Variants at APOE Influence Risk of Deep and Lobar Intracerebral Hemorrhage

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Objective: Prior studies investigating the association between APOE alleles ε2/ε4 and risk of intracerebral hemorrhage (ICH) have been inconsistent and limited to small sample sizes, and did not account for confounding by population stratification or determine which genetic risk model was best applied.

Methods: We performed a large-scale genetic association study of 2189 ICH cases and 4041 controls from 7 cohorts, which were analyzed using additive models for ε2 and ε4. Results were subsequently meta-analyzed using a random effects model. A proportion of the individuals (322 cases, 357 controls) had available genome-wide data to adjust for population stratification.

Results: Alleles ε2 and ε4 were associated with lobar ICH at genome-wide significance levels (odds ratio [OR] = 1.82, 95% confidence interval [CI] = 1.50–2.23, p = 6.6 × 10^{-10}, and OR = 2.20, 95%CI = 1.85–2.63, p = 2.4 × 10^{-11}, respectively). Restriction of analysis to definite/probable cerebral amyloid angiopathy ICH uncovered a stronger effect. Allele ε4 was also associated with increased risk for deep ICH (OR = 1.21, 95% CI = 1.08–1.36, p = 2.6 × 10^{-4}). Risk prediction evaluation identified the additive model as best for describing the effect of APOE genotypes.

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Interpretation: APOE ε2 and ε4 are independent risk factors for lobar ICH, consistent with their known associations with amyloid biology. In addition, we present preliminary findings on a novel association between APOE ε4 and deep ICH. Finally, we demonstrate that an additive model for these APOE variants is superior to other forms of genetic risk modeling previously applied.

**Patients and Methods**

**Participating Studies**

Genotype and phenotype data for ICH cases and controls were provided by ISGC investigators from the following studies: North American (United States) multicenter Genetics of Cerebral Hemorrhage on Anticoagulation (GOCHA) Study, Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS), University of Cincinnati (Cincinnati, OH), the Hospital del Mar (Barcelona, Spain) ICH study (HM-ICH), Jagiellonian University (Krakow, Poland) Hemorrhagic Stroke Study (JUHSS), Lund University (Lund, Sweden) Hemorrhagic Stroke Study (LUHSS), Medical University of Graz (Graz, Austria) ICH study (MUG-ICH), and the Vall d’Hebron Hospital (Barcelona, Spain) ICH Study (VHH-ICH). All studies were approved by the Institutional Review Boards (IRB) or Ethics Committee (EC) of participating institutions, and all participating subjects provided informed consent for participation in this study, including APOE and genome-wide genotyping.

**Subjects**

Subjects enrolled in each study included primary acute ICH cases aged >55 years presenting to the emergency departments of participating institutions (all accredited stroke centers). Eligibility for study participation required neuroimaging (CT or MRI) confirmation of hemorrhagic stroke (Table 1). Exclusion criteria included the presence of trauma, brain tumor, hemorrhagic transformation of a cerebral infarction, vascular malformation, or any other perceived cause of secondary ICH. Only individuals of self-described European or European-American ancestry were included for analysis in each study. Individuals of African-American ancestry (63 lobar ICH cases, 110 deep ICH cases, and 297 controls) enrolled in GOCHA and GERFHS were analyzed as a separate cohort (US-AA) for replication purposes, with additional adjustment for recruitment site (GOCHA vs GERFHS).

