Supplementary Online Content

Marini S, Crawford K, Morotti A, et al; the International Stroke Genetics Consortium. Association of apolipoprotein E with intracerebral hemorrhage risk by race/ethnicity: a meta-analysis. *JAMA Neurol.* Published online February 6, 2019. doi:10.1001/jamaneurol.2018.4519

eMethods

This supplementary material has been provided by the authors to give readers additional information about their work.

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Apolipoprotein E and Intracerebral Hemorrhage: A Trans-Ethnic Meta-Analysis

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eMethods

Participating Studies

Case and control subjects included in the study were gathered from 3 multicenter studies in the US and from 8 distinct European sites participating in the ISGC, based on availability of directly ascertained APOE ε genotypes. US studies included The Genetics of Cerebral Hemorrhage with Anticoagulation (GOCHA) study[1], the Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) study[2], the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study[3]. European studies included The Hospital del Mar and Vall d'Hebron Hospital ICH studies [4,5] in Barcelona, Spain, the Jagiellonian University Hemorrhagic Stroke Study[6] in Krakow, Poland, the Lund Stroke Register study[7] in Lund, Sweden, the Edinburgh Stroke Study and LINCHPIN[8] study in Scotland, UK, the University Medical Center (UMC) Utrecht ICH study, and the Brescia Stroke Registry[9]. Because of variable sample sizes from contributing centers, data from the European studies (ISGC Europe) were analyzed together for association testing in meta-analysis, as done previously[10,11]. We analyzed primary ICH cases, CT or MRI confirmed, aged >18 years (GOCHA enrolled subjects aged > 50 years). ICH cases where there was evidence of secondary cause (such as trauma, tumor, hemorrhagic transformation of ischemic stroke, or vascular malformation) were excluded. More specific inclusion and exclusion criteria for each of the included studies are reported in eTable 1.

Phenotypic and Genetic variables

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Demographic variables, including self-identified race and ethnicity (according to the recommendation of the Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity[12]) were systematically obtained from structured patient and family member interview within each site[3,13]. Additional covariates previously associated with ICH[14] risk were also collected: medical history of hypertension, previous stroke, hypercholesterolemia, warfarin, antiplatelet and statin use, smoking history, and alcohol exposure (more than twice per week)[15].Given the heterogeneity among the studies, other variables were not available. Number of medications used to treat hypertension (taken in the 2 weeks before ICH onset or before the interview, for cases and controls respectively) and systolic and diastolic blood pressure readings (measured on enrollment with index ICH for cases, and at the time of interview with controls) were also available for ERICH participants. CT images on admission were analyzed at each participating site for hematoma classification as lobar (involving predominantly the cortex and underlying white matter), and non-lobar (involving predominately the basal ganglia, periventricular white matter, or internal capsule), following prespecified criteria[11].

APOE genotype was determined as part of an ongoing GWAS of ICH. Taqman (Applied Biosystems, Foster City, CA) and iPLEX (Sequenom, San Diego, CA) methodologies were adopted at the University of Miami and Massachusetts General Hospital genotyping centers, respectively for all the sample. The genotypes obtained for rs429358 (C/T) and rs7412 (C/T) were used to define the three standard human APOE ε haplotypes of ε2, ε3, and ε4[16]. Genome-wide data were available for a subgroup of subjects, from Affymetrix 6.0 in GERFHS, and Illumina HumanHap610-Quad in GOCHA and ISGC Europe. IRB approval was obtained at all participating centers, and informed consent was obtained from all participants or their legally authorized representative.

Population Stratification

Fifteen ancestry informative markers were selected among the polymorphisms directly genotyped in ERICH [17] (eTable 2). These markers, distributed across the genome, showed difference in allele frequency (δ) of at least 0.5 between any two of the recruited ancestral populations (African American, Hispanic American, non-Hispanic European). GWAS data for GOCHA, GERFHS, ISGC Europe samples were analyzed as previously described[10]. Briefly

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Standardized prespecified quality control procedures[18], imputation via IMPUTE2 v.2.2[19] and 1000 Genomes integrated reference panels (Phase I interim release in NCBI build 37), and post imputation filtering (MAF <0.01, IMPUTE2 information score <0.7) were implemented. Samples with < 90% call rates, or SNPs with call rates <95% or deviation from Hardy-Weinberg equilibrium at P-value < 2.5 × 10−4 were excluded. Based on these 15 selected markers, principal component analysis was implemented in GOCHA, GERFHS, ISGC Europe and ERICH subjects in accordance with previously published methods[20–22]. The first four principal components were included in regression models to adjust for population stratification. We have previously shown the reliability of this approach in defining ancestries of populations[17]. This PC analysis was not used to reclassify participants, as self-identified race/ethnicity may capture exposures that transcend genetic ancestry and could contribute to explain the stratification among different populations.

