Background: The APOE ε4 allele is a genetic risk factor for Alzheimer disease (AD), though the strength of the association varies by ethnic group. Polymorphisms in regulatory sequences of APOE have also been related to AD, but the effects are inconsistent across studies.

Methods: We examined the association between AD and variants in 3 APOE promoters and in the promoter of the adjacent APOC1 gene in African American and Caribbean Hispanic individuals. Polymorphisms tested were the −491A/T, −427T/C, and −219G/T (Th1/E47cs) in the APOE promoter and the HpaI variant in the APOC1 promoter. Using standard research criteria for AD, overall odds ratios were computed and repeated stratified by pres-
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Conclusion: These findings exclude a strong or independent influence of APOE or APOC1 promoter polymorphisms on the variation in APOE-related risk of AD in African American and Caribbean Hispanic individuals.

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Original Contribution

APOE and APOC1 Promoter Polymorphisms and the Risk of Alzheimer Disease in African American and Caribbean Hispanic Individuals

Benjamin Tycko, MD, PhD; Joseph H. Lee, PhD; Alejandra Ciappa, MD; Anjana Saxena, PhD; Chi-Ming Li, PhD; Lin Feng, BA; Alex Arriaga, BA; Yaakov Stern, PhD; Rafael Lantigua, MD; Neil Shachter, MD; Richard Mayeux, MD, MSc

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Conclusion: These findings exclude a strong or independent influence of APOE or APOC1 promoter polymorphisms on the variation in APOE-related risk of AD in African American and Caribbean Hispanic individuals.

Arch Neurol. 2004;61:1434-1439

Methods

Subjects and Diagnosis

Data were derived from participants in the Washington Heights-Inwood Columbia Ag-
ing Project identified from a random sample of healthy Medicare beneficiaries aged 65 years or older residing in northern Manhattan, NY, between 1991 and 1996. The sampling procedures have been described elsewhere. Participants underwent an in-person, structured interview of health and function in daily activities at the time of study entry followed by a standard medical history, physical and neurological examination, and neuropsychological battery. Participants were followed at approximately 18-month intervals, repeating the evaluations used at baseline at each follow-up.

Ethnic group was classified by self-report using the format of the 1990 US Census Bureau. First, each individual chose a particular racial or ethnic group. Then they were asked whether they were of Hispanic origin. Using this information, individuals were separated into 3 ethnic groups: African American, Hispanic, or white (non-Hispanic). For Hispanic individuals, we also asked their country of birth or origin. For those who agreed to participate, an in-person interview and a standardized assessment including a medical history, physical and neurological examination, and neuropsychological battery were completed. For cases, the diagnosis of AD was established at a consensus conference of physicians and neuropsychologists. The clinical diagnosis of AD was based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association.27 When available, all medical records and imaging studies were used in the evaluation, as were data from the initial and follow-up examinations. APOE genotypes were not available to the physicians at any point during the diagnostic process. Patients classified as having AD included only individuals with probable AD27 and those with a Clinical Dementia Rating Scale score of 1.0 or higher. The comparison group consisted of individuals who had not received a diagnosis of dementia or either possible or probable AD at any point during follow-up across the 7 years. Patients with Parkinson disease, stroke, or non-AD dementia were excluded from the current study. The Columbia University institutional review board reviewed and approved this project.

**STATISTICAL ANALYSIS**

APOE allele frequencies were determined by counting each allele and by calculating sample proportions. For comparison of cases and controls within and across ethnic groups, APOE allele frequencies were calculated for all subjects and compared by \( \chi^2 \) analysis. Logistic regression was used to compute the odds ratio for the association between AD and markers flanking APOE. Data were stratified by the presence or absence of an APOE \( \varepsilon 4 \) allele and by adjusting for differences in age and education. Logistic regression analyses were conducted separately for each ethnic group. We tested for Hardy-Weinberg equilibrium using \( \chi^2 \) analysis. In addition, we compared allele frequencies for APOE and adjacent markers in affected vs unaffacted individuals and tested statistical significance by \( \chi^2 \) analysis. Multivariate logistic regression was used to compute the odds ratio for the association between AD and APOE promoter polymorphisms, adjusting for age, sex, and education. To study whether the APOE \( \varepsilon 4 \) allele interacts genetically with the upstream markers, we conducted multivariate logistic regression, stratified by the presence or absence of this allele.

