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Genetic Variants in *CETP* Increase Risk of Intracerebral Hemorrhage

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Genetic Variants in *CETP* Increase Risk of Intracerebral Hemorrhage

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Main Body

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ABSTRACT

Objective

In observational epidemiologic studies, higher plasma high-density lipoprotein cholesterol (HDL-C) has been associated with increased risk of intracerebral hemorrhage (ICH). DNA sequence variants that decrease cholesteryl ester transfer protein (*CETP*) gene activity increase plasma HDL-C; as such, medicines that inhibit CETP and raise HDL-C are in clinical development. Here, we test the hypothesis that *CETP* DNA sequence variants associated with higher HDL-C also increase risk for ICH.

Methods

We performed two candidate-gene analyses of *CETP*. First, we tested individual *CETP* variants in a discovery cohort of 1149 ICH cases and 1238 controls from 3 studies, followed by replication in 1625 cases and 1845 controls from 5 studies. Second, we constructed a genetic risk score comprised of 7 independent variants at the *CETP* locus and tested this score for association with HDL-C as well as ICH risk.

Results

Twelve variants within *CETP* demonstrated nominal association with ICH, with the strongest association at the rs173539 locus (odds ratio (OR) 1.25, standard error (SE) 0.06, $p=6.0\times10^{-4}$) with no heterogeneity across studies ($I^2=0\%$). This association was replicated in patients of European ancestry (p=0.03). A genetic score of *CETP* variants found to increase HDL-C by ~2.85mg/dL in the Global Lipids Genetics Consortium was strongly associated with ICH risk (OR 1.86, SE 0.13, $p=1.39\times10^{-6}$).

Interpretation

Genetic variants in *CETP* associated with increased HDL-C raise the risk of ICH. Given ongoing therapeutic development in *CETP* inhibition and other HDL-raising strategies, further exploration of potential adverse cerebrovascular outcomes may be warranted.

INTRODUCTION

Serum levels of high density lipoprotein (HDL-C) are strongly and inversely associated with coronary artery disease (CAD) risk[1]. Of the many single nucleotide polymorphisms (SNPs) associated with HDL-C levels, those within cholesteryl ester transfer protein (*CETP*) have the strongest effect[2-4]. Inhibitory variants within *CETP* associated with increased HDL-C correlate with reduced risk of multiple cardiac risk factors, including metabolic syndrome and myocardial infarction (MI)[5-8]. Inhibitors of the CETP gene product, designed to raise HDL-C by limiting CETP-mediated exchange of cholesteryl esters and triglycerides between HDL and LDL/VLDL particles, are being investigated in ongoing Phase III trials as treatments to reduce CAD risk[9,10].

In contrast, substantial data suggest that elevations in HDL-C may increase risk of spontaneous intracerebral hemorrhage (ICH)[11,12].Furthermore, clinical trial data suggests an increased risk of ICH on statins despite a lack of significant differences in lipid levels[13,14]. Because of small sample sizes and confounding by environmental or medical exposures, prior studies have not been able to resolve this potentially paradoxical role of elevated HDL-C in ICH. While ICH comprises only 15-20% of all strokes, it accounts for 50% of all stroke-related mortality and 30% of total costs[15,16]. Blood pressure control remains the only available preventive strategy[17]. As HDL-C evolves as a cardiovascular treatment target and clinical trial data on therapeutic modifiers accrue, an improved mechanistic understanding of the pathways involved in hemorrhagic cerebrovascular disease could lead to alternative treatments and prevention strategies for ICH.

It is not known whether *CETP* inhibitors, which endeavor to produce a biological effect similar to known genetic variants in *CETP*, increase ICH risk. The objective of this study was to use genome-wide genotypes from individuals with and without ICH from the International Stroke

Genetics Consortium to test genetic variants within *CETP* for association with ICH risk, under the hypothesis that the HDL-raising effects of inhibitory variants within *CETP* will result in increased ICH. *CETP* genetic variants that impact HDL-C are unconfounded by other exposures, remain constant throughout life, and may be more reflective of long-term levels than periodic lipid measurements[18]. Thus, examination of *CETP* genetic variation constitutes a valuable causal inference tool to help strengthen or disclaim prior observations of association between elevated HDL-C and ICH, and could provide additional clues about potential adverse effects of pharmacologic *CETP* inhibition.

METHODS

Study Design

We performed a two-stage (discovery and replication) case-control candidate-gene association study using both genome-wide data and direct genotyping. The discovery phase utilized data from 3 genome-wide association studies of ICH, sampling patients of European ancestry (**Table 1**)[19]. Replication involved direct genotyping of variants of interest from individuals recruited through 5 case-control studies of ICH, with no overlap between individuals from the discovery phase (**Table 2**). Detailed description of discovery and replication case and control recruitment architectures can be found in **Supplementary Table S1**.

All studies had approval from the local institutional review board or ethics committee at each participating institution. Informed consent was obtained from all patients, their legally authorized representatives, or was waived via protocol-specific allowance.

Cases

ICH was defined as a new and acute neurological deficit with compatible brain imaging. Enrolled patients were adult consenting primary acute ICH cases that presented to participating institutions with confirmation of primary ICH through computed tomography or magnetic resonance imaging. Exclusion criteria included trauma, brain tumor, hemorrhagic transformation of a cerebral infarction, vascular malformation, or any other cause of secondary ICH in all participating studies.

Case Populations

ICH cases w3ere recruited across multiple centers participating in the International Stroke Genetics Consortium from sites in the USA and Europe. For the purposes of reducing

confounding by population stratification, only individuals of self-reported European (Caucasian) ancestry were included in the analysis. Likewise, several studies (GOCHA, ESS, LINCHPIN) recruited ICH patients with ICH in the presence of anticoagulation (typically warfarin) exposure. These individuals were excluded from analyses due to the etiopathological distinctness of warfarin-related primary ICH from other forms. Discovery case populations were enrolled according to methods previously described[19]. Replication cases were recruited from ISGC participating centers using similar criteria as discovery cases (**Supplementary Table S2**). Briefly, UMC Utrecht ICH study included additional screening for secondary ICH cases in follow-up. The Edinburgh Stroke Study recruited subjects aged > 55 years only, and specifically excluded individuals with antecedent illicit drug use or presentation > 1 week from onset of symptoms. The LINCHPIN study identified ICH cases aged > 16 with acute or chronic ICH from a prospective cohort of individuals living in the Lothian region of Scotland, UK.

