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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

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Abstract

Introduction: The APOEε4 allele is the single strongest genetic risk for late-onset Alzheimer's disease (AD). Prior work demonstrates that not only the APOEε4 allele varies by race/ethnicity but also the risk for AD and cognitive impairment conveyed by the APOEε4 allele varies by the

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Author Contributions

S.E.O., L.A.J., A.W.T., K.Y., and R.A.R. = conceptualization and design of study; acquisition, analysis, and interpretation of data; drafting and revising manuscript; final approval of version to be published; and agreement to be accountable for the accuracy and integrity of the work. R.C.B., N.P., J.R.H., and M.P. = design of study; acquisition and interpretation of data; drafting and revising manuscript; final approval of version to be published; and agreement to be accountable for the accuracy and integrity of the work. K.S. = acquisition of data; drafting and revising manuscript; and agreement to be accountable for the accuracy and integrity of the work.

Statement of Ethics

This study protocol was reviewed and approved by the UNTHSC IRB protocols UNTHSC 2016–128 and 2020–125. Each participant (or his/her legal representative) signed written informed consent to participate in the study.

Conflict of Interest Statement

SEO has multiple patents on precision medicine for neurodegenerative diseases and is the founding scientist of Cx Precision Medicine. No other authors reported any potential conflicts of interest.

racial/ethnic group as well as genetic ancestry. Here, we sought to examine the link between the APOEε4 and neuropsychological functioning among Mexican Americans (MAs).

Methods: Data were examined from 1,633 (852 MAs and 781 non-Hispanic Whites [NHWs]) participants of the Health & Aging Brain Study – Health Disparities (HABS-HD) and were enrolled with all requisite data to be included into the current analyses.

Results: The frequency of both ε4 and ε2 alleles was significantly lower among MAs as compared to NHWs. Among MAs, APOEε4 allele presence was associated specifically with poorer immediate and delayed memory (Wechsler Memory Scale – Third Edition [WMS-III] Logical Memory and Spanish-English Verbal Learning Test [SEVLT]). Among NHWs, APOEε4 allele presence was associated with poorer immediate and delayed memory as well as worse executive functioning (Trials B) and verbal fluency (Animal naming).

Discussion/Conclusion: The APOEε4 allele was associated with poorer cognition across multiple domains among NHWs; however, allele presence was specifically associated with poorer memory performance among MAs. When combined with prior work, the current findings demonstrate that the risk factors associated with cognitive dysfunction differ among MAs as compared to NHWs and require additional investigation.

Keywords

Alzheimer's disease; Mexican American; APOE4; Cognition; Health disparities

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative cause of dementia, which disproportionately impacts African Americans and Hispanics [1]. Despite the fact that Hispanics (65% of which are Mexican American [MA] [2]) will experience the greatest increase in AD and AD-related dementias by 2060 [1], this group remains underrepresented in AD research [3]. For example, 83% of the current participants in the National Institute of Aging (NIA) Alzheimer's Disease Centers database [4] and 90% of the Alzheimer's Disease Neuroimaging Initiative database are non-Hispanic White (NHW) [5]. However, our team has shown that MAs experience cognitive loss at significantly younger ages than NHWs and are often diagnosed at more advance stages of AD [6, 7]. To date, the underlying factors contributing to these health disparities remains limited. If effective, novel treatments are to be developed for AD among diverse populations, and this gap must be understood.

The APOEε4 allele is the single strongest genetic risk factor for late-onset AD. Corbo and Schacchi demonstrated in 1999 that APOEε4 frequencies vary substantially across the globe [8]. In our prior work, we have shown that the frequency of the APOEε4 allele is lower among MAs as compared to NHWs [9, 10]. This finding was independently reported by Campos et al. [11]. Gonzalez et al. [12] subsequently demonstrated that APOEε4 frequency was lower among MAs as compared to Dominicans, Central Americans, Cubans, and Puerto Ricans in the SOL/INCA study. However, fewer studies have explicitly examined the link between APOEε4 and neuropsychological functioning among Hispanic populations. In the HCHS/SOL study, the effect of APOEε4 allele on cognitive decline varied across six Latino backgrounds [13]. When examining the link between APOEε4 allele and cognitive test