A haplotype analysis was used to determine whether the haplotype frequencies including these genes in cases differed from those in unrelated controls. Because the genetic parameters (eg, mode of inheritance, disease allele frequencies, penetrance, etc) of late-onset sporadic AD remain unknown, we tested a heterogeneity model using the EHPlus program.29,30

**RESULTS**

**POPULATION CHARACTERISTICS AND ALLELE FREQUENCIES**

The mean ± SD age of the participants was 79.5 ± 6.6 years (range, 65-103 years) and did not differ by ethnic group. The number of years of formal education differed in the 2 groups, with the mean level of education being 9.6 years for African American participants and 5.9 years for Caribbean Hispanic participants. The individuals who de-
The allele frequencies of the −491A/T and the −219G/T promoter (Table 1), but there were no differences in the allele frequencies of the −427 allele in African American participants compared with Caribbean Hispanic participants.

We compared the allele frequencies of variants for APOE and APOC1 independently and, because of the differences in the allele frequencies, stratified by ethnic group. In the Caribbean Hispanic participants, the APOE ε4 allele was more frequent among patients with AD than controls (22.2% vs 11.5%; \( \chi^2 = 19.1; P < .001 \)). (The numbers of participants with each genotype are listed in Table 2.) On the other hand, in African American participants, there were no overall differences in the frequency of the APOE coding alleles between patients and controls. Nonetheless, compared with those without an ε4 genotype, the APOE ε4 homozygous genotype was associated with AD both in African American and Caribbean Hispanic participants, while the APOE ε4 heterozygous genotype was associated with AD only in Caribbean Hispanic participants (Table 2).

The APOC1 HpaI+ variant was also more frequent among patients with AD than controls but only in the Caribbean Hispanic participants (21.6% vs 13.9%; \( \chi^2 = 10.33; P < .001 \)). (The numbers of participants with each genotype are listed in Table 2.) We repeated this analysis stratifying by the presence or absence of APOE ε4. Considering both heterozygotes and homozygotes, the HpaI+...
variant was more frequent in Caribbean Hispanic patients with AD compared with controls but only in those individuals with an APOE ε4 allele (16.2% vs 10.6%; χ²=6.09; P=.01). (The numbers of participants with each genotype are listed in Table 2.) There were no differences in APOC1 HpaI allele frequencies between African American patients and controls, regardless of the presence or absence of APOE ε4.

ASSOCIATIONS BETWEEN APOE PROMOTER POLYMORPHISMS AND AD RISK

We compared the allele frequencies of each APOE promoter polymorphism between patients and controls, conducting the analysis separately in the African American and Caribbean Hispanic participants. Because the influence of such flanking polymorphisms may depend on the APOE coding polymorphism to which they are linked in cis, we also tabulated the allele frequencies in patients and controls stratified by the APOE ε4 allele. As shown in Table 3, none of the APOE upstream markers showed a significant association with AD.

Setting the β at 0.20 (80% power) and the α at .05, we calculated the lowest detectable odds ratios for the sample sizes for each ethnic group separately. For African American and Caribbean Hispanic participants, we had large enough samples to detect odds ratios of 2.0 with −491A/T, −219G/T, and APOC1. Because the frequency of a genotype containing the variant allele of −427TC was 10%, the lowest detectable odds ratio was 2.8 for African American participants and 2.5 for Caribbean Hispanic participants.