Neuroimaging

Stroke neurologists and neuroradiologists at each participating site performed the neuroimaging assessment. Following known differences in underlying biology, ICH was classified as lobar or non-lobar according to location[20]. ICH originating in the cortico-subcortical junction (with or without involvement of subcortical white matter) was defined as lobar, whereas ICH selectively involving the thalamus, internal capsule, basal ganglia, brainstem or cerebellum was defined as non-lobar.

Controls

Controls were ICH-free individuals >18 years of age were enrolled from the same populations that gave rise to the cases. Controls were confirmed to have no history of previous ICH by interview and/or medical record review. Control population age restrictions were identical to case population age restrictions for all included studies.

Control Populations

ICH-free controls were recruited from the same populations that gave rise to the ICH cases, through inpatient recruitment, ambulatory centers in the local communities, blood donation centers serving the same population, and in the case of the Lothian Birth Cohort, a population cohort study (**Supplementary Table S3**). The Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) and Ethic/Racial Variations of Intracerebral Hemorrhage (ERICH) studies[19,21] used random digit dialing, the Lothian Birth Cohort individuals were matched to case samples by local investigators[22], and UMC Utrecht identified controls from the local blood donor population. The remainder of studies used random selection from ambulatory clinics or geographically-matched populations where cases were being recruited.

Exposure: common genetic variants within *CETP*

In the discovery phase, we ascertained variants within *CETP* by means of genome-wide genotyping followed by imputation using methods and quality control procedures previously described[19]. Briefly, DNA was isolated from fresh or frozen peripheral whole blood collected from cases and controls at each participating institution at the time of consent, quantified with a quantification kit (Qiagen, Valencia, CA, USA), and normalized to a concentration of 30 ng/μL. Cases and controls were plated together and genotyped on Illumina 610 or Affymetrix 6.0 platforms. Standard quality controls for genome-wide data were applied, and the resulting set of individuals and SNPs were carried forward to imputation, that was completed using IMPUTE2 with 1000 Genomes-based reference panels (version March 2012)[23]. Post imputation exclusion filters were minor allele frequency (MAF) <0.01 and information score <0.5. SNPs were extracted from the *CETP* gene region according to the human genome reference GRCh38.p2 annotated location (http://www.ncbi.nlm.nih.gov), +/- 50 kilobases.

Independent Replication

CETP variants exceeding Bonferroni-corrected significance and without significant heterogeneity (I^2<40%) for association with ICH in the discovery phase were selected for replication[24]. Replication SNPs were chosen based on proxy status with index SNPs. Because replication of CETP variants was carried out as part of an ongoing GWAS of ICH, a constraint for the selection of replication SNPs was predicted genotyping success using both Sequenom iPLEX (Sequenom, San Diego, CA, USA) and Taqman (Applied Biosystems, Foster City, CA, USA) methodologies, which were employed at the MGH and University of Miami genotyping centers, respectively (**Table 2**). Ancestry informative markers were also genotyped to facilitate adjustment for population admixture.

Data Analysis

We present discrete variables as counts (percentage [%]) and continuous variables as mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate.

Population Structure

Principal component analysis was implemented in both discovery and replication to account for population structure, using genome-wide data in discovery and pre-specified ancestry-informative markers in replication[25,26]. Caucasian population outliers were identified and removed by visual inspection of plots generated with principal components 1 and 2, and these principal components were included as covariates in regression models fitted for association testing. In GERFHS and ERICH samples, further refinement of population structure was achieved using the ADMIXTURE software tool to remove outliers[27].

Association Testing

Prior to discovery association testing, SNPs within *CETP* were clumped into loci sharing linkage disequilibrium (LD) r^2>0.5 using PLINK to allow discrimination of semi-independent loci across the gene. Association testing for SNPs within the *CETP* locus and ICH risk was completed separately for all ICH, as well as for lobar and non-lobar hemorrhages. Logistic regression models were fitted assuming independent additive genetic effects for dosage of the minor allele (1-degree-of-freedom additive trend test), and adjusting for age, gender, and principal components 1 and 2. A similar analytic approach was undertaken for analysis of replication data, using additive allele genotype data rather than dosage.

Meta-Analysis

Fixed effects, inverse variance weighted meta-analysis was used to pool effect estimates across studies, assessing heterogeneity by computing Cochrane's Q (with corresponding p) and I^2 (percent of effect size attributable to heterogeneity). Identical meta-analysis procedures were used for pooling of effects across studies in discovery, replication, and across all studies[28].

Genetic Risk Score Analysis

Variants within the *CETP* locus with established association with HDL-C levels in the most recent Global Lipids Genetics Consortium (GLGC) analysis[29] (Global Lipids Genetics Consortium, "Biological and clinical insights from exome array analysis of lipids in > 300,000 individuals", under review) were extracted from the discovery dataset and tested for association with ICH using an additive multi-SNP genetic risk score approach using the GTX package (http://CRAN.R-project.org/package=gtx) in R (version 3.0). 10 variants surpassing exome array-wide significance ($p<2.1x10^{-7}$) and demonstrating independence using a sequential forward selection model in the GLGC dataset were identified, of which 7 were available in our ICH discovery dataset[30]. These 7 variants, on average, were associated with a 0.19 standard deviation increase in HDL-C (~2.85mg/dL) in the GLGC population ($p<1x10^{-200}$). This

corresponds to a proportion of variance explained of 0.032. ICH risk was predicted from summary statistics, weighted according to the established HDL-C effect and oriented to the HDL-C increasing allele.

Statistical Testing and Software

We used a conservative Bonferroni-corrected threshold for statistical significance of $p<0.004$, adjusted for the number of semi-independent loci within *CETP* with $r^2<0.5$ (12 tests in this analysis). Quality control procedures, genetic association testing for single variants, and score calculations were performed in SNPTest and PLINK v1.07[26,31]. Imputation was completed using IMPUTE2[23]. All other statistical analyses were performed in SAS 9.2 (SAS Institute, Cary, NC USA).

RESULTS

Following relevant exclusions during quality control and principal component analysis, 1149 ICH cases and 1238 controls from 3 case-control studies of ICH were included in the discovery phase, 43% of which were of the lobar ICH subtype (**Table 1**).

CETP Genetic Variants

After imputation using 1000 genomes reference panels and application of genome-wide quality control filters, a total of 390 common variants of MAF > 0.01 were extracted from the *CETP* gene and 50 kilobase flanking regions (**Supplementary Table S4**)[32]. These 390 variants were present either via array-based ascertainment or imputation in all 3 of the discovery datasets, and were used for association testing.

