Association of Apolipoprotein E4 and Haplotypes of the Apolipoprotein E Gene With Lobar Intracerebral Hemorrhage

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Background and Purpose—Conflicting reports in the literature exist with regard to the association of apolipoprotein E (apo E) alleles and lobar intracerebral hemorrhage (ICH). We genotyped 12 single-nucleotide polymorphisms in the 5′ upstream regulatory, exonic, and intronic regions of the apo E gene and performed genotype and haplotype association analyses.

Methods—We prospectively enrolled subjects with hemorrhagic stroke and matched them with 2 controls based on age, race, and sex. Each case was reviewed by a physician to determine case status and location of the ICH. Multivariate logistic-regression modeling with backward elimination was used to determine significant risk factors for lobar ICH. Associations at the genotype and haplotype levels and linkage disequilibrium were conducted according to standard statistical methods.

Results—Between May 1997 and December 2002, 315 cases of ICH were recruited, of whom 107 were lobar ICH cases matched to 205 controls. No association was found for apo E2, E3, or E4 with nonlobar ICH. Independent, significant risk factors for lobar ICH included apo E4, untreated hypertension, anticoagulant use, a first-degree relative with ICH, and high school education (compared with high school education). Treated hypercholesterolemia compared with “no history of hypercholesterolemia” was associated with a decreased risk of lobar ICH. Haplotype association analysis demonstrated a significant association of the apo E gene with lobar ICH among whites (P<0.0001) and blacks (P=0.0024).

Conclusions—Apo E4 is independently associated with lobar ICH but not nonlobar ICH. Haplotypes of the apo E gene are associated with lobar ICH. Untreated hypertension is a risk factor for lobar ICH. (Stroke. 2005;36:1874-1880.)

Key Words: apolipoproteins ■ intracerebral hemorrhage ■ genetics ■ epidemiology

Spontaneous intracerebral hemorrhage (ICH) occurs at an annual incidence rate of 15 to 19 per 100 000.1 ICH has been shown to have important genetic and environmental risk factors, including apolipoprotein E (apo E) alleles and hypertension.2-7

Conflicting results regarding the association of the apo E type e2 (apo E2) and/or e4 (apo E4) allele with lobar ICH have been reported.2-6 Greenberg et al3,6 reported an association between apo E4 and lobar ICH, but Yamada et al2 were unable to confirm the association in a Japanese population. Nicoll et al4 did not find an association with apo E4 but reported that apo E2 was associated with lobar ICH. McCarron and Nicoll5 reported that apo E2 was specific for cerebral amyloid angiopathy (CAA)-related hemorrhage. These studies, however, did not examine the potential effect of regulatory regions or nearby mutations.

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In a previous study, we found that having either an apo E4 or an apo E2 allele was a risk factor for lobar ICH, but the study had insufficient power to determine which of the alleles led to the association.6 No report of other polymorphisms of the apo E gene and the risk of lobar ICH exists. The −491 AA promoter polymorphism was found to increase amyloid deposition among subjects with apo E4 but not among those without an apo E4 allele.8 Given the shared findings of cerebral amyloid angiopathy in lobar ICH and in Alzheimer’s disease, we included promoter and regulatory region polymorphisms of the apo E gene into our analysis.

Association studies of common variants have been proposed as powerful approaches for identifying genetic variants
underlying complex diseases. A haplotype is defined as a combination of multiple alleles on 1 chromosome. Haplotype analysis refers to the simultaneous study of multiple alleles. Such studies are facilitated by linkage disequilibrium (LD) mapping, in which alleles at adjacent loci are inherited together because of their nonrandom gametic association. Thus, each single-nucleotide polymorphism (SNP) provides information on other mutations that are near the SNP. In addition, the effect of regulatory regions on disease-causing mutations may be observed. In this study, we performed haplotype analyses to assess the levels of association between SNPs on the apo E gene and lobar ICH.