ESTIMATED HAPLOTYPES AND AD RISK

We calculated haplotypes using the 3 loci (−219G/T-APOE-APOC1) that are in linkage disequilibrium to determine whether the distribution of haplotypes differed

Table 3. Genotype Frequencies of APOE Flanking Polymorphisms in Alzheimer Disease Cases and Controls*

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. (%) of Cases</th>
<th>No. (%) of Controls</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>No. (%) of Cases</th>
<th>No. (%) of Controls</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−491AT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>14 (8.4)</td>
<td>33 (10.6)</td>
<td>1.20 (0.60-2.50)</td>
<td>11 (10.1)</td>
<td>22 (11.3)</td>
<td>0.95 (0.43-2.10)</td>
</tr>
<tr>
<td>A/T</td>
<td>59 (35.3)</td>
<td>112 (36.0)</td>
<td>1.30 (0.68-2.60)</td>
<td>41 (37.6)</td>
<td>64 (33.0)</td>
<td>1.20 (0.70-2.00)</td>
</tr>
<tr>
<td>A/A</td>
<td>94 (56.3)</td>
<td>166 (53.4)</td>
<td>1.00 (Referent)</td>
<td>57 (52.3)</td>
<td>108 (55.7)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>ε4+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>6 (12.2)</td>
<td>11 (20.0)</td>
<td>1.70 (0.51-5.40)</td>
<td>6 (14.3)</td>
<td>10 (14.1)</td>
<td>1.10 (0.34-3.30)</td>
</tr>
<tr>
<td>A/T</td>
<td>18 (36.7)</td>
<td>20 (36.4)</td>
<td>1.90 (0.61-5.90)</td>
<td>19 (45.2)</td>
<td>30 (42.3)</td>
<td>1.20 (0.51-2.60)</td>
</tr>
<tr>
<td>A/A</td>
<td>25 (50.0)</td>
<td>24 (43.6)</td>
<td>1.00 (Referent)</td>
<td>17 (40.5)</td>
<td>31 (43.7)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>ε4−</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>8 (6.8)</td>
<td>22 (8.6)</td>
<td>1.20 (0.50-2.90)</td>
<td>5 (7.5)</td>
<td>12 (9.8)</td>
<td>0.80 (0.26-2.40)</td>
</tr>
<tr>
<td>A/T</td>
<td>41 (34.7)</td>
<td>92 (35.9)</td>
<td>1.30 (0.55-3.10)</td>
<td>22 (32.8)</td>
<td>34 (27.6)</td>
<td>1.20 (0.65-2.40)</td>
</tr>
<tr>
<td>A/A</td>
<td>69 (58.5)</td>
<td>142 (55.5)</td>
<td>1.00 (Referent)</td>
<td>40 (59.7)</td>
<td>77 (62.6)</td>
<td>1.00 (Referent)</td>
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<td>−427TC</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>1 (0.7)</td>
<td>1 (0.3)</td>
<td>1.90 (0.10-29.9)</td>
<td>2 (2.1)</td>
<td>1 (0.6)</td>
<td>3.50 (0.30-39.00)</td>
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<tr>
<td>T/C</td>
<td>11 (7.3)</td>
<td>30 (10.5)</td>
<td>0.70 (0.30-1.30)</td>
<td>4 (4.3)</td>
<td>16 (9.4)</td>
<td>0.44 (0.14-1.40)</td>
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<td>T/T</td>
<td>138 (92.0)</td>
<td>256 (89.2)</td>
<td>1.00 (Referent)</td>
<td>88 (93.6)</td>
<td>154 (90.1)</td>
<td>1.00 (Referent)</td>
</tr>
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<td>ε4+</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>0</td>
<td>1 (2.3)</td>
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<td>0</td>
<td>0</td>
<td>NA</td>
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<td>T/C</td>
<td>31 (7.0)</td>
<td>8 (15.4)</td>
<td>0.78 (0.10-1.70)</td>
<td>0</td>
<td>9 (13.0)</td>
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<tr>
<td>T/T</td>
<td>3911 (90.7)</td>
<td>44 (84.6)</td>
<td>1.00 (Referent)</td>
<td>35 (100.0)</td>
<td>56 (86.2)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>ε4−</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>0</td>