Single-SNP Association Testing

After testing all 390 SNPs within CETP clumped into regions sharing r^2>0.5, 12 loci demonstrating nominal association with ICH ($p<0.05$) were identified (**Supplementary Table S5**). Three of these loci surpassed Bonferroni-correction (**Table 3**) with residual r^2=0.25-0.39 between them. Among these, only rs173539 (odds ratio (OR) 1.25, standard error (SE) 0.06, $p=6.00\times10^{-4}$) met prespecified criteria for replication due to its homogeneity across discovery datasets (I^2=0%). Of note, rs173539 was in high LD with rs3764261 (r^2=0.98), the strongest associated SNP with HDL-C in published GWAS of lipid levels (**Figure 1**)[33]. Comparison of effects of the rs173539 locus on risk of lobar vs. non-lobar hemorrhage revealed no significant differences by ICH subtype (**Supplementary Table S6**).

Replication and Meta-analysis of the rs173539 Locus

1625 ICH cases and 1845 controls of Caucasian ancestry were available for replication. Following application of predictive algorithms for SNP genotype ascertainment success using both genotyping methodologies employed, four SNPs in LD with rs173539 locus were selected for replication genotyping according to the constraints described (**Tables 4 and 5**). Both rs173539 and rs3764261 were predicted to fail in one or both replication pools. All four selected SNPs were successfully genotyped in all replication datasets. All replication results showed minimal heterogeneity and consistent directions of effect, and two variants replicated at $p<0.05$. In meta-analysis, all four SNPs within the rs173539 locus chosen for replication were strengthened by addition of the replication SNP data, with minimal heterogeneity in the final total sample size of 2595 ICH cases and 3030 controls (**Table 5**).

Genetic Risk Score Analysis

An additive multi-SNP genetic risk score was constructed using independent HDL-association data[29]. 10 variants were selected, of which 7 were present in the ICH discovery dataset (**Table 6**). 3 variants were unavailable in the ICH dataset due to differences in genotyping platforms (exome array vs. GWAS array) between the two studies. The genetic risk score of these 7 variants demonstrated association with ICH (OR 1.86, SE 0.13, $p=1.39\times10^{-6}$).

DISCUSSION

Our results demonstrate an association between *CETP* gene variants in the rs173539 locus and risk of ICH, opposite in direction to their effect on risk of CAD and metabolic syndrome[5,7,8]. Furthermore, an aggregated score of variants within *CETP* that raise HDL-C is strongly associated with increased ICH risk. These results suggest that there may be substantial differences in the roles of lipids in the progression of cerebrovascular and cardiometabolic diseases. Novel therapies targeting *CETP* along with other approaches to increase HDL-C are currently under active investigation in an effort to reduce the risk of CAD[34]. Because the cerebral small vessel diseases that lead to ICH are common in the aging population and frequently coincide with risk factors for cardiometabolic disease[35,36], our observations supporting opposing effects of HDL-C on ICH and CAD underscore the need for a better understanding of which patients could be at increased risk of ICH on therapies aimed at increasing HDL-C.

Our findings support prior studies linking elevated HDL-C with increased risk of ICH. Unlike prior studies, however, our genetic approach limits confounding by dietary, environmental, or medication exposures. A recent meta-analysis of epidemiological studies examining associations between cholesterol levels and ICH found a dose-response relationship between HDL-C and ICH risk, with each 1mmol/L increase in HDL-C associated with a 17% increase in ICH risk[11]. This result was nullified when studies of subarachnoid hemorrhage patients were included, but strengthened by restriction to studies from the United States, highlighting the potential confounds of case misspecification and unmeasured environmental exposures in testing associations of this nature.

HDL-C appears to have a complex and context-dependent role in cerebrovascular disease. In contrast to ICH, elevated HDL-C is associated with reduced risk of ischemic stroke, particularly

strokes caused by large artery atherosclerotic disease, consistent with the observed associations of HDL-C in CAD[37]. However, Mendelian Randomization (MR) studies of genetic variants predisposing to elevated HDL-C have not demonstrated association with either ischemic stroke or CAD, suggesting the observed relationships may not be causal[38,39]. Unfortunately, the limited sample size of genetics efforts in ICH coupled with acute changes in lipid values around the time of ICH currently preclude the use of this MR approach in our analyses[40].

No study, including the present, has yet established a direct causal relationship between HDL-C and ICH risk. While associations between *CETP* genetic variants and ICH are almost certainly unidirectional due to the immutability of the genetic code, they still could impact an unseen risk factor that lies outside of the known HDL-C level determining effects of the gene. Even if causality can be ultimately established, the mechanism by which a CETP-mediated increase in HDL-C may worsen ICH risk remains unclear. Inhibition of CETP results in changes to HDL particle size and cholesterol efflux capacity in addition to the observed changes in HDL-C serum levels, and it may be through these accompanying changes in HDL function that ICH risk is conferred[41]. Furthermore, accumulating evidence suggests that HDL effects on endothelium are dynamic and modifiable, and can even become pro-inflammatory with the incorporation of serum amyloid A1, complement C3, and ceramides, resulting in altered immune regulation and reduced antioxidant effects[42,43]. It is therefore possible that elevated HDL-C provides a platform to further the vascular inflammatory processes that play a substantial role in the cerebral small vessel disease underlying ICH[44]. Further studies will be needed to dissect the pathways intersecting with HDL-C to clarify the foundational biology of its role in ICH.

Therapeutic development of small molecule and biologic compounds designed to raise HDL-C continue[45]. While the first wave of Phase III trials of *CETP* inhibitors were plagued by off-target

effects and futility[46], the REVEAL trial of anacetrapib was recently continued after unblinded interim review. Other HDL-raising strategies, including apolipoprotein-A1 (ApoA1)-rich reconstituted HDL particle infusions and ApoA1-mimetic peptides continue to be evaluated in preclinical and early-phase trials[45]. Given this pipeline of HDL-based therapeutic development, it is imperative that potential adverse clinical effects of such strategies be clarified. Early experiences with FDA-approved PCSK-9 inhibitors have led to predictions of widespread adoption of this new class of drugs and it is reasonable to expect that HDL-C targeted treatments would be no different, resulting in a potentially large population of aging individuals with pharmacologically-induced high HDL-C levels of uncertain long-term cerebrovascular risk[47]. The proportion of variance in HDL-C levels explained by our genetic risk score was 0.032. This is roughly commensurate with observed effects of statins, which in clinical trials raised HDL by 0.04-0.10[48]. With emerging HDL-C modifying strategies likely to exert more profound effects, the impact on ICH risk, if confirmed and verified to be causal, could be more substantial than indicated by our *CETP* genetic risk score.

