Association Between Apolipoprotein E Genotype and Alzheimer Disease in African American Subjects

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Background: The association between Alzheimer disease (AD) and genotypes at the apolipoprotein E (*APOE*) locus has been confirmed in numerous populations worldwide, but appears to be inconsistent in African American subjects.

Objective: To investigate the association between *APOE* genotypes and AD in elderly African American subjects.

Design: Clinic-based, multicenter case-control study and a family study.

Participants: A total of 338 African American probands meeting criteria for probable or definite AD, 301 cognitively healthy, elderly unrelated control subjects (spouses and community volunteers), and 108 siblings of 88 AD probands.

Main Outcome Measures: Odds of AD according to *APOE* genotype.

Results: Compared with individuals with the *APOE* ε3/ε3 genotype, the odds of having AD were signifi-

cantly increased among those with 1 or more copies of the ε4 allele; the odds ratio (OR) for the ε3/ε4 genotype was 2.6 (95% confidence interval [CI], 1.8-3.7), and the OR for the ε4/ε4 genotype was 10.5 (95% CI, 5.1-21.8). These risks decreased substantially after 68 years of age. The risk for AD was lower among individuals with the ε2/ε3 genotype (OR, 0.41; 95% CI, 0.22-0.79). The patterns of association were similar in men and women. These results obtained from comparisons of unrelated AD patients and controls were bolstered by results of analysis of family data that showed preferential transmission of the ε4 allele to demented siblings (*P*<<.001) and of the ε2 allele to nondemented siblings (*P*=.005).

Conclusions: The presence of 1 or 2 ε4 alleles is a determinant of AD risk in African American subjects. The age-related risk for decline associated with the ε4 allele and the apparent protective effect of the ε2 allele are similar to patterns observed in white subjects.

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A GENETIC BASIS for Alzheimer disease (AD) is well established.[1] Survival analysis suggests that the risk for AD is 2 to 3 times higher among first-degree relatives of patients with AD compared with nonrelatives.[2] This trend is evident in multiple ethnic groups, including white,[3-5] Hispanic,[6] and African American[6,7] subjects. Mutations in the amyloid precursor protein and presenilin 1 and 2 genes may be responsible for as much as 50% of familial (ie, autosomal dominant) AD beginning before 60 years of age[1,8-10]; however, these defects have a low epidemiological impact, accounting for less than 1% of patients worldwide.[11]

The genetic factor with the highest attributable risk for AD is apolipoprotein E (*APOE*). The *APOE* gene on chromosome 19q has 3 codominant alleles, ε2, ε3, and

ε4, differing by single-base substitutions in the coding region of the gene. The ancestral allele, ε4, is overrepresented and ε2 is underrepresented in AD.[12-14] In a genetically diverse group of white subjects, the odds of AD for those homozygous for ε4 and for ε3/ε4 heterozygotes are 14.9 and 3.2 times, respectively, greater than the odds associated with ε3 homozygosity.[13] The mean age of onset of AD is 2 decades earlier in ε4 homozygotes,[13-15] and the increased risk associated with the ε4 allele is greater in women than in men.[13,14,16,17] The *APOE* ε4 allele has also been found to increase AD risk in nonwhite populations, including Chinese and Japanese.[18,19]

Conclusions about genetic risk for AD in African American subjects are based on a few studies of relatively small samples. Results from community-based samples in northern Manhattan, NY, and Indianapo-

