


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

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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 \approx 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) ϵ 4 is involved in cholesterol shuttle/packaging pathways¹¹⁻¹⁶ and contributes the greatest increased risk to AD. In contrast, the APOE ϵ 2 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

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.

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.

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 HABDS-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 HABDS-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 HABDS-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* $\epsilon 4$ positivity was evaluated separately between the two populations, along with two *APOE* $\epsilon 4$ 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 Mexican- and non-Hispanic 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

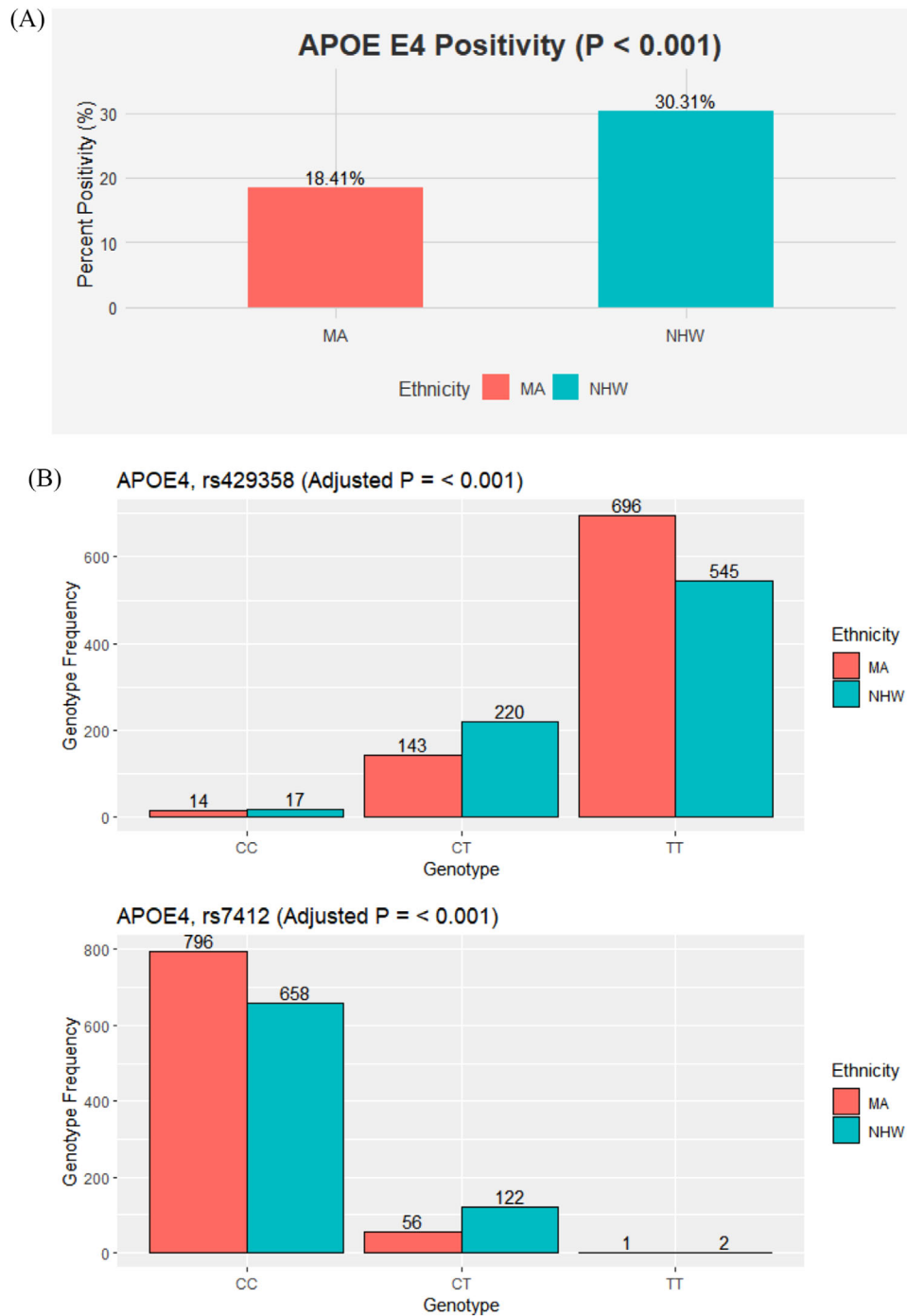


FIGURE 1 A, APOE ϵ 4 positivity among MA and NHW participants in HABS-HD. B, APOE ϵ 4 variant frequencies between MA and NHW participants in HABS-HD. APOE, apolipoprotein E; HABS-HD, Health and Aging Brain Study–Health Disparities; MA, Mexican American; NHW, non-Hispanic White

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

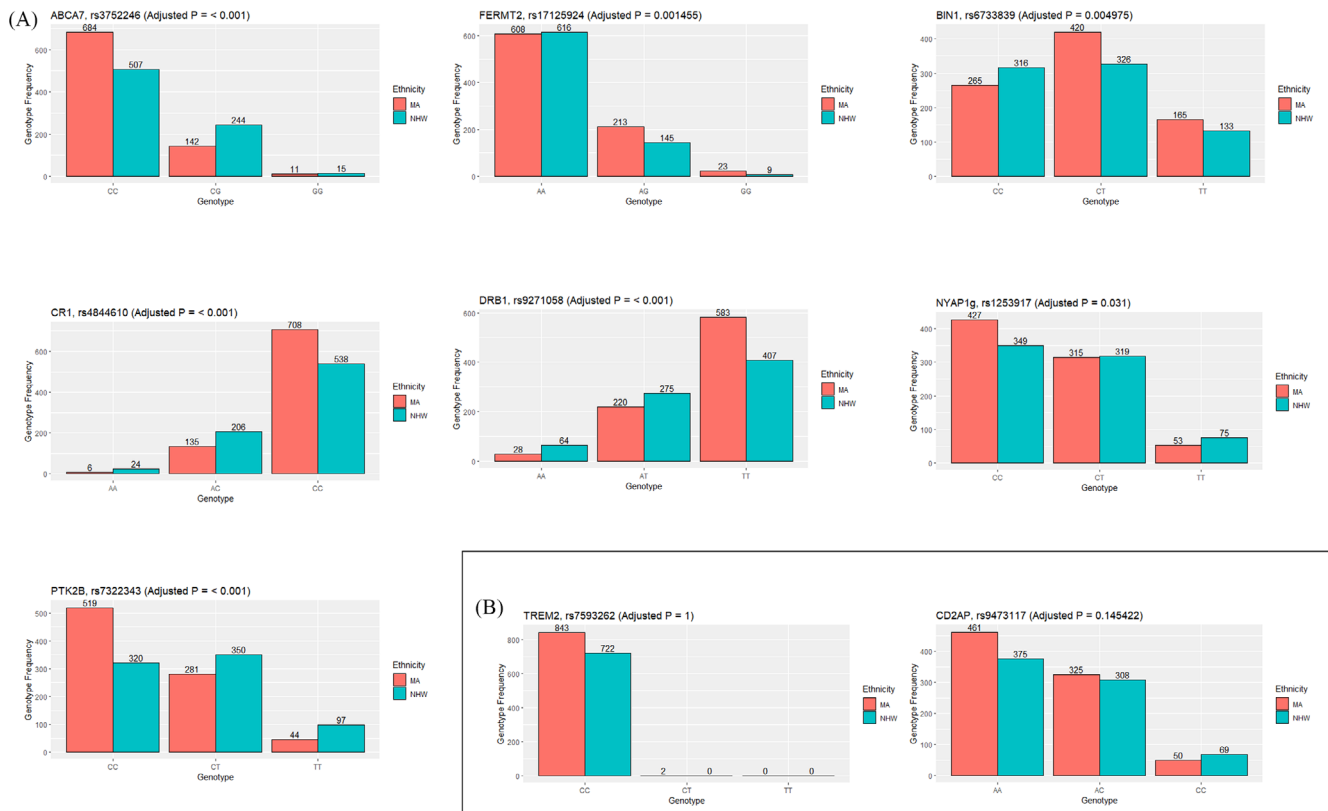


FIGURE 2 A, SNPs with a significant genotype frequency difference between ethnicities. B, SNPs with no significant genotype frequency difference between ethnicities. SNPs, single nucleotide polymorphisms

