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RESEARCH ARTICLE

Top Alzheimer's disease risk allele frequencies differ in HABS-HD Mexican- versus Non-Hispanic White Americans

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Abstract

INTRODUCTION: Here we evaluate frequencies of the top 10 Alzheimer's disease (AD) risk alleles for late-onset AD in Mexican American (MA) and non-Hispanic White (NHW) American participants enrolled in the Health and Aging Brain Study–Health Disparities Study cohort.

METHODS: Using DNA extracted from this community-based diverse population, we calculated the genotype frequencies in each population to determine whether a significant difference is detected between the different ethnicities. DNA genotyping was performed per manufacturers' protocols.

RESULTS: Allele and genotype frequencies for 9 of the 11 single nucleotide polymorphisms (two apolipoprotein E variants, *CR1*, *BIN1*, *DRB1*, *NYAP1*, *PTK2B*, *FERMT2*, and *ABCA7*) differed significantly between MAs and NHWs.

DISCUSSION: The significant differences in frequencies of top AD risk alleles observed here across MAs and NHWs suggest that ethnicity-specific genetic risks for AD exist. Given our results, we are advancing additional projects to further elucidate ethnicity-specific differences in AD.

KEYWORDS
Alzheimer's disease, dementia, diversity, genetics, health disparities, Hispanic, Mexican American, mild cognitive impairment

1 | BACKGROUND

1.1 | Alzheimer's disease and health disparities

Dementia is a broad term that encompasses a variety of cognitive dysfunction manifestations. Alzheimer's disease (AD) is the most common form of dementia, affecting one in nine people over the age of 65 in the United States, and resulting in about 135,000 deaths per year, according to the Centers for Disease Control in 2022.[1,2] AD is characterized by distinct pathological features such as the formation of extracellular plaques comprised of misfolded amyloid fragments and intracellular neurofibrillary tangles of hyperphosphorylated tau protein.[2,3]

AD has two distinct forms: familial early-onset and sporadic late-onset AD (LOAD). Familial early-onset AD is inherited in a Mendelian dominant fashion due to mutations in the amyloid precursor protein, presenilin 1, or presenilin 2 genes, disrupting proper amyloid cleavage pathways.[1–4] Familial early-onset AD is rare, representing ≈ 5% of diagnosed cases globally. In contrast, the pathogenesis and biological mechanisms underlying sporadic LOAD are not fully understood. This is likely due to the involvement and complex interplay among many environmental factors and genes with varying effect sizes across ethnicities/races.[5–7] Clinical signs and symptoms tend to present insidiously, only mildly affecting cognition and executive function at first, but slowly leading to significant memory loss, and/or disruptions to activities of daily living.[8] Typically, symptoms of cognitive impairment do not appear until normal physiology has been disrupted for decades.[2,9] Therefore, there is significant value in improving diagnostics and risk assessments for patients who are increasingly concerned about dementia due to factors such as early memory problems, family history, or increased awareness through their primary care provider. This will enable more affordable and less invasive preemptive screenings as well, for primary care patients who may not be aware of their risk status during normal checkups. Although the overall heritability for LOAD has been estimated at 60% to 80%,[10] known genetic risk variants only explain roughly half of the risk for disease.[5–7] Among the many genes that have been identified to be associated with increased AD risk, apolipoprotein (*APOE*) ε4 is involved in cholesterol shuttle/packaging pathways[11–16] and contributes the greatest increased risk to AD. In contrast, the *APOE* ε2 gene provides protection against AD.[17,18] Here we investigate other genes that contribute high risk.

The majority of AD studies to date have collected data from individuals of European ancestry, leaving many questions regarding other ethnicities.[4,19–21] Researchers are actively searching for a deeper understanding of race/ethnicity-specific etiology. As most of the literature related to AD/ADRD has been published on individuals of European ancestry, there is a critical need to investigate each race/ethnicity separately to determine top population-specific genetic risk factors.