As noted above, our study cannot determine whether the observed association between *CETP* and ICH risk is through HDL-C alone. While they exhibit their largest effect on HDL-C levels, *CETP* variants are also associated with low-density lipoprotein (LDL), triglycerides (TG), and total cholesterol (TC) levels[3]. While we cannot perform formal MR, the association between our HDL-C increasing genetic risk score at CETP and risk of ICH provides support for an HDL-specific effect. Even with this suggestion of HDL-C specificity, the composition of HDL particles can vary with respect to ratios of esterified to unesterified cholesterol as well as apolipoprotein content. Genetic variation that determines circulating HDL-C does not necessarily capture these secondary characteristics, which could have a substantial impact on biological effects.

An additional limitation of our study is the aggregation of case and control data across multiple sites, which could result in biases between cases and controls. We have attempted to control for study demographics and population structure in our regression analyses, and performed independent replication, but unmeasured confounding could still have impacted the observed associations. Related to this point, all analyses presented were in individuals of European ancestry due to small study populations, and therefore low statistical power, in individuals of other racial and ethnic backgrounds. As a result, our findings cannot be extended to minority populations at this time.

While our study utilized genomewide data for discovery and genetic risk score analyses, our approach was fundamentally a candidate gene study of *CETP*. Using GWAS data allowed for control of population stratification, which can be a major confounder in traditional candidate gene designs employing only direct genotyping. However, it was still based on an *a priori* hypothesis about *CETP* association with ICH. Therefore, the false discovery rate for association between variants at *CETP* and ICH risk, while stringently controlled using Bonferroni-correction at the *CETP* locus, may still be elevated in comparison with a standard GWAS. Due to the hypothesis-driven nature of our study, we by definition cannot provide novel results about lipid-related genetic loci that lie outside of the tested gene region.

Finally, the *CETP* gene contains several independent loci which have been associated with lipid levels and clinical endpoints[3,5,7,33]. This resulted in a more complex replication phase than would have been needed if the genetic architecture of the locus were centered about a single region of association. Coupled with the limitations of variant selection in our replication phase, we cannot distinguish a culprit variant to the exclusion of others. Although all variants chosen for replication demonstrated refined effect size estimates and greater statistical significance in meta-analysis with discovery data, replication was strongest for variants in slightly lower LD than the lead

variant from discovery, and with slightly higher between-study heterogeneity. Whether this observation represents true heterogeneity of effect at the replicated variants will depend on future validation and extension studies.

We have demonstrated an association between genetic variants in *CETP* and risk of ICH, and have shown that *CETP*'s HDL-C raising effects could play a role in the pathogenesis of ICH. Further work will be needed to identify how the biological pathways impacted by HDL-C may impart increased risk of hemorrhage. These pathways may yield crucial novel targets for prevention of ICH and the cerebral small vessel diseases that lead to vessel rupture.

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POTENTIAL CONFLICTS OF INTEREST

Nothing to disclose.

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FIGURE LEGENDS

Figure 1. ICH-associated variants in the rs173539 locus in *CETP*

Figure 1 Legend: Regional association plot of rs173539 and SNPs exhibiting r^2>0.5 in association with ICH. SNPs available for replication are circled. Mean recombination rate across the locus is represented by the continuous blue line. The rs3764261 variant identified was the leading SNP in prior genome-wide association studies of HDL-C. Chr = chromosome, cMMb = centimorgans per megabase, Mb = megabase.

TABLES

Table 1. Discovery populations

Variable	GOCHA		ISGC ICH Study		GERFHS	
	Cases	Controls	Cases	Controls	Cases	Controls
n	371	389	404	530	374	319
Age, mean (SD)	74 (10)	72 (8)	70 (13)	66 (16)	67 (15)	67 (14)
Female, n (%)	172 (46)	195 (50)	189 (47)	266 (50)	194 (52)	172 (54)
HTN, n (%)	274 (75)	227 (58)	278 (69)	247 (47)	241 (64)	166 (52)
T2D, n (%)	68 (18)	35 (9)	89 (22)	68 (13)	72 (19)	42 (13)
HL, n (%)	144 (39)	195 (50)	87 (22)	48 (9)	131 (35)	133 (42)
Smoking, n (%)	56 (15)	15 (4)	58 (14)	74 (14)	79 (21)	46 (14)
Genotyping Platform	Illumina 610	Illumina 610	Illumina 610	Illumina 610	Affymetrix 6.0	Affymetrix 6.0
Lobar, n (%)	205 (55)	-	135 (33)	-	156 (42)	-
Discovery totals	2387 individuals (1149 cases, 1238 controls), 43% lobar ICH					

Abbreviations: GERFHS = Genetic and Environmental Risk Factors for Hemorrhagic Stroke study; GOCHA = Genes and Outcomes of Cerebral Hemorrhage on Anticoagulation study; HL = Hyperlipidemia; HTN = Hypertension; ICH = Intracerebral hemorrhage; ISGC ICH study = International Stroke Genetics Consortium Intracerebral Hemorrhage Study; Lobar = Lobar ICH location; T2D = Type 2 Diabetes Mellitus

Table 2. Replication populations

Variable	MGH		ERICH		University of Brescia		UMC Utrecht		University of Edinburgh	
	Case	Ctrl	Case	Ctrl	Case	Ctrl	Case	Ctrl	Case	Ctrl
n	240	458	920	826	198	185	157	160	110	216
Age, n (SD)	76 (10)	69 (11)	69 (14)	68 (13)	69 (13)	63 (14)	62 (13)	56 (11)	75 (9)	76 (10)
Female, n (%)	96 (40)	206 (45)	397 (43)	371 (45)	81 (41)	85 (46)	66 (42)	67 (42)	59 (54)	118 (54)
Lobar , n (%)	120 (48)	-	380 (41)	-	82 (41)	-	60 (38)	-	61 (55)	-
Genotyping platform	iPLEX	iPLEX	Taq-man	Taq-man	iPLEX	iPLEX	iPLEX	iPLEX	iPLEX	iPLEX
Replication Totals	3470 individuals (1625 cases, 1845 controls), 42% lobar ICH									
Discovery + Replication Totals	5625 individuals (2595 cases, 3030 controls), 45% lobar ICH									

Abbreviations: Ctrl = Control; ERICH = Ethnic/Racial Variations of Intracerebral Hemorrhage; iPLEX = Sequenom MassARRAY iPLEX Platform; MGH = Massachusetts General Hospital; TaqMan = Applied Biosystems Taqman Genotyping Assay

Table 3. Discovery *CETP* loci demonstrating Bonferroni-significant association with ICH

Lead SNP	CHR	Tested allele	MAF	Effect direction	OR	SE	Discovery p	I^2
rs173539	16	T	0.31	+++	1.25	0.06	6.00E-4	0
rs820299	16	G	0.38	---	0.81	0.06	7.50E-4	48
rs158478	16	A	0.48	+++	1.21	0.06	1.48E-3	56

CHR = chromosome, MAF = minor allele frequency, OR = odds ratio, SE = standard error, SNP = single nucleotide polymorphism, + = variant increases ICH risk, - = variant decreases ICH risk.

