0	0	0	1	0	0
0	1	0	0	1	0	0	0	0
1	0	1	0	0	0	1	0	0
1	0	1	0	1	0	0	0	0
1	1	1	0	0	0	1	0	0
1	1	0	0	0	0	0	1	0
1	1	0	0	0	0	1	0	0

1	0	1	0	0	1	0	0	0
1	1	1	0	1	0	0	1	0
1	0	0	0	1	0	0	0	0

SNP7	SNP8	SNP9	SNP10
0	1	0	0
0	1	1	0
0	0	1	0
1	1	0	0
0	0	0	1
0	1	1	0
0	1	0	1
1	1	1	0
0	0	1	0
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1	0	0	0
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0	0	0	1
0	1	1	0
0	1	0	1
0	1	1	0
0	1	0	1
0	0	1	0
1	0	0	1
1	0	1	0
0	1	1	1
1	0	0	0
0	0	1	1
0	0	0	0
0	0	0	0
1	0	1	1
0	0	1	0
1	1	0	0
0	0	0	0
1	1	0	0
1	0	0	1
0	0	0	1

1	0	0	1
0	0	0	0
0	0	1	0

Appendix 1d. The output table of number of shared alleles

Pairs	STR1	STR2	STR3	STR4	STR5	STR6	STR7	STR8
1vs2	2	0	1	1	1	0	1	1
1vs3	1	0	1	0	1	0	1	1
1vs4	1	0	0	1	2	0	1	1
1vs5	0	0	0	0	0	0	2	1
1vs6	1	1	2	1	2	0	1	0
1vs7	1	1	1	1	2	0	1	1
1vs8	0	0	0	1	1	0	1	0
1vs9	0	0	1	1	0	0	2	0
1vs10	1	0	1	1	0	0	1	1
1vs11	0	0	1	1	2	0	0	0
1vs12	1	0	0	0	1	0	2	1
1vs13	0	0	2	1	0	0	1	1
1vs14	2	0	2	0	0	0	1	0
1vs15	0	0	1	1	1	0	1	0
1vs16	2	0	0	0	2	0	1	0
1vs17	1	0	1	0	1	0	0	1
1vs18	1	0	1	0	1	0	1	1
1vs19	1	0	0	1	1	0	1	0
1vs20	1	0	0	0	0	0	1	0
1vs21	0	0	0	0	1	0	1	1
1vs22	1	0	0	0	1	0	1	1
1vs23	1	0	1	1	1	1	1	1
1vs24	1	0	1	0	1	0	1	1
1vs25	0	1	1	1	0	0	0	1
1vs26	1	0	2	1	0	0	1	1
1vs27	1	0	1	1	1	0	0	1
1vs28	1	0	0	0	1	0	1	0
1vs29	1	1	2	0	1	0	1	1
1vs30	1	0	1	1	1	0	1	1
1vs31	1	0	2	0	1	0	1	1
1vs32	0	0	1	2	0	0	2	1
1vs33	1	0	1	1	1	0	1	1
1vs34	1	0	0	1	1	0	1	1
1vs35	1	0	0	1	0	0	1	0
1vs36	1	0	1	0	0	0	1	1
1vs37	0	0	1	0	0	0	1	1
1vs38	1	0	1	1	0	0	2	0
1vs39	1	0	1	0	1	0	1	2
1vs40	2	0	1	1	0	0	1	1
1vs41	0	0	1	1	0	0	1	1
1vs42	2	0	2	1	0	0	2	1
1vs43	1	0	0	0	1	0	2	1
1vs44	1	0	1	0	1	0	2	2
1vs45	1	0	1	1	2	0	2	2
1vs46	1	0	1	0	1	0	1	0
1vs47	1	0	1	1	1	0	1	0
1vs48	0	1	1	1	0	0	1	2

1vs49	0	0	2	1	1	0	1	1
1vs50	1	0	1	1	0	0	1	2
2vs3	1	0	0	0	1	1	1	1
2vs4	1	1	0	1	1	0	1	2
2vs5	0	0	0	0	0	0	1	2
2vs6	1	0	1	1	1	0	1	1
2vs7	1	0	0	1	1	0	2	1
2vs8	0	0	0	1	2	0	1	1
2vs9	0	1	0	1	0	0	1	0
2vs10	1	1	0	1	0	1	1	2
2vs11	0	1	1	1	1	2	1	0
2vs12	1	2	1	0	1	0	1	1
2vs13	0	0	1	1	0	0	2	1
2vs14	2	1	1	1	0	0	1	1
2vs15	0	0	0	0	1	0	1	1
2vs16	2	0	1	0	1	0	2	1
2vs17	1	1	0	0	2	1	1	2
2vs18	1	0	0	0	1	0	1	1
2vs19	1	1	0	2	1	0	2	1
2vs20	1	0	0	1	1	1	1	1
2vs21	0	1	0	1	1	1	1	1
2vs22	1	0	0	0	2	1	2	1
2vs23	1	0	1	2	1	0	1	1
2vs24	1	0	1	0	1	1	2	1
2vs25	0	0	0	1	1	1	1	1
2vs26	1	0	1	1	0	1	1	0
2vs27	1	0	0	1	1	2	1	2
2vs28	1	0	0	0	1	0	1	0
2vs29	1	0	1	0	1	0	1	2
2vs30	1	0	0	1	1	0	1	1
2vs31	1	0	1	0	1	1	2	1
2vs32	0	0	0	1	1	1	1	1
2vs33	1	0	0	1	1	0	1	1
2vs34	1	0	0	2	1	1	1	1
2vs35	1	0	0	1	0	0	2	1
2vs36	1	2	0	1	0	0	1	1
2vs37	0	1	1	1	1	1	1	1
2vs38	1	1	0	1	0	1	1	1
2vs39	1	0	1	1	1	0	2	1
2vs40	2	0	1	1	0	2	1	1
2vs41	0	1	1	0	1	0	0	0
2vs42	2	0	1	1	0	1	1	1
2vs43	1	0	0	0	1	1	1	1
2vs44	1	0	0	1	1	1	1	1
2vs45	1	1	1	0	1	1	1	1
2vs46	1	1	1	0	1	1	1	1
2vs47	1	1	0	1	1	0	1	1
2vs48	0	0	0	1	0	1	2	1

2vs49	0	0	1	0	1	0	1	1
2vs50	1	1	1	1	0	1	1	1
3vs4	1	0	1	0	1	0	0	1
3vs5	0	0	0	1	0	0	1	1
3vs6	1	0	1	0	1	1	2	0
3vs7	1	0	1	1	1	0	1	2
3vs8	1	1	0	0	1	1	0	1
3vs9	0	0	1	1	1	1	1	0
3vs10	2	1	2	0	0	1	2	1
3vs11	0	0	0	1	1	1	1	1
3vs12	1	0	0	1	2	1	1	1
3vs13	1	0	1	0	0	1	1	1
3vs14	1	0	1	1	1	1	2	0
3vs15	0	1	2	0	1	0	0	1
3vs16	1	0	0	1	1	1	1	0
3vs17	1	0	1	0	1	2	1	1
3vs18	1	0	1	0	2	1	0	2
3vs19	1	0	1	0	1	0	1	0
3vs20	1	0	1	1	1	0	0	0
3vs21	0	1	0	0	1	1	0	2
3vs22	1	0	1	1	1	2	1	2
3vs23	1	0	0	0	1	0	0	1
3vs24	1	0	0	2	2	1	1	1
3vs25	0	1	1	0	0	1	1	1
3vs26	1	1	1	0	1	1	0	0
3vs27	1	1	1	1	2	1	1	1
3vs28	1	0	1	0	1	1	0	1
3vs29	1	1	1	1	2	0	0	1
3vs30	1	0	2	1	1	1	2	1
3vs31	1	1	1	0	2	1	1	2
3vs32	0	1	2	0	0	1	1	1
3vs33	1	1	2	1	1	1	0	1
3vs34	1	1	1	0	1	1	2	2
3vs35	1	0	0	1	1	1	1	0
3vs36	1	0	2	1	1	0	0	2
3vs37	0	0	0	0	1	1	2	0
3vs38	1	1	1	0	1	2	1	0
3vs39	1	1	0	0	2	1	1	1
3vs40	1	0	0	0	1	1	0	1
3vs41	0	0	0	0	1	0	1	0
3vs42	1	0	1	0	1	1	1	2
3vs43	1	0	0	2	2	1	1	2
3vs44	1	0	1	1	2	2	1	1
3vs45	1	0	0	0	1	0	1	1
3vs46	1	0	0	1	1	1	0	1
3vs47	1	0	1	0	1	0	0	0
3vs48	0	0	1	1	1	0	1	1
3vs49	0	0	1	1	2	1	0	0

3vs50	1	0	0	1	0	0	0	1
4vs5	0	0	1	1	0	0	1	2
4vs6	2	1	0	2	2	1	0	1
4vs7	2	0	1	1	2	1	1	1
4vs8	1	0	1	1	1	1	1	1
4vs9	0	1	1	1	0	0	1	0
4vs10	1	1	1	0	0	1	0	2
4vs11	0	2	1	1	2	0	1	0
4vs12	2	1	0	1	1	0	1	1
4vs13	1	1	0	2	0	0	1	1
4vs14	1	1	0	0	0	0	0	1
4vs15	1	0	1	0	1	1	1	1
4vs16	1	0	1	0	2	0	1	1
4vs17	1	0	1	1	1	0	0	2
4vs18	1	1	1	1	1	1	2	1
4vs19	1	1	2	1	1	0	1	1
4vs20	1	1	1	0	0	0	1	1
4vs21	1	1	1	0	1	1	1	1
4vs22	2	1	1	0	1	0	1	1
4vs23	1	1	0	1	1	0	1	1
4vs24	2	0	1	0	1	0	1	1
4vs25	0	0	1	2	0	1	1	1
4vs26	1	0	0	2	0	0	2	0
4vs27	2	1	0	1	1	0	0	2
4vs28	2	0	2	1	1	1	1	0
4vs29	2	0	0	1	1	0	1	2
4vs30	2	1	1	1	1	0	0	1
4vs31	1	0	0	1	1	1	1	1
4vs32	1	0	1	1	0	0	1	1
4vs33	1	0	1	1	1	0	1	1
4vs34	1	0	1	1	1	0	0	1
4vs35	1	0	1	1	0	1	1	1
4vs36	1	1	1	0	0	1	1	1
4vs37	0	2	1	1	0	1	0	1
4vs38	1	1	1	2	0	0	1	1
4vs39	2	0	1	0	1	1	1	1
4vs40	1	1	1	1	0	0	1	1
4vs41	1	1	1	0	0	2	0	0
4vs42	1	0	0	1	0	0	1	1
4vs43	1	0	1	0	1	0	1	1
4vs44	2	1	0	0	1	0	1	1
4vs45	2	2	1	1	2	1	1	1
4vs46	1	0	1	1	1	0	1	1
4vs47	2	1	1	2	1	1	1	1
4vs48	1	0	1	1	0	0	1	1
4vs49	0	1	0	0	1	1	1	1
4vs50	2	2	0	1	0	1	1	1
5vs6	0	0	0	1	0	0	1	1

5vs7	0	0	1	1	0	0	1	1
5vs8	0	1	1	0	0	0	1	1
5vs9	1	0	1	1	0	0	2	0
5vs10	0	0	0	0	0	0	1	2
5vs11	1	0	1	1	0	0	0	0
5vs12	0	0	0	2	0	0	2	1
5vs13	0	0	0	1	0	1	1	1
5vs14	0	0	0	1	1	1	1	1
5vs15	0	1	0	0	1	0	1	1
5vs16	0	2	1	1	0	1	1	1
5vs17	1	1	1	1	0	0	0	2
5vs18	1	1	1	1	0	0	1	1
5vs19	1	0	1	0	1	1	1	1
5vs20	0	0	0	1	0	0	1	1
5vs21	1	0	1	0	1	0	1	1
5vs22	0	0	0	1	0	0	1	1
5vs23	0	1	0	0	0	0	1	1
5vs24	0	2	1	1	0	1	1	1
5vs25	2	0	1	1	0	0	0	1
5vs26	0	1	0	1	0	0	1	0
5vs27	0	0	0	1	0	0	0	2
5vs28	0	2	1	1	0	0	1	0
5vs29	0	0	0	2	0	2	1	2
5vs30	0	1	0	1	1	1	1	1
5vs31	1	0	0	1	0	0	1	1
5vs32	1	1	0	0	0	0	2	1
5vs33	1	1	0	1	1	0	1	1
5vs34	1	1	1	0	1	0	1	1
5vs35	1	1	1	1	0	0	1	1
5vs36	1	0	0	1	0	0	1	1
5vs37	0	0	1	1	0	0	1	1
5vs38	0	0	1	1	0	0	2	1
5vs39	0	1	1	0	0	0	1	1
5vs40	0	1	1	0	1	0	1	1
5vs41	0	0	1	0	0	0	1	0
5vs42	0	2	0	0	0	0	2	1
5vs43	1	2	1	1	0	0	2	1
5vs44	0	1	0	1	0	0	2	1
5vs45	0	0	1	1	0	0	2	1
5vs46	1	0	1	2	0	1	1	1
5vs47	0	1	1	1	1	0	1	1
5vs48	0	1	1	1	0	1	1	1
5vs49	1	1	0	1	0	0	1	1
5vs50	0	0	0	1	1	0	1	1
6vs7	2	1	1	1	2	1	1	0
6vs8	1	0	0	1	1	1	0	1
6vs9	0	0	1	1	0	1	1	1
6vs10	1	0	1	0	0	1	2	1

6vs11	0	1	1	1	2	0	1	1
6vs12	2	0	0	1	1	1	1	0
6vs13	1	1	2	2	0	1	1	1
6vs14	1	0	2	0	0	1	2	2
6vs15	1	0	1	0	1	1	0	1
6vs16	1	0	0	0	2	1	1	2
6vs17	1	0	1	1	1	1	1	1
6vs18	1	1	1	1	1	2	0	0
6vs19	1	1	0	1	1	0	1	1
6vs20	1	1	0	0	0	0	0	1
6vs21	1	0	0	0	1	1	0	0
6vs22	2	1	0	0	1	1	1	0
6vs23	1	1	1	1	1	0	0	0
6vs24	2	0	1	0	1	0	1	0
6vs25	0	1	1	2	0	1	1	0
6vs26	1	0	2	2	0	0	0	1
6vs27	2	1	1	1	1	0	1	1
6vs28	2	0	0	1	1	2	0	0
6vs29	2	1	2	1	1	0	0	1
6vs30	2	1	1	1	1	1	2	0
6vs31	1	0	2	1	1	1	1	0
6vs32	1	0	1	1	0	0	1	0
6vs33	1	0	1	1	1	1	0	0
6vs34	1	0	0	1	1	0	2	0
6vs35	1	0	0	1	0	2	1	1
6vs36	1	0	1	0	0	1	0	0
6vs37	0	1	1	1	0	1	2	1
6vs38	1	0	1	2	0	1	1	1
6vs39	2	0	1	0	1	2	1	0
6vs40	1	1	1	1	0	0	0	0
6vs41	1	1	1	0	0	1	1	0
6vs42	1	0	2	1	0	0	1	0
6vs43	1	0	0	0	1	0	1	0
6vs44	2	1	1	0	1	1	1	0
6vs45	2	1	1	1	2	1	1	0
6vs46	1	0	1	1	1	0	0	1
6vs47	2	0	1	2	1	1	0	1
6vs48	1	1	1	1	0	0	1	0
6vs49	0	1	2	0	1	2	0	1
6vs50	2	1	1	1	0	1	0	0
7vs8	1	0	1	1	1	0	1	1
7vs9	0	0	2	2	0	0	1	0
7vs10	1	0	1	0	0	1	1	1
7vs11	0	0	1	2	2	0	1	1
7vs12	2	0	0	1	1	0	1	1
7vs13	1	0	1	1	0	0	2	1
7vs14	1	0	1	1	0	0	1	0
7vs15	1	0	1	0	1	2	1	1

