Racial/ethnic variation of *APOE* alleles for lobar intracerebral hemorrhage

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Abstract

Objective

APOE ϵ 2 and ϵ 4 alleles have been associated with lobar intracerebral hemorrhage (ICH) in predominately white populations; we sought to evaluate whether this held true among black and Hispanic populations.

Methods

The Ethnic/Racial Variations of Intracerebral Hemorrhage study is a prospective, multicenter case-control study of ICH among white, black, and Hispanic participants. Controls were recruited to match cases based on age, ethnicity/race, sex, and geographic location. *APOE* genotyping and ICH location was determined blinded to clinical data.

Results

There were 907 cases of lobar ICH and 2,660 controls with *APOE* results. Both *APOE* ϵ 2 (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.1–2.0, $p = 0.01$) and *APOE* ϵ 4 (OR 2.0, 95% CI 1.5–2.6, $p < 1 \times 10^{-4}$) were associated with lobar ICH among white participants. Among black participants, neither *APOE* ϵ 2 (OR 1.0, 95% CI 0.7–1.5, $p = 0.97$) nor *APOE* ϵ 4 (OR 1.0, 95% CI 0.7–1.4, $p = 0.90$) were independent risk factors for lobar ICH. Similarly, among Hispanic participants, neither *APOE* ϵ 2 (OR 1.0, 95% CI 0.6–1.8, $p = 0.89$) nor *APOE* ϵ 4 (OR 1.2, 95% CI 0.8–1.7, $p = 0.36$) were associated with lobar ICH. Hypertension was a significant risk factor for lobar ICH in all 3 racial/ethnic groups.

Conclusion

In contrast to Caucasian patients, in which amyloid risk factors predominate in lobar ICH, we found that hypertension was the predominant risk factor for lobar ICH. While *APOE* alleles are a risk factor for lobar ICH in white patients, they appear to have a much lower effect in lobar ICH in African American and Hispanic American populations. This suggests *APOE* ϵ 2 and *APOE* ϵ 4 do not affect lobar ICH risk homogeneously across ethnic populations. In addition, hypertension has a prominent role in lobar ICH risk, particularly among minorities.

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Glossary

β = β -amyloid; CAA = cerebral amyloid angiopathy; CI = confidence interval; ERICH = Ethnic/Racial Variations of Intracerebral Hemorrhage; ICH = intracerebral hemorrhage; OR = odds ratio; SNP = single nucleotide polymorphism.

Intracerebral hemorrhage (ICH) is responsible for 10%–15% of strokes worldwide each year.¹ Among the major stroke types, ICH patients have the highest short-term² and long-term morbidity³ as well as the highest mortality.^{2,3} ICH is often categorized based on location: deep (ganglionic), lobar, cerebellar, and brainstem. Deep and lobar ICH are the most common locations affected, with relative frequencies varying greatly depending on race/ethnicity.⁴

Numerous risk factors for ICH have been identified: age,⁵ hypertension,^{4,6} anticoagulant use,^{7,8} heavy alcohol use,⁹ and cerebral amyloid angiopathy (CAA).^{10,11} CAA, resulting from amyloid protein deposition in cortical arterioles, occurs almost exclusively in cortical regions and the cerebellum.⁴ Presence of *APOE* ϵ 2 or *APOE* ϵ 4 alleles has been associated with increased risk of CAA^{12,13} and lobar ICH.^{14–17} Proposed mechanisms include alterations in amyloid processing and lipid metabolism.¹⁶ Prior studies, consisting mostly of white populations, have established significant differences in risk factors based on ICH location, with hypertension predominating in nonlobar ICH^{4,6} and *APOE* status predominating in lobar ICH in white patients.^{14–17} Because existing studies have drawn from predominantly white populations, applicability to minorities such as black and Hispanic patients is limited. We sought to evaluate whether the presence of *APOE* ϵ 2 and *APOE* ϵ 4 alleles were independent risk factors for lobar ICH in black and Hispanic populations.

Methods

Methods for the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH)¹⁸ study have been previously published.¹⁸ Briefly, the ERICH study is a multicenter case-control study of ICH in non-Hispanic white participants (hereafter “white participants”), non-Hispanic black participants (hereafter “black participants”), and Hispanic participants at 19 centers throughout the United States. Participants were 18 years or greater and fulfilled the criteria for ICH. In addition, participants had no evidence of trauma, vascular malformation or aneurysm, or brain tumor as a cause of the hemorrhage. Participants were excluded if they had evidence of malignancies leading to coagulopathy, hemorrhagic transformation of ischemic infarct, or hemorrhage secondary to dural venous sinus thrombosis.