1.2 | Top AD risk alleles in literature

Considering the fact that most literature on AD risk is derived from majority European populations, there is evidence to support that genetic risk scores are not transferable between ethnicities due to the differences in effect sizes for the genes and allele frequencies.[20] In 2019, Kunkle et al. published a large scale GWAS meta-analysis confirming 20 previously identified AD risk loci and identifying 5 new AD risk loci.[4] As a preliminary analysis, we chose to analyze the top 10 risk-conferring alleles (Table 1) from Kunkle et al. to compare and investigate whether their genotype frequencies are significantly different between Mexican American (MA) and non-Hispanic White (NHW) participants of the Health and Aging Brain Study–Health Disparities (HABS-HD) cohort. It was hypothesized that significant differences in the genotype frequencies of the top 10 AD risk alleles would exist when comparing MAs and NHWs, due to the differences in onset and clinical presentation of AD within these populations. Going forward, we intend to analyze additional AD risk alleles, and investigate frequencies of these risk alleles in other populations including Black Americans. Our future work will incorporate analysis delineating cases from controls based on confirmatory diagnosis from imaging data. This will provide better confidence in our results by leveraging neurodegenerative biomarker data to confirm pathology.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed literature using traditional databases such as PubMed to understand health disparities gaps in Alzheimer's disease (AD). Leveraging the comprehensive data collected in the Health and Aging Brain Study–Health Disparities (HABS-HD) cohort allows us to examine differences between Mexican American (MA) and Non-Hispanic White (NHW) participants' genetic data to determine whether top AD risk genes reported in the literature have different genotype frequencies, indicating an ethnicity-specific effect.
2. **Interpretation**: Our findings highlight a very important detail relating to AD health disparities research. We show that the top AD risk genes taken from prominent literature (using majority European population data), cannot be applied as-is to other ethnicities. We show significant differences in 9 of the 11 evaluated single nucleotide polymorphisms between MAs and NHWs.
3. **Future directions**: This article serves as preliminary data to elaborate on ethnicity-specific AD risk in HABS-HD.

2 | METHODS

2.1 | HABS-HD demographics

The HABS-HD study is conducted at University of North Texas Health Science Center–Institute for Translational Research to address National Institutes of Health (NIH) AD and ADRD (AD and related dementias) Research Implementation

TABLE 1 Top 10 genetic risk factors for sporadic late-onset Alzheimer's disease (AD) from Kunkle et al. Includes chromosomal position and known biological function.

AD risk gene	Chromosome	Biological function
APOE (apolipoprotein E)	19	Cholesterol shuttle/packaging
CR1 (complement receptor 1)	1	Immune system regulator
BIN1 (myc box-dependent-interacting protein 1)	2	Structural protein
DRB1 (major histocompatibility complex, class II, DR beta 1)	6	Immune system regulator
TREM2 (trigger receptor expressed on myeloid cells 2)	6	Immune system regulator
NYAP1 (neuronal tyrosine phosphorylated phosphoinositide-3-kinase adaptor 1)	7	Regulates neuronal morphogenesis
PTK2B (protein tyrosine kinase 2 beta)	8	MAP kinase signaling pathway and calcium regulation
FERMT2 (fermitin family homolog 2)	14	Component of extracellular matrix in mammalian cells and controller of cell shape change
ABCA7 (ATP binding cassette subfamily a member 7)	19	Lipid homeostasis and macrophage mediated phagocytosis
CD2AP (cluster of differentiation 2 associated protein)	6	Scaffolding molecule that regulates actin cytoskeleton

TABLE 2 Health and Aging Brain Study–Health Disparities cohort demographics.

Demographic characteristics of cohort	Mexican Americans	Non-Hispanic White Americans
N total	853	782
Mean age, years [mean (SD)]	63.83 (7.99)	69.35 (8.65)
Sex, % female	65.65%	54.48%
Education, years [mean (SD)]	9.51 (4.61)	15.50 (2.55)
Diabetes, % yes	36.34%	12.92%
Dyslipidemia, % yes	66.47%	63.94%
Hypertension, % yes	66.12%	59.59%
Normal cognition, % yes	75.73%	83.12%
MCI, % yes	16.65%	11%
Dementia, % yes	7.62%	5.88%

Note: For co-morbidity prevalence, data are provided by binary "yes/no" medical consensus.
Abbreviations: MCI, mild cognitive impairment; SD, standard deviation.

Milestones that call for investigations on AD and related dementia in diverse populations. This NIH-funded project is the most comprehensive study of AD among diverse community-dwelling populations.[14,22–27] The HABDS-HD is longitudinal, with replacement for attrition. For each participant in HABS-HD, the following is collected: extensive clinical history, neuropsychological evaluations, functional assessments, standard bloodwork, comprehensive AD biomarkers, genetic samples, and magnetic resonance imaging/positron emission tomography imaging at multiple time points.[27] In this study, we take a cross-sectional look at the genetic data available for MA ($n = 853$) and NHW ($n = 782$) participants to determine what genotype frequency differences may exist between ethnicities across the 11 single nucleotide polymorphisms (SNPs) of interest. Table 2 shows an overview of HABS-HD participant demographics analyzed in this study.