SUBJECTS AND METHODS

SETTING, SUBJECTS, AND *APOE* GENOTYPE

A total of 252 African American AD patients meeting the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association[24] for definite or probable AD were seen at 12 centers in the United States and Canada participating in the MIRAGE [Multi-Institutional Research in Alzheimer Genetic Epidemiology] Study. Details of the MIRAGE study design and diagnostic protocol have been reported elsewhere.[5,25] Of these patients, 225 (89.3%) were from 3 centers in the southeastern United States, including the University of Alabama, Birmingham; the Medical University of South Carolina, Charleston; and Morehouse School of Medicine, Atlanta, Ga. One hundred eleven cognitively normal spouses and elderly unrelated individuals drawn from the same base populations as the cases were identified based on a modified Telephone Interview Cognitive Screen score of at least 27 points. We sought the results of the Telephone Interview Cognitive Screen and testing of blood samples on living siblings of the AD probands. A second set of African American subjects (86 AD patients and 190 controls) was recruited at the Mayo Clinic in Jacksonville, Fla. All patients underwent evaluation by 1 clinician (N.R.G.-R.) and met criteria for probable AD.[24] Controls were volunteers from an elderly population being followed up longitudinally by means of annual psychometric examinations. We used a standard polymerase chain reaction procedure for *APOE* genotyping.[26] Ethnicity was self-defined. All subjects were non-Hispanic. Age and sex of the patients and unrelated controls are shown in **Table 1**. At the time of analysis, 88 MIRAGE patients with AD had at least 1 sibling available for study. Characteristics of the sibships included in the *APOE* analyses are shown in **Table 2**. Informed written consent was obtained from all subjects. Patients underwent consecutive ascertainment, not on the basis of family history of AD. We performed *APOE* genotyping after the diagnosis was established.

STATISTICAL METHODS

A χ^2 test was used to compare *APOE* allele frequencies between AD patients and unrelated controls. These comparisons were repeated for subjects stratified into 3 age groups ($\leq$70, 71-80, and $\geq$81 years). To examine the variability of the *APOE*-AD association across sites, we estimated an odds ratio (OR) for AD adjusted by the data set according to the presence or absence of at least 1 $\epsilon4$ allele using Mantel-Haenszel statistics.[27] We computed the test of homogeneity of ORs of Breslow and Day[28] to assess whether data sets could be pooled.

The influence of *APOE* genotype, age, and sex on the odds of development of AD was assessed using logistic regression procedures.[29] To accommodate the polychotomous classification of *APOE* genotype in the regression analysis, 3 indicator variables were constructed representing the genotype classes $\epsilon2/\epsilon2$ or $\epsilon2/\epsilon3$, $\epsilon2/\epsilon4$ or $\epsilon3/\epsilon4$, and $\epsilon4/\epsilon4$. These variables took on the value of 1 if the subject had the corresponding genotype, and zero otherwise. According to this scheme, the $\epsilon3/\epsilon3$ genotype was considered the referent. Age of onset of AD among cases and age at last examination among controls were assigned to an age variable. Nonlinear effects of age were considered by means of an age-squared term. We evaluated interaction among *APOE*, age, and sex by deriving product terms for each genotype with age, age squared, and sex. Models were evaluated using the LOGISTIC procedure in SAS version 6.12.[30] Logistic modeling analyses were repeated within the 3 age groups using cutoffs suggested by the full model before age stratification.

Sibship data were analyzed in 2 ways. In 1 approach, the odds of AD associated with *APOE* genotypes in sibships, taking into account age and sex, were computed using a logistic model with the generalized estimating equation[31] to allow for the correlation structure among siblings. Indicator variables and interaction terms were derived as described above. Models were estimated using the GENMOD procedure in SAS.[30] Sibship data were also evaluated using the Family-Based Association Test described by Rabinowitz and Laird[32] and implemented in a computer program.[33] The Family-Based Association Test is a generalized extension of the Sibship Disequilibrium Test, a nonparametric sign test developed for use with sibling pedigree data.[34] The Sibship Disequilibrium Test examines the association between the alleles of the marker and the trait by computing weighted probabilities for a specific marker allele transmitted from the parents to affected and unaffected siblings.

