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An Exploratory Study of APOE-ε4 Genotype and Risk of Alzheimer's Disease in Mexican Hispanics

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To the Editor:

Hispanics are 1.5 times more likely to develop Alzheimer's disease (AD) than White non-Hispanics[1]. A community-based study reported that the prevalence of AD is higher in Hispanics than in White non-Hispanics[2]. Interestingly, a recent study found that the average proportion of Amerindian genetic ancestry in AD cases was a third of that observed in the cognitively intact controls[3]. These findings suggest that Amerindian ancestry confers a protective effect against disease onset. Hispanics are a mixture of European, African, and Amerindian genomes, with percentages depending on the country of origin[4]. Individuals of Mexican origin generally are of Amerindian ancestry, while those of Caribbean origin, for example, have more African ancestry[5,6]. Therefore, the question arises as to whether Mexican Hispanics differ in their susceptibility to AD.

The Apolipoprotein E (APOE) gene, with its three common alleles (ε2, ε3, ε4), is involved in cholesterol transport and other biologic pathways potentially relevant to AD[7] and has been consistently associated with an increased risk of AD[8]. Studies indicate that the APOE genetic risk variants may not carry the same risk for Hispanics as for White non-Hispanics. A meta-analysis found an association between the APOE-ε4 allele and AD, although the risk conveyed by the APOE-ε4 allele frequency was found to be lower in Hispanics, predominately Caribbean origin, than in White non-Hispanics[9]. Another study of Hispanic Americans of predominantly Caribbean origin showed a smaller relative risk of AD conveyed by the APOE-ε4 allele in Hispanics than in White non-Hispanics[10]. To our

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Author Contributions:
Melissa Campos made substantial contributions to 1) the conception and design of the study and the analysis and interpretation of data; 2) the drafting of the article and its critical revision for important intellectual content; and 3) final approval of the version to be published. Dr. Edland made substantial contributions to 1) the conception and design of the study and the analysis and interpretation of data; 2) the drafting of the article and its critical revision for important intellectual content; and 3) final approval of the version to be published.
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knowledge, Mexican Hispanics have not been studied as a single group to determine the associated risk between the APOE-ε4 allele and AD onset.

METHODS

Self-identified Hispanic and White non-Hispanic volunteers were recruited for participation in the University of California, San Diego (UCSD) Shiley-Marcos Alzheimer Disease Research Center. Diagnoses was determined by two senior staff neurologists using standardized criteria. Cases had a diagnosis of probable or possible AD, while controls were diagnosed as cognitively normal. The UCSD Internal Review Board approved all procedures in this study.

An investigator, otherwise blinded to clinical and genotype data (M.C.), identified cases and controls in each ethno-racial group, and frequency matched them on age and education. APOE genotype was determined from peripheral blood per lab routine.

SPSS for Macintosh (PASW Statistics, Rel 16.0, Chicago: IBM Corporation) was used for statistical analyses. Logistic regression analyses controlling for the matching variables of age and education and including sex as a covariate were used to examine the odds ratio (OR) reflecting the likelihood of AD as a function of the presence of at least one APOE-ε4 allele for each ethno-racial group.

RESULTS

APOE-ε4 allele frequencies were greater in cases than controls for both ethno-racial groups. In addition, the APOE-ε4 allele frequency was lower in Mexican Hispanic cases (21.4%) compared to White non-Hispanics (42.9%). The ε4 allele frequency was highest in White non-Hispanic cases (42.9%).

In logistic regression analyses adjusting for age, education, and sex, there was no significant association within Mexican Hispanics (OR=2.04; confidence interval (CI) 0.59, 7.10; p=0.26), while APOE-ε4 was strongly associated with AD in White non-Hispanics (OR=3.77; CI 1.23, 11.57; p=0.02).

DISCUSSION

Mexican Hispanics are both less likely to carry an APOE-ε4 allele and have less of a risk for AD due to the ε4 allele than White non-Hispanics. These findings are consistent with Farrer et al., which reported similar APOE-ε4 allele frequencies between Hispanics and Caucasians, and moreover, found a significant association between APOE genotype and AD for Caucasians but not Hispanics[9]. The finding that the APOE-ε4 allele, one of the most important known risk factors for AD, is both less common among Hispanics and confers less risk is somewhat surprising given the general impression that AD risk is higher in Hispanics compared to White non-Hispanics[2].

A limitation of studies to date is their small sample size. This may have contributed to the lack of significance in the relationship between APOE and risk of AD in our study and other published studies involving Hispanic populations[9]. Further investigations with a larger sample size are warranted in order to elucidate the level of risk for AD associated with the APOE-ε4 allele in Hispanics. Understanding the source of this reduced risk may provide clues into how APOE genetic variants affect AD and may be a fruitful area for future investigation.

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Table 1

Apolipoprotein E (APOE) genotype and allele frequencies (%), odds ratios, and confidence intervals (CI) for cases and controls within Mexican Hispanic and White non-Hispanic groups.

	Mexican Hispanic		White Non-Hispanic	
APOE	**Cases (n=28)**	**Controls (n=28)**	**Cases (n=28)**	**Controls (n=28)**
Genotype Frequency				
ε2/ε3	3.6	10.7	7.1	7.1
ε2/ε4	3.6	0.0	7.1	0.0
ε3/ε3	60.7	64.3	25.0	57.1
ε3/ε4	25.0	25.0	42.9	32.1
ε4/ε4	7.1	0.0	17.9	3.6
Allele Frequency				
ε2	3.6	5.4	7.1	3.6
ε3	75.0	82.1	50.0	76.8
ε4	21.4	12.5	42.9	19.6
Odds Ratio[a]	2.04		3.77	
95% CI	0.59, 7.10		1.23, 11.57	

[a] Odds Ratio for subjects with at least one APOE-ε 4 allele.