2.2 | Genotyping and imputation methods

DNA was extracted from peripheral blood buffy coat samples ($n = 1635$) using the Mag-Bind Blood & Tissue DNA HDQ 96 Kit (Omega Bio-tek) and Hamilton Microlab STARlet automated liquid handler (Hamilton Company). Genotyping was performed per manufacturer's protocol using the Illumina Global Screening Array (GSA) based on Infinium HTS chemistry and analyzed with Genome Studio 2.0. Samples with call rates < 98% were re-typed or excluded. Quality control was performed according to literature standards and protocols used by our laboratory in previous publications.[28] Only *BIN1* was directly genotyped, while the remaining SNPs were imputed using Impute2 and 1000 Genomes Project Phase 3 data, with a linkage threshold of 0.8.[29–34]

2.3 | Statistical analysis

Statistical analysis was conducted to compare the allele and genotype frequencies on the top 10 risk-conferring genes from Kunkle et al.[4] among MAs and NHWs in the HABS-HD Study using R Studio (version 4.2.3). A Wilcoxon rank sum test was performed to evaluate the differences of genotype distributions between MA and NHW American populations for each gene. Bonferroni correction was applied to adjust for multiple testing of the 11 risk SNPs of the 10 genes, and an adjusted P value < 0.05 was considered significant. *APOE* ε4 positivity was evaluated separately between the two populations, along with two *APOE* ε4 variants.

To compare the linkage disequilibrium (LD) pattern of the genomic regions for each of the 11 SNPs between MA and NHW populations, LD and haplotype analysis was conducted using Haploview software (version 4.2).[35] Specifically, LD parameters D' and r^2 were estimated and haplotype blocks were identified, which were reported in LD heatmaps for each population. In addition, distributions on the haplotype blocks between the MA

TABLE 3 Genotype frequency differences for the top 10 AD risk genes in Mexcian- and non-Hispanc White Americans of the HABS-HD study.

Gene	rsNumber	Legend	Mexican Americans				Non-Hispanic Whites				*P*-value*
			Genotypic frequencies			*N*	Genotypic frequencies			*N*	
APOE+	N/A					853				782	<0.001**
APOE	rs429358	CC/CT/TT	14	143	696	853	17	220	545	782	<0.001**
APOE	rs7412	CC/CT/TT	796	56	1	853	658	122	2	782	<0.001**
CR1	rs4844610	AA/AC/CC	6	135	708	849	24	206	538	768	<0.001**
BIN1	rs6733839	CC/CT/TT	265	420	165	850	316	326	133	775	<0.005**
DRB1	rs9271058	AA/AT/TT	28	220	583	831	64	275	407	746	<0.001**
TREM2	rs75932628	CC/CT/TT	843	2	0	845	772	0	0	772	1.000
NYAP1	rs12539172	CC/CT/TT	427	315	53	795	349	319	75	743	0.031**
PTK2B	rs73223431	CC/CT/TT	519	281	44	844	320	350	97	767	<0.001**
FERMT2	rs17125924	AA/AG/GG	608	213	23	844	616	145	9	770	<0.002**
ABCA7	rs3752246	CC/GC/GG	684	142	11	837	507	244	15	766	<0.001**
CD2AP	rs9473117	AA/AC/CC	461	325	50	836	375	308	69	752	0.145

*Adjusted *P*-value.
**Significance at threshold $P < 0.05$.
Abbreviations: *ABCA7*, ATP binding cassette subfamily a member 7; AD, Alzheimer's disease; *APOE*, apolipoprotein E; *CR1*, complement receptor 1; *BIN1*, myc box-dependent-interacting protein 1; *CD2AP*, cluster of differentiation 2 associated protein; *DRB1*, major histocompatibility complex, class II, DR beta 1; *FERMT2*, fermitin family homolog 2; HABS-HD, Health and Aging Brain Study–Health Disparities; *NYAP1*, neuronal tyrosine phosphorylated phosphoinositide-3-kinase adaptor 1; PTK2B, protein tyrosine kinase 2 beta; *TREM2*, trigger receptor expressed on myeloid cells 2.

and NHW populations were compared using a chi-square test in Haploview.

3 | RESULTS

3.1 | SNP analysis

We found significant differences in genotype frequencies of 9 out of the 11 SNPs, demonstrated in Table 3. Notably, there was a significant difference in *APOE* ε4 positivity between NHWs (30.31%) and MAs (18.41%; Figure 1A). Figure 1B shows the genotype frequencies of the two *APOE* variants rs7412 (adjusted $P < 0.001$) and rs429358 (adjusted $P < 0.001$), between the two populations. Statistical analysis described in Section 2.3 showed statistically significant differences in frequencies of *APOE* (adjusted $P < 0.001$), complement receptor 1 (*CR1*; adjusted $P < 0.001$), myc box-dependent-interacting protein 1 (*BIN1*; adjusted $P = 0.004975$), major histocompatibility complex, class II, DR beta 1 (*DRB1*; adjusted $P < 0.001$), neuronal tyrosine phosphorylated phosphoinositide-3-kinase adaptor 1 (*NYAP1*; adjusted $P = 0.031$), protein tyrosine kinase 2 beta (*PTK2B*; adjusted $P < 0.001$), fermitin family homolog 2 (*FERMT2*; adjusted $P = 0.0011455$), and ATP binding cassette subfamily a member 7 (*ABCA7*; adjusted $P < 0.001$) between MAs and NHWs (Figure 2A). However, trigger receptor expressed on myeloid cells 2 (*TREM2*; adjusted $P = 1$), and cluster of differentiation 2 associated protein (*CD2AP*; adjusted $P = 0.145422$), did not show statistical significance (Figure 2B).