Standard protocol approvals, registrations, and patient consents

Approval was received from the ethical standards committee on human experimentation for all experiments with human participants. Informed consent was obtained from all study

participants or their legally authorized representative (consent for research). The study is registered in clinicaltrials.gov as NCT01202864.

Recruitment

Prior studies had identified the potential for survival and mild severity bias in the recruitment of cases, which led to modifications in recruitment procedures instituted for the current study. “Hot pursuit” recruitment, rather than retrospective recruitment, was utilized in patient identification.¹⁸ Almost all cases had a clinically drawn sample that was available for genetic testing. If a case did not have a clinically drawn sample, then a study test tube was used. The clinically drawn and study test tubes were otherwise handled in an identical fashion. ICH-free controls were identified through random digit dialing to match to cases by age, ethnicity/race, sex, and geographic location. Two random-digit dialing centers are used for the study. All controls were used in ethnicity-matched analyses.¹⁸

Imaging

CT images on admission, as well as follow-up scans during hospitalization, were analyzed for ICH location by a centralized neuroimaging core. Images in digital format were deidentified and were reviewed in a standardized fashion blinded to clinical evaluations. Intraparenchymal and intraventricular volumes are measured by planimetric analysis using Alice software (Parexel Corporation, Waltham, MA).

APOE genotypes

Blood samples were collected using a standardized blood collection kit with a unique study ID for each patient. *APOE* genotype was determined based on enzymatic digestion of PCR products, blinded to clinical evaluation. The 2 *APOE* single nucleotide polymorphisms (SNP) that exist at amino acid 112 and 158 of the *APOE* gene were targeted individually by the allele-specific Taqman probes (rs429358 and rs7412). The individual genotypes of the SNP assays at the 2 sites were then combined to create a single, standard *APOE* genotype. For analysis, genotypes were assigned based on carrier frequency, and individuals who were ϵ 2/ ϵ 4 heterozygotes were included in both the ϵ 2 and ϵ 4 analysis.

Demographic variables

High cholesterol was defined by interview as participant having ever been told by a doctor that he or she has high cholesterol. Heavy alcohol use was defined as greater than 2 drinks per day on average over a week. Education level was defined by self-report as less than high school, high school, or greater than high school.

Statistical analysis

Descriptive statistics were computed as means with SDs for continuous variables and as frequencies with percentages for categorical variables. First, age-adjusted logistic regression was computed, initially analyzing all cases and controls, then only cases and controls without hypertension, and last only cases and controls with hypertension. Next, multivariate modeling was performed with backward elimination, controlled for age, sex, hypertension, anticoagulant use, education level, alcohol use, diabetes, and *APOE* alleles with all variables with $p \leq 0.05$ retained. Finally, we performed a logistic regression using cases only, controlling for age, ethnicity, ICH volume, and presence of intraventricular hemorrhage, on the subset of lobar ICH cases to determine whether *APOE* $\epsilon 2$ or *APOE* $\epsilon 4$ status was associated with worse outcomes after lobar ICH, defined as a modified Rankin Scale score ≥ 4 at 3 months poststroke.

Data availability

Deidentified data from the ERICH study were made publicly available on October 1, 2017, through the NINDS Data Archive. In addition, an analysis dataset is available through request to the study. For more information, please contact daniel.woo@uc.edu.

Results

Table 1 provides demographic data. There were 907 cases of lobar ICH (401 white patients, 237 black patients, and 269 Hispanic patients) in the ERICH study, all with *APOE* genotypes available. These cases were compared with the 2,660 controls (979 white, 886 black, and 795 Hispanic) available at the time of analysis who did not have a history of ICH. All lobar ICH cases were planned to be matched to controls by age, race, sex, and geographic location. However, for the current analysis, matching was broken to increase power so controls for nonlobar ICH controls were included. We also performed a 1:1 matched analysis for age, race, and sex with the results generally similar but with borderline significance due to reduced power. In our current study, cases were compared to controls and adjusted for age, race, sex, and location as needed. Thus, 44% of the cases were white compared with 37% of the controls, 26% of cases were black vs 33% of controls, and 30% of both cases and controls were Hispanic ($p < 0.0001$). Collectively, the lobar ICH group was 4 years older than the control group on average, the lobar ICH group had a higher proportion of female participants than the control group, and higher proportions of lobar ICH cases were hypertensive, used anticoagulants, and used alcohol heavily, compared with the control group (table 1).