performance among older Hispanics residing in New Mexico, Romero and colleagues found no cross-sectional association; however, APOEε4 carriers demonstrated increased time on color Trails A and decreased total recall on the Fuld Object-Memory test over a 3-year period [14]. Here, we examined the link between APOEε4 allele presence and baseline neuropsychological test scores among MAs and NHWs of the community-based, multiethnic Health & Aging Brain Study – Health Disparities (HABS-HD) cohort [6, 15–17].

Methods

Participants and Assessment

The HABS-HD (formally the Health & Aging Brain study among Latino Elders, HABLE study) study is an ongoing, longitudinal, community-based project examining health disparities in mild cognitive impairment (MCI) and AD among Hispanic, MAs as compared to NHWs [6, 15–17] with recent expansion to enroll African Americans. HABS-HD methods have been published elsewhere [6] and are briefly outlined below. The data included in this study encompass MA and NHW participants since the recruitment of the African-American participants is ongoing. Inclusion criteria for the study includes (1) self-reported race/ethnicity of African-American, MA, or NHW, (2) willingness to provide blood samples, (3) capable of undergoing neuroimaging studies, (4) age of 50 years and above, and (5) fluent in English or Spanish. Exclusion criteria includes (1) type 1 diabetes, (2) the presence of active infection, (3) current/recent (12 month) cancer (other than skin cancer), (4) current severe mental illness that could impact cognition (other than depression), (5) recent (12 months) traumatic brain injury with loss of consciousness, (6) current/recent alcohol/substance abuse, (7) active severe medical condition that could impact cognition (e.g., end-stage renal failure, chronic heart failure, and chronic obstructive pulmonary disease), and (8) current diagnosis of dementia other than AD.

Participant recruitment for HABS-HD includes a community-based participatory research approach [18]. The community-based participatory research approach has been used successful as a recruitment modality for reaching underserved and minority populations. It involves collaborating with local communities through outreach (holding community events and seminars), word of mouth, marketing modalities (newspaper, television, and radio), and providing back information (clinical lab work, MRI clinical reads, and neuropsychological test results) to the participants and their health care providers. The HABS-HD protocol includes an interview, functional exam, blood draw for clinical labs and biobanking, neuropsychological testing, and 3T MRI of the brain. Amyloid and tau PET scans are ongoing for the full cohort. All aspects of the study protocol can be conducted in Spanish or English. The data are available to the scientific community through the UNTHSC Institute for Translational Research (ITR) website [19].

Interview and Neuropsychological Assessment

The HABS-HD protocol, includes a clinical interview and neuropsychological testing with the following battery: Mini-Mental State Exam (MMSE) [20], Wechsler Memory Scale – Third Edition (WMS-III) Digit Span (DS) and Logical Memory [21], Digit Symbol Substitution, Trail Making Test Parts A and B [22], Spanish-English Verbal Learning

Test (SEVLT) [23], Animal Naming (semantic fluency) [23], FAS (phonemic fluency) [24] as well as the American National Adult Reading Test (English speakers) [25] and Word Accentuation Test (Spanish speakers) [26]. An informant interview by clinicians with expertise in dementia to evaluate for functional declines conducted for completion of the Clinical Dementia Rating (CDR) Scale [27].

APOE genotyping was performed using commercially available TaqMan Genotyping Kits for rs429158 and rs7412 using the TaqMan GTXpress Master Mix (Thermo Fisher). Target amplification and detection was performed using the 7500 Real-Time PCR System (Applied Biosystems). Genotypes were called according to combined of allele amplification results at the two SNPs as follows (rs429358 and rs7412): ε2/ε2: T,T; ε2/ε3: T,CT; ε2/ε4: CT,CT; ε3/ε3: T/C; ε3/ε4: CT,C; and ε4/ε4: C,C. Positive controls (individuals of known, independently typed APOE genotypes) and negative controls were included on all runs. APOE genotypes frequencies were confirmed to be in the Hardy-Weinberg equilibrium.