Table 4. Discovery SNP rs173539 and local proxies in association with ICH risk

SNP	CHR	Tested allele	MAF	Effect direction	OR	SE	Discovery p	I^2
rs173539	16	T	0.31	+++	1.25	0.06	6.00×10^{-4}	0
-- rs247617 (r^2=0.99)	16	A	0.31	+++	1.24	0.06	8.74×10^{-4}	0
-- rs17231506 (r^2=0.99)	16	T	0.31	+++	1.23	0.06	9.13×10^{-4}	0
-- rs711752 (r^2=0.62)	16	A	0.42	++-	1.15	0.06	2.08×10^{-2}	14
-- rs708272 (r^2=0.61)	16	A	0.42	++-	1.15	0.06	2.23×10^{-2}	18

Association results for rs173539 in association with ICH risk, as well as four additional SNPs in linkage disequilibrium (LD) with rs173539 chosen for replication. CHR = chromosome, MAF = minor allele frequency, OR = odds ratio, SE = standard error, r^2 = degree of LD with rs173539. SNP = single nucleotide polymorphism, + = variant increases ICH risk, - = variant decreases ICH risk.

Table 5. Replication results for SNPs in LD with rs173539 and meta-analysis of all samples

	Replication					Discovery/Replication Meta-analysis				
SNP	Effect	OR	SE	p	I^2	Effect	OR	SE	p	I^2
rs247617	+++++	1.08	0.05	0.18	2	+++/+++++	1.13	0.04	$1.0x10^{-3}$	0
rs17231506	+++++	1.08	0.05	0.17	1	+++/+++++	1.13	0.04	$1.0x10^{-3}$	0
rs711752	++++-	1.12	0.05	0.03	7	++-/++++-	1.13	0.04	$1.0x10^{-3}$	0
rs708272	++++-	1.14	0.05	0.01	4	++-/++++-	1.14	0.04	$5.0x10^{-4}$	0

OR = odds ratio, SE = standard error, SNP = single nucleotide polymorphism, + = variant increases ICH risk, - = variant decreases ICH risk.

Table 6. ICH association results for variants of known HDL-C effect used to compute genetic risk score

SNP	Ref Allele	MAF	ICH OR	ICH Beta	ICH SE	ICH p	HDL Effect Allele	HDL Beta	HDL SE	Type
rs173539	T	0.31	1.25	0.222	0.065	0.0006	T	0.230	0.0028	Intergenic
rs3764261	A	0.31	1.23	0.210	0.063	0.0009	A	0.239	0.0028	Intergenic
rs247616	T	0.30	1.22	0.196	0.064	0.0023	T	0.242	0.0028	Intergenic
rs9989419	A	0.40	0.92	-0.079	0.059	0.1808	G	0.131	0.0026	Intergenic
rs5880	C	0.04	1.22	0.202	0.151	0.1812	G	0.258	0.0067	Nonsyn.
rs5882	G	0.32	1.06	0.057	0.065	0.3803	G	0.092	0.0028	Nonsyn.
rs7499892	T	0.19	1.02	0.022	0.076	0.7758	C	0.230	0.0033	Intronic

CETP = cholesterol ester transfer protein, HDL = High Density Lipoprotein, ICH = intracerebral hemorrhage, MAF = minor allele frequency, Nonsyn. = nonsynonymous, OR = odds ratio, Ref = reference, SE = standard error

SUPPLEMENTARY DATA

Genetic Variants in *CETP* Increase Risk of Intracerebral Hemorrhage

CD Anderson et al.

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Supplementary Table S1. ICH case and control recruitment architectures for participating studies

Study	Participating Centers	Population Ages	Case Recruitment	Control Recruitment
Brescia Stroke Registry	University of Brescia, Brescia, Italy	18+	Hospital-based, prospective	Regionally matched, hospital and ambulatory clinics
UMC Utrecht ICH Study	University Medical Center Utrecht, Utrecht, The Netherlands	18+	Hospital-based, prospective	Regionally matched, blood donor population
Edinburgh Stroke Study	Western General Hospital, Edinburgh, Scotland, UK	55+	Inpatient and outpatient hospital-based, prospective	N/A
LINCHPIN	Western General Hospital, Royal Infirmary of Edinburgh, St. John's Hospital at Howden, West Lothian, Scotland, UK	16+	Community-based in areas served by NHS Lothian Health Board, prospective with hot-pursuit and retrospective augmentation	N/A
Lothian Birth Cohort 1936	All centers serving the Lothian Area of Scotland	76 years old (cohort assessed at ages 70, 73, and 76)	N/A	Community population born in 1936 who took Scottish Mental Survey in 1947, living in Lothian, Scotland, UK
ERICH	19 centers in USA, based at University of Cincinnati	18+	Hospital-based, prospective with hot-pursuit	Regionally matched, random-digit-dialing
GOCHA	6 centers in USA, based at Massachusetts General Hospital	55+	Hospital-based, prospective	Regionally matched, ambulatory clinics
GERFHS	16 centers in the Greater Cincinnati/Northern Kentucky region of USA, based at University of Cincinnati	18+	Hospital-based, prospective	Regionally matched, random-digit-dialing
ISGC Europe	Hospital del Mar ICH study, Vall d'Hebron ICH study in Barcelona, Spain, Jagiellonian University Hemorrhagic Stroke Study in Krakow, Poland, Lund Stroke Register in Lund, Sweden	18+	Hospital-based, prospective	Regionally matched, hospital and ambulatory clinics

Supplementary Table S2. ICH case inclusion and exclusion criteria by recruitment site