Americans.^{2,9,38} By 2060, it is estimated that Hispanic/Latino Americans and Black Americans will make up $\approx 43\%$ 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* $\epsilon 4$ may be significant not only due to the difference in genotype frequencies, but because of *APOE* $\epsilon 4$'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* $\epsilon 4$ 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

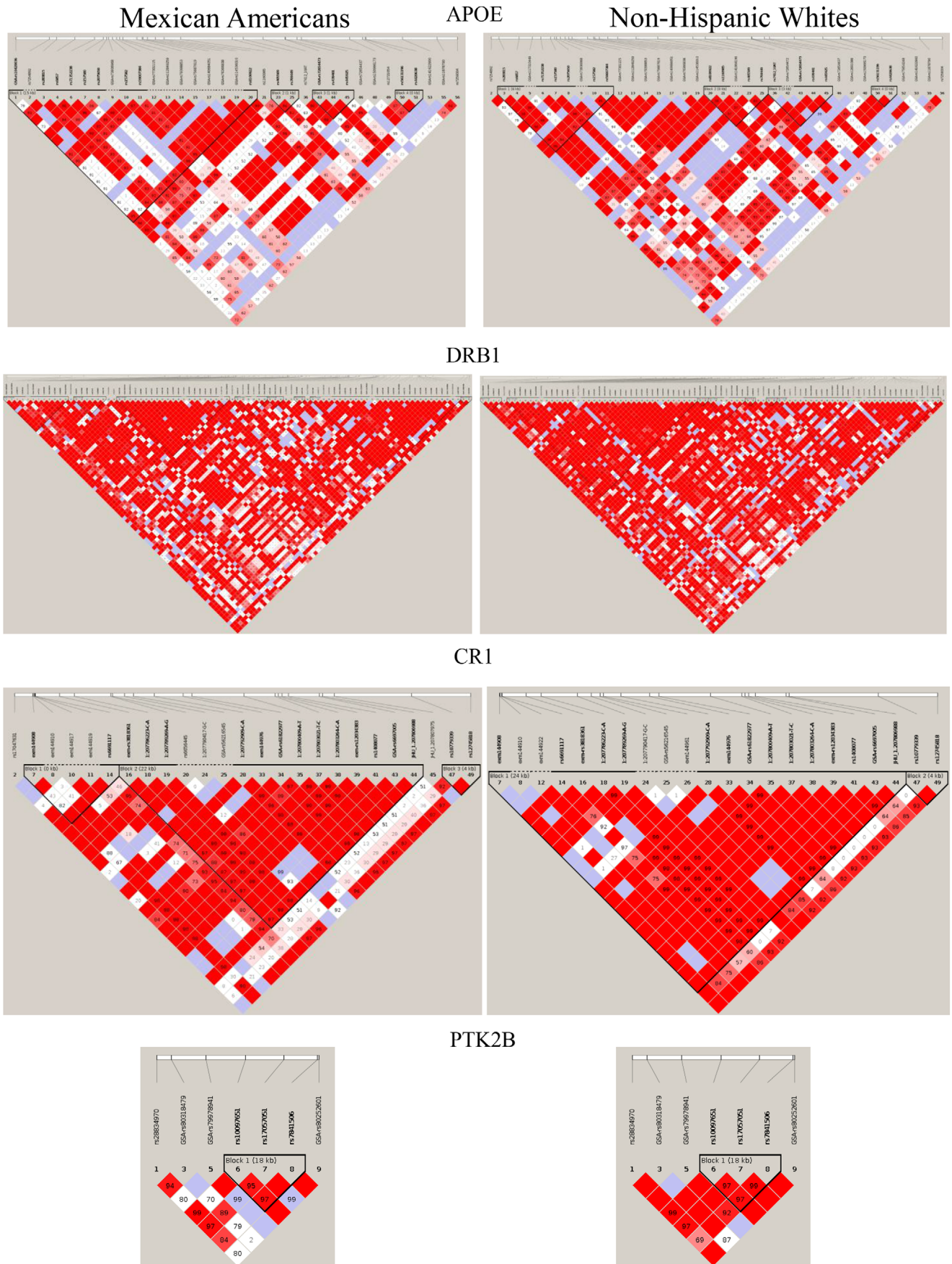


FIGURE 3 LD heatmaps for APOE, rs9271058 (DRB1), rs4844610 (CR1), rs73223431 (PTK2B); created by Haploview. Left, Mexican Americans; Right, non-Hispanic Whites. APOE, apolipoprotein E; LD, linkage disequilibrium