**Methods**

The methods of the Genetic and Environmental Risk Factors of Hemorrhagic Stroke Study have been published previously. The study was approved by the institutional review boards of all participating hospitals. All patients with a potential ICH or subarachnoid hemorrhage and residing within 50 miles of the University of Cincinnati are identified by surveillance of hospital emergency and radiology departments and hospital discharge diagnoses.

![Figure 1. LD correlation ($R^2$) and distribution ($D'$/H11032) between SNPs among whites. Abbreviations are as defined in text.](image1)

![Figure 2. LD correlation ($R^2$) and distribution ($D'$/H11032) between SNPs among blacks. The $R^2$ refers to how often the genotype at 1 marker is correlated with the corresponding pair's genotype. $D'$ refers to the level of LD between a pair of markers or how closely the genotype at 1 locus predicts the genotype at the second locus. SNPs rs157581, rs1160983, rs1160985, rs110984, and rs10119 are in the 5' upstream region. SNPs rs769446 and rs405509 are in the promoter region. The remaining SNPs are within the exons of the gene. Abbreviations are as defined in text.](image2)
ICH was defined as a nontraumatic, abrupt onset of severe headache, altered level of consciousness, and/or focal neurologic deficit associated with a focal collection of blood within the brain parenchyma not due to hemorrhagic conversion of a cerebral infarct. Patients were eligible if they were ≥18 years old and had no evidence of trauma or brain tumor as the cause of hemorrhage. Cases of vascular malformation related hemorrhage were excluded from the current analysis.

A subset of cases was approached for direct interview and genetic sampling. If the patient was unable to be interviewed, a proxy was interviewed. We recorded a history of hypertension as well as the 2 alleles that determine apo E status. A global statistical hypothesis. Less than high school and high school levels of education were compared with greater than high school education. Treated and untreated hypertension were compared with no hypertension, and treated and untreated hypercholesterolemia were compared with no hypercholesterolemia.

### Apo E SNPs
SNP selection was based on position and function, relative physical distance, and heterozygosity rates. Coding SNPs causing nonsynonymous (rs429358, rs7412, rs769452, and rs769455) and synonymous (rs157581 and rs1160983) changes and SNPs of promoter (rs769446 and rs405509) and 5' untranslated (rs440446, rs10119, rs1160984, and rs1160985) regions were chosen from the NCBI SNP database. Apo E alleles were determined by genotypes at rs429358 and rs7412.12 Cytosines at both loci equal apo E2, thymines at both equal apo E3, and thymine at the first allele at 1 locus predicts the allele at the other.

### Multivariate Analysis
The data were manipulated and analyzed with SAS software (SAS Institute). Univariate analyses were performed with exact conditional logistic regression modeling, and multivariable analyses were performed with conditional logistic modeling. Backward elimination was used for risk factors with significance levels of \( P < 0.10 \). Apo E2 and apo E4 were forced into the model. Analyses were performed for lobar and nonlobar ICH.

### Genetic Analysis
Case-control comparison was performed separately by race, with univariate comparisons performed by \( \chi^2 \). All SNPs were found to be in Hardy-Weinberg equilibrium except for rs1160983, which was dropped from the analysis. Haplotype construction, analysis, and LD determination were performed with PHASE and confirmed with EMLD, HAPLOSTATS, HAPLOVIEW, and HELIXTREE programs. SNPs were dropped from haplotype construction if their minor allele frequency was <5% (rs1160984, rs769452, and rs769455). Haplotypes were created and compared with the HELIXTREE program, with replication performed by the HAPLOVIEW program. Subhaplotypes were created with a \( D' \) cutoff of 0.70 as well as the 2 alleles that determine apo E status. A global statistical test for haplotype analysis was performed with the R/C method.13 Multiple comparison correction was performed with the Bonferroni method.