7vs16	1	0	1	1	2	0	2	0
7vs17	1	0	2	0	1	0	1	1
7vs18	1	0	2	0	1	1	1	2
7vs19	1	0	1	1	1	0	2	0
7vs20	1	0	0	1	0	0	1	0
7vs21	1	0	1	0	1	1	1	2
7vs22	2	0	0	1	1	0	2	2
7vs23	1	0	0	1	1	0	1	1
7vs24	2	0	1	1	1	0	2	1
7vs25	0	1	2	1	0	1	1	1
7vs26	1	0	1	1	0	0	1	0
7vs27	2	0	1	2	1	0	1	1
7vs28	2	0	1	0	1	1	1	1
7vs29	2	1	1	1	1	0	1	1
7vs30	2	0	1	2	1	0	1	1
7vs31	1	1	1	0	1	1	2	2
7vs32	1	0	1	1	0	0	1	1
7vs33	1	0	1	2	1	0	1	1
7vs34	1	0	0	1	1	0	1	2
7vs35	1	0	1	2	0	1	2	0
7vs36	1	0	1	1	0	2	1	2
7vs37	0	0	1	0	0	1	1	0
7vs38	1	0	2	1	0	0	1	0
7vs39	2	0	1	0	1	1	2	1
7vs40	1	0	1	1	0	0	1	1
7vs41	1	0	1	0	0	1	0	0
7vs42	1	0	1	1	0	0	1	2
7vs43	1	0	1	1	1	0	1	2
7vs44	2	0	1	1	1	0	1	1
7vs45	2	0	1	0	2	1	1	1
7vs46	1	0	1	1	1	0	1	1
7vs47	2	0	2	1	1	2	1	0
7vs48	1	1	2	2	0	0	2	1
7vs49	0	0	1	1	1	1	1	0
7vs50	2	0	0	2	0	1	1	1
8vs9	0	0	1	1	0	1	1	0
8vs10	1	1	0	0	0	0	0	1
8vs11	0	0	1	1	1	0	0	1
8vs12	1	0	0	0	1	1	1	0
8vs13	2	0	0	1	0	1	1	0
8vs14	0	0	0	0	0	1	0	1
8vs15	1	2	0	1	1	0	2	2
8vs16	0	1	1	0	1	1	1	1
8vs17	0	1	1	1	2	1	0	1
8vs18	0	1	1	0	1	1	1	1
8vs19	0	0	1	1	1	0	1	1
8vs20	0	0	0	0	1	0	2	1
8vs21	1	1	2	0	1	0	1	1

8vs22	1	0	0	1	2	1	1	1
8vs23	0	1	0	1	1	0	2	0
8vs24	1	1	1	0	1	0	1	0
8vs25	0	1	1	1	1	0	0	0
8vs26	0	2	0	1	0	0	1	0
8vs27	1	1	0	1	1	0	0	1
8vs28	1	1	1	1	1	1	2	1
8vs29	1	1	0	0	1	0	2	1
8vs30	1	1	0	1	1	1	0	0
8vs31	0	1	0	0	1	0	1	1
8vs32	1	2	0	1	1	0	1	0
8vs33	0	2	0	1	1	1	2	0
8vs34	0	2	0	1	1	0	0	1
8vs35	0	1	2	1	0	1	1	1
8vs36	0	0	0	0	0	0	2	1
8vs37	0	0	1	0	1	0	0	1
8vs38	0	1	1	1	0	1	1	1
8vs39	1	2	1	0	1	1	1	0
8vs40	0	1	1	2	0	0	1	0
8vs41	1	0	1	1	1	1	0	0
8vs42	0	1	0	1	0	0	1	1
8vs43	0	1	1	0	1	0	1	1
8vs44	1	1	0	0	1	1	1	0
8vs45	1	0	1	0	1	0	1	0
8vs46	0	0	1	0	1	0	2	2
8vs47	1	1	1	1	1	0	2	1
8vs48	1	1	1	1	0	0	1	0
8vs49	0	1	0	0	1	1	2	1
8vs50	1	0	0	1	0	0	2	0
9vs10	0	1	1	0	0	0	1	0
9vs11	1	1	1	2	0	0	0	1
9vs12	0	1	0	1	1	1	2	0
9vs13	0	0	1	1	0	1	1	1
9vs14	0	2	1	1	1	1	1	1
9vs15	0	0	1	0	0	0	1	0
9vs16	0	0	1	1	0	1	1	1
9vs17	0	0	2	0	0	1	0	0
9vs18	1	0	2	0	1	1	1	0
9vs19	0	0	1	1	0	0	1	1
9vs20	0	0	0	1	1	0	1	0
9vs21	1	1	1	0	0	0	1	0
9vs22	0	0	0	1	0	1	1	0
9vs23	1	0	0	1	0	0	1	1
9vs24	0	0	1	1	1	0	1	0
9vs25	1	0	2	1	0	0	0	1
9vs26	1	0	1	1	2	0	1	1
9vs27	0	0	1	2	1	0	0	0
9vs28	0	0	1	0	0	1	1	0

9vs29	0	0	1	1	1	0	1	0
9vs30	0	0	1	2	0	1	1	0
9vs31	0	0	1	0	1	0	1	0
9vs32	0	0	1	1	0	0	2	0
9vs33	1	0	1	2	0	1	1	1
9vs34	1	0	0	1	0	0	1	0
9vs35	0	0	1	2	1	1	1	0
9vs36	1	1	1	1	1	0	1	0
9vs37	1	1	1	0	1	0	1	0
9vs38	0	1	2	1	1	1	2	0
9vs39	0	0	1	0	1	1	1	0
9vs40	0	0	1	1	1	0	1	0
9vs41	0	0	1	0	1	0	1	0
9vs42	0	0	1	1	2	0	2	0
9vs43	1	0	1	1	1	0	2	0
9vs44	0	0	1	1	1	1	2	0
9vs45	0	1	1	0	0	0	2	0
9vs46	0	0	1	1	0	0	1	0
9vs47	0	1	2	1	0	0	1	0
9vs48	0	0	2	2	1	0	1	0
9vs49	2	0	1	1	1	1	1	0
9vs50	0	1	0	2	0	0	1	0
10vs11	0	1	0	0	0	1	1	0
10vs12	1	1	0	0	0	0	1	1
10vs13	1	0	1	0	1	0	1	1
10vs14	1	1	1	1	0	0	2	1
10vs15	0	1	2	1	0	1	0	1
10vs16	1	0	0	0	0	0	1	1
10vs17	1	0	1	0	0	1	1	2
10vs18	1	0	1	0	0	1	0	1
10vs19	1	0	1	1	0	0	1	1
10vs20	1	0	1	1	0	0	0	1
10vs21	0	2	0	1	0	2	0	1
10vs22	1	0	1	0	0	1	1	1
10vs23	1	0	0	1	1	0	0	1
10vs24	1	0	0	0	0	1	1	1
10vs25	0	1	1	0	0	2	1	1
10vs26	1	1	1	0	0	1	0	0
10vs27	1	1	1	0	0	1	1	2
10vs28	1	0	1	0	1	1	0	0
10vs29	1	1	1	0	0	0	0	2
10vs30	1	0	2	0	0	0	2	1
10vs31	1	1	1	0	0	2	1	1
10vs32	0	1	2	1	1	1	1	1
10vs33	1	1	2	0	0	0	0	1
10vs34	1	1	1	1	0	1	2	1
10vs35	1	0	0	0	1	1	1	1
10vs36	1	1	2	1	0	1	0	1

10vs37	0	1	0	1	0	2	2	1
10vs38	1	2	1	0	1	1	1	1
10vs39	1	1	0	1	0	1	1	1
10vs40	1	0	0	0	0	1	0	1
10vs41	0	0	0	1	0	1	1	0
10vs42	1	0	1	0	0	1	1	1
10vs43	1	0	0	0	0	1	1	1
10vs44	1	0	1	1	0	1	1	1
10vs45	1	1	0	1	0	1	1	1
10vs46	1	0	0	0	1	1	0	1
10vs47	1	1	1	0	0	1	0	1
10vs48	0	0	1	0	0	0	1	1
10vs49	0	0	1	1	0	1	0	1
10vs50	1	1	0	0	0	1	0	1
11vs12	0	1	0	1	1	0	0	0
11vs13	0	1	1	1	0	0	1	1
11vs14	0	1	1	1	0	0	1	1
11vs15	0	0	0	0	1	0	0	1
11vs16	0	0	1	1	2	0	1	1
11vs17	0	0	1	0	1	1	1	0
11vs18	1	1	1	0	1	0	1	1
11vs19	0	1	1	1	1	0	1	0
11vs20	1	1	0	1	0	1	0	0
11vs21	1	1	1	0	1	1	0	1
11vs22	0	1	0	1	1	1	1	1
11vs23	0	1	1	1	1	0	0	0
11vs24	0	0	2	1	1	1	1	0
11vs25	1	0	1	1	0	1	2	0
11vs26	0	0	1	1	0	1	1	1
11vs27	0	1	0	2	1	2	1	0
11vs28	0	0	1	0	1	0	0	1
11vs29	0	0	1	1	1	0	0	0
11vs30	0	1	0	2	1	0	1	0
11vs31	0	0	1	0	1	1	1	1
11vs32	0	0	0	1	0	1	0	0
11vs33	1	0	0	2	1	0	0	0
11vs34	1	0	0	1	1	1	1	1
11vs35	0	0	1	2	0	0	1	0
11vs36	1	1	0	1	0	0	0	1
11vs37	1	2	2	0	0	1	1	0
11vs38	1	1	1	1	0	1	0	0
11vs39	0	0	2	0	1	0	1	0
11vs40	0	1	2	1	0	2	0	0
11vs41	0	1	2	0	0	0	0	0
11vs42	0	0	1	1	0	1	0	1
11vs43	1	0	1	1	1	1	0	1
11vs44	0	1	0	1	1	1	0	0
11vs45	0	2	2	0	2	1	0	0

11vs46	0	0	2	1	1	1	0	1
11vs47	0	1	1	1	1	0	0	0
11vs48	0	0	1	2	0	1	1	0
11vs49	1	1	1	1	1	0	0	0
11vs50	0	2	1	2	0	1	0	0
12vs13	1	0	0	1	0	1	1	1
12vs14	1	1	0	1	1	1	1	0
12vs15	1	0	0	0	1	0	1	0
12vs16	1	0	1	1	1	1	1	0
12vs17	1	1	0	1	1	1	0	1
12vs18	1	0	0	1	2	1	1	1
12vs19	1	1	0	0	1	0	1	0
12vs20	1	0	0	1	1	0	1	0
12vs21	1	1	0	0	1	0	1	1
12vs22	2	0	0	1	1	1	1	1
12vs23	1	0	0	0	1	0	1	1
12vs24	2	0	0	1	2	0	1	2
12vs25	0	0	0	1	0	0	0	1
12vs26	1	0	0	1	1	0	1	0
12vs27	2	0	0	1	2	0	0	1
12vs28	2	0	0	1	1	1	1	0
12vs29	2	0	0	2	2	0	1	1
12vs30	2	0	0	1	1	1	1	2
12vs31	1	0	0	1	2	0	1	1
12vs32	1	0	0	0	0	0	2	2
12vs33	1	0	0	1	1	1	1	1
12vs34	1	0	0	0	1	0	1	1
12vs35	1	0	0	1	1	1	1	0
12vs36	1	2	0	1	1	0	1	1
12vs37	0	1	0	1	1	0	1	0
12vs38	1	1	0	1	1	1	2	0
12vs39	2	0	0	0	2	1	1	1
12vs40	1	0	0	0	1	0	1	1
12vs41	1	1	0	0	1	0	1	0
12vs42	1	0	0	0	1	0	2	1
12vs43	1	0	1	1	2	0	2	1
12vs44	2	0	0	1	2	1	2	1
12vs45	2	1	0	1	1	0	2	1
12vs46	1	1	0	2	1	0	1	0
12vs47	2	1	0	1	1	0	1	0
12vs48	1	0	0	1	1	0	1	1
12vs49	0	0	0	1	2	1	1	0
12vs50	2	1	0	1	0	0	1	1
13vs14	0	0	2	0	0	1	1	1
13vs15	1	0	1	0	0	0	1	0
13vs16	0	0	0	0	0	2	2	1
13vs17	0	0	1	1	0	1	1	1
13vs18	0	1	1	1	0	1	1	1

13vs19	0	1	0	1	0	1	2	0
13vs20	0	2	0	0	0	0	1	0
13vs21	1	0	0	0	0	0	1	1
13vs22	1	1	0	0	0	1	2	1
13vs23	0	1	1	1	1	0	1	1
13vs24	1	0	1	0	0	1	2	1
13vs25	0	0	1	2	0	0	1	1
13vs26	0	0	2	2	0	0	1	1
13vs27	1	1	1	1	0	0	1	1
13vs28	1	0	0	1	1	1	1	0
13vs29	1	0	2	1	0	1	1	1
13vs30	1	1	1	1	0	1	1	1
13vs31	0	0	2	1	0	0	2	1
13vs32	1	0	1	1	1	0	1	1
13vs33	0	0	1	1	0	1	1	1
13vs34	0	0	0	1	0	0	1	1
13vs35	0	0	0	1	1	1	2	0
13vs36	0	0	1	0	1	0	1	1
13vs37	0	1	1	1	0	0	1	0
13vs38	0	0	1	2	1	1	1	0
13vs39	1	0	1	0	0	1	2	1
13vs40	0	1	1	1	0	0	1	1
13vs41	1	1	1	0	0	0	0	0
13vs42	0	0	2	1	0	0	1	1
13vs43	0	0	0	0	0	0	1	1
13vs44	1	1	1	0	0	1	1	1
13vs45	1	1	1	1	0	0	1	1
13vs46	0	0	1	1	1	1	1	0
13vs47	1	0	1	2	0	0	1	0
13vs48	1	0	1	1	1	1	2	1
13vs49	0	1	2	0	0	1	1	0
13vs50	1	1	1	1	1	0	1	1
14vs15	0	0	1	0	1	0	0	1
14vs16	2	0	0	1	0	1	1	2
14vs17	1	0	1	0	0	1	1	1
14vs18	1	0	1	0	1	1	0	0
14vs19	1	0	0	1	1	0	1	1
14vs20	1	0	0	2	1	0	0	1
14vs21	0	1	0	1	1	0	0	0
14vs22	1	0	0	1	0	1	1	0
14vs23	1	0	1	1	0	0	0	0
14vs24	1	0	1	1	1	0	1	0
14vs25	0	0	1	0	0	0	1	0
14vs26	1	0	2	0	1	0	0	1
14vs27	1	0	1	1	1	0	1	1
14vs28	1	0	0	0	0	1	0	0
14vs29	1	0	2	1	1	1	0	1
14vs30	1	0	1	1	1	2	2	0