3.2 | Haplotype analysis

LD heatmaps for MA and NHW populations are reported in Figures 3 and 4, MA on the left and NHW on the right. Because of the Illumina GSA genotyping protocol, the number of SNPs typed can be different in each genomic region, resulting in different sizes of the LD heatmaps for each of targeted SNPs. Only LD heatmaps with > 3 SNPs typed in surrounding genetic region were reported, which were *APOE* (one heatmap for rs429358 and rs7412 due to proximal loci within *APOE* gene region), *CR1* (rs4844610), *BIN1* (rs6733839), *DRB1* (rs9271058), *PTK2B* (rs73223431), *FERMT2* (rs17125924), *ABCA7* (rs3752246), *CD2AP* (rs9473117). For each of the above genes, haplotype association results between MA and NHW populations on the identified haplotype blocks are reported in File S1 in supporting information. Both LD heatmaps and haplotype association results indicated systematic differences in the genomic regions of the targeted SNPs between the two populations.

4 | DISCUSSION

Based on our findings, 9 out of the 11 SNPs evaluated showed significant genotype frequency differences between MAs and NHWs enrolled in the HABS-HD cohort. With consideration to the fact that the evaluated SNPs confer the top AD risks as known in the literature, the results suggest that a systemic and population-specific difference in genetic etiology for AD pathogenesis exists, calling for a need to discriminate the different genetic risk profiles of minorities in