Racial/ethnic variations in diabetes, education level, and *APOE* alleles were also noted (table 1). A significantly higher proportion of black patients with lobar ICH had diabetes mellitus, compared with black controls. Although higher

proportions of controls had education beyond high school in all 3 racial/ethnic groups, the proportions for the lobar ICH cases varied considerably among the racial/ethnic groups (60.7% for white participants, 38.7% for black participants, and 19.5% for Hispanic participants). Overall, women were more likely to have lobar ICH compared with controls (table 1). The *APOE* $\epsilon 2$ genotype was more common among white lobar ICH patients (23.2%) compared with white controls (17.5%), as well as compared with black patients (19.8%) and Hispanic patients (8.9%). Overall, a significantly higher proportion of lobar ICH patients had the *APOE* $\epsilon 4$ genotype (34% vs 28% of controls). This was largely driven by the differences in white lobar ICH patients compared with white controls.

In multivariate analysis, both *APOE* $\epsilon 2$ and *APOE* $\epsilon 4$ genotypes were independently associated with lobar ICH (table 2) in the white subgroup, and neither *APOE* $\epsilon 2$ nor *APOE* $\epsilon 4$ was independently associated with lobar ICH in the black or Hispanic subgroups, which corroborates the univariate analysis. In a post hoc power analysis, based on our total numbers of black and Hispanic patients, we would have been able to detect an odds ratio (OR) of 1.08 in black patients and 1.07 in Hispanic patients with 80% power.

Multivariate analysis also demonstrated that not being educated beyond high school was associated with between a 2.5- and 5-fold increased odds for lobar ICH, with the highest odds among Hispanic participants with less than a high school education. In addition, hypertension was independently associated with lobar ICH for all 3 racial/ethnic subgroups, with OR as high as 2.6 for black participants and 2.4 for Hispanic participants, compared with 1.7 for white participants. Anticoagulant use was associated with a 6-fold risk for lobar ICH in black participants, compared with a 3-fold risk for Hispanic participants and a 2-fold risk for white participants.

Because lobar ICH occurred approximately 8 years earlier in life among black and Hispanic participants, compared with white participants, and age was not a confounder for increased risk of lobar ICH, we repeated the analysis for the 408 cases and 812 controls over 70 years old. For this older group, the *APOE* $\epsilon 2$ genotype was not associated with increased risk for lobar ICH (OR 1.2, 95% confidence interval [CI] 0.9–1.7, $p = 0.28$) when all racial/ethnic subgroups were combined, and there was no association in any of the racial/ethnic subgroups. The *APOE* $\epsilon 4$ genotype was associated with increased risk for lobar ICH in the white subgroup over 70 years of age (OR 2.6, 95% CI 1.9–3.8, $p < 0.0001$), whereas it was not associated with higher ICH risk in the black (OR 1.4, 95% CI 0.8–2.6, $p = 0.26$) or Hispanic subgroups (OR 1.5, 95% CI 0.8–2.8, $p = 0.16$). In a post hoc power analysis for this over 70-year-old subgroup, we would have been able to detect an OR of 1.09 for black and Hispanic participants with 80% power.

Table 1 Baseline patient demographics of lobar intracerebral hemorrhage compared with controls with *APOE* results in the Ethnic/Racial Variations of Intracerebral Hemorrhage study