### Results
Between May 1997 and December 2002, 315 cases of ICH were enrolled. Of these, 112 had a lobar ICH, of whom 5 had experienced a prior hemorrhage, leaving 107 cases. Of these, 86 were white; 19, black; 1, white Hispanic; and 1, Asian. Of these, 98 had 2 matching controls and 9 had 1 matching control.

None of the individual polymorphisms were associated with lobar ICH after controlling for multiple testing (see online supplement). LD was determined for each pair of polymorphisms for whites and blacks (Figures 1 and 2). Normalized disequilibrium (\( D' \) ranges from −1 to 1) is a measure of how closely 2 polymorphisms are observed to occur together. A \( D' \) close to 0 or equal to 1 suggests that the allele at 1 locus predicts the allele at the other.

## Table 1. Univariate and Multivariate Odds Ratios (ORs) and (95% Confidence Intervals) for Lobar ICH

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases, no. (%)</th>
<th>Controls, no. (%)</th>
<th>Univariate OR</th>
<th>Multivariate OR</th>
<th>Multivariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated hypertension</td>
<td>33 (32.4)</td>
<td>75 (40.1)</td>
<td>0.77 (0.42–1.38)</td>
<td>0.88 (0.44–1.78)</td>
<td>0.7229</td>
</tr>
<tr>
<td>Untreated hypertension</td>
<td>13 (12.8)</td>
<td>14 (7.5)</td>
<td>1.79 (0.64–5.09)</td>
<td>3.59 (1.09–11.80)</td>
<td>0.0351</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (8.8)</td>
<td>28 (15.0)</td>
<td>0.52 (0.20–1.25)</td>
<td>Not included</td>
<td>...</td>
</tr>
<tr>
<td>Moderate alcohol use</td>
<td>20 (19.6)</td>
<td>61 (32.6)</td>
<td>0.52 (0.26–1.00)</td>
<td>0.59 (0.30–1.16)</td>
<td>0.1270</td>
</tr>
<tr>
<td>Frequent alcohol use</td>
<td>9 (8.8)</td>
<td>6 (3.2)</td>
<td>2.36 (0.68–9.26)</td>
<td>3.45 (0.89–13.41)</td>
<td>0.0732</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>16 (15.7)</td>
<td>7 (3.7)</td>
<td>5.68 (1.96–20.00)</td>
<td>8.55 (2.57–28.40)</td>
<td>0.0005</td>
</tr>
<tr>
<td>First-degree relative with ICH</td>
<td>6 (5.9)</td>
<td>2 (1.1)</td>
<td>6.00 (1.07–60.79)</td>
<td>22.71 (2.96–174.18)</td>
<td>0.0027</td>
</tr>
<tr>
<td>Less than high school education</td>
<td>23 (22.6)</td>
<td>27 (14.4)</td>
<td>2.25 (1.07–4.82)</td>
<td>1.76 (0.75–4.10)</td>
<td>0.1935</td>
</tr>
<tr>
<td>High school education</td>
<td>43 (42.2)</td>
<td>71 (38.0)</td>
<td>1.54 (0.88–2.72)</td>
<td>1.92 (0.99–3.71)</td>
<td>0.0533</td>
</tr>
<tr>
<td>Treated hypercholesterolemia</td>
<td>7 (6.9)</td>
<td>30 (16.0)</td>
<td>0.36 (0.12–0.95)</td>
<td>0.23 (0.07–0.80)</td>
<td>0.0210</td>
</tr>
<tr>
<td>Untreated hypercholesterolemia</td>
<td>13 (12.8)</td>
<td>32 (17.1)</td>
<td>0.64 (0.29–1.32)</td>
<td>0.73 (0.33–1.62)</td>
<td>0.4350</td>
</tr>
<tr>
<td>Prior ischemic stroke</td>
<td>7 (6.9)</td>
<td>3 (1.6)</td>
<td>4.13 (0.93–24.98)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Apo E2</td>
<td>21 (20.6)</td>
<td>61 (32.6)</td>
<td>1.49 (0.77–2.90)</td>
<td>1.22 (0.57–2.64)</td>
<td>0.6122</td>
</tr>
<tr>
<td>Apo E4</td>
<td>39 (38.2)</td>
<td>48 (25.7)</td>
<td>1.85 (1.06–3.26)</td>
<td>2.25 (1.18–4.28)</td>
<td>0.0139</td>
</tr>
</tbody>
</table>