<td>1 (0.4)</td>
<td>NA</td>
<td>2 (3.4)</td>
<td>1 (0.9)</td>
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<tr>
<td>T/C</td>
<td>8 (7.5)</td>
<td>22 (9.4)</td>
<td>0.42 (0.33-1.80)</td>
<td>4 (6.8)</td>
<td>7 (6.6)</td>
<td>1.10 (0.30-3.80)</td>
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<tr>
<td>T/T</td>
<td>99 (92.5)</td>
<td>212 (90.2)</td>
<td>1.00 (Referent)</td>
<td>53 (89.9)</td>
<td>98 (92.5)</td>
<td>1.00 (Referent)</td>
</tr>
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<td>−219GT</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>38 (16.5)</td>
<td>61 (17.0)</td>
<td>1.10 (0.68-1.70)</td>
<td>9 (6.3)</td>
<td>20 (8.0)</td>
<td>0.72 (0.30-1.65)</td>
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<tr>
<td>G/T</td>
<td>114 (49.6)</td>
<td>168 (46.8)</td>
<td>0.89 (0.59-1.60)</td>
<td>50 (35.2)</td>
<td>99 (39.4)</td>
<td>0.80 (0.52-1.20)</td>
</tr>
<tr>
<td>G/G</td>
<td>78 (33.9)</td>
<td>130 (36.2)</td>
<td>1.00 (Referent)</td>
<td>83 (58.5)</td>
<td>132 (52.6)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>ε4+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>14 (17.5)</td>
<td>19 (25.7)</td>
<td>1.10 (0.40-2.90)</td>
<td>5 (9.4)</td>
<td>16 (17.6)</td>
<td>0.50 (0.16-1.50)</td>
</tr>
<tr>
<td>G/T</td>
<td>53 (66.3)</td>
<td>36 (48.6)</td>
<td>2.10 (0.90-4.90)</td>
<td>27 (50.9)</td>
<td>42 (46.2)</td>
<td>1.00 (0.50-2.10)</td>
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<tr>
<td>G/G</td>
<td>13 (16.3)</td>
<td>19 (25.7)</td>
<td>1.00 (Referent)</td>
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<td>33 (36.3)</td>
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<tr>
<td>T/T</td>
<td>24 (16.0)</td>
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<td>1.00 (0.54-1.70)</td>
<td>4 (4.5)</td>
<td>4 (2.5)</td>
<td>1.60 (0.40-6.60)</td>
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<tr>
<td>G/T</td>
<td>61 (40.7)</td>
<td>132 (46.3)</td>
<td>0.80 (0.50-1.20)</td>
<td>23 (25.8)</td>
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<tr>
<td>G/G</td>
<td>65 (43.3)</td>
<td>111 (38.9)</td>
<td>1.00 (Referent)</td>
<td>62 (69.7)</td>
<td>99 (61.9)</td>
<td>1.00 (Referent)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not able to be calculated.
*Confidence intervals are from the univariate analysis; values corrected for age, sex, and education are given in the text.
in patients and controls. Among Caribbean Hispanic participants, −219G/T and APOE together showed a significant difference in patients and controls in the estimated haplotype distribution ($\chi^2 = 35.40; P < .001$), while APOE-APOC1 did not ($\chi^2 = 7.00; P = .22$). The 3 loci examined together also indicated significant differences between patients and controls ($\chi^2 = 33.44; P < .001$), driven primarily by the −219GT-APOE haplotype. We then recomputed the P values using Monte Carlo methods based on 5000 replicates to minimize the influence of less-frequent haplotypes. The P values for the haplotypes using the 2 loci (−219G/T-APOE) and the 3 loci (−219G/T-APOE-APOC1) remained unchanged at .00001 and .0004, respectively. Among African American participants, on the other hand, none of the estimate haplotypes differed significantly between cases and controls for the same 3 sets of analyses.