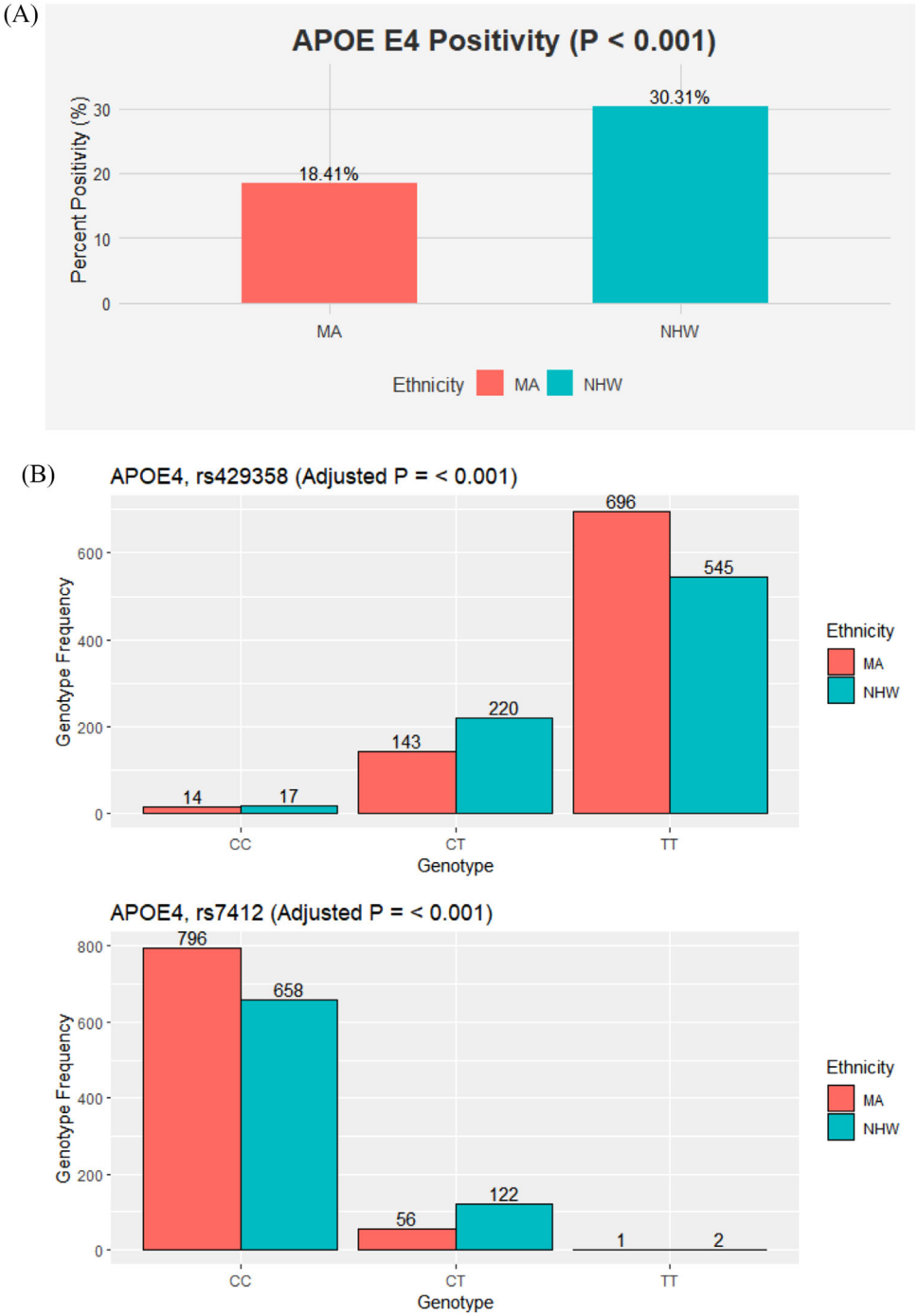

FIGURE 1 A, *APOE* ε4 positivity among MA and NHW participants in HABS-HD. B, *APOE* ε4 variant frequencies between MA NHW participants in HABS-HD. *APOE*, apolipoprotein E; HABS-HD, Health and Aging Brain Study–Health Disparities; MA, Mexican American; NHW, non-Hispanic White

independent large-scale GWAS studies. This is a critical knowledge gap in the field of AD genetics.

The gene functions in Table 1 can be grouped into either cholesterol shuttling (*APOE*, *ABCA7*), immune regulating (*CR1*, *DRB1*, *TREM2*, *ABCA7*), morphogenesis (*BIN1*, *NYAP1*, *FERMT2*, *CD2AP*), or cell signaling (*PTK2B*). We found a significant difference between MA and NHW Americans in nine of these risk loci, many of which are related to either inflammatory mediation, cell signaling or morphogenesis, or lipid homeostasis. It should be noted that the effect size is greatest from these top risk loci, despite additional risk alleles being discovered.[20] In general, SNPs are not conserved among ethnic groups, but genes are moderately conserved, and gene/protein network pathways are highly conserved.[5–7,36,37] This work suggests there are specific AD endophenotypes that may be ethnicity specific.

Underserved ethnic/racial groups, especially MA and Black Americans, tend to suffer from a higher burden of AD than NHW

