Apolipoprotein E and Alzheimer's Disease: Ethnic Variation in Genotypic Risks

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The presence of the apolipoprotein ε4 (apo ε4) allele significantly increases the risk of Alzheimer's disease. Whether this is due to biological effects of the apo ε4 protein or reflects linkage disequilibrium with an as yet unidentified Alzheimer's disease susceptibility gene is of critical importance. In a community study in northern Manhattan we found a fivefold increase in the risk of Alzheimer's disease among African-Americans, Hispanics, and whites homozygous for apo ε4. Overall, the risk between Alzheimer's disease and apo ε4 heterozygosity was also increased by twofold, but the association was somewhat weaker for African-Americans than for Hispanics and whites. In contrast, the apo ε2/ε3 genotype was associated with an eightfold increased risk of Alzheimer's disease in African-Americans but it was associated with reduced risk in whites. Variability in the strength and type of association between Alzheimer's disease and the apo E polymorphisms in the three ethnic groups could not be fully explained by age differences. The allelic frequency of apoε*4 was significantly higher in patients than control subjects in all ethnic groups at age 70 or younger, reflecting the higher proportion of apo ε4 homozygotes, but this difference diminished with increasing age. The allelic frequency of apoε*2 for African-Americans and Hispanics, but not whites, was significantly higher in patients than control subjects, but only after age 70. Though these findings need confirmation, they suggest that modifier genes or environmental factors may interact selectively with apo ε4 in African-Americans to weaken the association with Alzheimer's disease or that the apo E allelic system is in linkage disequilibrium with a nearby, as yet unidentified Alzheimer's disease susceptibility locus.

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Among the three common polymorphisms of apolipoprotein (apo) E, ε2, ε3, and ε4, the prevalence of the ε4 allele has been found to be increased among white patients with Alzheimer's disease (AD) compared to healthy control subjects [1–8], while the presence of an apo ε2 allele may provide protection [9]. Both the increased risk of AD associated with apo ε4 and the decreased risk associated with apo ε2 may diminish with age, however [9]. Because the genetic locus for apo E is on chromosome 19 within the region linked to late-onset familial AD [10] and because of the consistent association of AD with apo ε4 in both familial and sporadic disease, it has been proposed that the presence of one or more apo ε4 alleles increases susceptibility to AD. While arguments for a direct effect of a particular allelic variant of the apo E protein on the neuronal pathology have been made [1], the increased risk of AD conferred by apo ε4 might alternatively reflect linkage disequilibrium with a nearby AD susceptibility gene.

The association between apo ε4 and AD has been examined primarily in white populations from the United States and Europe. However, apo E has been extensively investigated in populations worldwide because of its role in lipid metabolism and ischemic cardiovascular disease [11]. The highest frequency of apo ε4 occurs among Finns, Icelandics, Sudanese, Nigerians, and African-Americans [12, 13]. Preliminary data from our community-based study [8] suggested that apo ε4 was not associated with AD among African-Americans. In that small study, the degree of association between apo ε4 and AD among Hispanics appeared to be intermediate between that in African-Americans and that in whites, consistent with the known African admixture in Hispanics of Caribbean origin [14]. The lack of a clear association be-

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tween AD and apo ε4 among African-Americans raised the possibility that apo ε4 might be in linkage disequilibrium with another AD susceptibility locus, or alternatively, that African-Americans might have a modifier gene (or genes) or environmental exposures that alter the biological effect of apo ε4. With this background, we conducted a larger case-control study based in the same community to test the hypothesis that the association of AD with the apo E allelic system differs among African-Americans, whites, and Hispanics.

Materials and Methods

Subjects and Setting

Patients were identified from a community-based dementia registry from a number of sources: regional hospitals (including inpatient and outpatient services), private practitioners in the community, federal and state health agencies, health maintenance organizations, and senior centers. Control subjects were recruited from the same source as patients and received identical interviews and clinical assessments (described below), which included a structured interview of family history. The refusal rate for both case patients and control subjects was less than 20% using the registry. We previously reported the development of our diagnostic methods and its relationship to the cultural and educational demographics of this community [15, 16]. None of the control subjects were spouses or relatives of case patients.