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lis, Ind, suggest that the association between the $\epsilon4$ allele and AD is substantially weaker in African American than in white subjects.[20,21] Risk for AD was not associated with *APOE* genotype in a study of black Africans in Nigeria.[22] A worldwide meta-analysis of the relationship between *APOE* and AD revealed considerable heterogeneity in the pattern of association across individual data sets of African American subjects.[13] Of the 12 data sets containing African American subjects, 10 had fewer than 30 subjects, and the others had 78 and 260. Tang and colleagues[23] reported that the relative risk for AD associated with 1 or more copies of the $\epsilon4$ allele was significantly increased in white, but not in African American or Hispanic, subjects. In the absence of the $\epsilon4$ allele, however, the cumulative risk for AD to 90 years of age (adjusted for sex and education) was higher among Af-

rican American (relative risk, 4.4) than among white subjects. This latter finding is consistent with a recent study showing that lifetime risk for AD is higher in relatives of African American probands with AD than in relatives of white probands, but this increased risk is not explained entirely by the $\epsilon4$ allele.[7] In the current study, we evaluated the *APOE* genotype in a large panel of African American patients with probable AD and 2 comparison groups, ie, siblings of the patients and ethnically matched, unrelated cognitively normal control subjects using case-control and family-based association approaches.

RESULTS

The ORs for AD associated with the $\epsilon4$ allele varied from 3.1 to 8.4 across sites (Table 1). However, these differ-

mozygotes at all ages. However, the ORs, which are remarkably high in middle age (eg, 50 years of age, 80.6; 60 years of age, 29.5), are greatly diminished in later years (eg, 80 years of age, 4.0; 90 years of age, 1.4). Without age stratification, the odds of AD among subjects with the ε3/ε4 genotype are 2.6 (95% CI, 1.8-3.7). The pattern of association between age and the ε3/ε4 genotype on AD risk is parabolic; relative to the ε3/ε3 genotype, the odds of AD among subjects with the ε3/ε4 genotype is greater than 5.0 before 60 years of age, decreases to 2.3 from 70 to 80 years of age, and steadily increases thereafter. Although the best-fitting regression model suggests a parabolic relationship between age and AD risk among ε4 heterozygotes, the risk increase after 80 years of age is not significant. The *APOE* genotype associations were not different among men and women. We performed age-stratified logistic regression analysis using cutoffs at 69 and 78 years suggested by the inflection points in the curve for ε4 heterozygotes from the full model (Figure 1) to compare ORs across age groups. **Figure 2** shows that among persons younger than 69 years, ε4 heterozygosity increased odds of AD risk 7.0 times compared with ε3 homozygosity, whereas the odds are only 1.8 and 2.6 for persons 69 to 78 years and 79 years or older, respectively. The ORs for the older groups are marginally significantly higher than 1.0. Among persons 79 years and older, the 3.3-fold increased odds of AD associated with ε4 homozygosity are not significantly different from the baseline odds for ε3 homozygosity or from the odds for the ε2/ε4 and ε3/ε4 genotypes.

We also analyzed *APOE* genotype distributions in 88 sibships consisting of an AD proband and at least 1 unaffected sibling. When we assumed an additive model, results of the Family-Based Association Test analysis showed that AD siblings were significantly more likely to have the ε4 allele (P<<.001) and less likely to have the ε2 allele (P=.005) than their unaffected siblings. Other genetic models yielded similar results. A logistic regression analysis using the generalized estimating equation showed that AD was more likely to develop in siblings heterozygous or homozygous for the ε4 allele compared with siblings with the ε3/ε3 genotype (P=.008 and P<<.001, respectively). These results, similar to the findings from the case-control analysis, suggest that the ε3/ε4 and ε4/ε4 genotypes confer an increased risk for AD among African American subjects.

COMMENT

In this multicenter study of African American patients, the odds of AD were increased nearly 4-fold among those

ences were not significantly different (Breslow-Day test for homogeneity, P=.94). Therefore, we conducted subsequent analyses on the pooled data.