ICH location was assigned based on admission CT scan by stroke neurologists at each participating site. ICH isolated to the cortex (with or without involvement of subcortical white matter) was defined as lobar ICH, while ICH selectively involving the thalamus, basal ganglia, or brainstem was defined as deep (nonlobar) ICH. Multiple concurrent bleeds involving deep and lobar territories were defined as mixed ICH and represented an exclusion criterion. Similarly, subjects presenting with evidence of prior bleeds in a different location than the index (enrollment) ICH were excluded from analysis. Cerebellar hemorrhages were also not analyzed in the present study. Individuals with CT scans of insufficient quality for location determination were excluded from all analyses. When ICH location assignment was not clear, the scan was reviewed by a group of...
<table>
<thead>
<tr>
<th></th>
<th>GOCHA</th>
<th>GERFHS</th>
<th>JUHSS</th>
<th>MUG-ICH</th>
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<td>Subjects, n</td>
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<td>Lobar ICH 203, Deep ICH 337, Controls 1304</td>
<td>Lobar ICH 102, Deep ICH 130, Controls 429</td>
<td>Lobar ICH 77, Deep ICH 114, Controls 1023</td>
</tr>
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<td>64.3 (17.1)</td>
<td>63.2 (13.3)</td>
<td>70.2 (13.2)</td>
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<td>45</td>
<td>48</td>
<td>45</td>
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<td>45</td>
<td>48</td>
<td>0.13</td>
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<td></td>
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<td>ApoE ε4, MAF 0.21</td>
<td>ApoE ε2, MAF 0.13</td>
<td>ApoE ε4, MAF 0.13</td>
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<td>ApoE ε4, MAF 0.21</td>
<td>ApoE ε2, MAF 0.13</td>
<td>ApoE ε4, MAF 0.13</td>
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<tr>
<td>HM-ICH</td>
<td>Lobar ICH 66, Deep ICH 103, Controls 185</td>
<td>Lobar ICH 42, Deep ICH 89, Controls 161</td>
<td>Lobar ICH 43, —, Controls 87</td>
<td>Lobar ICH 63, Deep ICH 110, Controls 297</td>
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<td>Age, mean (SD)</td>
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<td>74.5 (9.4)</td>
<td>72.6 (6.5)</td>
<td>63.4 (17.5)</td>
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<td>Hypertension (%)</td>
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<td>ApoE ε2, MAF 0.11</td>
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<td>ApoE ε4, MAF 0.21</td>
<td>ApoE ε2, MAF 0.13</td>
<td>ApoE ε4, MAF 0.13</td>
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</table>

**GERFHS** = Genetic and Environmental Risk Factors for Hemorrhagic Stroke Study at the University of Cincinnati (Cincinnati, OH); **GOCHA** = Multicenter North-American (US) Genetics of Cerebral Hemorrhage on Anticoagulation Study; **HM-ICH** = Hospital del Mar (Barcelona, Spain) ICH Study; **ICH** = intracerebral hemorrhage; **JUHSS** = Jagiellonian University (Krakow, Poland) Hemorrhagic Stroke Study; **LUHSS** = Lund University (Lund, Sweden) Hemorrhagic Stroke Study; **MAF** = minor allele frequency; **MUG-ICH** = Medical University of Graz (Graz, Austria) ICH Study; **SD** = standard deviation; **US-AA** = African-American subjects recruited in the United States (Boston, MA, and Cincinnati, OH) as part of the GOCHA and GERFHS studies; **VHH-ICH** = Val d’Hebron Hospital (Barcelona, Spain) ICH Study.
study neurologists and neuroradiologists for consensus. Scans lacking a consensus location were excluded from analysis. All readers interpreting neuroimaging data were blinded to clinical and APOE genotype information.

Recorded clinical characteristics included history of hypertension (clinical diagnosis of hypertension or history of antihypertensive drug use), pre-ICH exposure to warfarin, antiplatelet agents and statins, first-degree relative history of ICH, and alcohol and tobacco use.

Controls were enrolled from the same population as the cases at each participating institution, and included only individuals aged >55 years at time of enrollment. Controls were confirmed to have no medical history of ICH, Alzheimer’s disease, or pre-enrollment dementia by means of interview and review of medical records. Recorded clinical characteristics were identical to ICH cases.

Cerebral Amyloid Angiopathy-Related ICH
In order to determine the specificity of APOE alleles for ICH related to cerebral amyloid angiopathy (CAA), we separately analyzed definite and/or probable CAA ICH cases and possible CAA cases for association with e2 or e4. A total of 223 lobar ICH cases from the GOCHA cohort had pathology and/or MRI gradient-echo (GRE) data available for analysis. Microbleed presence and location was assessed for these individuals according to validated protocols. Briefly, MRI with GRE images (repetition time [TR] = 750msec/echo time [TE] = 50msec/slice thickness = 5–6mm/interslice gap = 1mm) was performed using a 1.5-T magnet. Cortical (lobar) and deep hemorrhages were classified as microbleeds according to their size (diameter < 5mm). All MRI analyses were performed and recorded without knowledge of clinical or genetic information. Only MRI scans obtained within 90 days from the index ICH were considered for analysis.

Definite/probable CAA was defined as lobar ICH in the presence of confirmed CAA pathology and/or microbleeds confined to the lobar brain region (n = 82). Possible CAA included all remaining lobar ICH cases lacking pathology and lobar microbleeds (n = 141). Each group was matched with separate hemorrhage-free controls based on age (within 5 years of the age of the index ICH case), gender, and hypertension status in a 1:2 casecontrol ratio.