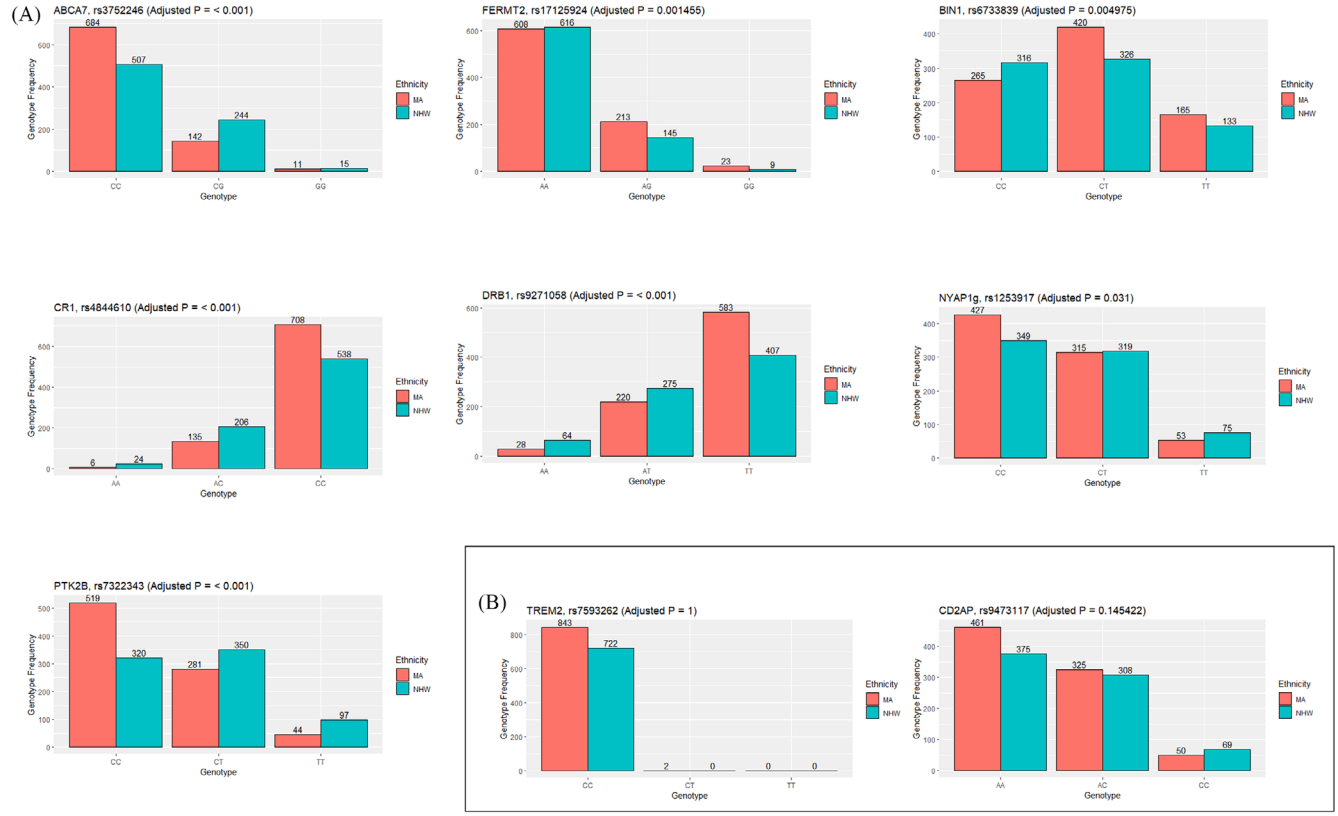

FIGURE 2 A, SNPs with a significant genotype frequency difference between ethnicities. B, SNPs with no significant genotype frequency difference between ethnicities. SNPs, single nucleotide polymorphisms

Americans.[2,9,38] By 2060, it is estimated that Hispanic/Latino Americans and Black Americans will make up ≈ 43% of the US population.[38] Despite the fact that AD has a variety of associated risk factors including genetics, lifestyle, and environmental,[12,39–42] it is unclear why diverse ethnic groups experience such large differential health outcomes compared to NHWs. Additionally, many questions remain about the implication of different genes, proteins, pathways, and related networks in disease manifestation.[2–4,20–22,24,43–46] Further investigation into these pathways may also aid accurate diagnosis. Currently, there is no curative treatment for AD that has proven effective. The most recent US Food and Drug Administration–approved medication (aducanumab) caused significant controversy due to extremely high cost, and adverse effects, ranging from brain swelling to brain hemorrhage being noted in 41% of patients during clinical trials.[47–50] Additionally, it has been noted that aducanumab studies contained under-representation of diverse populations, adding further uncertainty to the safety in these population.[51] Conventional AD treatment options involve the use of nootropics to enhance cognition, but they do not reverse the course of the disease.[52] Further work in this direction will aid in reducing health disparities among minorities, who carry increasing burdens of disease.

The HABS-HD team has published literature on the differences in AD endophenotype and how there may be racial/ethnicity-specific etiological subcategories of AD depending on the genetics, ancestry, and disease progression.[53] MAs tend to have a higher prevalence of diabetes, metabolic dysfunction, and immune dysregulation.[14,24,26,28,53–55] Black Americans also tend to have a higher prevalence of hypertension and cardiovascular disease.[2,21,56–58] By investigating ethnicity-specific risk at the level of genes and their networks, we aim to uncover the mechanisms potentially involved in ethnicity-specific risk, as it contributes to differential manifestations with varying etiology, in our future work.

Notably, our findings related to *APOE* ε4 may be significant not only due to the difference in genotype frequencies, but because of *APOE* ε4's normal physiological function. *APOE* is highly expressed in the liver and in brain astrocytes, where normally it is responsible for cholesterol packaging and transportation; however, the *APOE* ε4 risk allele has been shown to alter the blood–brain barrier (BBB) function independent of AD pathology, due to reduced pericyte coverage and increased leakage.[13,59–61] Increased leakage of the BBB can have immune-modulating effects as well as cardiovascular health implications due to changes in how lipids enter and exit the central nervous system via circulating peripheral blood, and how they interact with antigen-presenting cells.[62–66] This supports the idea that there may be AD endophenotypes based on a combination of subclinical factors, that is, dysfunctional inflammatory mediation or dyslipidemia.

Focusing on understanding the genetic differences between different ethnic/racial groups can help researchers and clinicians create