	Black			Hispanic			White			Total		
	Case, n = 237	Control, n = 886	p Value	Case, n = 269	Control, n = 795	p Value	Case, n = 401	Control, n = 979	p Value	Case, n = 907	Control, n = 2,660	p Value
Age, y, mean (SD)	62.2 (15.2)	58.0 (11.9)	0.0001	62.4 (15.5)	58.7 (13.6)	0.0006	70.7 (13.4)	68.5 (13.0)	0.0039	66.0 (15.1)	62.1 (13.7)	<0.0001
Female	118 (49.8)	401 (45.3)	0.21	129 (48.0)	327 (41.1)	0.0506	195 (48.6)	435 (44.4)	0.16	442 (48.7)	1,163 (43.7)	0.0088
Hypertension	194 (82.9)	536 (60.6)	<0.0001	184 (70.8)	378 (47.6)	<0.0001	268 (67.2)	507 (51.8)	<0.0001	646 (72.3)	1,421 (53.5)	<0.0001
Diabetes	71 (30.3)	194 (21.9)	0.0070	80 (30.0)	216 (27.2)	0.38	68 (17.0)	157 (16.0)	0.65	219 (24.3)	567 (21.3)	0.06
High cholesterol	85 (38.0)	361 (40.8)	0.43	112 (44.4)	372 (47.2)	0.45	197 (52.1)	513 (52.4)	0.93	394 (46.1)	1,246 (47.0)	0.67
Anticoagulant use	18 (7.6)	12 (1.4)	<0.0001	26 (9.7)	21 (2.6)	<0.0001	53 (13.2)	63 (6.4)	<0.0001	97 (10.7)	96 (3.6)	<0.0001
Smoking												
Current	59 (25.0)	219 (24.7)		41 (15.4)	93 (11.7)		39 (9.8)	90 (9.2)		139 (15.4)	402 (15.1)	
Former	65 (27.5)	247 (27.9)		79 (29.7)	258 (32.5)		169 (42.4)	405 (41.4)		313 (34.7)	910 (34.2)	
Never	112 (47.5)	420 (47.5)	0.99	146 (54.9)	444 (55.9)	0.26	191 (47.9)	483 (49.4)	0.86	449 (49.8)	1,347 (50.7)	0.91
Education												
< High school	51 (21.7)	81 (9.1)		134 (51.3)	188 (23.8)		36 (9.0)	25 (2.6)		221 (24.7)	294 (11.1)	
High school	93 (39.6)	195 (22.0)		76 (29.1)	174 (22.0)		121 (30.3)	147 (15.0)		290 (32.4)	516 (19.4)	
> High school	91 (38.7)	610 (68.9)	<0.0001	51 (19.5)	429 (54.2)	<0.0001	243 (60.7)	807 (82.4)	<0.0001	385 (43.0)	1846 (69.5)	<0.0001
Heavy alcohol use	22 (9.4)	33 (3.7)	0.0003	26 (9.9)	16 (2.0)	<0.0001	21 (5.3)	53 (5.4)	0.91	69 (7.7)	102 (3.9)	<0.0001
APOE												
Presence of ε2	47 (19.8)	170 (19.2)	0.82	24 (8.9)	69 (8.7)	0.90	93 (23.2)	171 (17.5)	0.0141	164 (18.1)	410 (15.4)	0.06
Presence of ε4	89 (37.6)	332 (37.5)	0.98	71 (26.4)	167 (21.0)	0.07	150 (37.4)	234 (23.9)	<0.0001	310 (34.2)	733 (27.6)	0.0002

Table 2 Multivariate analysis of white/black/Hispanic subgroups modeled with *APOE* allele

Variables	Black				Hispanic				White			
	Model with ε2		Model with ε4		Model with ε2		Model with ε4		Model with ε2		Model with ε4	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Hypertension	2.61 (1.78, 3.82)	<0.0001	2.61 (1.79, 3.82)	<0.0001	2.39 (1.71, 3.33)	<0.0001	2.36 (1.69, 3.29)	<0.0001	1.69 (1.31, 2.18)	<0.0001	1.70 (1.32, 2.20)	<0.0001
Anticoagulant use	6.31 (2.84, 14.00)	<0.0001	6.33 (2.85,14.06)	<0.0001	3.39 (1.71, 6.75)	0.0005	3.36 (1.69, 6.70)	0.0006	2.00 (1.34, 3.00)	0.0008	2.11 (1.40, 3.18)	0.0004
< High school education	3.06 (1.97, 4.74)	<0.0001	3.06 (1.97, 4.74)	<0.0001	5.26 (3.56, 7.75)	<0.0001	5.24 (3.56, 7.73)	<0.0001	4.49 (2.62, 7.70)	<0.0001	4.65 (2.70, 8.01)	<0.0001
High school education	2.86 (2.03, 4.04)	<0.0001	2.86 (2.03, 4.04)	<0.0001	3.29 (2.17, 5.00)	<0.0001	3.28 (2.16, 4.98)	<0.0001	2.59 (1.95, 3.45)	<0.0001	2.52 (1.89, 3.36)	<0.0001
> High school education	Reference		Reference		Reference		Reference		Reference		Reference	
Heavy alcohol use	2.51 (1.37, 4.60)	0.0030	2.50 (1.37, 4.59)	0.0030	8.18 (3.88, 17.26)	<0.0001	8.17 (3.87, 17.23)	<0.0001	NS	NS	NS	NS
Female	NS	NS	NS	NS	1.50 (1.09, 2.06)	0.0131	1.50 (1.09, 2.06)	0.0132	NA	NS	NS	NS
<i>APOE</i> ε2 allele	0.99 (0.67, 1.46)	0.97	NA	NA	1.04 (0.60, 1.81)	0.89	NA	NA	1.48 (1.10, 1.99)	0.0106	NA	NA
<i>APOE</i> ε4 allele	NA	NA	0.98 (0.71, 1.35)	0.90	NA	NA	1.19 (0.82, 1.71)	0.36	NA	NA	1.97 (1.51, 2.56)	<0.0001

Abbreviations: CI = confidence interval; OR = odds ratio.