Genotyping
All DNA samples were isolated from fresh or frozen blood, quantified using a quantification kit and normalized to a concentration of 30ng/μl. Two genotype-determining variants in APOE, rs7412, and rs429358, were independently genotyped using 2 separate assays. The allelic reads from the 2 assays were then translated to APOE genotypes (e3/e3, e3/e4, e4/e4, e3/e2, e2/e2, and e2/e4). All genotyping personnel were blinded to clinical and neuroimaging data. Genotype and phenotype data were subsequently submitted to the Coordinating Center (Massachusetts General Hospital) for analysis. All case and control groups were found to be in Hardy-Weinberg equilibrium for APOE genotypes. Genome-wide genotyping was performed on a subset of the GOCHA samples (322 cases, 357 controls) using the Illumina 610-Quad array. Genotypes were called using BeadStudio v 3.2.

Statistical Analysis

INDIVIDUAL STUDIES. Single-study level data were initially analyzed by logistic regression under independent additive genetic models. Our multivariate model included the following variables: age, gender, pre-ICH history of hypertension, number of i4 alleles (0, 1, or 2), and number of e2 alleles (0, 1, or 2). Subsequent analyses also adjusted for warfarin or antiplatelet agent exposure at time of ICH, smoking history (ever smoker), alcohol use (>1 drink/week), family history of ICH, pre-ICH history of ischemic stroke, and pre-ICH history of hyperlipidemia or statin exposure. None of the additional covariates modified the results from the initial regression model (data not shown). We therefore extracted results from the previously described model (adjusting for age, gender, and pre-ICH hypertension) for subsequent meta-analysis (see Meta-Analysis). Differences in effect sizes comparing lobar vs deep ICH and definite/probable CAA vs possible CAA were assessed using the Breslow-Day test.

META-ANALYSIS. Results from multivariate models for individual studies were combined using a conservative inverse variance random effects model (DerSimonian-Laird). Results from individuals with genome-wide data were entered separately as an independent study. This allowed direct comparison of results from studies controlling for population stratification with those without control. Meta-analysis heterogeneity was quantified by computing Cochrane’s Q and corresponding p and I² (percent of effect size attributable to heterogeneity). Heterogeneity was considered to be significant for heterogeneity p < 0.10 (due to the conservative nature of Cochrane’s test) or I² > 0.20. We decided to set the threshold for significance in the initial meta-analysis at the genome-wide level (p < 5 × 10⁻⁸). This threshold is equivalent to the estimated Bonferroni correction for all independently testable common variants (minor allele frequency > 0.01) in the human genome (ie, not correlated by linkage disequilibrium on the basis of HapMap and sequencing data). All analyses were performed using the R statistical software v 2.10.0 (http://www.r-project.org).

GENETIC MODELING. We reanalyzed all available data under dominant and recessive models, and compared predictive power for disease status to the initial results from the additive model. Comparison of predictive power for different genetic models was carried out using both a likelihood ratio test (LRT)-based method and by analyzing receiver operator characteristic (ROC) curves for disease status prediction. Both analyses returned very similar results.

POPULATION STRATIFICATION. To determine whether the frequency of APOE alleles varies across different populations, a finding that could lead to confounding due to population stratification, we extracted MAF data for European control individuals from all genetic studies of APOE listed in PubMed (www.pubmed.gov) as of December 1, 2010 (Supporting Table S1). These data were subsequently correlated with latitude and
longitude of their geographic position in Europe using a linear regression method. This analysis included size of the cohort and number of studies performed in each region as covariates.

We were able to control for population stratification in samples with available genome-wide data (322 cases, 357 controls) using PLINK v. 1.07 (http://pngu.mgh.harvard.edu/~purcell/plink) to perform principal component analysis (PCA) in accordance with previously published methods. Principal components 1 and 2 were extracted from the PCA results and entered as additional covariates in logistic regression analysis for these samples.

Results

Lobar ICH

We meta-analyzed 931 lobar ICH cases and 3744 controls from 7 studies, and found significant genome-wide association between lobar ICH risk and ε2 (odds ratio \[ OR = 1.82, p = 6.6 \times 10^{-10} \]) and ε4 (OR = 2.20, \[ p = 2.4 \times 10^{-11} \]) (Fig 1A, B). We identified no evidence of heterogeneity among studies (Table 2).