14vs31	1	0	2	0	1	0	1	0
14vs32	0	0	1	0	0	0	1	0
14vs33	1	0	1	1	1	1	0	0
14vs34	1	0	0	1	1	0	2	0
14vs35	1	0	0	1	1	1	1	1
14vs36	1	1	1	2	1	0	0	0
14vs37	0	1	1	1	1	0	2	1
14vs38	1	1	1	0	1	1	1	1
14vs39	1	0	1	1	1	1	1	0
14vs40	2	0	1	0	2	0	0	0
14vs41	0	0	1	0	1	0	1	0
14vs42	2	0	2	0	1	0	1	0
14vs43	1	0	0	1	1	0	1	0
14vs44	1	0	1	2	1	1	1	0
14vs45	1	1	1	0	0	0	1	0
14vs46	1	0	1	1	0	0	0	1
14vs47	1	1	1	0	1	0	0	1
14vs48	0	0	1	1	1	0	1	0
14vs49	0	0	2	1	1	1	0	1
14vs50	1	1	1	1	1	0	0	0
15vs16	0	1	0	0	1	0	1	1
15vs17	0	1	1	1	1	0	0	1
15vs18	0	1	1	0	1	1	1	1
15vs19	0	0	1	0	2	0	1	1
15vs20	0	0	1	0	0	0	2	1
15vs21	1	1	0	0	2	1	1	1
15vs22	1	0	1	1	1	0	1	1
15vs23	0	1	0	0	1	0	2	0
15vs24	1	1	0	0	1	0	1	0
15vs25	0	1	1	0	0	1	0	0
15vs26	0	2	1	0	0	0	1	0
15vs27	1	1	1	0	1	0	0	1
15vs28	1	1	1	1	1	1	2	1
15vs29	1	1	1	0	1	0	2	1
15vs30	1	1	2	0	2	0	0	0
15vs31	0	1	1	0	1	1	1	1
15vs32	1	2	2	1	0	0	1	0
15vs33	0	2	2	0	2	0	2	0
15vs34	0	2	1	0	2	0	0	1
15vs35	0	1	0	0	0	1	1	1
15vs36	0	0	2	0	0	2	2	1
15vs37	0	0	0	0	0	1	0	1
15vs38	0	1	1	0	0	0	1	1
15vs39	1	2	0	0	1	1	1	0
15vs40	0	1	0	1	1	0	1	0
15vs41	2	0	0	2	0	1	0	0
15vs42	0	1	1	0	0	0	1	1
15vs43	0	1	0	0	1	0	1	1

15vs44	1	1	1	0	1	0	1	0
15vs45	1	0	0	1	1	1	1	0
15vs46	0	0	0	0	1	0	2	2
15vs47	1	1	1	0	2	2	2	1
15vs48	2	1	1	0	0	0	1	0
15vs49	0	1	1	1	1	1	2	1
15vs50	1	0	0	0	1	1	2	0
16vs17	1	1	1	0	1	1	1	1
16vs18	1	1	1	0	1	1	1	0
16vs19	1	0	1	0	1	1	2	1
16vs20	1	0	0	1	0	0	1	1
16vs21	0	0	1	0	1	0	1	0
16vs22	1	0	0	1	1	1	2	0
16vs23	1	1	0	0	1	0	1	0
16vs24	1	2	1	1	1	1	2	0
16vs25	0	0	1	0	0	0	1	0
16vs26	1	1	0	0	0	0	1	1
16vs27	1	0	0	1	1	0	1	1
16vs28	1	2	1	0	1	1	1	0
16vs29	1	0	0	1	1	1	1	1
16vs30	1	1	0	1	1	1	1	0
16vs31	1	0	0	0	1	0	2	0
16vs32	0	1	0	0	0	0	1	0
16vs33	1	1	0	1	1	1	1	0
16vs34	1	1	0	0	1	0	1	0
16vs35	1	1	1	1	0	1	2	1
16vs36	1	0	0	1	0	0	1	0
16vs37	0	0	1	0	0	0	1	1
16vs38	1	0	1	0	0	1	1	1
16vs39	1	1	1	1	1	1	2	0
16vs40	2	1	1	0	0	0	1	0
16vs41	0	0	1	0	0	0	0	0
16vs42	2	2	0	0	0	0	1	0
16vs43	1	2	1	1	1	0	1	0
16vs44	1	1	0	1	1	1	1	0
16vs45	1	0	1	0	2	0	1	0
16vs46	1	0	1	1	1	1	1	1
16vs47	1	1	1	0	1	0	1	1
16vs48	0	1	1	1	0	1	2	0
16vs49	0	1	0	1	1	1	1	1
16vs50	1	0	0	1	0	0	1	0
17vs18	1	1	2	1	1	1	0	1
17vs19	2	1	1	0	1	0	1	1
17vs20	1	0	0	0	1	0	0	1
17vs21	0	0	1	0	1	1	0	1
17vs22	1	0	0	1	2	2	1	1
17vs23	1	1	0	0	1	0	0	1
17vs24	1	1	1	0	1	1	1	1

17vs25	1	0	2	1	1	1	1	1
17vs26	1	1	1	1	0	1	0	0
17vs27	1	0	1	0	1	1	2	2
17vs28	1	1	1	2	1	1	0	0
17vs29	1	0	1	1	1	0	0	2
17vs30	1	1	1	0	1	1	1	1
17vs31	2	0	1	1	1	1	1	1
17vs32	1	1	1	0	1	1	0	1
17vs33	1	1	1	0	1	1	0	1
17vs34	1	1	0	0	1	1	1	1
17vs35	2	1	1	0	0	1	1	1
17vs36	1	1	1	0	0	0	0	1
17vs37	0	0	1	1	1	1	1	1
17vs38	1	0	2	1	0	2	0	1
17vs39	1	1	1	0	1	1	1	1
17vs40	1	1	1	1	0	1	0	1
17vs41	0	1	1	1	1	0	0	0
17vs42	1	1	1	0	0	1	0	1
17vs43	1	1	1	0	1	1	0	1
17vs44	1	1	1	0	1	2	0	1
17vs45	1	0	1	1	1	0	0	1
17vs46	2	1	1	1	1	1	0	1
17vs47	1	1	2	1	1	0	0	1
17vs48	0	1	2	0	0	0	1	1
17vs49	0	1	1	0	1	1	0	1
17vs50	1	0	0	0	0	0	0	1
18vs19	1	1	1	0	1	0	1	0
18vs20	1	1	0	0	1	0	1	0
18vs21	1	0	1	0	1	1	1	2
18vs22	1	1	0	0	1	1	1	2
18vs23	1	2	0	0	1	0	1	1
18vs24	1	1	1	0	2	0	1	1
18vs25	1	0	2	1	0	1	1	1
18vs26	1	1	1	1	1	0	2	0
18vs27	1	1	1	0	2	0	0	1
18vs28	1	1	1	1	1	2	1	1
18vs29	1	0	1	1	2	0	1	1
18vs30	1	2	1	0	1	1	0	1
18vs31	1	0	1	2	2	1	1	2
18vs32	0	1	1	0	0	0	1	1
18vs33	2	1	1	0	1	1	1	1
18vs34	2	1	0	0	1	0	0	2
18vs35	1	1	1	0	1	2	1	0
18vs36	2	0	1	0	1	1	1	2
18vs37	0	1	1	1	1	1	0	0
18vs38	1	0	2	1	1	1	1	0
18vs39	1	1	1	0	2	2	1	1
18vs40	1	2	1	0	1	0	1	1

18vs41	0	1	1	0	1	1	0	0
18vs42	1	1	1	0	1	0	1	2
18vs43	2	1	1	0	2	0	1	2
18vs44	1	2	1	0	2	1	1	1
18vs45	1	1	1	1	1	1	1	1
18vs46	1	0	1	1	1	0	1	1
18vs47	1	1	2	1	1	1	1	0
18vs48	0	1	2	0	1	0	1	1
18vs49	1	2	1	0	2	2	1	0
18vs50	1	1	0	0	0	1	1	1
19vs20	1	1	1	1	0	0	1	1
19vs21	0	0	1	1	2	0	1	0
19vs22	1	1	1	0	1	0	2	0
19vs23	1	1	0	2	1	0	1	1
19vs24	1	0	1	0	1	1	2	0
19vs25	1	0	1	1	0	0	1	1
19vs26	1	0	0	1	0	0	1	0
19vs27	1	1	0	1	1	0	1	1
19vs28	1	0	2	0	1	0	1	0
19vs29	1	0	0	0	1	1	1	1
19vs30	1	1	1	1	2	0	1	0
19vs31	2	0	0	0	1	0	2	0
19vs32	1	0	1	1	0	0	1	0
19vs33	1	0	1	1	2	0	1	1
19vs34	1	0	1	2	2	0	1	0
19vs35	2	0	1	1	0	0	2	1
19vs36	1	1	1	1	0	0	1	0
19vs37	0	1	1	1	0	0	1	1
19vs38	1	0	1	1	0	0	1	1
19vs39	1	0	1	1	1	0	2	0
19vs40	1	1	1	1	1	0	1	0
19vs41	0	2	1	0	0	0	0	0
19vs42	1	0	0	1	0	0	1	0
19vs43	1	0	1	0	1	0	1	0
19vs44	1	1	0	1	1	0	1	0
19vs45	1	1	1	0	1	0	1	0
19vs46	2	1	1	0	1	1	1	1
19vs47	1	0	1	1	2	0	1	1
19vs48	0	0	1	1	0	1	2	0
19vs49	0	1	0	0	1	0	1	1
19vs50	1	1	0	1	1	0	1	0
20vs21	0	0	0	1	0	0	1	0
20vs22	1	1	2	1	1	0	1	0
20vs23	1	1	0	1	0	0	2	0
20vs24	1	0	0	1	1	0	1	0
20vs25	0	0	0	0	1	0	0	0
20vs26	1	0	0	0	1	0	1	0
20vs27	1	1	0	1	1	1	0	1

20vs28	1	0	1	0	0	0	2	0
20vs29	1	0	0	1	1	0	2	1
20vs30	1	1	1	1	0	0	0	0
20vs31	1	0	0	0	1	0	1	0
20vs32	0	0	1	0	1	0	1	0
20vs33	1	0	1	1	0	0	2	0
20vs34	1	0	1	1	0	0	0	0
20vs35	1	0	0	1	1	0	1	2
20vs36	1	0	1	2	1	0	2	0
20vs37	1	1	0	1	2	0	0	1
20vs38	2	0	0	0	1	0	1	2
20vs39	1	0	0	1	1	0	1	0
20vs40	1	1	0	0	1	1	1	0
20vs41	0	1	0	0	2	0	0	0
20vs42	1	0	0	0	1	0	1	0
20vs43	1	0	0	1	1	0	1	0
20vs44	1	1	0	2	1	0	1	0
20vs45	1	1	0	0	0	1	1	0
20vs46	1	0	0	1	0	0	2	1
20vs47	1	0	0	0	0	0	2	2
20vs48	0	0	0	1	1	1	1	0
20vs49	0	1	0	1	1	0	2	1
20vs50	1	1	0	1	0	1	2	0
21vs22	1	0	0	0	1	1	1	2
21vs23	0	0	0	1	1	0	1	1
21vs24	1	0	1	0	1	1	1	1
21vs25	1	1	1	0	0	2	0	1
21vs26	0	1	0	0	0	1	1	0
21vs27	1	1	0	0	1	1	0	1
21vs28	1	0	1	0	1	1	1	1
21vs29	1	1	0	0	1	0	1	1
21vs30	1	0	0	0	2	0	0	1
21vs31	0	1	0	0	1	2	1	2
21vs32	1	1	0	0	0	1	1	1
21vs33	1	1	0	0	2	0	1	1
21vs34	1	1	0	1	2	1	0	2
21vs35	0	0	2	0	0	1	1	0
21vs36	1	1	0	1	0	1	1	2
21vs37	0	1	1	1	0	2	0	0
21vs38	0	2	1	0	0	1	1	0
21vs39	1	1	1	1	1	1	1	1
21vs40	0	0	1	0	1	1	2	1
21vs41	1	0	1	0	0	1	0	0
21vs42	0	0	0	0	0	1	1	2
21vs43	1	0	1	0	1	1	1	2
21vs44	1	0	0	1	1	1	1	1
21vs45	1	1	1	0	1	1	1	1
21vs46	0	0	1	0	1	1	1	1

21vs47	1	1	1	0	2	1	1	0
21vs48	1	0	1	0	0	0	1	1
21vs49	1	0	0	0	1	1	1	0
21vs50	1	1	0	0	1	1	1	1
22vs23	1	1	0	0	1	0	1	1
22vs24	2	0	0	1	1	1	2	1
22vs25	0	0	0	0	1	1	1	1
22vs26	1	0	0	0	0	1	1	0
22vs27	2	1	0	1	1	1	1	1
22vs28	2	0	1	1	1	1	1	1
22vs29	2	0	0	1	1	0	1	1
22vs30	2	1	1	1	1	1	1	1
22vs31	1	0	0	0	1	1	2	2
22vs32	1	0	1	0	1	1	1	1
22vs33	1	0	1	1	1	1	1	1
22vs34	1	0	1	0	1	1	1	2
22vs35	1	0	0	1	0	1	2	0
22vs36	1	0	1	1	0	0	1	2
22vs37	0	1	0	0	1	1	1	0
22vs38	1	0	0	0	0	2	1	0
22vs39	2	0	0	0	1	1	2	1
22vs40	1	1	0	1	0	1	1	1
22vs41	1	1	0	1	1	0	0	0
22vs42	1	0	0	0	0	1	1	2
22vs43	1	0	0	1	1	1	1	2
22vs44	2	1	0	1	1	2	1	1
22vs45	2	1	0	0	1	0	1	1
22vs46	1	0	0	1	1	1	1	1
22vs47	2	0	0	0	1	0	1	0
22vs48	1	0	0	1	0	0	2	1
22vs49	0	1	0	1	1	1	1	0
22vs50	2	1	0	1	0	0	1	1
23vs24	1	1	1	0	1	0	1	1
23vs25	0	0	0	1	0	0	0	2
23vs26	2	1	1	1	0	0	1	0
23vs27	1	1	0	1	1	0	0	1
23vs28	1	1	0	0	2	0	2	0
23vs29	1	0	1	0	1	0	2	1
23vs30	1	2	0	1	1	0	0	1
23vs31	1	0	1	0	1	0	1	1
23vs32	0	1	0	1	1	0	1	1
23vs33	1	1	0	1	1	0	2	2
23vs34	1	1	0	2	1	0	0	1
23vs35	1	1	0	1	1	0	1	0
23vs36	1	0	0	1	0	0	2	1
23vs37	1	1	1	1	0	0	0	0
23vs38	1	0	0	1	1	0	1	0
23vs39	1	1	1	1	1	0	1	1

23vs40	1	2	1	1	0	0	1	1
23vs41	0	1	1	0	0	0	0	0
23vs42	1	1	1	1	0	0	1	1
23vs43	1	1	0	0	1	1	1	1
23vs44	1	2	0	1	1	0	1	1
23vs45	1	1	1	0	1	0	1	1
23vs46	1	0	1	0	2	0	2	0
23vs47	1	1	0	1	1	0	2	0
23vs48	0	1	0	1	0	0	1	1
23vs49	1	2	1	0	1	0	2	0
23vs50	1	1	2	1	0	0	2	1
24vs25	0	0	1	0	0	1	1	1
24vs26	1	1	1	0	1	1	1	0
24vs27	2	0	0	1	2	1	1	1
24vs28	2	2	1	0	1	0	1	0
24vs29	2	0	1	1	2	1	1	1
24vs30	2	1	0	1	1	0	1	2
24vs31	1	0	1	0	2	1	2	1
24vs32	1	1	0	0	0	1	1	2
24vs33	1	1	0	1	1	0	1	1
24vs34	1	1	0	0	1	1	1	1
24vs35	1	1	1	1	1	0	2	0
24vs36	1	0	0	1	1	0	1	1
24vs37	0	0	2	0	1	1	1	0
24vs38	1	0	1	0	1	1	1	0
24vs39	2	1	2	0	2	0	2	1
24vs40	1	1	2	0	1	1	1	1
24vs41	1	0	2	0	1	0	0	0
24vs42	1	2	1	0	1	1	1	1
24vs43	1	2	1	2	2	1	1	1
24vs44	2	1	0	1	2	1	1	1
24vs45	2	0	2	0	1	0	1	1
24vs46	1	0	2	1	1	2	1	0
24vs47	2	1	1	0	1	0	1	0
24vs48	1	1	1	1	1	1	2	1
24vs49	0	1	1	1	2	0	1	0
24vs50	2	0	1	1	0	0	1	1
25vs26	0	1	1	2	0	1	1	0
25vs27	0	1	1	1	0	1	1	1
25vs28	0	0	1	1	0	1	0	0
25vs29	0	2	1	1	0	0	0	1
25vs30	0	0	1	1	0	0	1	1
25vs31	1	1	1	1	0	2	1	1
25vs32	1	1	1	1	1	1	0	1
25vs33	1	1	1	1	0	0	0	2
25vs34	1	1	0	1	0	1	1	1
25vs35	1	0	1	1	0	1	1	0
25vs36	1	0	1	0	0	1	0	1