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eTable 1. ICH Case Inclusion and Exclusion Criteria by Recruitment Site

Study	Inclusion Criteria	Exclusion Criteria	Control Recruitment
Brescia Stroke Registry. (University of Brescia, Brescia, Italy)	(Hospital-based, prospective, +18 y/o) • Acute hospitalization for ICH • CT or MRI confirmation of ICH • Age > 18	• Head trauma • Brain tumor • Ischemic stroke • Vascular malformation • Other cause of secondary ICH	• Regionally matched, hospital and ambulatory clinics
UMC Utrecht ICH Study (University Medical Center Utrecht, Utrecht, The Netherlands)	(Hospital-based, prospective, +18 y/o) • Acute hospitalization for ICH • CT confirmation of ICH • Age > 18	• Head trauma • Brain tumor • Ischemic stroke • Vascular malformation • Other cause of secondary ICH present on admission or in follow-up	• Regionally matched, blood donor population
Edinburgh – ESS (Western General Hospital, Edinburgh, Scotland, UK)	(Inpatient and outpatient hospital-based, prospective, +55 y/o) • Acute hospitalization for ICH • CT or MRI confirmation of ICH • Age > 55	• Head trauma • Brain tumor • Ischemic stroke • Vascular malformation • Presentation > 1 week from ICH • Antecedent drug use • Primary coagulopathy	• N/A
Edinburgh – LINCHPIN (Western General Hospital, Royal Infirmary of Edinburgh, St. John's Hospital at Howden, West Lothian, Scotland, UK)	(Community-based in areas served by NHS Lothian Health Board, prospective with hot-pursuit and retrospective augmentation, +16 y/o) • Symptomatic ICH (acute or chronic)	• Head trauma • Brain tumor • Ischemic stroke with hemorrhagic transformation • Vascular malformation • Other cause of secondary ICH	• N/A

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	• CT or MRI confirmation of acute or chronic ICH • Age > 16 • Resident in area served by NHS Lothian Health Board at time of ICH		
ERICH (19 centers in USA, based at University of Cincinnati)	(Hospital-based, prospective with hot-pursuit, +18 y/o) • Acute hospitalization for ICH • CT or MRI confirmation of ICH • Age > 18	• Head trauma • Brain tumor • Ischemic stroke • Vascular malformation • Other cause of secondary ICH	• Regionally matched, random-digit-dialing
GOCHA (6 centers in USA, based at Massachusetts General Hospital)	(Hospital-based, prospective, +55 y/o) • Acute hospitalization for ICH • CT or MRI confirmation of ICH • Age > 55	• Head trauma • Brain tumor • Ischemic stroke • Vascular malformation • Other cause of secondary ICH	• Regionally matched, ambulatory clinics
GERFHS (16 centers in the Greater Cincinnati/Northern Kentucky region of USA, based at University of Cincinnati)	(Hospital-based, prospective, +18 y/o) • Acute hospitalization for ICH • CT or MRI confirmation of ICH • Age > 18	• Head trauma • Brain tumor • Ischemic stroke • Vascular malformation • Other cause of secondary ICH	• Regionally matched, random-digit-dialing
ISGC Europe ICH studies (Hospital del Mar, Vall d'Hebron Hospital, Jagiellonian University, Lund University)	(Hospital-based, prospective, +18 y/o) • Acute hospitalization for ICH • CT or MRI confirmation of ICH • Age > 18	• Head trauma • Brain tumor • Ischemic stroke • Vascular malformation • Other cause of secondary ICH	• Regionally matched, hospital and ambulatory clinics
* Lothian Birth Cohort 1936			• Community population born in 1936 who took Scottish Mental