Deep ICH

We separately analyzed definite/probable CAA ICH cases (n = 82) and possible CAA ICH cases (n = 141) samples in the subset of the GOCHA lobar ICH cases with available pathology and/or MRI data (n = 223). We then compared effect sizes in order to determine the specificity of the APOE association to definite/probable CAA (Table 3). Definite/probable CAA was associated with both ε4 (OR = 3.08, \[ p < 0.001 \]) and ε2 (OR = 2.89, \[ p < 0.001 \]), while no association was evident for possible CAA (ε4: OR = 1.21, \[ p = 0.46 \]; and ε2: OR = 1.02, \[ p = 0.57 \]). Effect-size point estimates and 95% confidence intervals [CIs] were significantly larger for definite/probable CAA ICH compared to possible CAA ICH for both ε4 (\[ p = 0.012 \]) and ε2 (\[ p = 0.032 \]).

We meta-analyzed 1085 deep ICH cases and 3657 controls from 6 studies, and found an association between deep ICH risk and ε4 (OR = 1.21, 95% CI = 1.08–1.36). This association failed to surpass the predefined genome-wide
significance threshold \( p = 2.6 \times 10^{-4} \). No association was identified for \( e_2 \) (OR = 1.07, 95% CI = 0.86–1.33, \( p = 0.54 \)) (see Fig 1C, D). We identified no evidence of meta-analysis heterogeneity (see Table 2). To explore whether the inclusion of misclassified lobar ICH cases in the group of deep ICH category might have generated a spurious association for \( e_4 \), we reanalyzed brainstem ICH cases (less likely to represent misdiagnosed lobar ICH due to the anatomic location and smaller average ICH volume) separately from the rest of the deep ICH cases. We then compared effect sizes and looked for meta-analysis heterogeneity that might indicate differential effects due to misclassification bias. The OR for \( e_4 \) in brainstem ICH (OR = 1.21) was identical to our meta-analysis estimate for deep ICH, and we identified no evidence of heterogeneity between studies (heterogeneity \( p = 0.99, I^2 = 0.00, 95\% CI = 0.00–0.00 \)). Comparison of effect sizes for \( e_4 \) in lobar ICH vs deep ICH resulted in a statistical significant difference (\( p < 0.001 \)).

**Table 2: Meta-Analysis: Association of APOE Alleles with Lobar and Deep ICH**

<table>
<thead>
<tr>
<th>Allele</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>( p )</th>
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<tr>
<td>Lobar ICH</td>
<td></td>
<td></td>
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<tr>
<td>e2</td>
<td>931</td>
<td>3744</td>
<td>1.82</td>
<td>1.50–2.23</td>
<td>6.6 \times 10^{-10}</td>
<td>0.98</td>
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<tr>
<td>e4</td>
<td>931</td>
<td>3744</td>
<td>2.20</td>
<td>1.85–2.63</td>
<td>2.4 \times 10^{-11}</td>
<td>0.99</td>
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<td>Deep ICH</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>e2</td>
<td>1085</td>
<td>3657</td>
<td>1.07</td>
<td>0.86–1.33</td>
<td>0.54</td>
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<tr>
<td>e4</td>
<td>1085</td>
<td>3657</td>
<td>1.21</td>
<td>1.08–1.36</td>
<td>2.6 \times 10^{-4}</td>
<td>0.97</td>
</tr>
</tbody>
</table>

CI = confidence interval; ICH = intracerebral hemorrhage; \( I^2 \) = percentage of meta-analysis effect size due to heterogeneity; OR = odds ratio.

**Replication in African-American Individuals**

We attempted replication of observed associations in 63 lobar ICH cases, 110 deep ICH cases, and 297 controls of U.S. African-American ancestry (US-AA) enrolled in GOCHA and GERFHS. We observed replication of associations between lobar ICH and both \( e_2 \) (OR = 1.99, 95% CI = 1.10–3.61, \( p = 0.036 \)) and \( e_4 \) (OR = 2.10, 95% CI = 1.09–4.03, \( p = 0.012 \)). Inclusion of US-AA samples in meta-analysis with European ancestry samples did not introduce significant heterogeneity (\( p = 0.99, I^2 = 0.0 \)). While we did not replicate the