25vs37	0	0	1	1	1	2	1	0
25vs38	0	1	2	2	0	1	0	0
25vs39	0	1	1	0	0	1	1	1
25vs40	0	0	1	1	0	1	0	1
25vs41	0	0	1	0	1	1	0	0
25vs42	0	0	1	1	0	1	0	1
25vs43	1	0	1	0	0	1	0	1
25vs44	0	0	1	0	0	1	0	1
25vs45	0	0	1	1	0	1	0	1
25vs46	1	0	1	1	0	1	0	0
25vs47	0	0	2	2	0	1	0	0
25vs48	0	1	2	1	0	0	1	1
25vs49	1	0	1	0	0	1	0	0
25vs50	0	0	0	1	0	1	0	1
26vs27	1	1	1	1	1	1	0	0
26vs28	1	1	0	1	0	0	1	0
26vs29	1	1	2	1	1	0	1	0
26vs30	1	1	1	1	0	0	0	0
26vs31	1	1	2	1	1	1	1	0
26vs32	0	2	1	1	0	2	1	0
26vs33	1	2	1	1	0	0	1	0
26vs34	1	2	0	1	0	1	0	0
26vs35	1	1	0	1	1	0	1	0
26vs36	1	0	1	0	1	0	1	0
26vs37	1	0	1	1	1	1	0	1
26vs38	1	1	1	2	1	1	1	0
26vs39	1	2	1	0	1	0	1	1
26vs40	1	1	1	1	1	1	1	0
26vs41	0	0	1	0	1	0	0	1
26vs42	1	1	2	1	2	2	1	0
26vs43	1	1	0	0	1	1	1	0
26vs44	1	1	1	0	1	1	1	1
26vs45	1	0	1	1	0	0	1	1
26vs46	1	0	1	1	0	1	1	0
26vs47	1	1	1	2	0	0	1	0
26vs48	0	1	1	1	1	0	1	1
26vs49	1	1	2	0	1	0	1	1
26vs50	1	0	1	1	0	0	1	1
27vs28	2	0	0	0	1	0	0	0
27vs29	2	1	1	1	2	0	0	2
27vs30	2	1	1	2	1	0	1	1
27vs31	1	1	1	0	2	1	1	1
27vs32	1	1	1	1	0	1	0	1
27vs33	1	1	1	2	1	0	0	1
27vs34	1	1	0	1	1	1	1	1
27vs35	1	0	0	2	1	0	1	1
27vs36	1	0	1	1	1	0	0	1
27vs37	0	1	0	0	1	1	1	1

27vs38	1	1	1	1	1	1	0	1
27vs39	2	1	0	0	2	0	1	1
27vs40	1	1	0	1	1	2	0	1
27vs41	1	1	0	0	1	0	0	0
27vs42	1	0	1	1	1	1	0	1
27vs43	1	0	0	1	2	1	0	1
27vs44	2	1	2	1	2	1	0	1
27vs45	2	1	0	0	1	1	0	1
27vs46	1	0	0	1	1	1	0	1
27vs47	2	0	1	1	1	0	0	1
27vs48	1	0	1	2	1	1	1	1
27vs49	0	1	1	1	2	0	0	1
27vs50	2	1	0	2	0	1	0	1
28vs29	2	0	0	1	1	0	2	0
28vs30	2	1	1	0	1	1	0	0
28vs31	1	0	0	1	1	1	1	1
28vs32	1	1	1	0	1	0	1	0
28vs33	1	1	1	0	1	1	2	0
28vs34	1	1	1	0	1	0	0	1
28vs35	1	1	1	0	1	2	1	0
28vs36	1	0	1	0	0	1	2	1
28vs37	0	0	1	1	0	1	0	0
28vs38	1	0	1	1	1	1	1	0
28vs39	2	1	1	0	1	2	1	0
28vs40	1	1	1	1	0	0	1	0
28vs41	1	0	1	1	0	1	0	0
28vs42	1	2	0	0	0	0	1	1
28vs43	1	2	1	0	1	0	1	1
28vs44	2	1	0	0	1	1	1	0
28vs45	2	0	1	1	1	1	1	0
28vs46	1	0	1	1	2	0	2	1
28vs47	2	1	1	1	1	1	2	0
28vs48	1	1	1	0	0	0	1	0
28vs49	0	1	0	0	1	2	2	0
28vs50	2	0	0	0	0	1	2	0
29vs30	2	0	1	1	1	1	0	1
29vs31	1	1	2	1	2	0	1	1
29vs32	1	1	1	0	0	0	1	1
29vs33	1	1	1	1	1	0	2	1
29vs34	1	1	0	0	1	0	0	1
29vs35	1	0	0	1	1	0	1	1
29vs36	1	0	1	1	1	0	2	1
29vs37	0	0	1	1	1	0	0	1
29vs38	1	1	1	1	1	0	1	1
29vs39	2	1	1	0	2	0	1	1
29vs40	1	0	1	0	1	0	1	1
29vs41	1	0	1	0	1	0	0	0
29vs42	1	0	2	0	1	0	1	1

29vs43	1	0	0	1	2	0	1	1
29vs44	2	0	1	1	2	0	1	1
29vs45	2	0	1	1	1	0	1	1
29vs46	1	0	1	2	1	1	2	1
29vs47	2	0	1	1	1	0	2	1
29vs48	1	1	1	1	1	1	1	1
29vs49	0	0	2	1	2	0	2	1
29vs50	2	0	1	1	0	0	2	1
30vs31	1	0	1	0	1	0	1	1
30vs32	1	1	2	1	0	0	1	2
30vs33	1	1	2	2	2	1	0	1
30vs34	1	1	1	1	2	0	2	1
30vs35	1	1	0	2	0	1	1	0
30vs36	1	0	2	1	0	0	0	1
30vs37	0	1	0	0	0	0	2	0
30vs38	1	0	1	1	0	1	1	0
30vs39	2	1	0	0	1	1	1	1
30vs40	1	2	0	1	1	0	0	1
30vs41	1	1	0	0	0	0	1	0
30vs42	1	1	1	1	0	0	1	1
30vs43	1	1	0	1	1	0	1	1
30vs44	2	2	1	1	1	1	1	1
30vs45	2	1	0	0	1	0	1	1
30vs46	1	0	0	1	1	0	0	0
30vs47	2	1	1	1	2	0	0	0
30vs48	1	1	1	2	0	0	1	1
30vs49	0	2	1	1	1	1	0	0
30vs50	2	1	0	2	1	0	0	1
31vs32	1	1	1	0	0	1	1	1
31vs33	1	1	1	0	1	0	1	1
31vs34	1	1	0	0	1	1	1	2
31vs35	2	0	0	0	1	1	2	0
31vs36	1	0	1	0	1	1	1	2
31vs37	0	0	1	1	1	2	1	0
31vs38	1	1	1	1	1	1	1	0
31vs39	1	1	1	0	2	1	2	1
31vs40	1	0	1	0	1	1	1	1
31vs41	0	0	1	0	1	1	0	0
31vs42	1	0	2	0	1	1	1	2
31vs43	1	0	0	0	2	1	1	2
31vs44	1	0	1	0	2	1	1	1
31vs45	1	0	1	1	1	1	1	1
31vs46	2	0	1	1	1	1	1	1
31vs47	1	0	1	1	1	1	1	0
31vs48	0	0	1	0	1	0	2	1
31vs49	0	0	2	0	2	1	1	0
31vs50	1	0	1	0	0	1	1	1
32vs33	0	2	2	1	0	0	1	1

32vs34	0	2	1	1	0	1	1	1
32vs35	1	1	0	1	1	0	1	0
32vs36	0	0	2	0	0	0	1	1
32vs37	0	0	0	0	1	1	1	0
32vs38	0	1	1	1	1	1	2	0
32vs39	1	2	0	0	0	0	1	1
32vs40	0	1	0	1	0	1	1	1
32vs41	1	0	0	1	1	0	1	0
32vs42	0	1	1	1	0	2	2	1
32vs43	0	1	0	0	0	1	2	1
32vs44	1	1	1	0	0	1	2	1
32vs45	1	0	0	1	0	0	2	1
32vs46	1	0	0	0	1	1	1	0
32vs47	1	1	1	1	0	0	1	0
32vs48	1	1	1	1	0	0	1	1
32vs49	0	1	1	1	0	0	1	0
32vs50	1	0	0	1	0	0	1	1
33vs34	2	2	1	1	2	1	0	1
33vs35	1	1	0	2	0	1	1	0
33vs36	2	0	2	1	0	0	2	1
33vs37	0	0	0	0	0	0	0	0
33vs38	1	1	1	1	0	1	1	0
33vs39	1	2	0	0	1	1	1	1
33vs40	1	1	0	1	1	0	1	1
33vs41	0	0	0	0	0	0	0	0
33vs42	1	1	1	1	0	0	1	1
33vs43	2	1	0	1	1	0	1	1
33vs44	1	1	1	1	1	1	1	1
33vs45	1	0	0	0	1	0	1	1
33vs46	1	0	0	1	1	0	2	0
33vs47	1	1	1	1	2	0	2	0
33vs48	0	1	1	2	0	0	1	1
33vs49	1	1	1	1	1	1	2	0
33vs50	1	0	0	2	1	0	2	1
34vs35	1	1	0	1	0	0	1	0
34vs36	2	0	1	1	0	0	0	2
34vs37	0	0	0	1	0	1	2	0
34vs38	1	1	0	1	0	1	1	0
34vs39	1	2	0	1	1	0	1	1
34vs40	1	1	0	1	1	1	0	1
34vs41	0	0	0	0	0	0	1	0
34vs42	1	1	0	1	0	1	1	2
34vs43	2	1	0	0	1	1	1	2
34vs44	1	1	0	1	1	1	1	1
34vs45	1	0	0	0	1	0	1	1
34vs46	1	0	0	0	1	1	0	1
34vs47	1	1	0	1	2	0	0	0
34vs48	0	1	0	1	0	0	1	1

34vs49	1	1	0	0	1	0	0	0
34vs50	1	0	0	1	1	0	0	1
35vs36	1	0	0	1	1	1	1	0
35vs37	0	0	1	0	1	1	1	1
35vs38	1	0	1	1	2	1	1	2
35vs39	1	1	1	0	1	2	2	0
35vs40	1	1	1	1	1	0	1	0
35vs41	0	0	1	0	1	1	0	0
35vs42	1	1	0	1	1	0	1	0
35vs43	1	1	1	1	1	0	1	0
35vs44	1	1	0	1	1	1	1	0
35vs45	1	0	1	0	0	1	1	0
35vs46	2	0	1	1	1	0	1	1
35vs47	1	1	1	1	0	1	1	2
35vs48	0	1	1	2	1	0	2	0
35vs49	0	1	0	1	1	2	1	1
35vs50	1	0	0	2	0	1	1	0
36vs37	0	1	0	1	1	1	0	0
36vs38	1	1	1	0	1	0	1	0
36vs39	1	0	0	1	1	1	1	1
36vs40	1	0	0	0	1	0	1	1
36vs41	0	1	0	0	1	1	0	0
36vs42	1	0	1	0	1	0	1	2
36vs43	2	0	0	1	1	0	1	2
36vs44	1	0	1	2	1	0	1	1
36vs45	1	1	0	0	0	1	1	1
36vs46	1	1	0	1	0	0	2	1
36vs47	1	1	1	0	0	2	2	0
36vs48	0	0	1	1	2	0	1	1
36vs49	1	0	1	1	1	1	2	0
36vs50	1	1	0	1	1	1	2	1
37vs38	1	1	1	1	1	1	1	1
37vs39	0	0	2	1	1	1	1	1
37vs40	0	1	2	0	1	1	0	0
37vs41	0	1	2	0	2	1	1	1
37vs42	0	0	1	0	1	1	1	0
37vs43	0	0	1	0	1	1	1	0
37vs44	0	1	0	1	1	1	1	1
37vs45	0	2	2	1	0	1	1	1
37vs46	0	0	2	1	0	1	0	1
37vs47	0	1	1	1	0	1	0	1
37vs48	0	0	1	0	1	0	1	1
37vs49	1	1	1	0	1	1	0	2
37vs50	0	2	1	0	0	1	0	1
38vs39	1	1	1	0	1	1	1	0
38vs40	1	0	1	1	1	1	1	0
38vs41	0	0	1	0	1	0	1	0
38vs42	1	0	1	1	1	1	2	0

38vs43	1	0	1	0	1	1	2	0
38vs44	1	0	1	0	1	2	2	0
38vs45	1	1	1	1	0	0	2	0
38vs46	1	0	1	1	1	1	1	1
38vs47	1	1	2	2	0	0	1	2
38vs48	0	0	2	1	1	0	1	0
38vs49	0	0	1	0	1	1	1	1
38vs50	1	1	0	1	0	0	1	0
39vs40	1	1	2	0	1	0	1	1
39vs41	1	0	2	0	1	1	0	1
39vs42	1	1	1	0	1	0	1	1
39vs43	1	1	1	0	2	0	1	1
39vs44	2	1	0	1	2	1	1	2
39vs45	2	0	2	0	1	1	1	2
39vs46	1	0	2	0	1	0	1	0
39vs47	2	1	1	0	1	1	1	0
39vs48	1	1	1	0	1	0	2	2
39vs49	0	1	1	0	2	2	1	1
39vs50	2	0	1	0	0	1	1	2
40vs41	0	1	2	1	1	0	0	0
40vs42	2	1	1	1	1	1	1	1
40vs43	1	1	1	0	1	1	1	1
40vs44	1	2	0	0	1	1	1	1
40vs45	1	1	2	0	0	1	1	1
40vs46	1	0	2	0	0	1	1	0
40vs47	1	1	1	1	1	0	1	0
40vs48	0	1	1	1	1	1	1	1
40vs49	0	2	1	0	1	0	1	0
40vs50	1	1	1	1	1	1	1	1
41vs42	0	0	1	0	1	0	1	0
41vs43	0	0	1	0	1	0	1	0
41vs44	1	1	0	0	1	0	1	1
41vs45	1	1	2	1	0	1	1	1
41vs46	0	1	2	0	0	0	0	0
41vs47	1	0	1	0	0	1	0	0
41vs48	2	0	1	0	1	0	0	1
41vs49	0	1	1	1	1	1	0	1
41vs50	1	1	1	0	0	1	0	1
42vs43	1	2	0	0	1	1	2	2
42vs44	1	1	1	0	1	1	2	1
42vs45	1	0	1	0	0	0	2	1
42vs46	1	0	1	0	0	1	1	1
42vs47	1	1	1	1	0	0	1	0
42vs48	0	1	1	1	1	0	1	1
42vs49	0	1	2	0	1	0	1	0
42vs50	1	0	1	1	0	0	1	1
43vs44	1	1	0	1	2	1	2	1
43vs45	1	0	1	0	1	0	2	1