The *APOE* allele and genotype distributions were significantly different among patients and controls (**Table 3**), although each group is in Hardy-Weinberg equilibrium (cases, χ^2=2.0 [P=.74]; controls, χ^2=0.15 [P>.99]). The ε3/ε4 and ε4/ε4 genotypes confer increased odds of AD, whereas the ε2/ε3 genotype is protective. Stratified analysis demonstrated a progressively smaller difference in the frequency of the ε4 allele, and the ε4/ε4 genotype in particular, between patients and controls with age. In contrast, the frequency of the ε3/ε4 genotype was substantially higher among patients compared with controls in the youngest and oldest age cohorts, but this difference was much smaller among subjects aged 71 to 80 years. The protective effect of the ε2/ε3 genotype was evident in all age cohorts.

Logistic regression analysis showed that the ε2/ε3 genotype is protective (OR, 0.41; 95% confidence interval [CI], 0.22-0.79), and these odds do not vary with age (**Figure 1**). The ε4 homozygotes have significantly increased odds (OR=10.5; 95% CI, 5.1-21.8) of AD compared with ε3 ho-

Table 3. *APOE* Genotype and Allele Distributions in Patients With AD and Controls by Age*

Age Group, y	*APOE* Genotype						Significance	*APOE* Allele			Significance
	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4		ε2	ε3	ε4	
≤70											
AD cases (n = 124)	0	1 (0.8)	2 (1.6)	32 (25.8)	52 (41.9)	37 (29.8)	$\chi^2_5 = 66.0$; $P \ll .001$	3 (1.2)	117 (47.2)	128 (51.6)	$\chi^2_2 = 79.4$; $P \ll .001$
Controls (n = 132)	1 (0.8)	23 (17.4)	2 (1.5)	71 (53.8)	30 (22.7)	5 (3.8)		27 (10.2)	195 (73.9)	42 (15.9)	
71-80											
AD cases (n = 156)	0	8 (5.1)	8 (5.1)	51 (32.7)	67 (42.9)	22 (14.1)	$\chi^2_5 = 20.4$; $P = .001$	16 (5.1)	177 (56.7)	119 (38.1)	$\chi^2_2 = 19.0$; $P \ll .001$
Controls (n = 136)	1 (0.7)	14 (10.3)	6 (4.4)	66 (48.5)	45 (33.1)	4 (2.9)		22 (8.1)	191 (70.2)	59 (21.7)	
≥81											
AD cases (n = 58)	1 (1.7)	4 (6.9)	3 (5.2)	21 (36.2)	24 (41.1)	5 (8.6)	$\chi^2_5 = 13.0$; $P = .02$	9 (7.8)	70 (60.3)	37 (31.9)	$\chi^2_2 = 11.2$; $P = .003$
Controls (n = 33)	0	8 (24.2)	2 (6.1)	17 (51.5)	4 (12.1)	1 (3.0)		12 (18.2)	46 (69.7)	8 (12.1)	
Total											
AD cases (n = 338)	1 (0.3)	13 (3.8)	13 (3.8)	104 (30.8)	143 (42.3)	64 (18.9)	$\chi^2_5 = 84.7$; $P \ll .001$	28 (4.1)	364 (53.8)	284 (42.0)	$\chi^2_2 = 92.0$; $P \ll .001$
Controls (n = 301)	3 (1.0)	45 (15.0)	10 (3.3)	154 (51.2)	79 (26.2)	10 (3.3)		61 (10.1)	432 (71.8)	109 (18.1)	

*Data are given as number (percentage). Percentages have been rounded and may not sum to 100. *APOE* indicates apolipoprotein E locus; AD, Alzheimer disease.
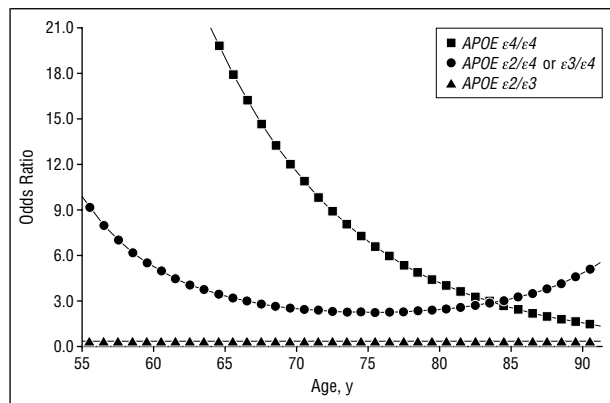