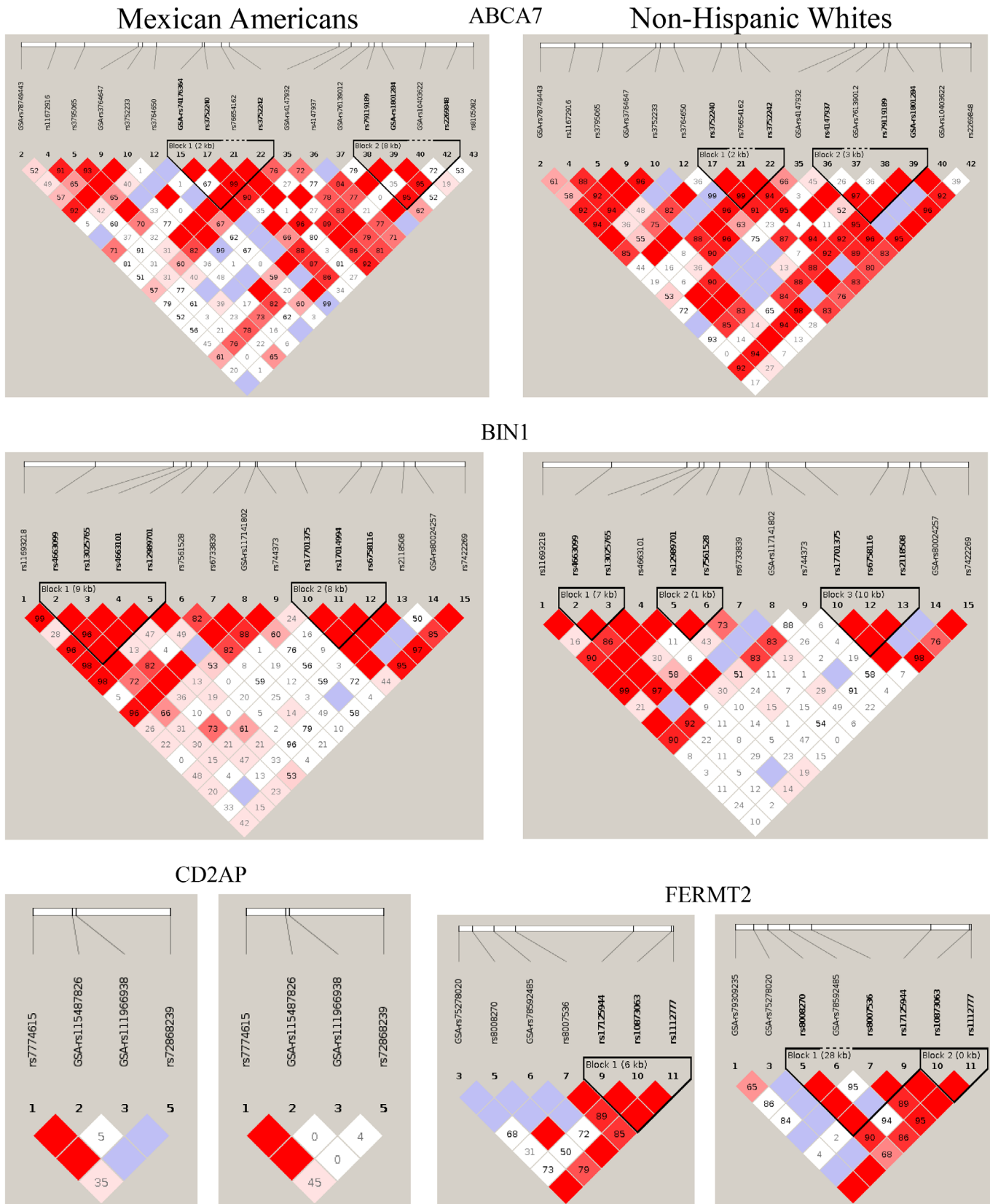


FIGURE 4 LD heatmaps for rs3752246 (ABCA7), rs6733839 (BIN1), rs9473117 (CD2AP), rs17125924 (FERMT2); created by Haploview. Left, Mexican Americans; Right, non-Hispanic Whites. LD, linkage disequilibrium

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 2060³⁸ 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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REFERENCES

1. World Health Organization. Dementia fact sheet. 2020.
2. Alzheimer's Association Report. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2022;18(4):700–789.
3. Barber R. The genetics of Alzheimer's disease. *Scientifica*. 2012;2012:217–240.
4. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates A β , tau, immunity and lipid processing. *Nat Genet [Internet]*. 2019;51(3):414–430. <http://www.nature.com/articles/s41588-019-0358-2>
5. Martin AR, Gignoux CR, Walters RK, et al. Human demographic history impacts genetic risk prediction across diverse populations. *Am Hum Genet*. 2017;100(4):635–649.
6. Martin AR, Gignoux CR, Walters RK, et al. Demographic History Impacts Genetic Risk Prediction across Diverse Populations. *Am Hum Genet*. 2017;100(4):635–649. Epub 2017 Mar 30. doi:10.1016/j.ajhg.2017.03.004. Erratum in: *Am J Hum Genet*. 2020 Oct 1;107(4):788–789. PMID: 28366442; PMCID: PMC5384097.
7. McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet*. 2008;9:356–369.