Not included indicates not included in the final model; NS, not significant. Multivariate ORs are given for factors in the final model. Factors such as treated hypertension were included in the final model despite being nonsignificant because they were comparison factors for significant ones, such as untreated hypertension. Apo E2 was forced into the model because its association was a primary hypothesis. Less than high school and high school levels of education were compared with greater than high school education. Treated and untreated hypertension were compared with no hypertension, and treated and untreated hypercholesterolemia were compared with no hypercholesterolemia.
Table 2 presents the prevalence and univariate and multivariate risks for lobar ICH. The rs769455 locus was significant for both whites and blacks. The most common haplotypes containing apo E2, E3, and E4 did not demonstrate significant associations with lobar ICH. Table 4 presents pairwise haplotype analyses among whites and blacks. Additional haplotype analyses are available in the online supplement.

**Discussion**

Controversial literature exists with regard to the association of apo E alleles and lobar ICH. We report that apo E4 is independently associated with lobar ICH. We support this finding with an overall haplotype association of the apo E gene with lobar ICH.

These differences may help explain some of the conflicting findings in the literature. Although we did not find an association between the apo E2 allele and lobar ICH, we did find that haplotypes that contained the apo E2 allele were associated with lobar ICH and that the most common haplotypes that contained apo E4 were not associated with lobar ICH. Thus, if the populations studied by Nicoll et al and McCarron and Nicoll
containing a large proportion of these haplotypes, an association of apo E2 with lobar ICH could be found.

One hypothesis to explain these findings is that mutations of the regulatory regions may affect risk. Our study is the first report on the 5′ upstream regulatory and promoter regions of the apo E gene and the risk of ICH and is congruent with prior studies reporting that mutations of the promoter region may mediate the risk of Alzheimer disease.14–16

The question arises as to whether or not the haplotype association is being driven primarily by apo E4 or apo E3 alleles. If there were no additional risk or modifying risk by the other polymorphisms in the haplotype, then the risks accorded by apo E4 or apo E3 would be relatively uniform across haplotypes, and the most common haplotypes would be the most likely to demonstrate the effect, given a higher power to detect an association. However, we have found that the most common haplotypes had no association with risk, which reinforces the possibility that other polymorphisms may affect risk. This hypothesis requires confirmation through biologic studies of the relation of mutations in these regions with apo E production and/or function.

The biologic mechanism of the association of apo E with lobar ICH may be explained through their association with CAA. CAA occurs in 50% to 79% of patients with Alzheimer disease, which has also been associated with apo E4.17,18 In addition to the studies described earlier, McCarron and Nicoll3 reported that the risk of apo E2 with CAA occurred among subjects with and without Alzheimer disease, whereas the association of apo E4 with CAA was correlated with concomitant Alzheimer disease. This suggests that apo E2 is a specific risk factor for CAA-related hemorrhage, whereas apo E4 is related to CAA in general.

The amyloid precursor protein is cleaved by α-secretase, leaving a transmembrane portion of the protein ranging in length from 37 to 42 amino acids. Researchers have found that β-amyloid-42 is significantly elevated in Alzheimer disease patients and their first-degree relatives.19 McCarron et al20 reported that patients with CAA-related hemorrhage were more reactive to β-amyloid-42. Rosand et al21 reported an association of apo E2 among 41 patients with warfarin-related ICH compared with 66 controls, in which 7 of 11 subjects had pathologic evidence of CAA. In animal models, knockin mice with human apo E4 developed amyloid plaques as well as CAA, whereas apo E3 knockin mice developed almost no CAA or parenchymal plaques.22

We were surprised to find that untreated hypertension was a significant risk factor for lobar ICH. Previously, we reported that hypertension appeared to be a significant risk factor for nonlobar ICH but not lobar ICH.7 Later, we reported that untreated hypertension was a greater risk factor than treated hypertension for ICH.10 With double the sample size of our initial report, we included treated and untreated hypertension into the analysis and found that untreated hypertension was a significant risk factor for lobar ICH.