Diagnostic Classification

Cognitive diagnoses were assigned algorithmically (decision tree) and verified at consensus review as follows: normal control = no cognitive complaints, CDR sum of boxes score of 0, and cognitive tests scores broadly within normal limits (i.e., performance greater than that defined as meeting diagnostic criteria for MCI [i.e., ≤1.5 standard deviations below the normative range]); MCI: cognitive complaint (self or other), CDR sum of boxes score between 0.5 and 2.0, and at least one cognitive test score falling ≤1.5 standard deviation below normative ranges; dementia: CDR sum of boxes score ≥2.5 and at least 2 cognitive test scores 2 standard deviation below normative ranges.

Statistical Analyses

Statistical Analyses were conducted in SPSS 25 (IBM). Linear regression models were run with age, education, gender, and APOEε4 (presence vs. absence) as predictor variables and raw neuropsychological test scores as the outcome variable. Analyses were conducted using the entire cohort and then split by ethnicity. Statistical significance was set at $p < 0.05$.

Results

As of November 2021, a total of 1,633 participants were enrolled with all requisite data to be included into the current analyses (852 MAs and 781 NHWs). The MA group was significantly younger ($p < 0.001$) and obtained fewer years of formal education ($p < 0.001$) than NHWs. There was also a significant gender difference between groups with a higher number of females included among those who self-reported as MA ($p < 0.001$). In regard to neuropsychological test performance, mean differences were found between ethnic groups with MAs performing lower across all cognitive domains ($p < 0.001$) (see Table 1).

APOE allele frequency groups are presented in Table 2. In the full cohort, ε2 allele frequency was 11.1%, whereas ε4 frequency was 24.1%. However, MAs had lower frequency of both ε2 ($\chi^2 = 28.41$, $p < 0.001$) and ε4 ($\chi^2 = 31.59$, $p < 0.001$) alleles when compared to NHWs. ε2 allele frequency was 6.6% among MAs as compared to 15.9% among NHWs, and ε4 frequency was 18.4% among MAs as compared to 30.3% among

NHWs. Additional breakdown was as follows: ε2/ε2 MA 0.1% versus NHW 0.3%; ε2/ε3 MA 5.7% versus NHW 13.2%; ε2/ε4 MA 0.8% versus NHW 2.4%; ε3/ε4 MA 15.9% versus NHW 25.7%; and ε4/ε4 MA 1.6% versus NHW 2.2%.

In the full cohort, APOEε4 allele presence was associated with significantly poorer neuropsychological test performance in the domains of immediate memory (WMS-III Logical Memory I (LM1), $t = -3.29$, $p < 0.001$; SEVLT Trials 1–5 Total, $t = -3.38$, $p < 0.001$), delayed memory (WMS-III Logical Memory II (LM2), $t = -3.73$, $p < 0.001$; SEVLT 30 min delayed recall, $t = -3.49$, $p < 0.001$), and verbal fluency (Animal Naming, $t = -2.18$, $p = 0.03$) (see Table 3).

Among MAs, APOEε4 presence was significantly associated only with immediate (WMS-III LM1, $t = -3.44$, $p < 0.001$; SEVLT Trials 1–5, $t = -2.29$, $p = 0.004$) and delayed memory (WMS-III LM2, $t = -2.91$, $p = 0.004$; SEVLT delayed recall $t = -2.40$, $p = 0.02$). Among NHWs, APOEε4 allele presence was significantly associated with immediate (WMS-III LM1, $t = -2.63$, $p = 0.009$; SEVLT Trials 1–5, $t = -3.34$, $p < 0.001$) and delayed memory (WMS-III LM2, $t = -3.34$, $p < 0.001$; SEVLT delayed recall, $t = -3.19$, $p = 0.001$), executive functioning (Trails B, $t = 3.07$, $p = 0.002$; WMS-III DS, $t = -2.06$, $p = 0.04$ and trend toward significance on Trails A, $t = 1.76$, $p = 0.08$), and language (Animal Naming, $t = -2.41$, $p = 0.02$) (see Table 3).