8. Reisberg B, Finkel S, Overall J, et al. The Alzheimer's Disease Activities of Daily Living International Scale (ADL-IS). *Int Psychogeriatr*. 2001;13(2):163–181.
9. Alzheimer's Association. Alzheimer's Association 2022 Alzheimer's disease facts and figures. *Special Report- More Than Normal Aging: Understanding Cognitive Impairment [Internet]*. Alzheimer's Association; 2022. [cited 2022 Sep 27]. <https://www.alz.org/media/Documents/alzheimers-facts-and-figures-special-report.pdf>
10. Gatz M, Reynolds CA, Fratiglioni L, et al. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry*. 2006;63(2):168–174.
11. Zhang C, Hu R, Zhang G, et al. A weighted genetic risk score based on four APOE-Independent Alzheimer's disease risk loci may supplement APOE E4 for better disease prediction. *J Mol Neurosci*. 2019;69(3):433–443.
12. Mur J, McCartney DL, Walker RM, et al. DNA methylation in APOE: the relationship with Alzheimer's and with cardiovascular health. *Alzheimers Dement*. 2020;6(1):e12026.
13. Jackson RJ, Meltzer JC, Nguyen H, et al. APOE4 derived from astrocytes leads to blood–brain barrier impairment. *Brain*. 2021;145(10):3582–3593.
14. O'Bryant SE, Barber RC, Philips N, et al. The Link between APOE4 presence and neuropsychological test performance among Mexican Americans and Non-Hispanic whites of the multiethnic Health & Aging