Figure 1. Relative odds of Alzheimer disease according to apolipoprotein E (*APOE*) genotype and age among unrelated African American subjects. We generated these odds from a logistic regression model for subjects with the ε2/ε2 or ε2/ε3, ε2/ε4 or ε3/ε4, and ε4/ε4 genotypes relative to the group with the ε3/ε3 genotype. Curves were derived from a model that included *APOE* dummy variables, age, age-squared term, and second-order interaction terms involving *APOE* variables and age.
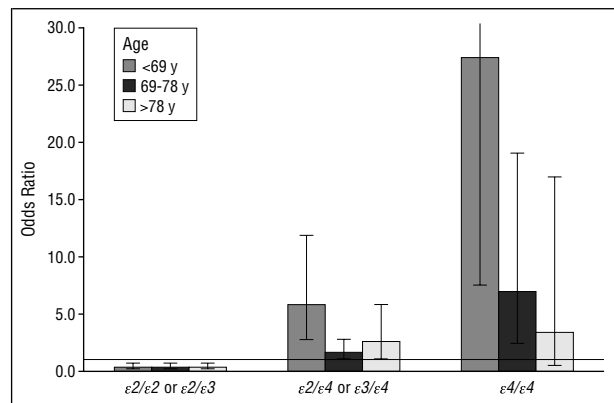

Figure 2. Relative odds of Alzheimer disease according to apolipoprotein E (*APOE*) genotype and age group among unrelated African American subjects. Within each age group, odds were generated from a logistic regression model for subjects with the ε2/ε2 or ε2/ε3, ε2/ε4 or ε3/ε4, and ε4/ε4 genotypes relative to the group with the ε3/ε3 genotype. Error bars represent 95% confidence intervals; horizontal line, odds ratio of 1.0 (referent).

having at least 1 *APOE* ε4 allele compared with subjects with the ε3/ε3 genotype. This elevated risk was present in patients with ε4 heterozygosity and homozygosity, but varied substantially and generally decreased with age. We also found that the odds of AD were 2.4 times lower among subjects with the ε2/ε3 genotype, again compared with those with the ε3/ε3 genotype. The patterns of association were similar in men and women. These results obtained from comparisons of samples of unrelated AD patients and controls were bolstered from analysis of family data showing preferential transmission of the ε4 allele to demented siblings and of the ε2 allele to nondemented siblings.

Previous studies of the *APOE* association in community-based samples of African American subjects re-ported a significant but much weaker effect of ε4 homozygosity on AD risk.[20,21] There was no apparent association with the ε3/ε4 genotype in either of these investigations. In contrast, the ε2/ε3 genotype is more frequent and the ε3/ε4 genotype is less frequent among patients in the Indianapolis study compared with the patients in our sample (**Table 4**). Aside from these 2 published studies, African American subjects have not been a focus of other investigations of the *APOE*-AD association. A meta-analysis[13] evaluated the primary data contributed by 40 research teams, including those of Tang and colleagues[21] and a subset of the Indianapolis cohort,[35] as well as 2 other community-based samples,[36,37] and 1 clinic-based series[12] consisting of 20 to 30 African American subjects each. The odds of carrying at least 1 ε4 allele

Table 4. _APOE_ Genotype and Allele Distributions in Patients With AD and Controls in Studies of African American Patients*