43vs46	1	0	1	1	1	1	1	1
43vs47	1	1	1	0	1	0	1	0
43vs48	0	1	1	1	1	0	1	1
43vs49	1	1	0	1	2	0	1	0
43vs50	1	0	0	1	0	0	1	1
44vs45	2	1	0	0	1	0	2	2
44vs46	1	0	0	1	1	1	1	0
44vs47	2	1	1	0	1	0	1	0
44vs48	1	1	1	1	1	0	1	2
44vs49	0	2	1	1	2	1	1	1
44vs50	2	1	0	1	0	0	1	2
45vs46	1	0	2	1	1	0	1	0
45vs47	2	1	1	1	1	1	1	0
45vs48	1	0	1	0	0	1	1	2
45vs49	0	1	1	1	1	1	1	1
45vs50	2	2	1	0	0	2	1	2
46vs47	1	0	1	1	1	0	2	1
46vs48	0	0	1	1	0	1	1	0
46vs49	0	0	1	1	1	0	2	1
46vs50	1	0	1	1	0	0	2	0
47vs48	1	1	2	1	0	0	1	0
47vs49	0	1	1	0	1	1	2	1
47vs50	2	1	0	1	1	1	2	0
48vs49	0	1	1	1	1	0	1	1
48vs50	1	0	0	2	1	1	1	2
49vs50	0	1	1	1	0	1	2	1

STR9	STR10	STR11	STR12	STR13	STR14	STR15	STR16	STR17
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2	2	1	0	0	2	0	1	1
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2	2	1	1
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2	2	1	2

Appendix 1e. The output table of Simulated *K*

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4	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
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31	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0
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34	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0
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239	0	0	0	0	0	0	0	0

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315	0	0	0	0	0	0	0	0
316	0	0	0	0	0	0	0	0
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318	0	0	0	0	0	0	0	0
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11	6	8	4	3	3	1	0	0
9	7	7	5	5	1	1	0	0
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8	7	8	5	2	0	2	0	0
9	7	7	4	6	4	0	0	0
3	13	7	4	5	1	0	0	0
10	5	12	6	4	0	1	0	0
11	13	5	1	5	3	1	0	0

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9	10	11	8	0	2	1	0	0
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9	8	7	7	6	2	0	0	0

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7	5	5	8	2	3	0	1	0
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7	8	11	5	0	3	2	0	0
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7	6	5	11	6	3	1	0	0
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9	9	9	10	3	1	1	0	0
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9	7	11	7	4	1	0	0	0
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11	6	3	8	2	3	2	0	0
8	12	5	5	1	2	1	0	0
7	7	10	8	2	1	0	0	0
9	11	9	3	4	1	0	1	0
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4	7	10	11	4	4	0	0	0
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9	12	7	4	4	2	1	0	0
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6	6	10	6	5	3	1	0	0
7	3	14	4	6	2	1	0	0
5	11	9	6	7	1	2	1	0
8	14	5	3	1	1	1	1	0

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5	6	9	6	5	3	0	0	0
8	4	11	7	3	2	2	0	0
6	14	9	6	4	1	1	0	0
8	6	7	9	6	2	1	0	0
11	9	6	9	5	2	1	0	0
9	4	12	8	3	3	2	0	0
9	11	6	7	6	1	1	0	0
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Appendix 1f. The output table of Simulated X

X	0	1	2	3	4	5	6	7
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3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0
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17	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0
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30	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0
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34	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0
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45	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0
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49	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0
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0	1	0	0	0	0	0	0	0

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2	0	0	0	0	0	0	0	0
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0	2	0	0	0	0	0	0	0

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4	1	0	0	0	0	0	0	0
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1	0	0	0	0	1	0	0	0
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1	1	0	0	0	0	0	0	0
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0	1	2	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
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0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
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0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0

3	0	0	0	0	0	0	0	0
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1	1	0	0	0	0	0	0	0
0	1	1	0	0	0	0	0	0
1	2	0	0	0	0	0	0	0
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0	1	0	0	0	0	0	0	0
0	1	0	0	0	0	0	0	0
1	1	1	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
0	0	1	0	0	0	0	0	0
1	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	1	0	1	0	0	0	0	0
1	0	0	0	0	0	0	0	0
0	1	0	1	0	0	0	0	0
0	1	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0

44	45	46	47	48	49	50	51	52
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0	0	0	0	0	0	0	0	0

0	0	0	0	0	0	0	0	0

0	0	0	0	0	0	0	0	0

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0	0	0	0	0	0	0	0	0

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0	0	0	0	0	0	0	0	0
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0	0	0	0	0	0	0	0	0

53	54	55	56	57	58	59	60
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0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0

0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0

0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0

0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0

0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0

0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0

0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0

0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0

0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0

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0	0	0	0	0	0	0	0

Appendix 1g. The example script of R file

```
library(mixIndependR)
`SNP10+STR20_ul_2020` <- read.csv("~/Appendix 1a.csv", row.names=1)
x <- `SNP10+STR20_ul_2020`
rm(counta)
###basic genetics
p <- AlleleFreq(x)
G0 <-GenotypeFreq(x,p,expect = T)
G <- GenotypeFreq(x,p,expect = F)
HWE_chi<-HWE.Chisq(G,G0,rescale.p = T,simulate.p.value = T,2000)
##G/colSums(G)

h<-Heterozygous(x)
H_hwe<-RxpHetero(h,p,HWE = T)
H <- RxpHetero(h,p,HWE = F)
#H <- colSums(h)/nrow(h)
ObsDist_K<-FreqHetero(h)
ExpDist_K<- DistHetero(H)
AS<-AlleleShare_Table(x)
ObsDist_X<-FreqAlleleShare(AS)
e0<-ExpProAlleleShare(p)
e <-RealProAlleleShare(AS)
ExpDist_X<-DistAlleleShare(e)
##Figure
library(ggplot2)
df_K <- ComposPare_K(h,ExpDist_K,trans = F)
df_X <- ComposPare_X(AS,ExpDist_X,trans = F)

ggplot(df_K,aes(x=freq))+
```

```
  geom_histogram(aes(y=..density..,color=OvE,fill=OvE),alpha=0.5,binwidth = 1,position = "identity")+
  ggtitle("Distribution of No. of Heterozyous loci for Simualted mix Data")+
  xlab("No. of Heterozygous Loci(K)")+ylab("Density/Probability")+
  stat_function(data=ExpDist_K,mapping = aes(x=K,y=Density),fun = splinefun(ExpDist_K$K,ExpDist_K$Density),color="Red")


df_K_T <-ComposPare_K(h,ExpDist_K,trans = T)
table(df_K_T$K_io)
table(df_K_T$K_ie)
chisq.test(df_K_T$K_io,df_K_T$K_ie)


##Significance test####
nrow(x)
Simu_K <- Simulate_DistK(H,50,500)
Simu_X <- Simulate_DistX(e,25,500)
?Dist_SimuChisq
Simu_K
Simu_X
ObsDist_X$Frequency[21:41]


chisq.test(ObsDist_K$Frequency[12:23],p=ExpDist_K$Density[12:23],simulate.p.value = T,rescale.p = T,B=2000) ##19.073
chisq.test(ObsDist_X$Frequency[21:41],p=ExpDist_X$Density[21:41],simulate.p.value = T,rescale.p = T,B=2000) ##23.633


x2<-Dist_SimuChisq(Simu_K,ExpDist_K$Density,2000)
x2_X<-Dist_SimuChisq(Simu_X,ExpDist_X$Density,2000)
P<-ecdf(x2)
P(19.073)
```

```
plot(P)
P2 <- ecdf(x2_X)
P2(23.633)
plot(P2)
write.csv(p,"~/Appendix 1b.csv")
write.csv(h,"~/Appendix 1c.csv")
write.csv(AS,"~/Appendix 1d.csv")
write.csv(Simu_K,"~/Appendix 1e.csv")
write.csv(Simu_X,"~/Appendix 1f.csv")
```

Appendix 2a. Simulated Linked 100 SNPs of 500 Individuals

Sample ID	SNP_L 1	SNP_L 1	SNP_L 2	SNP_L 2	SNP_L 3	SNP_L 3	SNP_L 4	SNP_L 4
Ind 1	1	1	0	0	0	0	0	0
Ind 2	1	1	0	0	0	0	0	0
Ind 3	1	1	0	0	0	0	0	0
Ind 4	1	1	0	0	0	0	0	0
Ind 5	1	1	0	0	0	0	1	0
Ind 6	1	1	0	0	0	0	0	0
Ind 7	0	1	0	0	1	0	0	0
Ind 8	1	1	0	0	0	0	1	0
Ind 9	1	1	0	0	0	0	0	0
Ind 10	1	1	0	0	0	0	1	1
Ind 11	1	1	0	0	0	0	0	0
Ind 12	1	1	0	0	0	0	0	0
Ind 13	1	1	0	0	0	0	0	0
Ind 14	1	1	0	0	0	0	0	0
Ind 15	1	1	0	0	0	0	0	0
Ind 16	1	1	0	0	0	0	0	0
Ind 17	1	1	0	0	0	0	0	0
Ind 18	1	1	0	0	0	0	0	0
Ind 19	1	1	0	0	0	0	0	0
Ind 20	1	1	0	0	0	0	0	0
Ind 21	1	1	0	0	0	0	0	0
Ind 22	1	0	0	0	0	1	0	0
Ind 23	1	1	0	0	0	0	0	0
Ind 24	1	1	0	0	0	0	0	0
Ind 25	1	1	0	0	0	0	0	0
Ind 26	1	1	0	0	0	0	0	0
Ind 27	1	1	0	0	0	0	0	0
Ind 28	1	1	0	0	0	0	0	0
Ind 29	1	1	0	0	0	0	0	0
Ind 30	1	1	0	0	0	0	0	0
Ind 31	1	1	0	0	0	0	0	0
Ind 32	1	1	0	0	0	0	0	0
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SNP_L 27	SNP_L 28	SNP_L 28	SNP_L 29	SNP_L 29	SNP_L 30	SNP_L 30	SNP_L 31	SNP_L 31
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SNP_L 99	NP_L 100	NP_L 100
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Appendix 2b. Simulated Unlinked 100 SNPs of 500 Individuals

Sample ID	SNP 1	SNP 1	SNP 2	SNP 2	SNP 3	SNP 3	SNP 4	SNP 4
Ind 1	0	0	0	0	0	0	0	0
Ind 2	0	0	0	0	0	0	0	0
Ind 3	0	0	0	0	0	0	0	0
Ind 4	0	0	0	0	0	0	0	0
Ind 5	0	0	0	0	0	0	0	0
Ind 6	0	0	0	0	0	0	0	0
Ind 7	0	0	0	0	0	0	0	0
Ind 8	0	0	0	0	0	0	0	0
Ind 9	0	0	0	0	1	0	0	0
Ind 10	0	0	0	0	0	0	0	0
Ind 11	0	0	0	0	0	0	0	0
Ind 12	0	0	0	0	0	0	0	0
Ind 13	0	0	0	0	0	0	0	0
Ind 14	0	0	0	0	0	0	0	0
Ind 15	0	0	0	0	0	0	0	0
Ind 16	0	0	0	0	0	0	0	0
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Ind 48	0	0	0	0	0	0	0	0
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Ind 273	0	0	0	0	0	0	0	0
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SNP 32	SNP 32	SNP 33	SNP 33	SNP 34	SNP 34	SNP 35	SNP 35	SNP 36
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SNP 36	SNP 37	SNP 37	SNP 38	SNP 38	SNP 39	SNP 39	SNP 40	SNP 40
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SNP 68	SNP 68	SNP 69	SNP 69	SNP 70	SNP 70	SNP 71	SNP 71	SNP 72
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SNP 81	SNP 82	SNP 82	SNP 83	SNP 83	SNP 84	SNP 84	SNP 85	SNP 85
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SNP 86	SNP 86	SNP 87	SNP 87	SNP 88	SNP 88	SNP 89	SNP 89	SNP 90
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SNP 90	SNP 91	SNP 91	SNP 92	SNP 92	SNP 93	SNP 93	SNP 94	SNP 94
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Appendix 2c. Simulated Linked 100 STRs of 500 Individuals

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Sample 3	12	13	17	16	15	16	14	14	14	24	20
Sample 4	4	15	17	15	10	25	18	12	17	14	18
Sample 5	9	10	16	17	5	24	12	16	16	18	16
Sample 6	14	9	16	17	11	9	12	15	11	17	12
Sample 7	3	9	18	16	17	10	15	14	15	23	22
Sample 8	11	5	17	18	17	3	16	18	25	18	20
Sample 9	13	20	16	17	13	15	12	16	25	19	9
Sample 10	6	17	17	16	19	7	13	16	12	21	9
Sample 11	19	10	17	16	15	13	14	13	16	11	0
Sample 12	14	11	15	17	17	9	15	11	22	12	10
Sample 13	19	6	15	16	11	21	15	13	16	15	16
Sample 14	14	7	16	17	20	18	13	15	18	15	20
Sample 15	12	15	17	17	15	23	15	14	18	26	19
Sample 16	8	13	16	18	18	18	14	16	21	21	21
Sample 17	11	13	17	18	17	23	16	16	18	16	16
Sample 18	16	7	17	17	11	13	18	15	20	12	9
Sample 19	10	13	18	15	22	8	19	15	14	15	15
Sample 20	11	14	17	14	14	21	16	13	9	20	17
Sample 21	3	16	15	15	2	21	14	13	12	22	10
Sample 22	8	16	14	18	4	25	17	14	16	14	9
Sample 23	10	10	16	17	8	15	11	13	17	22	13
Sample 24	16	14	16	17	18	18	18	14	24	13	23
Sample 25	15	15	18	16	11	11	17	16	17	17	12
Sample 26	14	12	16	16	15	13	16	16	26	20	19
Sample 27	14	13	16	15	4	12	13	15	12	18	10
Sample 28	9	5	16	16	19	17	15	15	11	18	16
Sample 29	11	13	18	15	17	12	16	16	17	7	-2
Sample 30	8	17	16	15	23	15	15	13	19	17	7
Sample 31	3	8	15	16	13	14	17	16	19	19	8
Sample 32	16	10	13	17	13	15	14	16	21	20	11
Sample 33	7	6	17	17	19	7	14	17	17	28	7
Sample 34	14	13	16	17	20	13	16	17	16	14	21
Sample 35	12	7	18	16	14	10	16	16	14	18	12
Sample 36	18	10	15	15	10	14	13	13	23	10	10
Sample 37	9	6	14	15	7	8	12	16	20	13	15
Sample 38	10	4	17	16	11	10	14	15	18	16	18
Sample 39	17	18	16	15	20	13	10	16	27	20	19
Sample 40	11	12	16	17	16	17	18	15	20	23	21
Sample 41	2	9	18	18	15	12	15	16	11	17	8
Sample 42	17	9	15	19	4	14	15	17	17	20	13
Sample 43	9	8	15	16	12	5	15	16	14	21	10
Sample 44	7	13	17	16	14	3	18	16	18	7	28
Sample 45	16	7	17	17	12	22	15	15	17	17	14
Sample 46	8	10	18	15	16	13	18	16	17	21	14
Sample 47	12	3	18	17	15	12	18	16	14	14	11

Sample 48	12	5	16	16	9	11	14	15	17	16	5
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Sample 50	5	12	16	16	15	17	16	17	22	23	11
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Appendix 2d. Simulated Unlinked 100 STRs of 500 Individuals

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Sample 6	34	33	29	27	25	28	30	31	30	29	18
Sample 7	30	28	31	30	25	25	30	32	32	31	43
Sample 8	29	32	28	28	28	27	32	30	32	29	43
Sample 9	28	33	27	28	31	26	31	28	30	29	41
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Appendix 2e. Real Data of 151 Markers (149 SNPs and 2 STRs) of 2504 Individuals

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HG00097_HG00097	0	1	0	1
HG00099_HG00099	1	1	1	1
HG00100_HG00100	0	0	0	0
HG00101_HG00101	0	0	0	0
HG00102_HG00102	0	1	0	1
HG00103_HG00103	0	0	0	0
HG00105_HG00105	0	1	0	1
HG00106_HG00106	0	1	0	1
HG00107_HG00107	0	1	0	1
HG00108_HG00108	0	0	0	0
HG00109_HG00109	0	0	0	0
HG00110_HG00110	0	1	0	1
HG00111_HG00111	0	0	0	0
HG00112_HG00112	0	0	0	0
HG00113_HG00113	0	1	0	1
HG00114_HG00114	0	1	0	1
HG00115_HG00115	0	1	0	1
HG00116_HG00116	0	1	0	1
HG00117_HG00117	0	0	0	0
HG00118_HG00118	0	1	0	1
HG00119_HG00119	0	0	0	0
HG00120_HG00120	0	0	0	0
HG00121_HG00121	0	1	0	1
HG00122_HG00122	0	0	0	0
HG00123_HG00123	0	0	0	0
HG00125_HG00125	0	0	0	0
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HG00127_HG00127	0	1	0	1
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HG00130_HG00130	0	1	0	1
HG00131_HG00131	0	0	0	0
HG00132_HG00132	0	1	0	1
HG00133_HG00133	0	1	0	1
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Package 'mixIndependR'

October 7, 2020

Type Package

Title Genetics and Independence Testing of Mixed Genetic Panels

Version 0.3.0

Author Bing Song

Maintainer Bing Song <bingsong@my.unthsc.edu>

Depends R (>= 3.6.0)

Imports stats (>= 3.3),utils (>= 3.2.3), stringr, ggplot2

Description Developed to deal with multi-locus genotype data, this package is especially designed for those panel which include different type of markers. Basic genetic parameters like allele frequency, genotype frequency, heterozygosity and Hardy-Weinberg test of mixed genetic data can be obtained. In addition, a new test for mutual independence which is compatible for mixed genetic data is developed in this package.