Study	Inclusion Criteria	Exclusion Criteria
Brescia Stroke Registry	• 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
UMC Utrecht ICH Study	• 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
Edinburgh - ESS	• 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
Edinburgh - LINCHPIN	• Symptomatic ICH (acute or chronic) • CT or MRI confirmation of acute or chronic ICH • Age > 16 • Resident in area served by NHS Lothian Health Board at time of ICH	• Head trauma • Brain tumor • Ischemic stroke with hemorrhagic transformation • Vascular malformation • Other cause of secondary ICH
ERICH	• 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
GOCHA	• 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
GERFHS	• 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
ISGC Europe ICH studies (Hospital del Mar, Vall d'Hebron Hospital, Jagiellonian University, Lund University)	• 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

Supplementary Table S3. Control inclusion and exclusion criteria by recruitment site

Study	Ascertainment Methods	Inclusion Criteria
Brescia Stroke Registry	• Screened and collected from the same hospital as ICH cases	• Absence of stroke history, confirmed through interview and review of medical records
UMC Utrecht ICH Study	• Blood donors presenting to the same hospital as ICH cases, from same surrounding population	• Healthy blood donor as confirmed through screening questionnaires at the donation facility
Edinburgh - Lothian Birth Cohort 1936	• Individuals in Lothian born in 1936, totaling 1091 participants in Wave 1 at age 70 years, with follow-up waves at ages 73 and 76	• Random selection matched 2:1 with ICH cases from ESS and LINCHPIN, confirmed stroke-free at age 76
ERICH	• Ascertained through random digit dialing in the regions surrounding centers where cases were recruited, age > 18	• Absence of ICH history confirmed through interview at the time of consent
GOCHA	• Screened and collected from ambulatory clinics at the same centers that recruited cases, age > 55	• Absence of ICH history confirmed through interview at the time of consent
GERFHS	• Ascertained through random digit dialing in the Greater Cincinnati-Northern Kentucky region where cases were recruited, age > 18	• Absence of ICH history confirmed through interview at the time of consent
ISGC Europe ICH studies (Hospital del Mar, Vall d'Hebron Hospital, Jagiellonian University, Lund University)	• Screened and collected from ambulatory clinics at the same centers that recruited cases, age > 18	• Absence of ICH history confirmed through interview at the time of consent

Supplementary Table S4. Discovery phase association results for all SNPs in *CETP*

SNP	OR	SE	P	Direction	I2
rs173539	1.25	0.06	0.00060	+++	0
rs183130	1.24	0.06	0.00066	+++	0
rs820299	0.81	0.06	0.00075	---	48.1
rs3764261	1.23	0.06	0.00086	+++	0
rs247617	1.24	0.06	0.00087	+++	0
rs17231506	1.23	0.06	0.00091	+++	0
rs821840	1.24	0.07	0.00111	+++	0
rs56156922	1.24	0.07	0.00111	+++	0
rs12446515	1.24	0.07	0.00123	+++	0
rs158478	1.21	0.06	0.00148	+++	56
rs72786786	1.24	0.07	0.00178	+++	0
rs60545348	0.82	0.07	0.00200	---	36.2
rs158479	1.20	0.06	0.00228	+++	14.9
rs247616	1.22	0.06	0.00229	+++	0
rs12597002	0.82	0.07	0.00248	---	36.8
rs708273	0.82	0.07	0.00272	---	11.7
rs4369653	0.83	0.07	0.00390	---	51.7
rs12149545	1.20	0.06	0.00467	+++	0
rs158477	1.19	0.06	0.00542	+++	41
rs56228609	1.19	0.07	0.00904	+++	0
rs4784745	0.85	0.06	0.00973	---	0
rs4784741	1.17	0.06	0.01014	+++	16.6
rs291044	0.85	0.06	0.01180	---	0
rs12444012	1.16	0.06	0.01211	++-	26.5
rs12720926	1.16	0.06	0.01338	+++	0
rs291043	0.86	0.06	0.01340	---	0
rs11508026	1.16	0.06	0.01611	+++	3.8
rs7187261	1.46	0.16	0.01636	+++	0
rs711752	1.15	0.06	0.02079	++-	14
rs708272	1.15	0.06	0.02231	++-	18.5
rs289751	1.50	0.18	0.02310	++-	19.3
rs711751	0.87	0.06	0.02725	---	0
rs4783962	0.86	0.07	0.02749	---	0
rs12447839	0.86	0.07	0.02944	---	0
rs11860407	1.14	0.06	0.03670	+++	0
rs12708980	1.13	0.06	0.03748	+++	0
rs891144	1.80	0.29	0.03975	+++	0
rs4587963	0.87	0.07	0.04051	---	0
rs2033254	1.13	0.06	0.04137	+++	0

rs71387147	0.77	0.13	0.04162	---	0
rs247618	0.86	0.07	0.04195	---	0
rs12447924	0.87	0.07	0.04207	---	0
rs1800775	1.12	0.06	0.04412	+++	0
rs289746	1.16	0.07	0.04637	+++	30.5
rs1800776	0.79	0.12	0.04787	---	14.4
rs7187275	1.36	0.16	0.05059	+++	0
rs12934552	0.84	0.09	0.05069	---	0
rs3816117	1.12	0.06	0.05256	+++	0
rs12708985	1.18	0.09	0.05326	+++	0
rs13337445	0.80	0.12	0.05934	--+	58.5
rs1122390	0.87	0.07	0.05950	---	0
rs289742	1.18	0.09	0.06317	+++	0
rs12447620	1.17	0.09	0.06683	+++	0
rs1800777	1.31	0.16	0.07862	+++	27.7
rs17369163	0.81	0.12	0.07962	--+	41.9
rs1800774	1.11	0.06	0.08460	+++	0
rs4784751	1.12	0.06	0.08496	++-	25.9
rs7197864	0.85	0.09	0.08917	---	0
rs17290922	0.85	0.09	0.08959	---	0
rs4784750	1.11	0.06	0.10300	++-	22.6
rs1651663	1.12	0.07	0.10340	++-	0
rs7205459	0.86	0.09	0.10340	---	0
rs35926917	0.82	0.12	0.10970	--+	30
rs74023630	0.86	0.10	0.11230	---	0
rs9936680	0.83	0.12	0.11520	--+	27
rs158617	1.15	0.09	0.11720	+++	0
rs72786778	0.78	0.16	0.11730	+--	0
rs158480	1.15	0.09	0.12480	+++	0
rs56208677	1.21	0.12	0.12670	+++	0
rs12924030	0.87	0.09	0.12750	---	0
rs77751805	1.41	0.23	0.12930	+++	0
rs12445252	1.10	0.07	0.13250	++-	12.7
rs12444396	1.10	0.07	0.13630	++-	22.1
rs12923459	0.91	0.06	0.13720	---	0
rs9924087	0.84	0.12	0.13980	--+	35
rs289734	0.89	0.08	0.14040	---	0
rs1436425	1.10	0.07	0.14810	+++	0
rs17231534	0.80	0.15	0.15140	--+	31.6
rs74021897	1.10	0.07	0.15200	+++	0
rs289736	1.13	0.09	0.15400	++-	0
rs1684576	1.09	0.06	0.16500	++-	43.4
rs72778371	0.89	0.08	0.16690	--+	0