Diagnosis

A physician elicited the medical and neurological history and conducted a standardized physical and neurological examination. All ancillary information, including medical charts and reports of laboratory studies, were included in the evaluation, but data regarding apo E genotypes were shielded from the clinical diagnostic process. A standardized neuropsychological battery that measured performance in memory, orientation, abstract reasoning, language, and construction and measurement of activities of daily living was used to determine whether subjects met the cognitive and functional criteria for dementia. All clinical information was reviewed at a diagnostic conference of physicians and neuropsychologists to arrive at consensus diagnosis. The diagnosis of AD was based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition—revised [17], and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association [18]. The majority of patients were alive at the time of this investigation, but data were also available on 16 patients with postmortem confirmation of diagnoses identified in the same registry.

Family History Assessment

A structured family history interview for AD and other neurological disorders in first-degree relatives (parents and full siblings) was obtained. An initial screening question when answered affirmatively triggered a set of follow-up questions designed to ascertain historical information necessary for diagnosis. Operational criteria were then applied to the answers to the follow-up questions, to arrive at a diagnosis that was scaled according to the degree of certainty. The categories "definite," "probable," "possible," and "uncertain" required more than one affirmative response to the symptoms. The "doubtful" category was reserved for relatives with an affirmative response to the screening question but a negative response to all other symptoms. "Unknown" was reserved for family members where no information was available (i.e., an "unknown" response to the screening question). The reliability of this interview has been reported [19].

Ethnic Group

For ethnic group classification, we used the format suggested by the 1990 US Census Bureau [20]. The 1990 census allows for the identification of Hispanics as a cultural group with further designation of African-American or black, white, and other. We separated subjects into three ethnic groups according to self-report: African-American, Hispanic, and white (non-Hispanic), based on direct interview with the subjects or a family member.

Genomic DNA Amplification and Restriction Isotyping of Apo E

Genomic DNA was amplified by polymerase chain reaction (PCR), using reaction conditions modified from those described by Hixson and Vernier [21]. Briefly, each amplification contained 200 ng of genomic DNA, 25 pmol of each primer [21], 10% dimethyl sulfoxide, and 0.5 unit of Taq DNA polymerase (Boehringer Mannheim) in a final volume of 25 μl. Initial denaturation was at 94°C for 5 minutes, followed by 40 cycles of annealing at 65°C for 30 seconds, extension at 72°C for 30 seconds, denaturation at 94°C for 1 minute, followed by a final extension at 72°C for 10 minutes. The amplification product (10 μl) was then digested with 10 units of CfoI (Boehringer Mannheim) for 3 hours at 37°C and electrophoresed for 15 hours at 300 V through a 20% polyacrylamide gel. The genotypes were determined by the sizes of DNA fragments present, viewed, and photographed under ultraviolet light after staining with 0.5 μg/ml of ethidium bromide. All genotypes were determined without knowledge of patient-control status.

Data Analysis

Allele frequencies for patients with AD and control subjects were determined by counting alleles and calculating sample proportions. Frequencies of apo E genotypes in patients and control subjects were compared using the χ^2 test and the approximate test based on the normal approximation to the binomial distribution [22]. We estimated both simple and stratified (by ethnic group) odds ratios (ORs) [22] for AD associated with the presence of the apo ε4 and ε2 alleles (homozygous and heterozygous), using subjects with the apo ε3/ε3 genotype as the reference group. The frequencies for the demographic categories, including ethnic groups, were compared among case patients and control subjects using χ^2 analyses and Fisher's exact tests [22]. Tests for homogeneity [22] were also used to measure the degree of variability across the ethnic groups. This statistic has a χ^2 distribution under the null hypothesis of a consistent (homogeneous) association. Thus, the value of χ is increased when groups are inhomogeneous. Both univariate and multivariate ORs for AD associated with apo ε4 and ε2 were also calculated from logistic regression [23], adjusting for age and ethnic group.