A limitation of our analysis is that survival bias may have affected our results. However, we have reported that our interviewed cases were similar to noninterviewed cases with respect to major risk factors.10,11 In addition, interrater agreement on assessment of the location of ICH was not evaluated and may have led to misclassification bias. Multiple testing is always a limitation in genetic association studies, particularly with haplotype analyses. Finally, the haplotype analysis was not adjusted for the presence of other factors, because individual haplotype assignment would include additional assumptions that may be less reliable. Independent confirmation of our findings in a different cohort is required.

Our study confirms and extends the literature supporting an association of apo E4 with lobar ICH. It further demonstrates that inclusion of polymorphisms of the 5′ upstream and promoter into haplotypes yields a significant association with lobar ICH, suggesting that other mutations in the region may affect risk.

**Acknowledgments**

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**References**


<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Frequency</th>
<th>No.</th>
<th>Frequency</th>
<th>No.</th>
<th>P</th>
<th>D'</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Whites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T,C (apo E3)</td>
<td>0.684</td>
<td>118</td>
<td>0.786</td>
<td>266</td>
<td>0.0187</td>
<td></td>
</tr>
<tr>
<td>C,C (apo E4)</td>
<td>0.229</td>
<td>39</td>
<td>0.141</td>
<td>48</td>
<td>0.0211</td>
<td></td>
</tr>
<tr>
<td>T,T (apo E2)</td>
<td>0.086</td>
<td>15</td>
<td>0.073</td>
<td>25</td>
<td>0.645</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall P=0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Blacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T,C (apo E3)</td>
<td>0.771</td>
<td>28</td>
<td>0.757</td>
<td>53</td>
<td>0.881</td>
<td></td>
</tr>
<tr>
<td>C,C (apo E4)</td>
<td>0.076</td>
<td>3</td>
<td>0.143</td>
<td>10</td>
<td>0.224</td>
<td></td>
</tr>
<tr>
<td>T,T (apo E2)</td>
<td>0.153</td>
<td>6</td>
<td>0.100</td>
<td>7</td>
<td>0.346</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall P=0.554</td>
<td></td>
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</table>

CI indicates confidence interval.


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**Editorial Comment**

**Epistasis Is Coming Are We Ready?**

For physicians and patients, the central challenge of human genetics is unraveling the genetic architecture of human diseases. Depending on the disease, this architecture can range from simple to complex. In the so-called mendelian diseases, 1 mutation in a single gene is sufficient to cause disease, whereas more complex diseases may involve changes in single genes, multiple genes, or even combinations of alleles within the same gene. The payoff for successful disease-gene discovery is likely to be enormous, leading to novel biologic discoveries and innovative interventions that can alleviate human suffering. The search so far, however, has been slower than we would all like. The nagging problem is that for most common diseases, the culprit gene variants contribute only a small proportion of disease risk. Successful studies must therefore detect relatively weak associations, and finding weak associations requires very large samples of patients.