rs5030708	0.77	0.19	0.17420	--+	0
rs12448528	0.90	0.08	0.17550	---	0
rs11862052	1.13	0.09	0.17610	+++	0
rs9989419	0.92	0.06	0.18080	+--	0
rs5880	1.22	0.15	0.18120	++-	33.3
rs117398617	0.90	0.08	0.18750	--+	5.5
rs891140	0.92	0.06	0.18850	--+	33.2
rs1875236	1.16	0.11	0.19390	+++	0
rs11644475	1.33	0.22	0.19900	++-	44.9
rs289735	1.09	0.07	0.20350	+--	59
rs4471669	1.09	0.07	0.20370	+++	0
rs11644171	1.09	0.07	0.20530	++-	34.7
rs7203984	1.10	0.08	0.20690	-++	61.6
rs289750	1.09	0.07	0.20860	+--	61.5
rs1875235	1.15	0.11	0.21210	+++	0
rs78921879	1.13	0.10	0.22040	++-	0
rs1684575	1.08	0.06	0.22380	++-	78.5
rs289749	1.09	0.07	0.22420	+--	64.5
rs9925054	0.93	0.06	0.22660	---	0
rs1549669	0.93	0.06	0.23250	---	0
rs166017	1.08	0.07	0.25260	++-	32
rs289714	1.10	0.08	0.25690	+++	0
rs7200805	0.81	0.19	0.26620	---	0
rs37025	0.93	0.06	0.27070	--+	0
rs289741	1.07	0.07	0.27560	+++	0
rs28504436	1.08	0.07	0.28780	++-	0
rs1672865	1.06	0.06	0.29450	++-	79.6
rs4783961	1.06	0.06	0.29560	-++	70.3
rs72773107	1.17	0.15	0.30590	+++	0
rs61738710	0.87	0.13	0.30930	--+	0
rs7194225	0.88	0.12	0.31030	--+	43.4
rs9921780	1.06	0.06	0.31310	+-+	46.7
rs172337	1.12	0.12	0.32300	++-	0
rs247610	0.94	0.06	0.32320	---	0
rs13339199	1.14	0.13	0.32340	-++	24.2
rs193695	0.94	0.06	0.32410	+--	0
rs12924331	1.06	0.06	0.32650	+-+	46.6
rs289743	1.07	0.07	0.32800	+++	0
rs34218679	1.09	0.09	0.32910	-++	0
rs247614	1.07	0.07	0.33000	++-	0
rs74931918	1.17	0.16	0.33020	+++	0
rs190324	0.94	0.06	0.33060	--+	0
rs56816073	1.07	0.07	0.33200	++-	0

rs9925265	1.06	0.06	0.33440	+-+	38.7
rs821470	0.94	0.06	0.34020	--+	57.2
rs289718	1.06	0.07	0.34430	+++	0
rs289719	1.06	0.07	0.34430	+++	0
rs72780003	1.13	0.13	0.34750	-++	35.5
rs1167742	0.94	0.06	0.34760	--+	55.5
rs247611	1.06	0.07	0.35030	++-	6.7
rs16965077	0.87	0.15	0.35110	---	0
rs56353889	1.06	0.07	0.35280	++-	6.6
rs173537	1.06	0.07	0.35650	++-	11.2
rs1651666	0.94	0.06	0.36570	--+	49.6
rs193694	1.08	0.09	0.37040	++-	28.2
rs4474668	1.06	0.07	0.37100	++-	10.2
rs866038	1.06	0.07	0.37100	++-	10.2
rs861884	1.06	0.07	0.37480	++-	8.7
rs4783965	0.94	0.08	0.37950	---	0
rs5882	1.06	0.06	0.38030	+++	0
rs117910159	0.85	0.18	0.38260	+--	0
rs12920974	0.95	0.07	0.38690	---	0
rs955513	0.95	0.06	0.38930	-+-	16
rs117427818	1.14	0.15	0.39120	++-	39.8
rs75911530	1.21	0.23	0.39520	++-	0
rs34946873	1.11	0.12	0.39740	+-+	55
rs247612	1.06	0.07	0.39750	++-	0
rs1820787	1.06	0.07	0.39760	++-	0
rs736274	1.08	0.10	0.40520	+++	0
rs247613	1.06	0.07	0.40650	++-	0
rs16970107	0.94	0.07	0.41030	--+	48.4
rs2133783	1.05	0.07	0.41850	++-	23.6
rs952440	1.05	0.07	0.41850	++-	23.6
rs37024	0.95	0.06	0.42090	-+-	4.7
rs1864163	0.95	0.07	0.42110	-+-	0
rs289716	1.05	0.07	0.42210	+++	0
rs16965150	0.84	0.22	0.42370	0	0
rs2115429	0.94	0.08	0.42840	-+-	0
rs37023	1.05	0.07	0.42950	++-	35.2
rs289715	1.08	0.09	0.43000	+++	0
rs12720873	1.16	0.20	0.44100	++-	0
rs16942393	0.96	0.06	0.44590	+--	0
rs8058353	1.13	0.16	0.44950	+++	0
rs8059595	1.13	0.16	0.44950	+++	0
rs36229787	0.95	0.07	0.45140	--+	0
rs28495885	0.93	0.10	0.45220	-+-	0