License GPL (>= 2)

Encoding UTF-8

LazyData true

RoxygenNote 7.1.1

Suggests testthat, knitr, rmarkdown

NeedsCompilation no

VignetteBuilder knitr

Repository CRAN

Date/Publication 2020-10-07 12:40:06 UTC

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`AlleleFreq` *Calculate Allele Frequency*

Description

Calculate Allele Frequency

Usage

```
AlleleFreq(x)
```

Arguments

`x`	a dataset of alleles. Type needs to be Homogeneous. Each row denotes each sample. One allele in one cell.In the (2r-1)th column, there is the other allele on the same locus from that in the 2r-th column; noted: no column for ID, make row.names=1 when importing.

Details

This function calculates the allele frequencies of one dataset.

Value

a matrix of allele frequencies. Each row denotes each allele; each column denotes each marker. The order of makers follows x.

Examples

```
x <- data.frame(STR1=c(12,13,13,14,15,13,14,12,14,15),
                STR1_1=c(12,14,13,15,13,14,13,12,14,15),
                SNP1=c("A","T","A","A","T","A","A","T","T","A"),
                SNP1_1=c("A","T","T","T","A","T","A","A","T","T"))
AlleleFreq(x)
```

`AlleleShare_Table` *Calculate numbers of sharing alleles each pair at each locus*

Description

Calculate numbers of sharing alleles each pair at each locus

Usage

```
AlleleShare_Table(x,replicate=TRUE)
```

Arguments

`x`	a dataset of alleles. Each row denotes each individual.One allele in one cell.In the (2r-1)th column, there is the same locus with the 2r-th column; noted: no column for ID, make row.names=1 when importing.
`replicate`	a logical variable. if replicate is TRUE, the pairs are formed with replicates; if FALSE, the pairs are formed without replicate.

Details

This function calculates the numbers of shared alleles between each pair of individuals for a dataset.Output a table and Usually followed by write.csv(as.data.frame(y),file = "~/*.csv") to export the results.

Value

y a matrix of numbers of shared alleles. Each row denotes each pair; Each column denotes each locus.

Examples

```
x <- data.frame(STR1=c(12,13,13,14,15,13,14,12,14,15),
                STR1_1=c(12,14,13,15,13,14,13,12,14,15),
                SNP1=c("A","T","A","A","T","A","A","T","T","A"),
                SNP1_1=c("A","T","T","T","A","T","A","A","T","T"))
AlleleShare_Table(x,replicate=TRUE)
```

ComposPare_K *Generate Comparison Observed and Expected No. of Heterozygous Loci.*

Description

Generate Comparison Observed and Expected No. of Heterozygous Loci.

Usage

```
ComposPare_K(h,Ex,trans)
```

Arguments

h	a double made up of "0" and "1" where 1 means heterozygous and 0 means homozygous; Outcome of function "Heterozygous"; Each column denotes each locus and each row denotes each individual.
Ex	a dataframe of expected density, outcome of function "DistHetero", on each possible total number of heterozygous loci.
trans	a logic variable, if True, the outcome is a dataframe of n x 2. n is the number of individuals of original imported database. First column is the observed No. of Heterozygous Loci and the second is the expected one. If False, the dataframe is 2n x 2, where n is the number of individuals of original imported database. The first column is a categorical variable denoting the frequency is observed or expected value; the second column is the frequency of No. of heterozygous loci.

Details

This function generates a dataframe in which the observed and expected heterozygous loci for each sample are included. The observed ones are calculated from the original dataset. However, the expected ones are simulated according to the expected probability with the same sample size as observed sample.

Value

a dataframe of observed and expected No. of heterozygous loci for each individual.

Examples

```
h<-matrix(rbinom(20,1,0.5),nrow=5)
Ex <- data.frame(K=c(0:5),Density=rnorm(6,mean = 0.5,sd=0.05))
ComposPare_K(h,Ex,trans = TRUE)
```

ComposPare_X *Generate Comparison Observed and Expected No. of Shared Alleles.*

Description

Generate Comparison Observed and Expected No. of Shared Alleles.

Usage

```
ComposPare_X(AS,Ex,trans=TRUE)
```

Arguments

AS	a double made up of "0","1" and "2" denoting number of shared alleles; Outcome of function "AlleleShare_Table"; Each column denotes each locus and each row denotes each pair of individuals.
Ex	a dataframe of expected density, outcome of function "DistAlleleShare", on each possible total number of shared Alleles.
trans	a logic variable, if True, the outcome is a dataframe of n x 2. n is the number of individuals of original imported database. First column is the observed No. of Heterozygous Loci and the second is the expected one. If False, the dataframe is 2n x 2, where n is the number of individuals of original imported database. The first column is a categorical variable denoting the frequency is observed or expected value; the second column is the frequency of No. of heterozygous loci.

Details

This function generates a dataframe in which the observed and expected shared alleles for each pair of individuals. The observed ones are calculated from the original dataset through "AlleleShare_Table". However, the expected ones are simulated according to the expected probability with the same sample size as the observed sample.

Value

a dataframe of observed and expected No. of shared alleles for each pair of individuals.

Examples

```
AS<-matrix(sample(c(0:2),20,replace=TRUE,prob=c(0.3,0.3,0.4)),nrow=5)
Ex <- data.frame(X=c(0:8),Density=rnorm(9,mean = 0.5,sd=0.05))
ComposPare_X(AS,Ex,trans = TRUE)
```

counta *Simple count including zero###*

Description

Simple count including zero###

Usage

```
counta(z, y)
```

Arguments

z	a vector you would like to check
y	an element you would like to count.(Even it is not included in z)

Details

This function counts how many the assigned elements there are in one vector.

Value

the times that y appears in z

Examples

```
z <-rbinom(20,1,0.5)
counta(z,0)
```

DistAlleleShare *Build Expected Distribution of Numbers of Shared Alleles*

Description

Build Expected Distribution of Numbers of Shared Alleles

Usage

```
DistAlleleShare(e)
```

Arguments

e	a matrix/dataframe of probability of shared alleles; outcome of "ExpProAlleleShare" or "RealProAlleleShare". Each row denotes each locus. The first column is the case of 0 shared alleles, the second column is the case of 1 shared alleles, the third column is the case of 2 shared alleles.

Details

This function build the expected distribution of numbers of shared alleles for known shared alleles of each pair of individuals.

Value

a dataframe of probabilities of each number of shared alleles(from 0 to 2*loci); the first column is No. of Shared Alleles; the Second Column is Expected Density

References

Chakraborty, R., Stivers, D. N., Su, B., Zhong, Y., & Budowle, B. (1999) <doi:10.1002/(SICI)1522-2683(19990101)20:8<1682::AID-ELPS1682>3.0.CO;2-Z>

Examples

```
e0<-data.frame("P0"=runif(5,min = 0,max = 0.5),"P1"=runif(5,0,0.5))
e<-data.frame(e0,"P2"=1-rowSums(e0))
DistAlleleShare(e)
```

`DistHetero` *Build Expected Distribution of Numbers of Heterozygous Loci*

Description

Build Expected Distribution of Numbers of Heterozygous Loci

Usage

```
DistHetero(H)
```

Arguments

`H`	a vector of average heterozygosity of each locus

Details

This function build the expected distribution of numbers of heterozygous loci for known heterozygosity of each loci.

Value

a dataframe of expected density on each possible total number of heterozygous loci.

References

Chakraborty, R. (1981, ISSN:0016-6731)

Examples

```
DistHetero(runif(10))
```

`Dist_SimuChisq` *Build a simulated distribution for Chi-Square*

Description

Build a simulated distribution for Chi-Square

Usage

```
Dist_SimuChisq(s,prob,b)
```

Arguments

`s`	a matrix of frequencies for each simulated sample. Each row for each sample.
`prob`	a vector of expected probability for each simulated sample.
`b`	the times of bootstrapping.

Details

This function build the distribution of Chi square statistics for simulated samples

Value

a vector of Chi-square statistics, length is the times of sampling.

Examples

```
require(mixIndependR)
h<-runif(10)
s<-Simulate_DistK(h,500,100)
Exp <- DistHetero(h)
Dist_SimuChisq(s,Exp$Density,10)
```

ExpProAlleleShare *Calculate the Expected Probability of 0,1 and 2 Shared Alleles###*

Description

Calculate the Expected Probability of 0,1 and 2 Shared Alleles###

Usage

```
ExpProAlleleShare(p)
```

Arguments

p	a matrix/double of frequency of alleles; Outcome of "AlleleFreq". Each column denotes each locus. Different alleles is ordered in different rows such as 11,11.3,12,12.2,13... and so on

Details

This function Calculates the Expected Probability of 0,1 and 2 Shared Alleles for a set of loci. Usually followed by write.csv(as.data.frame(y),file = "~/*.csv") to export the result of a n x3 matrix.

Value

a matrix/double of expected probabilities of 0,1 and 2 shared alleles for each locus. Each row denotes each locus. The first column denotes the probability of 0 shared alleles, the second denotes 1 shared allele, the third denotes 2 shared alleles.

References

Weir, B. S. (2004, ISSN:0022-1198)

Examples

```
a0<-matrix(runif(20),nrow=5)
a1<-colSums(a0)
a<-data.frame(STR1=a0[,1]/a1[1],STR2=a0[,2]/a1[2],STR3=a0[,3]/a1[3],STR4=a0[,4]/a1[4])
ExpProAlleleShare(a)
```

FreqAlleleShare *Build Observed Distribution of No. of Shared Alleles*

Description

Build Observed Distribution of No. of Shared Alleles

Usage

```
FreqAlleleShare(AS)
```

Arguments

AS	a matrix of number of shared alleles, made up with 0, 1 and 2, outcome of function "AlleleShare_Table". Rows for individuals, and columns for markers.

Details

This function build the observed distributions from observed Allele Share table, made up of 0,1 and 2.

Value

a dataframe of frequencies of each number of shared alleles(from 0 to 2*N0. of loci)

Examples

```
AS<-matrix(sample(c(0:2),20,replace=TRUE,prob=c(0.3,0.3,0.4)),nrow=5)
FreqAlleleShare(AS)
```

FreqHetero *Build Observed Distribution of No. of Heterozygous loci*

Description

Build Observed Distribution of No. of Heterozygous loci

Usage

```
FreqHetero(h)
```

Arguments

h	a dataframe of heterozygosity, made up with 0 and 1, outcome of function "Heterozygous" Rows for individuals, and columns for markers.

Details

This function build the observed distributions from observed heterozygosity table, made up of 0,1.

Value

a dataframe of frequencies of each number of heterozygous loci(from 0 to No. of loci)

Examples

```
h<-matrix(rbinom(20,1,0.5),nrow=5)
FreqHetero(h)
```

GenotypeFreq *Calculate Genotype Frequency###*

Description

Calculate Genotype Frequency###

Usage

```
GenotypeFreq(x,p,expect=TRUE)
```

Arguments

x	a dataset of alleles. Each row denotes each sample. One allele in one cell.In the (2r-1)th column, there is the other allele on the same locus from that in the 2r-th column; noted: no column for ID, make row.names=1 when importing.
p	a matrix of allele frequencies. Each row denotes each allele; each column denotes each marker. The order of markers follows x.
expect	a logic variable. If expect is true, the function will calculate the expected genotype probabilities. If false, calculate the observed genotype frequencies.

Details

This function calculates the observed or expected genotype frequency from dataset and allele frequency.#####

Value

y a matrix of genotype frequencies. Each row denotes each genotype; each column denotes each loci. The order of markers follows x; the genotypes are ordered by: from 1:l-th column, the genotypes are homozygous in order as : p1p1, p2p2,p3p3,...,plpl;from ll-th to u-th column, the genotypes are heterozygous in order as:choose(l,2) like: p1p2,p1p3,...,p1pl,p2p3,p2p4,...p2pl,...p(l-1)pl

References

Chakraborty, R., Srinivasan, M. R., & Daiger, S. P. (1993, ISSN:0002-9297).

Examples

```
require(mixIndependR)
x <- data.frame(STR1=c(12,13,13,14,15,13,14,12,14,15),
                STR1_1=c(12,14,13,15,13,14,13,12,14,15),
                SNP1=c("A","T","A","A","T","A","A","T","T","A"),
                SNP1_1=c("A","T","T","T","A","T","A","A","T","T"))
p <- AlleleFreq(x)
GenotypeFreq(x,p,expect=TRUE)
```

Heterozygous *Test heterozygosity at each locus*

Description

Test heterozygosity at each locus

Usage

```
Heterozygous(x)
```

Arguments

x	a dataset of alleles. Each row denotes each individual.One allele in one cell.In the (2r-1)th column, there is the same locus with the 2r-th column; noted: no column for ID, make row.names=1 when importing.

Details

This function test the heterozygosity of each individuals at each locus.Output a table and Usually followed by write.csv(as.data.frame(y),file = "~/*.csv") to export the results.

Value

a dataframe of heterozygosity.0 is homozygous;1 is heterozygous. Each row denotes each individual; Each column denotes each locus.