Discussion

The current findings demonstrate that not only is the APOEε4 allele frequency lower among MAs but also the link between the APOEε4 allele and neuropsychological test performance also varies. Specifically, APOEε4 presence is associated with poorer immediate and delayed memory among MAs only; however, among NHWs, APOEε4 allele presence is associated with poorer immediate and delayed memory as well as poorer executive functioning and language scores.

Prior work has shown that the impact conveyed on risk for AD by APOEε4 allele presence varies by the racial/ethnic group. In a study of 1,079 Medicare recipients, Tang et al. [28] found that (1) the APOEε4 frequency was lower among AAs and Hispanics as compared to NHWs and (2) APOEε4 was a risk factor for AD only among NHWs. Farrer et al. [29] conducted a meta-analysis and found APOEε4 increased risk for AD among NHWs, but the association was lower among both Hispanics and AAs. Morris et al. [30] found that presence of APOEε4 was associated with lower levels of CSF t-tau and $ptau_{181}$ among AAs; however, AAs without APOEε4 did not demonstrate differences in these markers from NHWs. Rajabli et al. [31] found that APOEε4 presence conveyed lower risk for AD among African genetic background as compared to European ancestral background regardless of the population. More recently, Griswold et al. [32] found individuals with European local ancestry expressed significantly higher brain APOE levels than those with African local genomic ancestry.

Few studies however have explicitly examined the link between APOEε4 allele frequency and detailed neuropsychological functioning among Hispanic populations. Romero and

colleagues examined the link between the APOEε4 allele and cognitive test performance at baseline and after the 3-year follow-up among 105 community-dwelling Hispanic adults aged 60 years and older residing in New Mexico [14]. In that study, there was no cross-sectional link between APOEε4 allele and cognitive test scores; however, after the 3-year follow-up, the APOEε4 allele was associated with increased time to complete color Trails A (i.e., poorer performance) as well as decreased total recall on the Fuld Object Memory test. In the Study of Latinos (HCHS/SOL), Granot-Hershkovitz et al. [13] examined data among 4,183 participants stratified by Latino background. In this study, APOEε4 allele presence was associated with significant cognitive decline, which was strongest among Cubans, whereas the APOEε2 allele was associated with reduced risk for MCI among Puerto Ricans. Amerindian genetic ancestry was found to protect from risk conferred by APOEε4 on significant cognitive decline [13]. Therefore, the current findings expand on the extant literature, demonstrating a memory-specific cross-sectional impact of the APOEε4 allele among MAs.

There are limitations to the current study. First, the current study reflects cross-sectional analyses; however, longitudinal assessments in the HABS-HD study are ongoing, and future work will examine the impact of APOEε4 on neuropsychological test performance over time. Second, genetic ancestry is not considered in the current analyses; however, GWAS was recently completed in this cohort, and therefore, future work will determine the impact of Amerindian and European ancestry on the impact of the APOEε4 allele on neuropsychological test performance. Prior work has shown a protective effect of the APOEε2 allele; however, this allele is also of lower frequency among MAs. Ongoing work is specifically examining if the APOEε2 allele conveys a protective effect in this cohort. Finally, the current study only examines data from MAs and NHWs; however, HABS-HD is currently enrolling 1,000 African Americans, and future work will examine this work across the three largest racial/ethnic groups in the USA. Future work will also examine the impact of APOEε4 on amyloid, tau, and neurodegeneration neuroimaging markers across all three racial/ethnic groups. Overall, the current findings extend upon the existing literature by documenting a memory-specific impact of APOEε4 among MAs.

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Data Availability Statement

The data are available to the scientific community through the UNTHSC ITR website [19].

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Table 1.