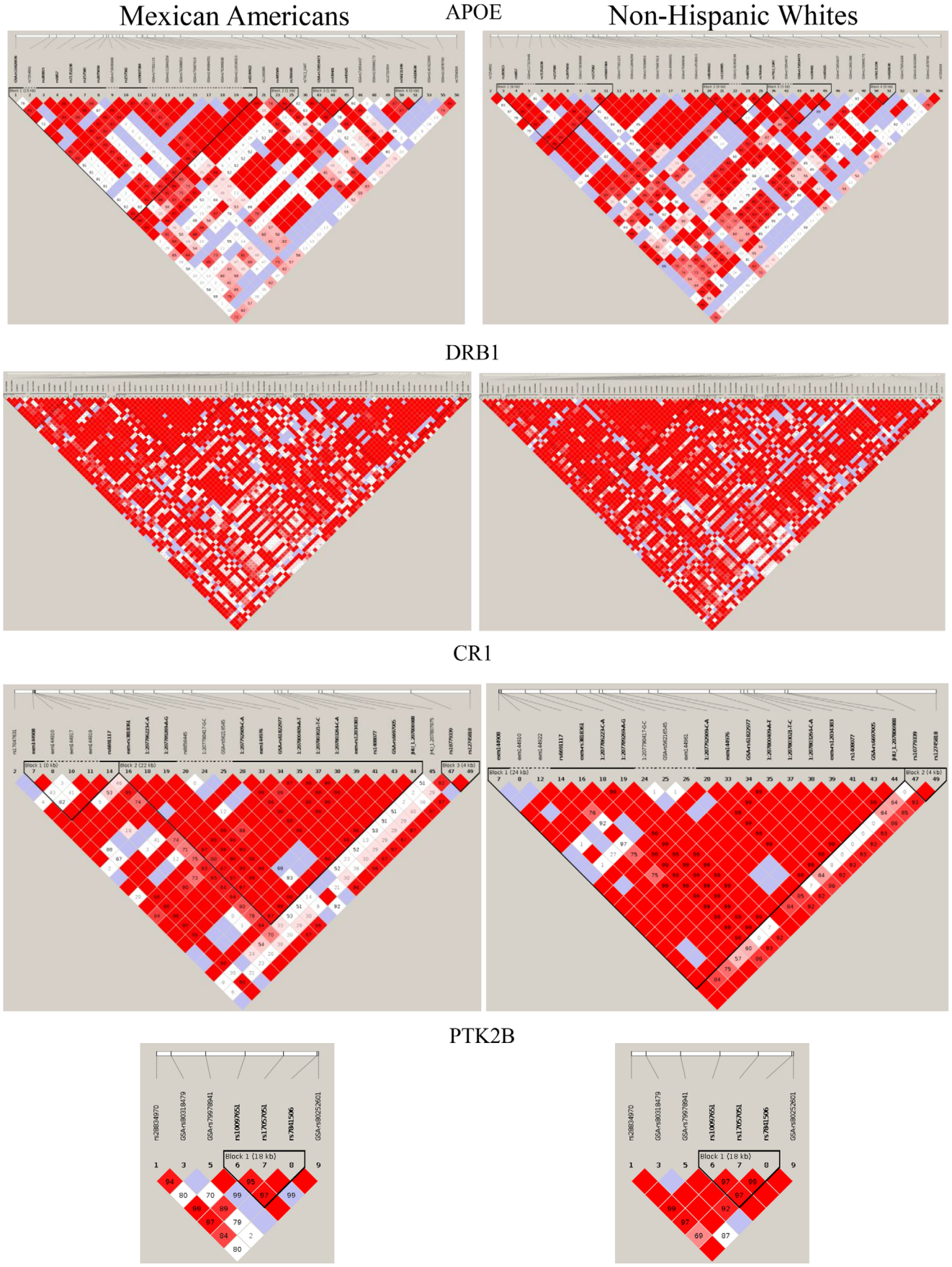

FIGURE 3 LD heatmaps for *APOE*, rs9271058 (*DRB1*), rs4844610 (*CR1*), rs73223431 (*PTK2B*); created by Haploview. Left, Mexican Americans; Right, non-Hispanic Whites. *APOE*, apolipoprotein E; LD, linkage disequilibrium