- Brain Study—Health Disparities cohort. *Dement Geriatr Cogn Disord*. 2022;51(1):26-31.
15. Mancera-Páez O, Estrada-Orozco K, Mahecha MF, et al. Differential methylation in APOE (Chr19; exon four; from 44,909,188 to 44,909,373/hg38) and increased apolipoprotein E plasma levels in subjects with MILD cognitive impairment. *Int J Mol Sci*. 2019;20(6):1394.
 16. Granot-Hershkovitz E, Tarraf W, Kurniansyah N, et al. APOE alleles' association with cognitive function differs across Hispanic/Latino groups and genetic ancestry in the study of Latinos—investigation of neurocognitive aging (HCHS/SOL). *Alzheimers Dement*. 2021;17(3):466-474.
 17. Kim YJ, Seo SW, Park SB, et al. Protective effects of APOE e2 against disease progression in subcortical vascular mild cognitive impairment patients: a three-year longitudinal study. *Sci Rep*. 2017;7(1):1910.
 18. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet*. 1994;7(2):180-184.
 19. Jun GR, Chung J, Logue MW, et al. Transethnic genome-wide scan identifies novel Alzheimer's disease loci. *Alzheimers Dement*. 2017;13(7):727-738.
 20. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet [Internet]*. 2022;54(4):412-436. <https://www.nature.com/articles/s41588-022-01024-z>
 21. Kunkle BW, Schmidt M, Klein HU, et al. Novel Alzheimer disease risk loci and pathways in African American individuals using the African genome resources panel: a meta-analysis. *JAMA Neurol*. 2021;78(1):102-113.
 22. O'Bryant SE, Zhang F, Petersen M, et al. Neurodegeneration from the AT(N) framework is different among Mexican Americans compared to Non-Hispanic Whites: a Health & Aging Brain among Latino Elders (HABLE) study. *Alzheimers Dement*. 2022;14(1):e12267. <https://onlinelibrary.wiley.com/doi/10.1002/dad2.12267>
 23. O'Bryant S, Petersen M, Hall J, et al. Characterizing plasma NFL in a community-dwelling multi-ethnic cohort: results from the HABLE study. *Alzheimers Dement*. 2022;18(2):240-250.
 24. O'Bryant SE, Zhang F, Petersen M, et al. Proteomic profiles of neurodegeneration among Mexican Americans and Non-Hispanic Whites in the HABS-HD study. *J Alzheimers Dis*. 2022;86(3):1243-1254.
 25. O'Bryant SE, Zhang F, Petersen M, et al. A blood screening tool for detecting mild cognitive impairment and Alzheimer's disease among community-dwelling Mexican Americans and Non-Hispanic Whites: a method for increasing representation of diverse populations in clinical research. *Alzheimers Dement*. 2021;18(1):77-87.
 26. Hall JR, Johnson LA, Zhang F, et al. Using fractional anisotropy imaging to detect mild cognitive impairment and Alzheimer's disease among Mexican Americans and Non-Hispanic Whites: a HABLE study. *Dement Geriatr Cogn Disord*. 2021;50(3):266-273.
 27. O'bryant SE, Johnson LA, Barber RC, et al. The Health & Aging Brain among Latino Elders (HABLE) study methods and participant characteristics. *Alzheimers Dement*. 2021;13(1):e12202.
 28. Pathak GA, Silzer TK, Sun J, et al. Genome-Wide methylation of mild cognitive impairment in Mexican Americans highlights genes involved in synaptic transport, Alzheimer's disease-precursor phenotypes, and metabolic morbidities. *J Alzheimers Dis*. 2019;72(3):733-749.
 29. Anderson CA, Pettersson FH, Clarke GM, Cardon LR, Morris AP, Zondervan KT. Data quality control in genetic case-control association studies. *Nat Protoc*. 2010;5(9):1564-1573.
 30. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience*. 2015;4(1):7.
 31. Alexander DH, Lange K. Enhancements to the ADMIXTURE algorithm for individual ancestry estimation. *BMC Bioinf*. 2011;12:246.