Descriptive statistics of cohort

	Total cohort (*N* = 1,614)	**MA (*N* = 853)**	**NHW (*N* = 781)**
Age, mean (SD), years	66.47 (8.76)	63.83 (7.98)	69.35 (8.65)**
Range	50–92	50–91	50–92
Education, mean (SD)	12.37 (4.81)	9.51 (4.61)	15.50 (2.55)**
Range	0–20	0–20	0–20
Gender, % female	61	66	54**
WMS-III DS, mean (SD)	13.69 (4.31)	11.43 (1.97)	16.15 (3.67)**
Range	0–29	0–25	6–29
Trail Making Test Part A, mean (SD)	43.96 (25.39)	50.79 (29.22)	36.53 (17.65)**
Range	15.00–150.00	16.00–150.00	15.00–150.00
Trail Making Test Part B, mean (SD)	128.59 (85.43)	161.17 (93.45)	93.77 (58.53)**
Range	25.00–300.00	25.00–300.00	25.00–300.00
FAS, mean (SD)	31.84 (12.25)	27.10 (10.99)	37.00 (11.45)**
Range	0–68	0–65	2–68
Animals, mean (SD)	17.48 (5.17)	16.27 (4.79)	18.81 (5.24)**
Range	0–37	0–33	0–37
WMS-III LM1, mean (SD)	35.23 (12.02)	30.74 (10.65)	40.11 (11.52)**
Range	0–69	0–58	0–69
WMS-III LM2, mean (SD)	21.29 (8.99)	18.48 (8.10)	24.33 (8.92)**
Range	0–44	0–41	0–44
SEVLT 1–5 total, mean (SD)	30.74 (9.08)	28.91 (8.32)	32.73 (9.44)**
Range	0–53	0–53	3–53
SEVLT delayed recall, mean (SD)	7.61 (3.46)	6.96 (3.30)	8.30 (3.48)**
Range	0–15	0–15	0–15

WMS, Wechsler Memory Scale; SEVLT, Spanish-English Verbal Learning Test. * $p < 0.05$.

** $p < 0.001$.

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Table 2.

APOE allele frequency by the ethnic group

	Genotype frequencies, %					
	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4
Total cohort	0.2	9.3	1.6	66.4	20.6	1.9
MA	0.1	5.7	0.8	75.7	15.9	1.6
NHW	0.3	13.2	2.4	56.3	25.7	2.2

Table 3.

Regression model of impact of APOEε4 allele presence on neuropsychological test scores (age, gender, and education as covariates)

	Total cohort	MA	NHW
WMS-III LM1	$t = -3.29$, $p < 0.001$	$t = -3.44$, $p < 0.001$	$t = -2.63$, $p = 0.009$
WMS-III LM2	$t = -3.73$, $p < 0.001$	$t = -2.91$, $p = 0.004$	$t = -3.34$, $p < 0.001$
SEVLT 1–5	$t = -3.38$, $p < 0.001$	$t = -2.29$, $p = 0.02$	$t = -3.20$, $p = 0.001$
SEVLT Delayed	$t = -3.49$, $p < 0.001$	$t = -2.40$, $p = 0.02$	$t = -3.19$, $p = 0.001$
Trials A	$t = 1.65$, $p = 0.10$	$t = 1.15$, $p > 0.05$	$t = 1.76$, $p = 0.08$
Trails B	$t = 1.53$, $p > 0.05$	$t = 0.40$, $p > 0.05$	$t = 3.07$, $p = 0.002$
WMS-III DS	t = −0.57, $p > 0.05$	$t = -0.52$, $p > 0.05$	$t = -2.06$, $p = 0.04$
FAS	$t = -0.16$, $p > 0.05$	$t = -0.64$, $p > 0.05$	$t = -0.38$, $p > 0.05$
Animals	$t = -2.18$, $p = 0.03$	$t = -0.95$, $p > 0.05$	$t = -2.41$, $p = 0.02$

WMS-III LM1, Wechsler Memory Scale 3rd Edition Logical Memory I (immediate memory); WMW-III LM2, Wechsler Memory Scale 3rd Edition Logical Memory II (delayed recall); SEVLT, Spanish-English Verbal Learning Test; DS, Digit Span.