Table 3 Multivariate risk of lobar intracerebral hemorrhage by *APOE* allele and stratified by hypertension history

	Black		Hispanic		White	
	OR (CI)	p Value	OR (CI)	p Value	OR (CI)	p Value
Age-adjusted logistic regressions						
Presence of $\epsilon 2$	1.04 (0.72, 1.49)	0.85	1.01 (0.62, 1.64)	0.98	1.40 (1.06, 1.87)	0.020
Age	1.03 (1.01, 1.04)	<0.0001	1.02 (1.01, 1.03)	0.0003	1.01 (1.00, 1.02)	0.0055
Presence of $\epsilon 4$	0.99 (0.74, 1.34)	0.97	1.31 (0.95, 1.81)	0.10	1.91 (1.49, 2.46)	<0.0001
Age	1.03 (1.01, 1.04)	<0.0001	1.02 (1.01, 1.03)	0.0004	1.01 (1.00, 1.02)	0.0038
Age-adjusted logistic regression, no hypertension in either of case/control						
Presence of $\epsilon 2$	1.65 (0.76, 3.57)	0.20	1.27 (0.57, 2.87)	0.56	2.11 (1.36, 3.27)	0.0009
Age	1.02 (0.99, 1.05)	0.16	1.01 (0.99, 1.03)	0.19	1.02 (1.00, 1.03)	0.0154
Presence of $\epsilon 4$	0.61 (0.29, 1.26)	0.18	1.09 (0.59, 2.01)	0.79	1.45 (0.96, 2.19)	0.08
Age	1.02 (0.99, 1.05)	0.16	1.01 (0.99, 1.03)	0.20	1.02 (1.01, 1.03)	0.0091
Age-adjusted logistic regressions, both case and control are hypertensive						
Presence of $\epsilon 2$	0.90 (0.59, 1.36)	0.62	0.97 (0.52, 1.82)	0.92	1.14 (0.77, 1.66)	0.52
Age	1.01 (1.00, 1.03)	0.06	1.01 (0.99, 1.02)	0.37	1.00 (0.99, 1.01)	0.96
Presence of $\epsilon 4$	1.15 (0.82, 1.62)	0.41	1.32 (0.89, 1.96)	0.17	2.36 (1.70, 3.27)	<0.0001
Age	1.01 (1.00, 1.03)	0.06	1.01 (0.99, 1.02)	0.41	1.00 (0.99, 1.01)	0.99

Abbreviations: CI = confidence interval; OR = odds ratio.

In age-adjusted logistic regression, neither *APOE* $\epsilon 2$ nor *APOE* $\epsilon 4$ emerged as risk factors for hypertensive black participants, nonhypertensive black participants, hypertensive Hispanic participants, or nonhypertensive Hispanic participants (table 3). In the white hypertensive subgroup, the *APOE* $\epsilon 2$ allele was associated with lobar ICH, but it was not associated with lobar ICH for nonhypertensive white participants. Conversely, *APOE* $\epsilon 4$ was associated with lobar ICH in nonhypertensive white participants, but it was not associated with lobar ICH for hypertensive white participants.

Pertaining to outcome data, *APOE* $\epsilon 2$ and *APOE* $\epsilon 4$ were not associated with worse clinical outcomes at 3 months (table 4). Race/ethnicity was similarly not associated with a worse clinical outcome for lobar ICH. Age, lobar ICH volume, and presence of intraventricular hemorrhage were all independently associated with poor outcomes (modified Rankin Scale score ≥ 4).

As previously stated, we also performed a 1:1 matched analysis for age, race, and sex. Demographic information from this matched analysis is summarized in table 5. Multivariate analysis of white, black, and Hispanic subgroups modeled with *APOE* allele for this 1:1 matched analysis is available in table 6. Finally, the matched analysis of the multivariate risk of lobar ICH by *APOE* allele and stratified by hypertension history is described in table 7.