 32. Alexander DH, Novembre J, Lange K. Fast model-based estimation of ancestry in unrelated individuals. *Genome Res*. 2009;19(9):1655-1664.
 33. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen W-M. Robust relationship inference in genome-wide association studies. *Bioinformatics*. 2010;26(22):2867-2873.
 34. Atkinson EG, Maihofer AX, Kanai M, et al. Tractor uses local ancestry to enable the inclusion of admixed individuals in GWAS and to boost power. *Nat Genet*. 2021;53(2):195-204.
 35. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics*. 2005;21(2):263-265.
 36. Graham SE, Clarke SL, Wu KHH, et al. The power of genetic diversity in genome-wide association studies of lipids. *Nature*. 2021;600(7890):675-679.
 37. Khullar S, Wang D. Predicting gene regulatory networks from multi-omics to link genetic risk variants and neuroimmunology to Alzheimer's disease phenotypes. *Biorxiv [Preprint]*. 2021;20:2021.06.21.449165. PMID: 34189529; PMCID: PMC8240682. doi:10.1101/2021.06.21.449165
 38. Vespa J, Medina L, Armstrong DM. Demographic Turning Points for the United States: Population Projections for 2020 to 2060 Population Estimates and Projections Current Population Reports [Internet]. 2018. www.census.gov/programs-surveys/popproj
 39. Basavarajappa BS, Subbanna S. Histone methylation regulation in neurodegenerative disorders. *Int J Mol Sci*. 2021;22(9):4654.
 40. Horvath H, Horvath S. DNA methylation age of human tissues and cell types [Internet]. *Genome Biol*. 2013;14:R115. <http://genomebiology.com/14/10/R115>
 41. Salameh Y, Bejaoui Y, el Hajj N. DNA methylation biomarkers in aging and age-related diseases. *Front Genet*. 2020;11:171.
 42. Walker RM, Bermingham ML, Vaheer K, et al. Epigenome-wide analyses identify DNA methylation signatures of dementia risk. *Alzheimers Dement*. 2020;12(1):e12078.
 43. Dumitrescu L, Mahoney ER, Mukherjee S, et al. Genetic variants and functional pathways associated with resilience to Alzheimer's disease. *Brain*. 2020;143(8):2561-2575.
 44. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet*. 2019;51(3):404-413.
 45. Heath L, Earls JC, Magis AT, et al. Manifestations of Alzheimer's disease genetic risk in the blood are evident in a multiomic analysis in healthy adults aged 18 to 90. *Sci Rep*. 2022;12(1):6117.
 46. Gan C-L, Zhang T, Lee TH. The genetics of Alzheimer's disease in the Chinese population. *Int J Mol Sci*. 2020;21(7):2381.
 47. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-related imaging abnormalities in 2 Phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. *JAMA Neurol*. 2022;79(1):13.
 48. Woloshin S, Kesselheim AS. What to know about the Alzheimer drug aducanumab (aduhelm). *JAMA Intern Med*. 2022;182(8):892.
 49. Mahase E. Aducanumab: 4 in 10 high dose trial participants experienced brain swelling or bleeding. *Br Med J*. 2021;375:n2975.
 50. Barakos J, Purcell D, Suhy J, et al. Detection and management of amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with anti-amyloid beta therapy. *J Prev Alzheimers Dis*. 2022;9(2):211-220.
 51. Padala SP, Yarns BC. Under-represented populations left out of Alzheimer's disease treatment with aducanumab: commentary on ethics. *J Alzheimers Dis Rep*. 2022;6(1):345-348.
 52. Zec RF, Burkett NR. Non-pharmacological and pharmacological treatment of the cognitive and behavioral symptoms of Alzheimer disease. *NeuroRehabilitation*. 2008;23:425-438.
 53. O'Bryant SE, Petersen M, Hall J, Johnson L. APOEε4 genotype is related to brain amyloid among Mexican Americans in the HABS-HD study. *Front Neurol*. 2022;13:834685.