Results

Characteristics of Study Population

Data from 145 patients with AD and 206 healthy elderly unrelated control subjects were ascertained. Patients and control subjects did not differ by gender (AD: 39.2% men; controls: 42.2% men). In all ethnic groups combined, patients were slightly older (75.3 ± 10.5 [range, 46–96] years) than control subjects (72.5 ± 7.8 [range, 46–93] years, $p < 0.05$). Also African-American and Hispanic subjects were older than Caucasians (Table 1). Patients also had less education (AD: 8.2 ± 5.6 years; controls: 9.4 ± 4.7 years; $p < 0.05$) than did control subjects.

Apo E Allelic Frequencies and Genotypes

There was a significant difference in the distribution of apo E alleles among the three ethnic groups within the control group ($\chi^2 = 17.5$, 4*df*, $p < 0.001$, see Table 1). The apo ε4 allele frequency was higher in African-American than in Hispanic or white control subjects, and both African-Americans and Hispanics had a lower frequency of apo ε2 than did white control subjects. The genotype distributions for control subjects within each ethnic group were in Hardy-Weinberg equilibrium (Table 2). Among patients the distribution of apo E alleles also differed across ethnic groups ($\chi^2 = 9.5$, *df*4, $p = 0.05$), with higher frequencies of both apo ε4 and ε2 in African-Americans than in the other two ethnic groups. Among patients, neither a family history of dementia in a first-degree relative nor a history of onset of AD after age 65 was related to any apo E genotype.

Measures of Association: Odds Ratios

Combining all three ethnic groups, the OR adjusted for age and ethnic group for AD associated with homozygosity for apo ε4 was 5.1 (95% confidence interval [CI]: 1.7–15.0; $p < 0.005$) and that for heterozygosity was 2.1 (95% CI: 1.2–3.2; $p < 0.005$). Within each ethnic group, we estimated the OR for AD associated with each individual apo E genotype (see Table 2). There was a strong association between AD and apo

Table 1. Distributions of Apo E Genotypes among Patients with Alzheimer's Disease and Control Subjects by Ethnic Groups[a]

Ethnic Groups	N	Age (yr)	Apo*ε3	Apo*ε4	Apo*ε2
African-American					
Alzheimer's disease	41	76 (8.8)	0.56	0.32	0.12
Control	57	74 (5.8)[b]	0.74	0.24	0.02
Hispanic					
Alzheimer's disease	61	76 (9.4)	0.70	0.24	0.06
Control	90	74 (7.1)[b]	0.84	0.12	0.03
White					
Alzheimer's disease	43	71 (9.9)	0.71	0.27	0.02
Control	59	70 (11.6)	0.84	0.09	0.07

[a]Allelic frequencies differed significantly between case patients and control subjects within and across ethnic groups. See text for explanation.
[b]Significant difference within each stratum ($p < 0.05$).

Table 2. Odds Ratios for Alzheimer's Disease Associated with Apo E Genotype by Ethnic Group[a]