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(All centers serving the Lothian Area of Scotland)			Survey in 1947, living in Lothian, Scotland, UK

* This study was used to recruit controls for the Edinburgh – ESS and Edinburgh – LINCHPIN cases

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eTable 2. Ancestry Informative Markers Selected

AIM	Chromosome	position (GRCh37.p13)	A1	A2	Allele frequencies		
					AFR	AMR	EUR
rs7581299	2	179900720	T	C	0.749	0.660	0.370
rs11725412	4	38277754	A	G	0.215	0.464	0.063
rs12640848	4	71506412	A	G	0.967	0.660	0.331
rs1423099	5	75427518	T	C	0.930	0.568	0.264
rs4463276	6	145055331	A	G	0.088	0.376	0.771
rs13259288	8	4483059	T	G	0.822	0.478	0.764
rs12679427	8	72242674	T	C	0.437	0.424	0.724
rs10962599	9	16795286	T	C	0.977	0.651	0.274
rs10840311	11	9854857	T	C	0.726	0.601	0.352
rs3019657	11	134511647	A	G	0.696	0.496	0.871
rs550338	12	24512037	A	G	0.697	0.460	0.764
rs200354	14	99375321	T	G	0.336	0.476	0.829
rs12913832	15	28365618	A	G	0.972	0.798	0.364
rs2216594	19	33533258	A	G	0.048	0.347	0.676
rs801712	22	47090243	C	G	0.251	0.477	0.795

AIM: ancestry informative marker; A1 and A2: allele frequency; AFR: Afro-American; AMR: Mixed American; EUR: European

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eTable 3. Comparison Between With Subjects With and Without Ancestry Informative Markers Available for Population Stratification Analysis

	GENETIC DATA for population stratification		
	available (n 7452)	**not available (n 5672)**	p value
Male sex, n (%)	4140 (55.6%)	3013 (53.1%)	**0.003**
Age, median (IQR)	66 (54-76)	68 (58-77)	**<0.001**
Cases, n (%)	4069 (54.6)	2225 (39.2)	**<0.001**
ICH location			**<0.001**
Lobar ICH, n (%)	1408/6202 (34.7)	897/6202 (41.9)	
Non-lobar ICH, n (%)	2654/6202 (65.3)	1243/6202 (58.1)	
Hypertension, n (%)	4609/12481 (67.2)	3359/12481 (59.7)	
Self-reported race/ethnicity, n (%)			**<0.001**
white	3594/12449 (52.8)	4971/12449 (88.2)	
blacks	1730/12449 (25.4)	550/12449 (9.8)	
Hispanics	1486/12449 (21.8)	118/12449 (2.1)	
APOE ε4 allele count, n (%)			**<0.001**
	5310 (71.3)	4346 (76.6)	
	1909 (25.6)	1197 (21.1)	
	233 (3.1)	129 (2.3)	
APOE ε2 allele count, n (%)			0.53
	6251 (83.9)	4842 (85.4)	
	1137 (15.3)	780 (13.8)	
	64 (0.9)	50 (0.9)	

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eTable 4. Frequencies of Additional Diseases and Risk Factors Among Cases and Controls of the Available Data

	Controls	**Cases**	**p value***
Smoking, n (%)	2084 (36.2)	1959 (35.3)	0.170
Alcohol use, n (%)	2414 (47.0)	2087 (41.4)	< 0.001
Previous CV ischemic event, n (%)	371 (7.7)	636 (12.6)	< 0.001
Hypercholesterolemia, n (%)	2748 (46.3)	2315 (40.1)	< 0.001
Statin use, n (%)	1209 (26.6)	1220 (22.7)	< 0.001
Antiplatelet use, n (%)	1186 (35.5)	1655 (32.7)	0.005
Warfarin use, n (%)	404 (6.5)	793 (13.0)	< 0.001
Hypertension, n (%)	3404 (53.0)	4564 (75.3)	< 0.001
Male sex, n (%)	3590 (52.6)	3562 (56.6)	< 0.001
Age, median (IQR)	66 (56-75)	67 (56 -78)	< 0.001