54. Silzer T, Barber R, Sun J, et al. Circulating mitochondrial DNA: new indices of type 2 diabetes-related cognitive impairment in Mexican Americans. *PLoS One*. 2019;14(3):e0213527.
55. King KS, Vintimilla RM, Braskie MN, et al. Vascular risk profile and white matter hyperintensity volume among Mexican Americans and Non-Hispanic Whites: the HABLE study. *Alzheimers Dement*. 2022;14(1):e12263. <https://onlinelibrary.wiley.com/doi/10.1002/dad2.12263>
56. Logue MW, Schu M, Vardarajan BN, et al. A comprehensive genetic association study of Alzheimer disease in African Americans [Internet]. *Arch Neurol*. 2011;68:1569-1579. <https://jamanetwork.com/>
57. Liu J, Zhao W, Ware EB, Turner ST, Mosley TH, Smith JA. DNA methylation in the APOE genomic region is associated with cognitive function in African Americans. *BMC Med Genomics*. 2018;11(1):43.
58. Tajuddin SM, Hernandez DG, Chen BH, et al. Novel age-associated DNA methylation changes and epigenetic age acceleration in middle-aged African Americans and whites. *Clin Epigenetics*. 2019;11(1):119.
59. Soto I, Graham LC, Richter HJ, et al. APOE stabilization by exercise prevents aging neurovascular dysfunction and complement induction. *PLoS Biol*. 2015;13(10):1-33.
60. Montagne A, Nation DA, Sagare AP, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature*. 2020;581(7806):71-76.
61. Bell RD, Winkler EA, Singh I, et al. Apolipoprotein e controls cerebrovascular integrity via cyclophilin A. *Nature*. 2012;485(7399):512-516.
62. Villegas-Llerena C, Phillips A, Reitboeck PG, Hardy J, Pocock JM. Microglial genes regulating neuroinflammation in the progression of Alzheimer's disease. *Curr Opin Neurobiol*. 2016;36:74-81.
63. Schwabe T, Srinivasan K, Rhinn H. Shifting paradigms: the central role of microglia in Alzheimer's disease. *Neurobiol Dis*. 2020;143:104962.
64. Agarwal M, Khan S. Plasma lipids as biomarkers for Alzheimer's disease: a systematic review. *Cureus*. 2020;12(12):e12008.
65. Hampel H, Caraci F, Cuello AC, et al. A path toward precision medicine for neuroinflammatory mechanisms in Alzheimer's disease. *Front Immunol*. 2020;11:456.
66. McQuade A, Blurton-Jones M. Microglia in Alzheimer's disease: exploring how genetics and phenotype influence risk. *J Mol Biol*. 2019;431:1805-1817.
67. Thornton RLJ, Glover CM, Cené CW, Glik DC, Henderson JA, Williams DR. Evaluating strategies for reducing health disparities by addressing the social determinants of health. *Health Aff*. 2016;35(8):1416-1423.
68. Aranda MP, Kremer IN, Hinton L, et al. Impact of dementia: health disparities, population trends, care interventions, and economic costs. *J Am Geriatr Soc*. 2021;69(7):1774-1783.
69. Barnett JH, Lewis L, Blackwell AD, Taylor M. Early intervention in Alzheimer's disease: a health economic study of the effects of diagnostic timing. *BMC Neurol*. 2014;14:101.
70. Cannon JS, Kilburn MR, Karoly LA, Mattox T, Muchow AN, Buenaventura M. Investing early: taking stock of outcomes and economic returns from early childhood programs. *Rand Health Q*. 2018;7(4):6.

SUPPORTING INFORMATION

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

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