Examples

```
x <- data.frame(STR1=c(12,13,13,14,15,13,14,12,14,15),
                STR1_1=c(12,14,13,15,13,14,13,12,14,15),
                SNP1=c("A","T","A","A","T","A","A","T","T","A"),
                SNP1_1=c("A","T","T","T","A","T","A","A","T","T"))
Heterozygous(x)
```

HWE.Chisq *Test the Hardy Weinberg Equilibrium with Chi-square test####*

Description

Test the Hardy Weinberg Equilibrium with Chi-square test####

Usage

```
HWE.Chisq(x,x0,rescale.p=FALSE,simulate.p.value=FALSE,B)
```

Arguments

x	a matrix of observed genotype frequencies. Each row denotes each genotype; each column denotes each loci. The order of markers follows x; the genotypes are ordered by: from 1:l-th column, the genotypes are homozygous in order as : p1p1, p2p2,p3p3,...,plpl;from ll-th to u-th column, the genotypes are heterozygous in order as:choose(l,2) like: p1p2,p1p3,...,p1pl,p2p3,p2p4,...p2pl,...p(l-1)pl
x0	a matrix of expected Probabilities;each row denotes each genotype; each column denotes each loci. The order of markers follows x; the genotypes are ordered by: from 1:l-th column, the genotypes are homozygous in order as : p1p1, p2p2,p3p3,...,plpl;from ll-th to u-th column, the genotypes are heterozygous in order as:choose(l,2) like: p1p2,p1p3,...,p1pl,p2p3,p2p4,...p2pl,...p(l-1)pl
rescale.p	a logical scalar; if TRUE then p is rescaled (if necessary) to sum to 1. If rescale.p is FALSE, and p does not sum to 1, an error is given.
simulate.p.value	a logical indicating whether to compute p-values by Monte Carlo simulation.
B	an integer specifying the number of replicates used in the Monte Carlo test.

Details

This function check the Hardy Weinberg Equilibrium from observed and expected distribution with Chi-square test#####

Value

y a list of result of chi-square test, $chi $pvalue; chi and pvalue are vectors of chi square statistics/ p values. Orders follows x.

Examples

```
require(mixIndependR)
x <- data.frame(STR1=c(12,13,13,14,15,13,14,12,14,15),
                STR1_1=c(12,14,13,15,13,14,13,12,14,15),
                SNP1=c("A","T","A","A","T","A","A","T","T","A"),
                SNP1_1=c("A","T","T","T","A","T","A","A","T","T"))
p <- AlleleFreq(x)
```

```
g <- GenotypeFreq(x,p,expect=FALSE)
g0 <- GenotypeFreq(x,p,expect=TRUE)
HWE.Chisq(g,g0,rescale.p=FALSE,simulate.p.value=TRUE,2000)
```

HWE.Fisher *Test the Hardy Weinberg Equilibrium with Fisher's exact test###*

Description

Test the Hardy Weinberg Equilibrium with Fisher's exact test###

Usage

```
HWE.Fisher(p,H,y)
```

Arguments

p	a matrix of allele frequency;each row denotes allele; each column denotes each loci;
H	a vector of number of Heterozygotes on each loci; length is number of loci.
y	a matrix of observed genotype Densities(Not count). Each row denotes each genotype; each column denotes each loci. The order of markers follows x; the genotypes are ordered by: from 1:l-th column, the genotypes are homozygous in order as : p1p1, p2p2,p3p3,...,plpl;from ll-th to u-th column, the genotypes are heterozygous in order as:choose(l,2) like: p1p2,p1p3,...,p1pl,p2p3,p2p4,...p2pl,...p(l-1)pl

Details

This function check the Hardy Weinberg Equilibrium with Fisher's exact Test.#####

Value

a vector of p-values of Fisher's test; ordered by the order of loci in p or x

References

Weir, B. S. (1996, ISBN:9780878939022)

Examples

```
x <- data.frame(STR1=c(12,13,13,14,15,13,14,12,14,15),
                STR1_1=c(12,14,13,15,13,14,13,12,14,15),
                SNP1=c("A","T","A","A","T","A","A","T","T","A"),
                SNP1_1=c("A","T","T","T","A","T","A","A","T","T"))
p <-AlleleFreq(x)
G <- GenotypeFreq(x,p,expect = FALSE)
h <- Heterozygous(x)
```

```
H <- RxpHetero(h,p,HWE = FALSE)
HWE.Fisher(p,H,G/colSums(G))
```

`mixIndependK` *Quick pvalue of total number of heterozygous loci*

Description

Quick pvalue of total number of heterozygous loci

Usage

```
mixIndependK(x,t,B)
```

Arguments

`x`	a dataset of alleles. Each row denotes each individual.One allele in one cell.In the (2r-1)th column, there is the same locus with the 2r-th column; noted: no column for ID, make row.names=1 when importing.
`t`	times of simulation in "Simulate_DistK" and "Simulate_DistX".
`B`	times of bootstrapping in Chi Squares Test.

Details

This function is a summary of pipeline for number of heterozygous loci (K), and generates the p-value of K for the target dataset.

Value

pvalue (1-cumulative probabilities) for the number of heterozygous loci(K)

Examples

```
x0 <- data.frame(STR1=c(12,13,13,14,15,13,14,12,14,15),
                 STR1_1=c(12,14,13,15,13,14,13,12,14,15),
                 SNP1=c("A","T","A","A","T","A","A","T","T","A"),
                 SNP1_1=c("A","T","T","T","A","T","A","A","T","T"),
                 STR2=c(10,12,11,9,10,12,11,12,12,10),
                 STR2_1=c(10,9,11,11,10,12,10,10,12,9),
                 SNP2=c("C","C","G","G","G","G","C","G","G","C"),
                 SNP2_1=c("C","C","G","G","C","G","C","C","G","G"))
mixIndependK(x0,10,10)
```

`mixIndependX` *Quick pvalue of total number of shared alleles*

Description

Quick pvalue of total number of shared alleles

Usage

```
mixIndependX(x,t,B)
```

Arguments

`x`	a dataset of alleles. Each row denotes each individual.One allele in one cell.In the (2r-1)th column, there is the same locus with the 2r-th column; noted: no column for ID, make row.names=1 when importing.
`t`	times of simulation in "Simulate_DistK" and "Simulate_DistX".
`B`	times of bootstrapping in Chi Squares Test.

Details

This function is a summary of pipeline for number of shared alleles(X), and generates the p-value of K for the target dataset.

Value

pvalue (1-cumulative probabilities) for the number of shared alleles(K)

Examples

```
x0 <- data.frame(STR1=c(12,13,13,14,15,13,14,12,14,15),
                 STR1_1=c(12,14,13,15,13,14,13,12,14,15),
                 SNP1=c("A","T","A","A","T","A","A","T","T","A"),
                 SNP1_1=c("A","T","T","T","A","T","A","A","T","T"),
                 STR2=c(10,12,11,9,10,12,11,12,12,10),
                 STR2_1=c(10,9,11,11,10,12,10,10,12,9),
                 SNP2=c("C","C","G","G","G","G","C","G","G","C"),
                 SNP2_1=c("C","C","G","G","C","G","C","C","G","G"))
mixIndependX(x0,10,10)
```

RealProAlleleShare *Calculate the Real Probability of 0,1 and 2 Shared Alleles###*

Description

Calculate the Real Probability of 0,1 and 2 Shared Alleles###

Usage

```
RealProAlleleShare(AS)
```

Arguments

AS	a matrix/double of no. of Shared alleles, made up with 0,1 and 2; Outcome of "AlleleShare_Table". Each column denotes each locus. Each row denotes each individual.

Details

This function Calculates the density of 0,1 and 2 Shared Alleles for a set of loci. Usually followed by write.csv(as.data.frame(y),file = "~/*.csv") to export the result of a n x3 matrix.

Value

a matrix/double of real density of 0,1 and 2 shared alleles for each locus. Each row denotes each locus. The first column denotes the probability of 0 shared alleles, the second denotes 1 shared allele, the third denotes 2 shared alleles.

Examples

```
AS<-matrix(sample(c(0:2),20,replace=TRUE,prob=c(0.3,0.3,0.4)),nrow=5)
RealProAlleleShare(AS)
```

RxpHetero *Calculate Real or Expected Average Heterozygosity at each locus*

Description

Calculate Real or Expected Average Heterozygosity at each locus

Usage

```
RxpHetero(h,p,HWE)
```

Arguments

h	a dataset of heterozygosity, made up with 0 and 1. Output of function "Heterozygous". Each row denotes each individual. Each row denotes each locus.
p	a dataset of allele frequency, Output of function "AlleleFreq". Each row denotes each allele, and each column denotes each locus.
HWE	a logic variable. When TRUE, this function will calculate the expected heterozygosity under Hardy-Weinberg Equilibrium: H= 1-sum(q_i^2); q_i is the allele frequency; If FALSE, this function calculate the average heterozygosity from real heterozygosity table.

Details

This function calculate average heterozygosity at each locus.Output a vector of number of loci.

Value

a vector of average heterozygosity on each loci.

References

Chakraborty, R., & Jin, L. (1992, ISSN:1432-1203) <doi:10.1007/BF00197257>

Examples

```
x <- data.frame(STR1=c(12,13,13,14,15,13,14,12,14,15),
                STR1_1=c(12,14,13,15,13,14,13,12,14,15),
                SNP1=c("A","T","A","A","T","A","A","T","T","A"),
                SNP1_1=c("A","T","T","T","A","T","A","A","T","T"))
require(mixIndependR)
h <- Heterozygous(x)
p <- AlleleFreq(x)
RxpHetero(h,p,HWE=TRUE)
```

Simulate_DistK — *Generate a Bundle of Simulated distributions for No. of heterozygous loci with known heterozygosites*

Description

Generate a Bundle of Simulated distributions for No. of heterozygous loci with known heterozygosites

Usage

```
Simulate_DistK(H,m,t)
```

Arguments

H	a vector of average heterozygosity of each loci. Length of H is the number of loci.
m	the sample size you want, usually similar to the real sample size.
t	the number of samples you want to build

Details

This function generates multinomial distribution for loci known the heterozygosity and build the simulated distribution for no. of heterozygous loci.

Value

a matrix of frequencies of No. of Heterozygous Loci. Each row denotes each simulated sample; Each column denotes each No. of Heterozygous loci, from 0 to length of H.

Examples

```
Simulate_DistK(runif(10),500,100)
```

Simulate_DistX *Build a simulated distribution for No. of Shared Alleles*

Description

Build a simulated distribution for No. of Shared Alleles

Usage

```
Simulate_DistX(e,m,t)
```

Arguments

e	a matrix of Probability of Sharing 2,1 or 0 alleles at each loci. Each row denotes each locus. Three columns denote sharing 0,1 or 2 alleles.
m	the sample size you want, usually similar to the real sample size.
t	the number of samples you want to build/ the times to generate a sample

Details

This function generates multinomial distribution for loci known the Allele Frequency and Expected Probability of Shared 2,1 or 0 alleles

Value

y a matrix of frequencies of No. of shared alleles. Each row denotes each simulated sample; Each column denotes each No. of shared alleles, from 0 to 2e length of e.

Examples

```
e0<-data.frame("P0"=runif(5,min = 0,max = 0.5),"P1"=runif(5,0,0.5))
e<-data.frame(e0,"P2"=1-rowSums(e0))
Simulate_DistX(e,500,10)
```