Discussion

Our study found that *APOE* $\epsilon 2$ and *APOE* $\epsilon 4$ alleles were not significantly associated with lobar ICH in black and Hispanic participants, even when the analysis was limited to older age. In white participants, we found *APOE* $\epsilon 2$ and *APOE* $\epsilon 4$ alleles to be independent risk factors for lobar ICH, as has been well-established.¹⁹ Hypertension was a significant risk factor for lobar ICH, particularly in the black and Hispanic subgroups. We also found that there was a differential effect of the risk of *APOE* alleles on risk of lobar ICH among white participants, depending on prior history of hypertension. One explanation could be that *APOE* $\epsilon 2$ increases the risk of hypertensive lobar ICH, whereas *APOE* $\epsilon 4$ increases the risk of CAA-related (nonhypertensive) lobar ICH. Both alleles remain risk factors for lobar ICH among white participants, but they do not appear to be associated with increased lobar ICH risk in black or Hispanic participants.

The *APOE* $\epsilon 2$ and *APOE* $\epsilon 4$ alleles have been proposed to have a variety of cerebrovascular consequences that result in increased risk for ICH. *APOE* $\epsilon 2$ and *APOE* $\epsilon 4$ alleles have been shown to have more β -amyloid ($A\beta$) deposition in cerebrovascular vessel walls, predisposing them to CAA-associated ICH.^{20,21} *APOE* $\epsilon 4$ results in higher resting cerebral blood flow in older adults²² coupled with $A\beta$ vessel wall deposition, and this was thought to be the rationale for association of *APOE* $\epsilon 4$ alleles with higher lobar ICH rates. An

Table 4 Outcome at 3 months against *APOE* status in lobar intracerebral hemorrhage (ICH)

	OR (CI)	p Value
Outcome at 3 months against presence of <i>APOE</i> ε2 logistic regression		
Presence of ε2	1.33 (0.87, 2.04)	0.19
Black	1.32 (0.86, 2.03)	0.21
Hispanic	1.28 (0.85, 1.91)	0.24
White	Reference	Reference
Age	1.05 (1.04, 1.06)	<0.0001
ICH volume	2.15 (1.80, 2.57)	<0.0001
IVH	1.70 (1.17, 2.46)	0.0052
Outcome at 3 months against presence of <i>APOE</i> ε4 logistic regression		
Presence of ε4	1.01 (0.71, 1.42)	0.98
Black	1.30 (0.85, 2.00)	0.23
Hispanic	1.23 (0.82, 1.83)	0.32
White	Reference	Reference
Age	1.05 (1.04, 1.06)	<0.0001
ICH volume	2.17 (1.81, 2.59)	<0.0001
IVH	1.67 (1.16, 2.43)	0.0063

Abbreviations: CI = confidence interval; IVH = intraventricular hemorrhage; OR = odds ratio.

additional proposed mechanism for lobar ICH in *APOE* ε2 is the lower affinity for low-density lipoprotein receptor compared with *APOE* ε4 and *APOE* ε3 alleles.^{20,23} Our results suggest that *APOE* function does not differ across racial and ethnic groups, but rather amyloid-dependent hemorrhage pathogenesis may be relatively underrepresented as a lobar ICH mechanism in black and Hispanic patients, compared with white patients, and therefore any future therapeutics that target amyloid biology in an effort to reduce ICH risk could be met with less clinical effect in these minority populations. In addition, efforts to aggressively treat hypertension in minority populations may ameliorate lobar ICH risk to a greater degree than would be expected in white populations with a higher prevalence of CAA-related lobar ICH.

Some classification of ICH systems regard most lobar ICH as the result of CAA.²⁴ Indeed, our own study group had previously reported in a predominately white ICH population that the attributable risk for lobar ICH was high for *APOE* alleles, with minimal contribution from hypertension.²⁴ However, several other studies have demonstrated both treated and untreated hypertension as risk factors for lobar ICH.^{6,25,26} Untreated hypertension is an important risk factor for lobar ICH in black and Hispanic patients.⁶ Our study supports the view that hypertension is an important independent risk factor for lobar ICH across white, black, and Hispanic groups.

Our finding that less than a high school education is associated with a 3- to 5-fold risk of lobar ICH across white, black,

and Hispanic participants is congruent with previous research.^{27,28} Lower education levels are thought to reflect socioeconomic status and issues related to health care access.²⁹ As previously hypothesized,²⁷ the strength of its association with lobar ICH varied across groups in our study. All the racial/ethnic groups demonstrated a high risk of less than high school education compared with greater than or equal to high school education.

Regarding alcohol use, previous studies have been difficult to compare given variable definitions of heavy alcohol use. Our study demonstrated a clear increased risk of lobar ICH in the black and Hispanic groups for frequent alcohol use.

Our study has several limitations. We allowed for self-report of race and did not use genotyped ancestry informative markers to verify self-report in this analysis. Even if this analysis was conducted and we could discriminate between African ancestral Hispanic participants and Amerindian ancestry, we could not discriminate within groups. For example, although people of Puerto Rican, Peruvian, and Mexican descent might all identify as Hispanic, their genetic differences may be variable.