PROTEIN-REPORTER ASSAYS FOR FUNCTIONAL EFFECTS OF THE −219G/T POLYMORPHISM

The −219G/T promoter polymorphism has been reported to produce modest but significant effects on allel-specific APOE messenger RNA expression and our haplotype analysis suggested a possible influence of −219T promoter polymorphism in conjunction with the adjacent loci. We tested whether the −219G vs −219T sequence variants could cause differences in APOE transcription when they were present in the context of a minimal APOE promoter sequence. Accordingly, we cloned a series of matched 806-bp promoter fragments, extending from −773 to +33 relative to the transcriptional start site and containing either the −219G or −219T alleles, upstream of the luciferase reporter gene. These were transfected into HepG2 cells in multiple repeated experiments. As expected, this minimal promoter region strongly stimulated expression of the luciferase reporter gene. However, although the T allele of the −219GT polymorphism gave slightly reduced APOE promoter activity, this reduction was within the range of error of the assay. As a positive control, a plasmid containing an artificial point mutation, introduced at another site in the promoter sequence, showed significantly reduced activity.

The PrD1 plasmid contained the APOE promoter with G at position −219. The PrD3 and PrD10 plasmids were dependent but identical clones, both with a T at position −219. The PrD2 plasmid was an artificial mutant allele with −219T and an additional T-C substitution at position −97. Each experiment consisted of triplicate determinations of luciferase activity divided by β-galactosidase activity. The mean values of luciferase/β-galactosidase obtained with the PrD2, PrD3, and PrD10 plasmids in each experiment were then normalized to the mean value obtained in that experiment with the PrD1 plasmid. For luciferase/β-galactosidase, the mean ± SD value for G (PrD1) was 1; Tmut (PrD2), 0.40 ± 0.12 (16 experiments); T (PrD3), 0.78 ± 0.35 (17 experiments); and T (PrD10), 0.80 ± 0.34 (9 experiments). In all experiments, the pGL3-Basic vector lacking any promoter cassette gave luciferase/β-galactosidase values at least 10-fold less than the PrD1 plasmid.

Since the first report of an association between an APOE promoter polymorphism and AD, there has been considerable interest in testing whether regulatory polymorphisms near APOE might also affect AD susceptibility. Polymorphisms in regulatory sequences would presumably exert their effects by altering APOE messenger RNA expression in cis. Several studies published to date have yielded inconsistent results, but it may be important to continue to test this hypothesis in additional populations. We examined multiple polymorphisms upstream of APOE and the promoter of the adjacent APOC1 gene for associations with AD in a large cohort of Caribbean Hispanic and African American participants with extensive clinical follow-up.

Our findings have both positive and negative aspects. We found no convincing evidence of an independent association with AD for any variant in the promoter of APOE. In contrast, for the HpaI variant of the APOC1 polymorphism, we find evidence for a weak association with AD that was modified significantly by the presence or absence of an APOE ε4 allele. A haplotype analysis using the loci spanning −219G/T to APOC1 yielded a significant difference in the haplotype distribution between cases and controls but only in Caribbean Hispanic participants. However, there was no significant association with any of the loci individually or as haplotypes among African American participants. Among the markers we have tested, the −219GT polymorphism lies closest to the APOE transcriptional start site. Previously, slight differences in allele-specific expression of APOE messenger RNA in the brains of individuals with different −219GT genotypes were reported. Although we could not detect significant allele-specific differences in promoter activity in transfection assays using a minimal APOE promoter sequence, this may be owing to insufficient precision of this type of assay. Given the continuing interest in functional polymorphisms within human regulatory sequences, better assays for small effects of single-nucleotide polymorphisms in human promoter sequences are needed. Indeed, Stengard et al have observed subtle phenotypic variation in lipid metabolism using information from additional sequence variation surrounding the APOE locus. A similar approach to investigate phenotypic variation in AD may be warranted.

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REFERENCES

tence of [this cluster] is to be expected" and that it is merely "an outlier"?

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Error in Byline. In the Original Contribution by Tycko et al titled “APOE and APOC1 Promoter Polymorphisms and the Risk of Alzheimer Disease in African American and Caribbean Hispanic Individuals,” published in the September issue of the ARCHIVES (2004;61:1434-1439), an author name was omitted from the byline at article submission. The byline should have read Benjamin Tycko, MD, PhD; Joseph H. Lee, PhD; Alejandra Ciappa, MD; Anjana Saxena, PhD; Chi-Ming Li, PhD; Lin Feng, BA; Lin Yang, MD; Alex Arriaga, BA; Yaakov Stern, PhD; Rafael Lantigua, MD; Neil Shachter, MD; Richard Mayeux, MD, MSc.