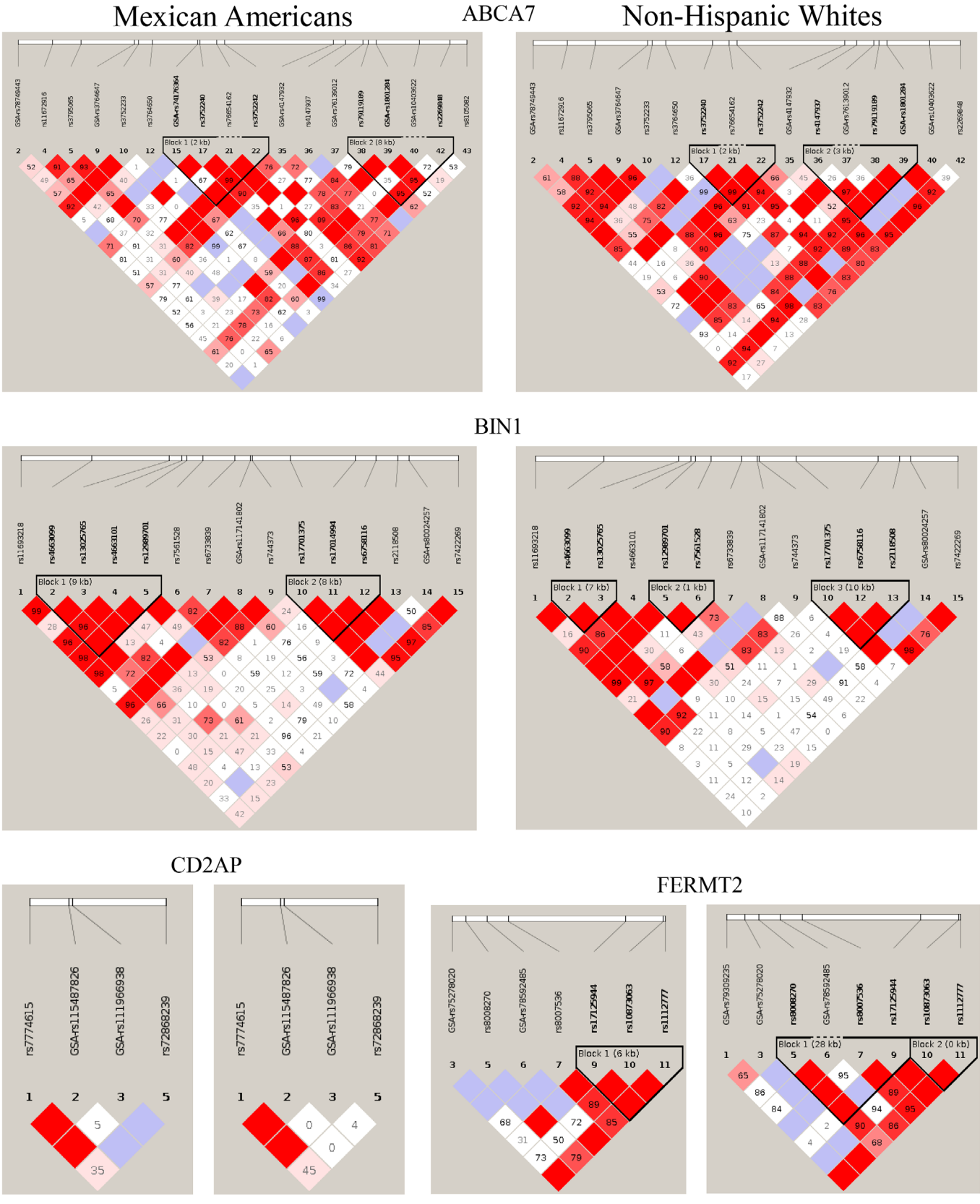

FIGURE 4 LD heatmaps for rs3752246 (*ABCA7*), rs6733839 (*BIN1*), rs9473117 (*CD2AP*), rs17125924 (*FERMT2*); created by Haploview. Left, Mexican Americans; Right, non-Hispanic Whites. LD, linkage disequilibrium

more accurate risk profiling, resulting in better health outcomes for patients, as well as significantly reduced AD health-care–associated costs.[2,67–70] Our future work will evaluate the risks contributed by gene and protein networks and associated genetic and epigenetic modifications, to help us understand what factors are most deleterious to an individual's health and whether these factors show ethnicity-specific effects.

In conclusion, the findings of the present analysis demonstrate the need for ethnicity-specific diagnostics to evaluate risk more accurately in minority populations. Discovering that 9 of the top 11 AD risk alleles have significantly different frequencies between MA and NHW Americans proves an imperative direction for the future of AD research: studies prioritizing and examining results between the different ethnicities is essential to pave the path for equitable diagnosis and treatment options. These genotypic frequency disparities lead us directly to the health disparities we may likely find when looking at treatment and disease progression outcomes between the two groups; this is not to account for the environmental, racial, financial, language, and transportation barriers that affect their health care as well. Given the projected increase in the Hispanic population by 2060[38] and a respective increase in AD burden, the medical research community must focus AD research on determining why there are ethnicity-specific disparities and prioritize projects that help bridge these gaps. Our next goal will be to evaluate the gene–protein networks more closely, and ultimately, contribute to the development of genetic and epigenetic ethnicity-specific risk stratification models, to reduce health disparities in AD literature.

5 | LIMITATIONS AND FUTURE DIRECTIONS

The study of AD genetics continues to present a challenge due to the low prevalence of certain rare variants in community-based populations, reducing statistical power. For example, rare variant *TREM2*, a functionally significant marker, was found not to be of significantly different allele frequency between MAs and NHWs. As the HABS-HD study continues to enroll more participants, we aim to repeat our analysis on the entire cohort of several thousand participants once the data are available. Our future studies will take this work further, using the genetic and epigenetic data we have collected to construct genetic risk score algorithms.

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CONFLICT OF INTEREST STATEMENT

The authors do not report any conflicts of interest relating to the work in this article. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects enrolled in HABS-HD consented to their participation and the study was approved by UNTHSC Institutional Review Board.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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