* $\chi 2$ test and Mann Whitney u test; CV: cerebrovascular

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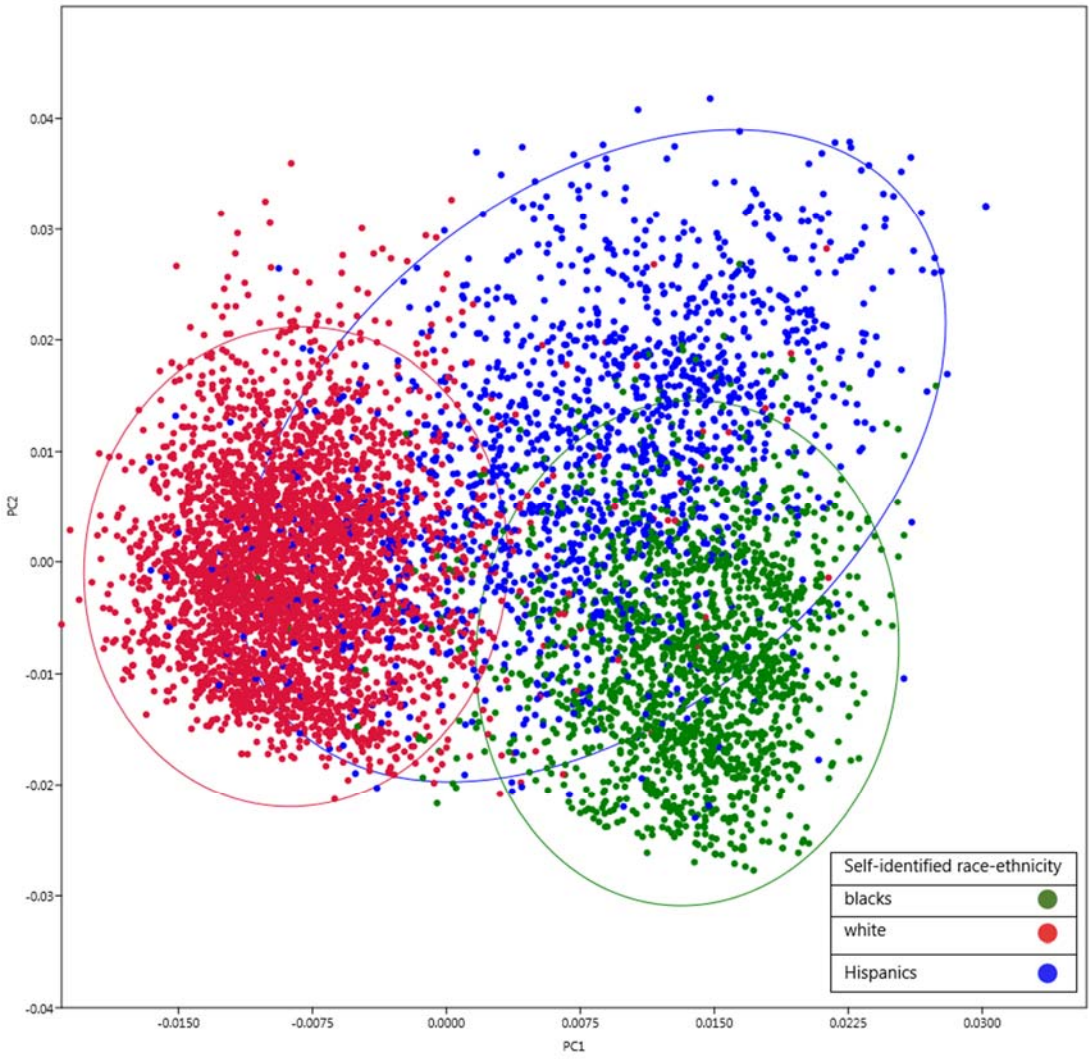
eFigure. Distribution of Subjects in Principal Component (PA) Space and the Relation with Self-identified Race and Ethnicity (Ellipses Cluster 95% of PC Analysis Data)



		Ellipses clusters (cluster of 95% data based on PC space)					
		white	Hispanics	blacks	Hispanics - blacks	Hispanics- white	blacks - white
Self-identified race-ethnicity	blacks	-	41	-		30	-
	white	-	38	3	43	-	-
	Hispanics	26	-	19	-	-	-

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