**Table 3: Association of APOE Alleles with CAA-Related ICH**

<table>
<thead>
<tr>
<th>Allele</th>
<th>Cases</th>
<th>Controls</th>
<th>MAF (Cases)</th>
<th>MAF (Controls)</th>
<th>OR</th>
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<th>( p )</th>
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<tr>
<td>e2</td>
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<td>0.07</td>
<td>2.89</td>
<td>1.57–5.33</td>
<td>5.2 \times 10^{-4}</td>
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<tr>
<td>e4</td>
<td>82</td>
<td>164</td>
<td>0.25</td>
<td>0.12</td>
<td>3.08</td>
<td>1.68–5.63</td>
<td>4.6 \times 10^{-4}</td>
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<tr>
<td>e2</td>
<td>141</td>
<td>282</td>
<td>0.09</td>
<td>0.07</td>
<td>1.02</td>
<td>0.63–1.65</td>
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<tr>
<td>e4</td>
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<td>282</td>
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<td>0.12</td>
<td>1.21</td>
<td>0.74–1.99</td>
<td>0.46</td>
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See Woo et al. \textsuperscript{12}

CAAs = cerebral amyloid angiopathy; CI = confidence interval; ICH = intracerebral hemorrhage; MAF = minor allele frequency; OR = odds ratio.
association between ε4 and deep ICH (p = 0.21), the effect size estimate (OR = 1.15) was consistent with that observed in the European ancestry samples. Inclusion of US-AA samples in the deep ICH meta-analysis did not introduce significant heterogeneity (p = 0.99, I^2 = 0.0) and increased the level of significance of the observed association (p-value for all individuals = 1.0 x 10^{-4} vs p-value for Europeans only = 2.6 x 10^{-4}).

**Genetic Model Specification**

We repeated all analyses for lobar ICH under dominant and recessive genetic models and compared predictive performance with the additive model based on individual genotypes. Significance was assessed using the LRT and comparing ROC curves. Disease status (lobar ICH case vs control) before and after inclusion of principal components. No difference in significance was evident for deep ICH (141 cases, 357 controls) comparing unadjusted (ε2: OR = 1.89, p = 0.012; ε4: OR = 2.28, p = 0.010) and after (ε2: OR = 1.88, p = 0.010; ε4: OR = 2.28, p = 0.009) inclusion of principal components. No difference in results was evident for deep ICH (141 cases, 357 controls) comparing unadjusted (ε2: OR = 0.99, p = 0.67; ε4: OR = 1.19, p = 0.14) and PCA-adjusted analyses (ε2: OR = 0.98, p = 0.54; ε4: OR = 1.18, p = 0.15).

**Population Stratification at the APOE Locus**

The APOE locus demonstrated significant population stratification across the European continent in our review of previously published reports. ε2 was associated with both latitude (p = 0.025) and longitude (p = 0.001) across the European continent, while ε4 was associated with latitude (p < 0.001). Observed MAFs ranged from 0.01 (Siberia) to 0.15 (UK) for ε2 and from 0.06 (Southern Italy) to 0.27 (Finland) for ε4 (Fig S1).

We therefore reanalyzed lobar and deep ICH GOCHA individuals with genome-wide association (GWAS) data (GOCHA-GWAS), comparing results before and after inclusion of principal components. For lobar ICH, the results for GOCHA-GWAS (181 cases, 357 controls) were very similar before (ε2: OR = 1.89, p = 0.012; ε4: OR = 2.28, p = 0.010) and after (ε2: OR = 1.88, p = 0.010; ε4: OR = 2.28, p = 0.009) inclusion of principal components. No difference in results was evident for deep ICH (141 cases, 357 controls) comparing unadjusted (ε2: OR = 0.99, p = 0.67; ε4: OR = 1.19, p = 0.14) and PCA-adjusted analyses (ε2: OR = 0.98, p = 0.54; ε4: OR = 1.18, p = 0.15).

**Discussion**

Our analyses show strong associations between APOE variants and lobar ICH, providing the first evidence of association between sequence variants and intracerebral hemorrhage that surpass the genome-wide significance threshold. Furthermore, we have demonstrated that previously adopted genetic models of APOE and ICH (dominant and recessive) do not provide the best possible description of the increase in ICH risk associated with the ε2 and ε4 alleles. This additional finding is important for follow-up studies of the APOE locus, as it supports the existence of a dose-response relationship between the biological effect of APOE and lobar ICH risk, which is poorly understood at present. Finally, although APOE MAF clearly varies across populations, we were able to rule out population stratification as a possible source of confounding.