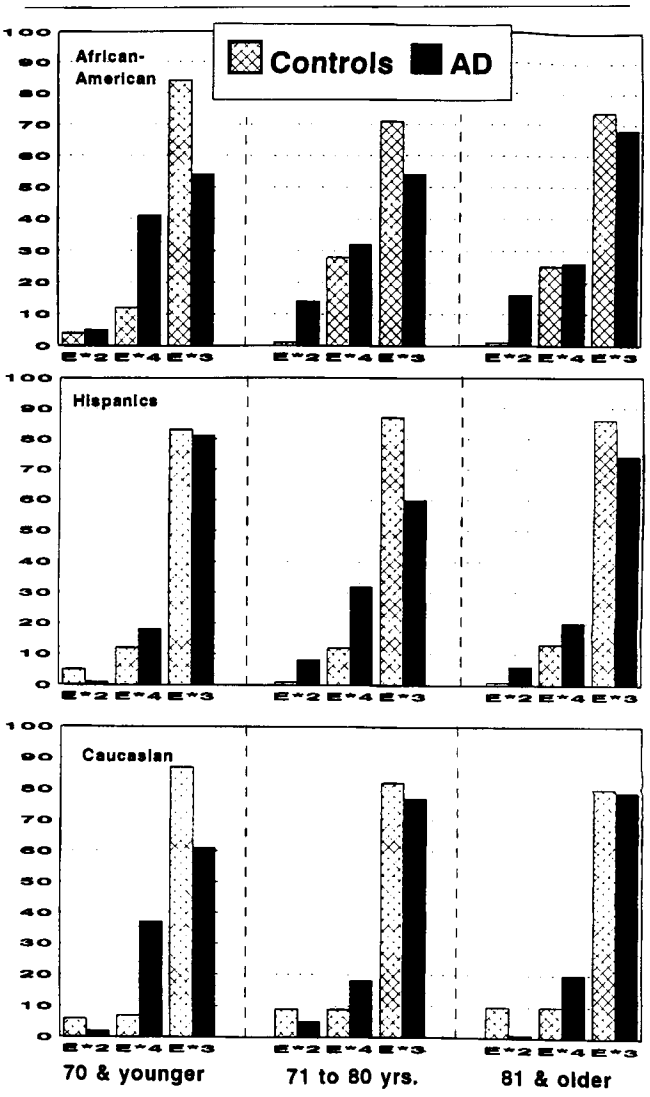
Ethnic Groups	ε3/ε3	ε2/ε3	ε2/ε2	ε4/ε2	ε3/ε4	ε4/ε4
African-American						
Alzheimer's disease	12	7	1	1	15	5
Control	30	2	0	0	23	2
Odds ratio	1.0 reference	8.8 (1.6–48.0)[b]	[c]	[c]	1.6 (0.6–4.2)	8.2 (1.3–51.0)[b]
Hispanic	N					
Alzheimer's disease	33	2	1	3	18	4
Control	65	5	0	0	18	2
Odds ratio	1.0 reference	0.8 (0.2–4.3)	[c]	[c]	2.0 (0.9–4.5)	4.2 (0.7–24.0)
White	N					
Alzheimer's disease	22	1	0	1	16	3
Control	42	8	0	1	7	1
Odds ratio	1.0 reference	0.2 (0.03–2.00)	[d]	1.9 (0.1–32.0)	4.4 (1.6–12.2)[b]	5.7 (0.6–58.0)

[a]All odds ratio estimates were computed and age adjusted by logistic regression. The numbers in parentheses indicate the 95% confidence interval for the odds ratio. The expected frequencies, given Hardy-Weinberg equilibrium, are provided for controls in each ethnic group. African-American—ε3/ε3 (55%), ε3/ε4 (35%), ε3/ε2 (3%), ε4/ε4 (6%), ε4/ε2 (.5%), ε2/ε2 (.5%); Hispanic—ε3/ε3 (70%), ε3/ε4 (22%), ε3/ε2 (5%), ε4/ε4 (2%), ε4/ε2 (.8%), ε2/ε2 (.2%); white—ε3/ε3 (70%), ε3/ε4 (15%), ε3/ε2 (12%), ε4/ε4 (1%), ε4/ε2 (1.5%), ε2/ε2 (.5%).
[b]Statistical significance, $p < 0.01$ for each.
[c]Odds ratio was not calculated because of an empty cell.
[d]No patients or control subjects were found with this genotype.

ε4/ε4 in all three ethnic groups. The OR for apo ε3/ε4 appeared to be stronger in whites (4.4) than in African-Americans (1.6) or Hispanics (2.0), although the statistical test for heterogeneity of this association did not demonstrate significance (χ^2_H = 2.2, 2*df*, $p > 0.05$). There was a positive association between AD and apo ε2/ε3 in African-Americans (OR = 8.8), and a negative association with this genotype in the other two ethnic groups (see Table 2: Hispanics, 0.8; whites, 0.2); this difference was statistically significant (χ^2_H = 8.9, 2*df*, $p < 0.05$).