Epistasis, broadly defined, is the interaction betweenalleles at different loci, or positions, in the genome. Most simply, a variant at 1 locus can prevent a variant at another locus from manifesting its effect.1,2 These combinations of variants may be in different genes, or they may be within the same gene, eg, within the regulatory and coding regions. Ultimately, epistatic interaction is synergistic, with an effect that differs from the simple sum of the effects of each individual allele. The analysis of haplotypes has become a widely used technique in the search for disease genes because it allows investigators to assess the disease contribution of large sections of a chromosome without having to test all of the single-nucleotide polymorphisms (SNPs) contained in those sections. Haplotypes, sets of SNPs contained within a given stretch of DNA along a chromosome, may hold the key to discovery of the gene variants that cause disease. When there is extensive linkage disequilibrium across a region containing a haplotype, it is likely that this region of DNA has been passed down from generation to generation nearly unchanged. As a result, large numbers of individuals across the population can share a small number of
haplotype variants. When this is the case, genotyping a few “tag” SNPs may serve to identify a large proportion of the genetic variation in the region of the haplotype. The genotype of a “tag” SNP will predict genotypes at multiple nearby SNPs. Theoretically, then, one can start by genotyping the “tag” SNPs in a region first, determine the haplotypes formed by the “tags,” and then assess whether a particular haplotype or set of “tags” is more commonly found among cases or controls. Once the culprit haplotype is found, investigators can then focus on finding the variants embedded within the haplotype.

Although the theoretical underpinning of this approach is far from straightforward or without controversy, it is nonetheless the basis of the International HapMap Project, which aims to develop a haplotype map of the human genome that can, among other things, supply information on all of the “tags” necessary to capture a large proportion of the variation across most of the genome (http://www.hapmap.org). The hope is that with these “tags” in hand, clinician scientists can then efficiently examine long stretches of the genome, or even the entire genome, in their study population by sticking to the “tags.”

The analysis of Woo et al uses haplotypes to ask a different question. Rather than picking “tags” as a means of efficiently discovering new gene regions of interest, they focused on the region of DNA containing the apolipoprotein E gene (APOE) and asked whether particular sets of SNPs might play a role in risk for the development of lobar intracerebral hemorrhage (ICH). In particular, they sought to determine whether regulatory variants that might influence gene expression interact with the coding variants responsible for the ε2 and ε4 alleles that have been well studied by their group and others.

This is an epistatic analysis. Woo et al are the first to ask such a question in lobar ICH, a disease that they have shown has both a strong genetic component and an important element of family aggregation. With just >200 chromosomes from cases for analysis, however, power is limited, particularly given the large number (26) of haplotypes studied. Furthermore, the small numbers make the haplotype results unstable—the frequency of any studied ε2 or ε4 haplotype among white subjects, for example, never exceeds 4.3%, and among controls the highest value is 5.1% (Table 2 in Woo et al).

So, could variation in regulatory sequences influence the effect of ε2 or ε4 on the risk of lobar ICH, perhaps through modulation of gene expression? If so, could a treatment that alters APOE gene expression reduce the risk of lobar ICH? Experiments in transgenic mice demonstrate that human apo ε4 promotes the development of cerebral amyloid angiopathy, a leading cause of ICH in the elderly, although similar studies of ε2 have not been reported. The confirmation of epistatic interactions at the level of human APOE, however, requires further study involving many more patients.

The Greater Cincinnati–Northern Kentucky investigators have been international leaders in assembling well-phenotyped cohorts of patients with ischemic and hemorrhagic stroke for genetic studies, but even a center as successful as theirs has only been able to assemble just >100 patients with lobar ICH for study. Genetic studies of epistatic interactions within APOE are likely to require 10 times as many patients, making the need for collaboration among centers essential for the future. Such collaboration will, of course, require the collection of common phenotypic information. Leaders in the field have recognized the need for this kind of common dataset for the study of another clinical manifestation of cerebrovascular disease, vascular cognitive impairment. A collaborative effort led by the National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network will establish minimal research datasets that can be completed at centers across the globe to facilitate future genetics studies. Initiatives like these are likely to serve future studies of the range of cerebrovascular disease.

As the cost of genotyping continues to plummet, the challenge of phenotyping becomes more and more pressing. A role for epistatic interactions in the genetic architecture of complex diseases like stroke may well be the rule rather than the exception. Thus, the challenge for the field of vascular neurology will be phenotyping large numbers of patients adequately and uniformly.

Acknowledgments

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References


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