Study	_APOE_ Genotype						_APOE_ Allele		
	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4	ε2	ε3	ε4
Sahota et al[20]									
AD cases (n = 60)	0	4 (6.7)	1 (1.7)	26 (43.3)	18 (30.0)	11 (18.3)	5 (4.2)	74 (61.7)	41 (34.2)
Controls (n = 216)	6 (2.8)	24 (11.1)	10 (4.6)	101 (46.8)	66 (30.6)	9 (4.2)	46 (10.6)	292 (67.6)	94 (21.8)
Tang et al[21]									
AD cases (n = 106)	3 (2.8)	16 (15.1)	2 (1.9)	49 (46.2)	26 (24.5)	10 (9.4)	24 (11.3)	140 (66.0)	48 (22.6)
Controls (n = 154)	1 (0.6)	16 (10.4)	3 (1.9)	77 (50.0)	55 (35.7)	2 (1.3)	21 (6.8)	225 (73.1)	62 (20.1)
Present study									
AD cases (n = 338)	1 (0.3)	13 (3.8)	13 (3.8)	104 (30.8)	143 (42.3)	64 (18.9)	28 (4.1)	364 (53.8)	284 (42.0)
Controls (n = 301)	3 (1.0)	45 (15.0)	10 (3.3)	154 (51.2)	79 (26.2)	10 (3.3)	61 (10.1)	432 (71.8)	109 (18.1)

*Data are given as number (percentage). Percentages have been rounded and may not sum to 100. _APOE_ indicates apolipoprotein E locus; AD, Alzheimer disease.

among those who had AD compared with cognitively normal controls were 3.0, 3.3, and 2.0, respectively, in these smaller data sets, whereas the odds were 0.9 in the larger data set contributed by Tang et al.[13] These findings suggest that variation in the pattern of association across studies of African American subjects are not merely due to whether the subjects were recruited in clinic- or community-based settings.

The disparity in the _APOE_-AD association observed in our study compared with the studies by Sahota et al[20] and Tang et al[21] could be due to differences between clinic- and community-based patients, such as severity of dementia or other concurrent illnesses. Recruitment bias of this sort might enrich a clinic-based sample for AD cases with particular genetic mechanisms associated with a more severe course of illness. Population stratification is an unlikely explanation, because the _APOE_ genotype distribution among controls was similar across studies (Table 4). Also, different patterns of association might be related to environmental or cultural factors. Approximately 92% of the patients in our study were recruited from 4 cities in the southeastern United States. Differences between the North and the South in vascular risk factors leading to attrition of subjects from the catchment area or to modification of _APOE_ genotype expression could account for the differences between the current and previous studies. For example, according to the Third National Health and Nutrition Examination Survey (1988-1991), 24% of the US population has hypertension.[38] The age-adjusted national prevalence is higher in non-Hispanic black subjects (32.4%) overall, and even higher for black subjects in the southeastern region of the country (35% for black men and 37.7% for black women).[39] Individuals with hypertension and the ε4 allele are more likely to die of serious coronary artery disease[40,41] before AD develops. Finally, lack of an effect among subjects with the ε3/ε4 genotype in the Indianapolis and Manhattan samples might be due to sample size; our study included more than twice the number of AD cases than the other 2 studies combined. However, this argument is weakened by the observation of a significantly higher proportion of the ε3/ε4 genotype among AD patients compared with controls within the Birmingham and Jacksonville sites. Each

of these sites had fewer subjects than the Indianapolis or Manhattan samples (data not shown).

Differences in the association between the ε4 allele and AD across studies of African American subjects may be attributed in part to an age effect. Our results suggest that the ε4 allele is a potent risk factor for AD among African American subjects before 70 years of age, but the effect diminishes dramatically thereafter. The AD patients in the cohort studied by Sahota et al[20] were 10 years older than those in our study (mean±SD age, 82.7±6.1 vs 72.8±8.6 years), and none was younger than 70 years. Most of the AD cases in the Manhattan sample (mean±SD age, 78±7.6 years) were also older than 70 years. The odds of AD among African American participants in our study 69 years and older with 1 or 2 ε4 alleles (Figure 2) are not significantly higher than the odds obtained by Sahota et al[20] or Tang et al.[21] Some evidence exists of an age effect in the study by Tang et al.[21] Among subjects in the youngest quartile (age, ≤69 years), the ε4 allele frequency differed significantly (42% in AD cases and 15% in controls), which they attributed to ε4 homozygotes. Sahota et al[20] also attempted to analyze the age effect by assigning subjects to 2 age groups, using 75 years as the cutoff. However, there were too few subjects (7 AD patients and 89 controls) younger than 75 years to detect the age effect that we have demonstrated.