Because the associations between AD and both apo ε2 and apo ε4 have been reported to vary with age [9], we performed two further analyses. First, we investigated the possibility that the age differences across the three ethnic groups explained the weaker association between the apo ε4/ε3 genotype and AD in African-Americans compared to that in Hispanics and whites. For this purpose we excluded patients and control subjects below the age of 65 and above the age of 85, thus eliminating the age differences among the three ethnic groups (African-Americans, 74.3 ± 5.4; Hispanics, 73.9 ± 5.2; whites, 74.7 ± 5.4; F = 1.4, $p > 0.05$). We then reestimated the OR associated with apo ε4/ε3 and apo ε2/ε3 using logistic regression to adjust for any residual age differences between patients and control subjects. The results of this analysis were very similar to those shown in Table 2. The OR for apo ε4/ε3 was 1.5 (95% CI: 0.5–4.7) in African-Americans, 2.6 (95% CI: 1.0–6.4) in Hispanics, and 3.9 (95% CI: 1.2–12.6) in whites. The OR for apo ε2/ε3 was 18.8 (95% CI: 4.7–74.8) in African-Americans, 0.6 (95% CI: 0.4–10.6) in Hispanics, and 0.2 (95% CI: 0.0–8.6) in whites.

Second, to clarify further the effect of age on the relationship between AD and apo E, we compared the allelic frequencies for apoε*2, ε*3, and ε*4 among patients and control subjects in all three ethnic groups across three age strata: age 70 and younger, age 71 to 80, and age 81 and older (Fig). At age 70 and younger, the allelic frequency for apo ε4 was significantly elevated among patients compared with control subjects in all three ethnic groups, possibly reflecting the higher frequency of apo ε4 homozygosity (6.5 vs 1.2%). In African-Americans and whites, the apoε*4 frequency in patients diminished with increasing age; this pattern was not apparent in Hispanics. In African-American control subjects, the apoε*4 frequency was higher among subjects over age 70 than among those age 70 or younger. The apoε*2 allelic frequency also differed over the three age groups. In African-Americans and Hispanics, the frequency of apoε*2 was significantly increased among patients compared with control subjects in the older age groups (see Fig; African-Americans age 71 and older: AD 15% vs controls 1.1%, $z = 2.9$, $p < 0.01$; and Hispanics age 71 and older: AD 7.1% vs controls 0.9%, $z = 2.3$, $p < 0.02$).



Frequencies for the three common apolipoprotein E alleles in patients with Alzheimer's disease (AD) *and a group of elderly control subjects from a community in northern Manhattan.* Solid bars *indicate patients with AD while the* cross-hatched bars *indicate controls. Ethnic groups are divided and identified in the upper left corner of each box and the groups are further subdivided into three age strata based on the distribution of subjects overall (≤70, 71–80, and ≥81). Patients with AD had a significantly higher frequency of apoε*4 in all three ethnic groups, but only in the lowest age stratum. In contrast, African-American and Hispanic patients with AD had significantly higher frequencies of apoε*2, but the number of subjects with this allele was relatively small.*

Among whites the frequency of apoε*2 was higher in control subjects than in patients in all age groups.

Discussion

Our findings indicate a uniform increased risk of AD among African-Americans, whites, and Hispanics homozygous for apo ε4. Apo ε4 heterozygosity was also associated with an increased risk of AD, but this association was somewhat weaker in African-Americans than

in the other two ethnic groups. The risk of AD was also increased for African-Americans with an apo ε2 allele, whereas it was decreased for whites with this polymorphism, as previously reported by Corder and coauthors [9]. These differences do not appear to be due to any disparity in age across the three ethnic groups because the ORs were virtually unchanged in the analysis involving subjects of comparable age. However, the results are based on a small number of subjects in each ethnic group and require confirmation. Nevertheless, there are at least three possible explanations for these results, each of which suggest new lines of inquiry into the complex genetics of AD.

First, it is possible that apo ε4 has a direct effect on AD susceptibility, but that African-Americans have either a modifier gene (or genes) or environmental exposures that "partially" protect them from the effects of the apo ε4 protein. Modifier genes or exposures might alter the effects of a single apo ε4 allele, but not the higher gene dose with two apo ε4 alleles. Thus, apo ε4 homozygosity was unequivocally associated with increased risk, while the effect of a single apo ε4 allele was not. To account for the positive association between AD and apo ε2 in African-Americans and the negative association between AD and apo ε2 in whites, however, this direct effect model would also require that there be modifier genes or risk factors affecting both apo ε4 and apo ε2, and in opposite directions. Studies to identify genes or exposures that modify the effects of the apo E proteins will be critical.