The strengths of our investigation include the multiple centers for recruitment and the multiethnic/multiracial patients studied with large sample sizes, allowing for the analysis of risk factors in white, black, and Hispanic

Table 5 Baseline patient demographics of lobar intracerebral hemorrhage compared to controls with *APOE* results in the Ethnic/Racial Variations of Intracerebral Hemorrhage study

	Black			Hispanic			White			Total		
	Case, n = 209	Control, n = 209	p Value	Case, n = 218	Control, n = 218	p Value	Case, n = 390	Control, n = 390	p Value	Case, n = 817	Control, n = 817	p Value
Age, y, mean (SD)	61.9 (14.0)	61.6 (13.9)	0.8581	61.4 (14.5)	60.7 (14.2)	0.6265	70.6 (13.1)	70.3 (12.7)	0.7301	65.9 (14.4)	65.5 (14.1)	0.5779
Female	107 (51.2)	107 (51.2)	Matched	110 (50.5)	110 (50.5)	Matched	188 (48.2)	188 (48.2)	Matched	405 (49.6)	405 (49.6)	Matched
Hypertension	171 (82.2)	131 (62.7)	<0.0001	150 (71.1)	107 (49.1)	<0.0001	264 (68.0)	207 (53.1)	<0.0001	585 (72.5)	445 (54.5)	<0.0001
Diabetes	65 (31.4)	45 (21.6)	0.0242	70 (32.4)	62 (28.4)	0.3691	65 (16.8)	64 (16.4)	0.8979	200 (24.7)	171 (21.0)	0.0749
High cholesterol	77 (39.1)	80 (38.3)	0.8672	94 (45.9)	112 (51.9)	0.2185	192 (52.2)	210 (53.9)	0.6448	363 (47.1)	402 (49.3)	0.3849
Anticoagulant use	15 (7.2)	1 (0.5)	0.0004	21 (9.6)	9 (4.1)	0.0232	52 (13.3)	35 (9.0)	0.0532	88 (10.8)	45 (5.5)	0.0001
Smoking												
Current	52 (25.0)	45 (21.5)		38 (17.6)	27 (12.4)		38 (9.8)	26 (6.7)		128 (15.8)	98 (12.0)	
Former	55 (26.4)	67 (32.1)		62 (28.7)	70 (32.1)		166 (42.8)	170 (43.6)		283 (34.9)	307 (37.6)	
Never	101 (48.6)	97 (46.4)	0.4140	116 (53.7)	121 (55.5)	0.2948	184 (47.4)	194 (49.7)	0.2784	401 (49.4)	412 (50.4)	0.0784
Education												
< High school	42 (20.2)	22 (10.5)		105 (49.3)	54 (25.0)		35 (9.0)	8 (2.1)		182 (22.5)	84 (10.3)	
High school	81 (38.9)	43 (20.6)		65 (30.5)	48 (22.2)		116 (29.8)	59 (15.1)		262 (32.4)	150 (18.4)	
> High school	85 (40.9)	144 (68.9)	<0.0001	43 (20.2)	114 (52.8)	<0.0001	238 (61.2)	323 (82.8)	<0.0001	366 (45.2)	581 (71.3)	<0.0001
Heavy alcohol use	19 (9.3)	8 (3.8)	0.0250	15 (7.0)	5 (2.3)	0.0197	21 (5.4)	19 (4.9)	0.7265	55 (6.8)	32 (3.9)	0.0093
APOE												
Presence of ε2	40 (19.1)	36 (17.2)	0.6120	19 (8.7)	25 (11.5)	0.3401	92 (23.6)	69 (17.7)	0.0419	151 (18.5)	130 (15.9)	0.1686
Presence of ε4	78 (37.3)	78 (37.3)	1.0000	51 (23.4)	46 (21.1)	0.5648	147 (37.7)	90 (23.1)	<0.0001	276 (33.8)	214 (26.2)	0.0008

Table 6 Multivariate analysis of white/black/Hispanic subgroups modeled with *APOE* allele