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Appendix 4. R Functions

```
AlleleFreq <- function(x){
    x <- as.matrix(x)
    m <- nrow(x)    #number of individuals
    n <- ncol(x)/2   #number of loci
Allele <- as.data.frame(table(x))   #####All alleles included####
  l <- nrow(Allele)   #####Number of Alleles
  p <- mat.or.vec(l,n)
  for (j in 1:n){
    a <- 2*j -1
    b <- 2*j
    for (k in 1:l){
      p[k,j] <- counta(x[,a:b],Allele[k,1])/(2*m)
    }
  }
  row.names(p) <- Allele[,1]
  M<-colnames(x)
  Ms <- rep.int(0,n)
  for (i in 1:n){
    Ms[i] <- M[2*i-1]
  }
  colnames(p)<-Ms
  return(p)
}
```

```
AlleleShare_Table <- function(x,replicate=TRUE)
{
  n <- nrow(x)
  m <- ncol(x)/2
  MakerTwo<-colnames(x)
  d <- mat.or.vec(2,n/2)
  if(replicate){
    d<-combn(n,2,simplify = TRUE)}else{
      if ((n %% 2) == 0){
        d[1,]<- sample(n,n/2,replace = FALSE)
        d[2,]<- sample(setdiff(c(1:n),d[1,]))
      }else{
        d[1,]<- sample(n,(n-1)/2,replace = FALSE)
        d[2,]<- sample(setdiff(c(1:n),d[1,]))[-1]
      }

    }

  p <- ncol(d) ###number of pairs####
  A.S. <- mat.or.vec(p,m)
  Name <- as.character(rep(NA, p))
  Namec <- rep.int(0,m)

  for (i in 1:p)
  {
    a <- as.character(x[d[1,i],])
    b <- as.character(x[d[2,i],])
    c <- rep.int(0,m)
```

```
  for (r in 1:m)
  {
    Namec[r]<-MakerTwo[(2*r-1)]
    if(identical(a[(2*r-1):(2*r)],b[(2*r-1):(2*r)])){
      c[r] <- 2
    }

    else{
      c[r]<-length(intersect(a[(2*r-1):(2*r)],b[(2*r-1):(2*r)]))
    }
  }
  A.S.[i,] <-c
  Name[i] <- str_c(d[1,i],d[2,i],sep = "vs")
 }

 colnames(A.S.) <- Namec
 row.names(A.S.)<- Name
 return(A.S.)
}
```

```
ComposPare_K <- function(h,Ex,trans)
{
  Obs_hetero<-data.frame(rowSums(h))
  colnames(Obs_hetero)<-c("K_io")
  Exp_hetero <- data.frame(sample(Ex$K,nrow(Obs_hetero),replace = T,prob = Ex$Density))
  colnames(Exp_hetero)<-c("K_ie")
  df<-as.data.frame(c(Obs_hetero,Exp_hetero))
  df_t <- data.frame(OvE=factor(rep(c("Obs", "Exp"),
each=nrow(Obs_hetero))),freq=(c(df$K_io,df$K_ie)))
  if(trans){
    return(df)
  }else{
      return(df_t)

  }
}
```

```
ComposPare_X <- function(AS,Ex,trans=TRUE)
{
  Obs_AS<-data.frame(rowSums(AS))
  colnames(Obs_AS)<-c("X_io")
  Exp_AS <- data.frame(sample(Ex$X,nrow(Obs_AS),replace = T,prob = Ex$Density))
  colnames(Exp_AS)<-c("X_ie")
  df<-as.data.frame(c(Obs_AS,Exp_AS))
  df_t <- data.frame(OvE=factor(rep(c("Obs", "Exp"),
each=nrow(Obs_AS))),freq=(c(df$X_io,df$X_ie)))
  if(trans){
    return(df)
  }else{
    return(df_t)
  }
}
```

```
counta <- function(z,y){
  return(sum(z==y,na.rm = TRUE))
}
```

```
Dist_SimuChisq <- function(s,prob,b){
  idx <-which(prob==0)
  if (length(idx)==0){
    prob <- prob
    s <- s
  }else{
    prob <- prob[-idx]
    s <- s[,-idx]
  }
  t <- nrow(s) ####times of sampling.######
  MyChisqValues <- replicate(t,0)
  for (k in 1:t){
    MyChisqValues[k] <- chisq.test(s[k,],p=prob,simulate.p.value = T,B=b)$statistic
  }
  return(MyChisqValues)
}
```

```
DistAlleleShare <- function(e)
{
  N <- nrow(e)
  P <- mat.or.vec(N,2*N+1)###generate the vetor/matrix for product####

  P[1,1] <- e[1,1]
  P[1,2] <- e[1,2]
  P[1,3] <- e[1,3]

  for (r in 2:N)
  {
    P[r,1] <- P[r-1,1]*e[r,1]
    P[r,2] <- P[r-1,1]*e[r,2]+P[r-1,2]*e[r,1]

    m <- 2*r-1

    for (k in 3:m)
    {
      P[r,k] <- P[r-1,k-2]*e[r,3]+P[r-1,k-1]*e[r,2]+P[r-1,k]*e[r,1]
    }
    P[r,2*r] <-P[r-1,2*r-2]*e[r,3]+P[r-1,2*r-1]*e[r,2]
    P[r,2*r+1] <- P[r-1,2*r-1]*e[r,3]
  }
  colnames(P)<-0:(ncol(P)-1)
  return(data.frame("X"=c(0:(2*N)),"Density"=P[N,]))
}
```

```
DistHetero <- function(H)
{
  N <- length(H)
  H_ <- 1-H

  P1 <- c(H_[1],H[1])

  P <- mat.or.vec(N,N+1)
  P[1,1] <- P1[1]
  P[1,2] <- P1[2]



  for (r in 2:N)
  {
    P[r,1] <- P[r-1,1]*H_[r]
    for (k in 2:N)
    {
      P[r,k] <- P[r-1,k]*H_[r]+P[r-1,k-1]*H[r]
    }
    P[r,N+1] <-P[r-1,N]*H[r]
  }
  return(data.frame("K"=c(0:N),"Density"=(P[N,])))
}
```

```
ExpProAlleleShare <- function(p)

{
  p1 <- colSums(p,na.rm = TRUE,dims =1)
  p2 <- colSums(p*p,na.rm = TRUE,dims =1)
  p3 <- colSums(p*p*p,na.rm = TRUE,dims =1)
  p4 <- colSums(p*p*p*p,na.rm = TRUE,dims =1)

  P0 <- 1-4*p2+4*p3+2*p2*p2-3*p4
  P1 <- 4*p2-4*p3-4*p2*p2+4*p4
  P2 <- 2*p2*p2-p4

  return(cbind(P0,P1,P2))
  print(cbind(P0,P1,P2))
}
```

```
FreqAlleleShare<- function(AS){
  n<-ncol(AS)
  X<-rowSums(AS)
  Frequency <- rep.int(0,(2*n+1))
  for (i in 1:(2*n+1)){
    Frequency[i] <- counta(X,(i-1))
  }
  X_io <- c(0:(2*n))
  df <- data.frame(X_io,Frequency)
  return(df)
}
```

```
GenotypeFreq <- function(x,p,expect = TRUE){
  x <- as.matrix(x)
  n <- ncol(p) ###number of loci;
  l <- nrow(p)  ###number of alleles;
  m <- nrow(x)  ####number of individuals/Samples;
  ll <- l+1
  c <- choose(l,2)+l   ####number of heterozygous and homozygous genotypes###
  cb <-combn(c(1:l),2)
  d<-row.names(p)
  het<-combn(d,2)
  homo <-matrix(c(combn(d,1),combn(d,1)),nrow = 2,byrow = T)
  Gn<-cbind(homo,het)
  y <- mat.or.vec(c,n)
  if(expect){
    for (i in 1:n){
      for (h in 1:l){
        y[h,i] <- p[h,i]^2
      }
      for (h in ll:c){
        y[h,i] <- 2*p[cb[1,(h-l)],i]*p[cb[2,(h-l)],i]
      }
    }
  }
  if(!expect){
    for (k in 1:n){
      a <- 2*k -1
      b <- 2*k
      for (j in 1:c){
```

```
      y[j,k] <- 0
      for (r in 1:m){
        if (setequal(x[r,a:b],Gn[,j])){
          y[j,k] <- y[j,k]+1
        }else{
          y[j,k] <- y[j,k]
        }
      }
    }
  }
  colnames(y) <- colnames(p)
  s <- ncol(Gn)
  G.Nam <- rep.int(s,0)
  for (g in 1:s){
    G.Nam[g]<- paste(Gn[1,g],Gn[2,g],sep = " ")
  }
  rownames(y) <- G.Nam
  return(y)
}
```

```
Heterozygous <- function(x){
  x <- as.matrix(x)
  n <- nrow(x)
  m <- ncol(x)
  y <- mat.or.vec(n,m/2)
  y
  for (i in 1:n){
    for (r in 1:(m/2)){
      if (x[i,(2*r)]==x[i,(2*r-1)])
        y[i,r] <-0
      else
        y[i,r] <-1
    }
  }
  M<-colnames(x)
  Ms <- rep.int(0,m/2)
  l <- m/2
  for (i in 1:l){
    Ms[i] <- M[2*i-1]
  }
  colnames(y)<-Ms
  rownames(y)<-rownames(x)
  return(y)
}
```

```
HWE.Chisq <- function(x,x0,rescale.p=FALSE,simulate.p.value=FALSE,B){
  n <- ncol(x)
  chi <- rep.int(0,n)
  pvalue <- rep.int(0,n)
  if(rescale.p){
    if (simulate.p.value){
      for (i in 1:n){
        ss <-x[,i]
        so <-x0[,i]
        cr <- 5/sum(ss)
        if(length(ss[which(so>cr)])>2){
          chi[i]<-chisq.test(ss[which(so>cr)],p=so[which(so>cr)]/sum(so[which(so>cr)]),rescale.p =
T,simulate.p.value = T, B=B)$statistic
          pvalue[i] <-
chisq.test(ss[which(so>cr)],p=so[which(so>cr)]/sum(so[which(so>cr)]),rescale.p =
T,simulate.p.value = T, B=B)$p.value
        }else{
          chi[i]<-chisq.test(ss[which(ss>0)],p=so[which(ss>0)]/sum(so[which(ss>0)]),rescale.p =
T,simulate.p.value = T, B=B)$statistic
          pvalue[i] <-chisq.test(ss[which(ss>0)],p=so[which(ss>0)]/sum(so[which(ss>0)]),rescale.p
= T,simulate.p.value = T, B=B)$p.value
        }
            }
    }else{
      for (i in 1:n){
        ss <-x[,i]
        so <-x0[,i]
        cr <- 5/sum(ss)
        if(length(ss[which(so>cr)])>2){
```

```
        chi[i]<-chisq.test(ss[which(so>cr)],p=so[which(so>cr)]/sum(so[which(so>cr)]),rescale.p =
T,simulate.p.value = F, B=B)$statistic

        pvalue[i] <-
chisq.test(ss[which(so>cr)],p=so[which(so>cr)]/sum(so[which(so>cr)]),rescale.p =
T,simulate.p.value = F, B=B)$p.value

      }else{

        chi[i]<-chisq.test(ss[which(ss>0)],p=so[which(ss>0)]/sum(so[which(ss>0)]),rescale.p =
T,simulate.p.value = F, B=B)$statistic

        pvalue[i] <-chisq.test(ss[which(ss>0)],p=so[which(ss>0)]/sum(so[which(ss>0)]),rescale.p
= T,simulate.p.value = F, B=B)$p.value

      }

      }

  }

   }else{

   if(simulate.p.value){

   for (i in 1:n){

     ss <-x[,i]

     so <-x0[,i]

     cr <- 5/sum(ss)

     if(length(ss[which(so>cr)])>2){

       chi[i]<-chisq.test(ss[which(so>cr)],p=so[which(so>cr)]/sum(so[which(so>cr)]),rescale.p =
F,simulate.p.value = T, B=B)$statistic

       pvalue[i] <-
chisq.test(ss[which(so>cr)],p=so[which(so>cr)]/sum(so[which(so>cr)]),rescale.p =
F,simulate.p.value = T, B=B)$p.value

     }else{

       chi[i]<-chisq.test(ss[which(ss>0)],p=so[which(ss>0)]/sum(so[which(ss>0)]),rescale.p =
F,simulate.p.value = T, B=B)$statistic

       pvalue[i] <-chisq.test(ss[which(ss>0)],p=so[which(ss>0)]/sum(so[which(ss>0)]),rescale.p =
F,simulate.p.value = T, B=B)$p.value

     }

     }
```

```
    }else{
   for (i in 1:n){
    ss <-x[,i]
    so <-x0[,i]
    cr <- 5/sum(ss)
    if(length(ss[which(so>cr)])>2){
      chi[i]<-chisq.test(ss[which(so>cr)],p=so[which(so>cr)]/sum(so[which(so>cr)]),rescale.p =
F,simulate.p.value = F, B=B)$statistic
      pvalue[i] <-
chisq.test(ss[which(so>cr)],p=so[which(so>cr)]/sum(so[which(so>cr)]),rescale.p =
F,simulate.p.value = F, B=B)$p.value
    }else{
      chi[i]<-chisq.test(ss[which(ss>0)],p=so[which(ss>0)]/sum(so[which(ss>0)]),rescale.p =
F,simulate.p.value = F, B=B)$statistic
      pvalue[i] <-chisq.test(ss[which(ss>0)],p=so[which(ss>0)]/sum(so[which(ss>0)]),rescale.p =
F,simulate.p.value = F, B=B)$p.value
    }
    }
    }
  }
  names(chi) <- colnames(x)
  names(pvalue) <- colnames(x)
  y <- list("chi"=chi,"pvalue"=pvalue)
  return(y)
  print(y)
  }
```

```
HWE.Fisher <- function(p,H,y){
  n<- colSums(y)[1] #####number of samples#####
  m <- ncol(y) ####number of loci#####
  p0 <- p*2*n
  Pr <- rep.int(0,m)
  for (i in 1:m){
    Pr[i]<-exp(lfactorial(n)+H[i]*log(2)+sum(lfactorial(p0[,i]))-lfactorial(2*n)-
sum(lfactorial(y[,i])))
  }
  names(Pr) <- colnames(y)
  return(Pr)

}
```

```
mixIndependK<-function(x,t,B){
  s <- nrow(x)
  p <- AlleleFreq(x)
  h <- Heterozygous(x)
  H <- RxpHetero(h,p,HWE = F)
  Obs_DistHetero<-FreqHetero(h)
  Exp_DistHetero<-DistHetero(H)
  prob<-Exp_DistHetero$Density
  obs<-Obs_DistHetero$Frequency
  idx <-which(prob==0)
  if (length(idx)==0){
    prob <- prob
    obs <- obs
  }else{
    prob <- prob[-idx]
    obs <- obs[-idx]
  }
  x20 <-chisq.test(obs,p=prob,simulate.p.value = T,B=B)
  s<-Simulate_DistK(H,s,t)
  x2<-Dist_SimuChisq(s,Exp_DistHetero$Density,B)
  P <- ecdf(x2)
  return(1-P(x20$statistic))
}
```

```
mixIndependX <- function(x,t,B){
  s <- nrow(x)/2
  AS <- AlleleShare_Table(x,replicate = F)
  Obs_DistAlleleShare<-FreqAlleleShare(AS)
  e <- RealProAlleleShare(AS)
  Exp_DistAlleleShare <- DistAlleleShare(e)
  prob<-Exp_DistAlleleShare$Density
  obs<-Obs_DistAlleleShare$Frequency
  idx <-which(prob==0)
  if (length(idx)==0){
    prob <- prob
    obs <- obs
  }else{
    prob <- prob[-idx]
    obs <- obs[-idx]
  }
  x20 <-chisq.test(obs,p=prob,simulate.p.value = T,B=B)
  s<-Simulate_DistX(e,s,t)
  x2<-Dist_SimuChisq(s,Exp_DistAlleleShare$Density,B)
  P <- ecdf(x2)
  return(1-P(x20$statistic))
}
```

```
RealProAlleleShare <-function(AS){
  l <-nrow(AS)
  n <-ncol(AS)
  Pro_real <- mat.or.vec(n,3)
  for (i in 1:n){
    Pro_real[i,1]<-counta(AS[,i],0)
    Pro_real[i,2]<-counta(AS[,i],1)
    Pro_real[i,3]<-counta(AS[,i],2)
  }
  row.names(Pro_real) <- colnames(AS)
  colnames(Pro_real) <- c("P0","P1","P2")
  return(Pro_real/l)
}
```

```
RxpHetero <- function(h,p,HWE){
  if (HWE){
    return(1-colSums(p*p))
  }else{
    return(colSums(h)/nrow(h))
  }
}
```

```
Simulate_DistK <- function(H,m,t){
  n <- length(H)
  OneSample <- mat.or.vec(n*t,m)
  Freq <- mat.or.vec(t,n+1) ####each row denotes each small sample, the column denotes the numbers of heterozygous loci: 0~n, the value in cell denotes how many individuals has such number of heterozygous loci.####
  ###build the function for count##
  countif <- function(z,y){
    conts <- 0
    s <- length(z)
    for (l in 1:s){
      if (z[l]==y){
        conts <-conts+1
      }
    }
    return(conts)
  }
  #####pick up m individuals t times, to make up the t small samples. ###
  for (i in 1:t){
    a <- ((i-1)*n)+1
    b <- i*n
    OneSample[(a:b),]<-replicate(m,rbinom(n,1,H))
    for (j in 0:n){
      Freq[i,j+1] <- countif(colSums(OneSample[(a:b),]),j)
    }
  }
  colnames(Freq) <- c(0:n)
  return(Freq)
}
```

```
Simulate_DistX <- function(e,m,t){
  n <- nrow(e)
  OneSample <- mat.or.vec(n*t,m)
  Freq <- mat.or.vec(t,2*n+1) ####each row denotes each small sample, the column denotes the numbers of shared alleles: 0~2n, the value in cell denotes how many individuals has such number of shared alleles.####
  ###build the function for count##
  countif <- function(z,y){
    conts <- 0
    s <- length(z)
    for (l in 1:s){
      if (z[l]==y){
        conts <-conts+1
      }
    }
    return(conts)
  }
  #####pick up m individuals t times, to make up the t small samples. ###
  for (j in 1:t){
    for (i in 1:n){
      OneSample[((j-1)*n+i),] <- replicate(m,sample(c(0,1,2),1,replace=T,prob = e[i,]))
    }
    a <- ((j-1)*n)+1
    b <- j*n
    N <- 2*n
    for (k in 0:N){
      Freq[j,k+1] <- countif(colSums(OneSample[(a:b),]),k)
    }
  }
```

```
  colnames(Freq) <- c(0:(2*n))
  return(Freq)
}
```

```
split_Genotype <- function(df,sep,dif){
  f_sep <- function(x){
    x %>% separate(names(x),c(names(x),paste(names(x),dif)),sep)
  }
  for (i in 1:ncol(df)){
    df %>% mutate(f_sep(df[i])) -> df
  }
  return(df[sort(names(df))])
}
```

Appendix 5. *ms* command lines

#####unlinked 20 STRs########

./ms 1000 20 -t 8.0| ./microsat > ./msat_Unlinked_500x20STR_unlinked.dat

######unlinked 10 SNPs########

./ms 1000 10 -s 1 >ms_500x10_SNP_unlinked.dat

######linked 10 SNPs########

./ms 1000 1 -s 10 >ms_500x10_SNP_link.dat

######linked 20 STRs########

./ms 1000 1 -t 160.0 | ./microsat -a 15 -l 20 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 0.05 >msat_500x20_STR_Linked_2Parts.dat

Appendix 6. *plink 1.9* command lines

plink --vcf 1kg.snp.str.chr4.vcf.gz --out mydata_chr4

plink --bfile mydata_chr4 --mind 0.1 --recode --out cleaned_chr4

plink --file cleaned_chr4 --maf 0.05 --recode --out cleaned_af0.05_chr4

plink --file cleaned_af0.05_chr4 --geno 0.1 --recode -out cleand_step3 ###Missing rate per SNP

plink --file cleand_step3 --hwe 0.001 --recode --out cleaned_step4

####plink --file mydata --me 0.05 0.1 --make-bed --out newdata

###plink --file data --impute-sex --make-bed --out newfile ###notneed###

plink --bfile newdata --r2 --ld-window-r2 0.6

plink --bfile newdata --r2 --ld-window-kb 10 --ld-window-r2 0.2

plink --chr 4 --bfile newdata --from-bp 10000 --to-bp 200000 --recode -out 10kto200k ####386 variants and 383 SNPs 3 indels