Our findings in the case-control sample of increased odds of AD among subjects with the ε3/ε4 and ε4/ε4 genotypes and decreased odds among those with the ε2/ε3 genotype are supported by the findings in the sibships. In contrast to conventional association designs, including those using population-based samples, the family-based approach minimizes biases due to population stratification (ie, cases and controls not representative of a single genetic population). The sibship design also controls for environmental exposures, especially those shared in early life. The Sibship Disequilibrium Test statistic evaluates the hypothesis of association, given linkage. In other words, a significant result from this test implies that the polymorphism under examination, or its immediate neighbor on the chromosome, is directly related to disease susceptibility.[34] Our results suggest that AD is more likely to develop in persons who inherit the ε4 allele compared with their siblings who do not. Con-

versely, the inheritance of the ε2 allele confers some protection against AD.

Our results need to be interpreted with caution. We may have reached the limits of even this comparatively large data set of African American subjects to fit complex models. Although our sample consisted of AD patients across the age spectrum, our sample in the group 80 years or older is less than half the size of the samples in the other age groups. Furthermore, the AD patients in this study may not be representative clinically or genetically of cases in the African American community. Clinic-based patients would be expected to have a higher genetic load (eg, higher frequency of the ε4 allele) than patients recruited from the community. However, this concern is lessened by the observation of a similar *APOE*-AD association among white clinic- and community-based samples.[13] The use of 3 sources of unrelated controls (spouses and age-matched individuals at the MIRAGE Study sites and community volunteers at the Jacksonville site) is another potential source of concern. Across sites, the controls are significantly different in sex ($P=.01$), but not in age or frequency of the ε4 allele. Moreover, with respect to the *APOE* genotype, our controls are similar to the controls in other community-based African American samples (Table 4).

CONCLUSIONS

In agreement with observations from an analysis of more than 11 000 white subjects of European descent,[13] the ε4 allele appears to be a potent risk factor for AD, and the ε2 allele confers a protective effect against AD in African American subjects. The association of the ε4 allele is age dependent in both ethnic groups, with the major effect of the ε4 allele occurring in persons younger than 70 years, although the patterns are not identical. A notable difference between the 2 ethnic groups is the interaction between sex and the *APOE* ε2/ε4 and ε3/ε4 genotypes. Among white subjects, the risk for AD was elevated in ε4 heterozygotes compared with ε3 homozygotes in women only. Lack of a sex interaction in our African American sample might be an issue of sample size or an indication that the factors that influence sex modification in heterozygotes are not equally frequent or do not work in the same manner in white and African American subjects. Cross-cultural comparisons of the impact of interactions between *APOE* and other factors on AD susceptibility should be pursued.

Author contributions: *Study concept and design* (Drs Graff-Radford, Green, Griffith, Williams, Hipps, Cupples, and Farrer); *acquisition of data* (Drs Graff-Radford, Green, Go, Hutton, Edeki, Bachman, Adamson, Willis, and Farrer); *analysis and interpretation of data* (Drs Graff-Radford, Haines, Cupples, and Farrer); *drafting of the manuscript* (Drs Graff-Radford, Go, and Farrer); *critical revision of the manuscript for important intellectual content* (Drs Graff-Radford, Green, Go, Hutton, Edeki, Bachman, Adamson, Griffith, Willis, Hipps, Haines, Cupples, and Farrer); *statistical expertise* (Drs Haines, Cupples, and Farrer); *obtained funding* (Drs Graff-Radford, Go, Willis, and Farrer); *administrative, technical, and material support* (Drs Green, Go, Hutton, Edeki, Bachman, Adamson, Griffith, Willis, Hipps, and Farrer); *study supervision* (Drs Go, Hutton, Edeki, Griffith, Hipps, Haines, and Farrer).

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