Variables	Black				Hispanic				White			
	Model with ε2		Model with ε4		Model with ε2		Model with ε4		Model with ε2		Model with ε4	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Hypertension	2.44 (1.43, 4.17)	0.0011	2.43 (1.43, 4.15)	0.0011	2.41 (1.42, 4.09)	0.0011	2.32 (1.38, 3.92)	0.0016	1.57 (1.14, 2.17)	0.0057	1.52 (1.10, 2.11)	0.0125
Anticoagulant use	21.81 (2.62, 181.76)	0.0044	21.08 (2.54, 175.00)	0.0048							1.79 (1.06, 3.02)	0.0299
< High school education	2.58 (1.30, 5.11)	0.0066	2.60 (1.31, 5.15)	0.0063	4.95 (2.70, 9.07)	<0.0001	4.77 (2.63, 8.65)	<0.0001	8.09 (3.03, 21.57)	<0.0001	8.30 (3.06, 22.46)	<0.0001
High school education	3.25 (1.84, 5.77)	<0.0001	3.16 (1.80, 5.53)	<0.0001	2.94 (1.63, 5.31)	0.0004	3.07 (1.70, 5.54)	0.0002	2.93 (1.93, 4.44)	<0.0001	2.76 (1.80, 4.21)	<0.0001
> High school education	Reference		Reference		Reference		Reference		Reference		Reference	
Heavy alcohol use					4.99 (1.40, 17.79)	0.0132	4.70 (1.33, 16.62)	0.0163				
APOE ε2 allele	0.85 (0.47, 1.53)	0.5804			0.59 (0.27, 1.27)	0.1763			1.58 (1.08, 2.31)	0.0195		
APOE ε4 allele			1.00 (0.61, 1.63)	0.9980			1.15 (0.63, 2.10)	0.6484			2.16 (1.50, 3.11)	<0.0001

Abbreviations: CI = confidence interval; OR = odds ratio.

Table 7 Multivariate risk of lobar intracerebral hemorrhage by *APOE* allele and stratified by hypertension history

	Black		Hispanic		White	
	OR (CI)	p Value	OR (CI)	p Value	OR (CI)	p Value
Logistic regressions against $\epsilon 2/\epsilon 4$, hypertensive status						
Presence of $\epsilon 2$	1.14 (0.69, 1.87)	0.6117	0.74 (0.40, 1.38)	0.3446	1.43 (1.01, 2.02)	0.0456
Presence of $\epsilon 4$	1.00 (0.66, 1.52)	1.0000	1.16 (0.72, 1.88)	0.5417	2.06 (1.49, 2.85)	<0.0001
Age-adjusted logistic regressions, no hypertension in either of case/control						
Presence of $\epsilon 2$	5.00 (0.58, 42.80)	0.1418	1.33 (0.30, 5.96)	0.7064	2.60 (0.93, 7.29)	0.0694
Presence of $\epsilon 4$	1.00 (0.20, 4.96)	1.0000	0.50 (0.15, 1.66)	0.2577	0.57 (0.24, 1.36)	0.2067
Age-adjusted logistic regressions, both case and control are hypertensive						
Presence of $\epsilon 2$	0.84 (0.43, 1.64)	0.6125	0.89 (0.34, 2.30)	0.8085	0.95 (0.52, 1.76)	0.8759
Presence of $\epsilon 4$	1.50 (0.83, 2.72)	0.1827	1.33 (0.63, 2.82)	0.4513	1.95 (1.15, 3.30)	0.0127

Abbreviations: CI = confidence interval; OR = odds ratio.

participants. Hispanic patients have been underrepresented in ICH literature, our study being among the first to include a genetic analysis of Hispanic ICH cases in a large scale. Therefore our results are more broadly applicable than previously reported literature on lobar ICH, which consisted of primarily white populations.

Our study found that *APOE* $\epsilon 2$ and *APOE* $\epsilon 4$ are not independent risk factors for lobar ICH in black and Hispanic populations. Although a small effect is possible, this finding suggests that other factors affect how *APOE* alleles lead to lobar ICH among white patients and challenges the notion that hypertension plays little role in lobar ICH. The complex interplay between *APOE* status and lobar ICH requires deeper investigation and analysis going forward.

Author contributions

Russell P. Sawyer: composition of manuscript and interpretation of the data. Padmini Sekar: analysis and interpretation of data with critical revision of manuscript for intellectual content. Jennifer Osborne: data acquisition with critical revision of manuscript for intellectual content. Steven J. Kittner: critical revision of manuscript for intellectual content. Charles J. Moomaw: critical revision of manuscript for intellectual content. Matthew L. Flaherty: critical revision of manuscript for intellectual content. Carl D. Langefeld: critical revision of manuscript for intellectual content. Christopher D. Anderson: critical revision of manuscript for intellectual content. Jonathan Rosand: critical revision of manuscript for intellectual content. Daniel Woo: study concept and design with critical revision of manuscript for intellectual content.

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