We have also found that the effect of ε2 and ε4 in lobar ICH appears to be predominantly associated with CAA-related ICH. The increase in effect size observed when analysis is restricted to definite/probable CAA suggests that different mechanisms account for hemorrhagic stroke in the presence or absence of pathological and neuroimaging markers of amyloid angiopathy. Of note, effect sizes associated with definite/probable CAA-related ICH are in line with those observed for ε4 in Alzheimer’s disease, consistent with the existence of shared biological pathways between the 2 conditions that do not necessarily extend to lobar ICH as a whole.

We found an association between ε4 APOE and deep ICH, although it did not achieve genome-wide significance. Previous findings in the PROGRESS trial implicated APOE variants in deep ICH, particularly in subjects of Asian ancestry. Our data extend this association to European-ancestry individuals. We are not able to rule out the possibility that lobar or CAA-related hemorrhages misclassified as deep hemorrhage might have generated a spurious association with ε4. However, our observation that ε4 is associated with brainstem ICH, with an effect size identical to that observed in the deep ICH cohort as a whole, supports the presence of a more fundamental mechanism linking ε4 and non-CAA-related ICH. APOE plays a critical role in redistributing lipids among central nervous system cells for normal lipid homeostasis, repairing injured neurons, maintaining synaptodendritic connections, neurite outgrowth, synaptic plasticity, mitochondrial resistance to oxidative stress, and glucose use by neurons and glial cells. In multiple pathways affecting neuropathology, APOE ε4 acts directly or in concert with age, head injury, oxidative stress, ischemia, and inflammation to alter disease onset,
progression, and prognosis. Mechanisms such as these could be involved in determining individual responses to ICH-associated oxidative and ischemic stress, driving the increased frequency of ε4 in deep ICH cases. Indeed, these biological phenomena could potentially play a role in both lobar and deep ICH. Future studies, however, will be required to clarify the biological implications of our findings.

Our review of publicly available data on APOE allele frequencies in Europeans confirmed an association between geography and the ε2/ε4 genotype. This observation raises the possibility of confounding due to
population stratification in our analyses. We were able to conclusively rule out population stratification only in the GOCHA-GWAS dataset via PCA. However, effect-size estimates within the GOCHA-GWAS data are entirely in line with those observed in the cohorts without population stratification control. This observation is inconsistent with the hypothesis that observed associations for APOE are due to confounding by population stratification. Furthermore, we provide evidence of replication in African Americans, in whom minor allele frequencies for ε2 and ε4 are different from those in European-ancestry cohorts (see Table 1). In light of these results, confounding due to population stratification is theoretically possible but unlikely in our analyses.

Prior meta-analyses of the effect of APOE alleles on ICH risk failed to identify genome-wide significant associations with lobar ICH or any role for ε4 in deep ICH.4,5 However, all studies included in prior meta-analyses had substantial limitations. Sample sizes were smaller compared to the present study, and the vast majority of individuals did not have ICH location information available for analysis, which likely resulted in loss of statistical power given the divergent effect sizes for both APOE alleles in deep and lobar ICH. Furthermore, prior studies and meta-analyses applied the dominant genetic model in their description of the effects of APOE alleles on ICH risk. Our own data demonstrate that the additive model is superior to the dominant model in the description of genetic risk at APOE. Model misspecification in prior studies likely further eroded statistical power. Finally, previous meta-analyses did not have direct access to individual-level data, thus limiting the harmonization in statistical methods that we employed in our study.

Our study has limitations. Despite the large number of cases and controls available for analysis, the association between ε4 and deep ICH did not achieve genome-wide significance. This result, therefore, must be considered preliminary. Similarly, while we were able to observe a significant difference in effect size for ε2 and ε4 when comparing definite/probable vs possible CAA, we do not have sufficient power to rule out any effect in the latter. Indeed, the estimated OR for ε4 in possible CAA-related ICH is very close to the one observed for deep ICH, thereby raising the possibility of shared mechanism between non CAA-related effects in both locations.

In summary, we have identified genome-wide significant associations between APOE ε2 and ε4 and lobar ICH. Additionally, we report preliminary findings on a novel association between ε4 and deep ICH. Future studies will be required to clarify the functional mechanisms underlying the effect of APOE variants on ICH.

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Potential Conflicts of Interest
Nothing to report.

References