The frequency of apo ε4 was higher among African-American control subjects than in control subjects from the other ethnic groups. A prevalence study [24] in this community found rates of dementia to be identical in the three ethnic groups. While the specific types of dementia were not described, preliminary analyses indicate no significant difference in the prevalence of AD by ethnic group [25]. Studies to determine whether other populations [12] with high frequencies of the apo ε4 allele manifest a relative excess of late-onset AD compared to those with lower apo ε4 frequencies would be important.

A second explanation for the different allelic associations of apo ε with AD among African-Americans and whites is that the associations are due to linkage disequilibrium, rather than to a direct effect of apo ε4. An AD susceptibility gene may be in linkage disequilibrium with apo ε4 in whites and with apo ε4 and ε2 in African-Americans. According to this model, the allelic variants at the putative AD susceptibility locus must have arisen early in the diversification of racial groups. Clearly, if apo ε4 is not itself the AD susceptibility gene but instead is in linkage disequilibrium with this gene, then studies to identify the true AD susceptibility locus should focus on other genes tightly linked to apo E.

Corder and coauthors [9] suggested that the independent, negative association with apo ε2 in whites provided evidence against linkage disequilibrium, because it would require association of apo ε4 with an allele increasing susceptibility to AD, and association of apo ε2 with an allele decreasing susceptibility to AD. We suggest an alternative explanation for the data in whites: An AD susceptibility allele may be in linkage disequilibrium both with apo ε4 and to a lesser extent, with apo ε3. This would also account for the lower risk in whites with apo ε2 than in those with either apo ε3 or apo ε4, and would be consistent with the different allelic associations in African-Americans.

The third possibility is that ethnic differences in the associations between AD and apo ε4 observed in this community study are due to differential survival among older patients with an apo ε4 allele. Our results indicate that the apo ε4 allelic frequency in patients diminishes with age. In whites, the apo ε4 allelic frequency in control subjects remained unchanged with age (≈10%), whereas in African-Americans it increased with advancing age (≈25%). This was not expected because the presence of an apo ε4 allele has been associated with increased risk of coronary artery disease, particularly that associated with mortality [26]. This may be due simply to the small number of African-Americans in this study who were 70 years or younger, but the allelic frequency in the older African-Americans is similar to that previously reported [12, 13]. Alternately, other genetic or environmental factors may contribute to the differences in lipid metabolism related to apo E and the association with heart disease [27, 28]. Prospective studies will be essential to clarify the relationship between apo ε4 and survival in the presence and absence of AD.

At least two hypotheses that implicate apo E in the etiology of AD have been advanced. Strittmatter and colleagues [1, 29] proposed apo E as a β-amyloid sequestering agent. Consistent with this position are the observations that apo E colocalizes with β-amyloid and that the degree of binding in vitro is greatest with the apo ε4 protein (homozygous > heterozygous). Another hypothesis forwarded by this group proposes that the absence of apo ε3 results in more rapid τ phosphorylation, leading to instability of the microtubule system in neurons and the formation of paired helical filaments and neurofibrillary tangles in AD [30]. The current findings of an association between AD and both apo ε4 and ε2 in African-Americans are perhaps more consistent with this hypothesis.

Uncovering a marker of genetic susceptibility to AD is of major public health importance because the disease is both common and costly. Given the variable prevalence of the major polymorphisms of apo E, it is possible that other populations may also differ with regard to the association between AD and apo E. The predictive value of a test for risk, however defined, will vary with the prevalence of AD and with the frequen-

cies of apo E polymorphisms in the population [22]. Published data to date imply that a test based on the apo E allele system might accurately assess AD risk in some populations. While this may be true, caution is warranted because data from populations with higher known frequencies of apo ε4 have not been thoroughly investigated with regard to the association with AD. As with any test for disease risk, individuals are likely to make important decisions concerning their lives based on the perception that they (or their family members) carry the disease gene or are at increased risk of developing the disease. Our data suggest that commercial initiatives to exploit apo E allelic analysis as an assessment of the risk of AD may be premature. Nevertheless, several lines of research are now open. A thorough analysis of DNA near the apo E locus for additional transcription units should be undertaken as well as a search for additional susceptibility or modifier loci and potential environmental factors in populations with higher apo ε4 allelic frequencies to identify factors or genes that modify the effect of an AD susceptibility gene.

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