rs7203286	0.95	0.06	0.45290	---	0
rs3764263	0.96	0.06	0.45570	-+-	0
rs12720897	0.91	0.13	0.45660	+-+	72.9
rs247606	1.07	0.08	0.45690	++-	57.5
rs193693	1.06	0.08	0.45940	++-	54.3
rs12708983	1.17	0.22	0.46050	++-	0
rs6499863	0.94	0.08	0.46090	-+-	0
rs2518058	1.06	0.08	0.46140	++-	59.3
rs2052880	0.96	0.06	0.46370	+-+	0
rs7185561	1.05	0.07	0.46480	++-	0
rs12720898	0.91	0.13	0.46540	+-+	74.7
rs289748	1.04	0.06	0.46790	-++	0
rs711747	0.96	0.06	0.46810	-+-	0
rs247609	1.05	0.07	0.46880	++-	24.3
rs12446867	1.05	0.07	0.46950	++-	0
rs17239354	0.91	0.13	0.46960	+-+	72.4
rs12373120	0.95	0.07	0.47300	--+	22
rs9931176	1.05	0.07	0.47440	++-	0
rs58124158	0.96	0.06	0.47870	--+	52.3
rs952439	1.06	0.08	0.48010	++-	56.9
rs821465	0.95	0.07	0.48170	-+-	0
rs1820788	1.05	0.07	0.48180	++-	27.5
rs12720918	0.96	0.07	0.48520	--+	0
rs37029	0.96	0.06	0.48530	-+-	0
rs37030	0.96	0.06	0.48530	-+-	0
rs1428847	0.96	0.06	0.48540	-+-	0
rs4784738	0.88	0.18	0.49100	+--	12.4
rs3903056	1.06	0.08	0.49130	++-	54.2
rs8059431	1.12	0.17	0.49370	++-	0
rs1167514	0.95	0.07	0.49730	+--	0
rs247608	1.06	0.09	0.49860	++-	58
rs289707	0.95	0.07	0.50100	-+-	0
rs289703	1.05	0.07	0.50320	++-	0
rs16942394	1.04	0.06	0.50340	+++	0
rs881598	1.06	0.08	0.50530	++-	49.8
rs2518056	0.96	0.06	0.50540	-+-	0
rs3812963	1.06	0.09	0.51130	-+-	10.4
rs62035509	0.95	0.08	0.51430	-+-	21.6
rs3794647	0.96	0.06	0.51640	-+-	0
rs711748	0.96	0.06	0.51640	-+-	0
rs37026	0.96	0.06	0.51740	-+-	0
rs289747	1.04	0.06	0.51790	++-	0
rs1801706	0.95	0.08	0.51820	--+	0

rs9924286	0.96	0.06	0.51890	-+-	0
rs9926292	0.96	0.06	0.51890	-+-	0
rs3794648	0.96	0.06	0.51910	-+-	7.3
rs4784749	0.95	0.08	0.52130	--+	27.1
rs2217332	1.06	0.08	0.52310	++-	56.9
rs7196436	0.91	0.15	0.52670	+--	0
rs12598913	0.96	0.06	0.52970	--+	55.5
rs17245715	0.94	0.10	0.53240	+--	9.6
rs1366544	1.05	0.08	0.53380	++-	57.2
rs4548848	0.96	0.06	0.53980	-+-	0
rs176532	0.96	0.07	0.54270	-+-	13.7
rs75429044	0.94	0.09	0.54520	-+-	0
rs2562126	1.05	0.08	0.55100	++-	50.5
rs55664802	0.95	0.09	0.55110	++-	63
rs74023644	0.91	0.16	0.55230	+--	0
rs74023645	0.91	0.16	0.55230	+--	0
rs16965220	0.96	0.06	0.55270	--+	56.5
rs3812964	0.97	0.06	0.55270	-+-	0
rs12596509	0.97	0.06	0.55320	-+-	0
rs708270	0.97	0.06	0.55320	-+-	0
rs711749	0.97	0.06	0.55320	-+-	0
rs821466	1.04	0.06	0.55600	+--	19.3
rs2518055	1.05	0.09	0.55830	++-	62.2
rs37031	0.97	0.06	0.55880	-+-	0
rs17369468	0.96	0.07	0.56980	--+	72.2
rs62035538	0.96	0.07	0.57000	--+	32.2
rs55634433	0.92	0.15	0.57080	+--	0
rs75974417	0.96	0.07	0.57220	--+	0
rs247607	1.05	0.08	0.57390	++-	62.3
rs5805	0.97	0.06	0.57750	-+-	4
rs56079121	0.95	0.09	0.58250	-+-	0
rs11076176	1.05	0.08	0.58280	-++	0
rs39718	0.97	0.06	0.58610	-+-	0
rs55726180	1.03	0.06	0.59180	+-+	34.5
rs58337780	0.92	0.16	0.59220	+--	0
rs12149572	1.03	0.06	0.59380	--+	15
rs1651665	0.97	0.07	0.59500	--+	65
rs9931252	0.95	0.09	0.59580	-+-	0
rs711746	0.97	0.06	0.59610	-+-	0
rs9932164	0.95	0.09	0.59750	-+-	0
rs289754	0.97	0.06	0.59820	+-+	0
rs9927820	1.03	0.06	0.59860	+-+	27
rs112039804	1.06	0.11	0.59940	-++	0

rs13330423	0.97	0.06	0.60360	--+	0
rs11863728	1.03	0.06	0.60370	+-+	26.3
rs12708968	0.95	0.10	0.60460	+--	4.2
rs12598522	1.03	0.06	0.60610	-0+	6.3
rs718620	0.95	0.10	0.60770	-+-	0
rs28168	0.97	0.06	0.60860	-++	2.4
rs17370142	0.95	0.10	0.62360	-+-	63.3
rs5808	0.97	0.06	0.62620	-++	6.6
rs13335668	0.95	0.10	0.62800	++-	63.4
rs72780004	0.97	0.07	0.62840	--+	0
rs1167741	0.97	0.06	0.63080	--+	0
rs37027	0.97	0.06	0.63100	-+-	25
rs66495554	1.03	0.07	0.63350	-+-	0
rs28880001	1.03	0.06	0.63540	+-+	20.7
rs12149414	1.03	0.06	0.63640	+-+	20.6
rs12149520	1.03	0.06	0.63640	+-+	20.6
rs3764262	1.03	0.06	0.63910	+-+	21.4
rs2399594	1.03	0.06	0.64040	+-+	0
rs56172892	0.95	0.10	0.64400	-+-	59.1
rs11866974	1.03	0.06	0.64440	+-+	12.7
rs2518054	1.04	0.09	0.64590	-+-	7
rs9927174	1.03	0.06	0.64680	+-+	18.9
rs76994065	0.94	0.14	0.65070	++-	30.4
rs56132500	1.06	0.12	0.65240	-++	0
rs9921645	1.03	0.06	0.65590	+-+	18.3
rs13333567	1.03	0.06	0.66610	+-+	11.2
rs62038195	1.03	0.06	0.66610	+-+	11.2
rs6499862	0.97	0.08	0.67060	-+-	0
rs58138751	1.06	0.13	0.67380	-++	0
rs112952893	1.04	0.09	0.67450	-++	0
rs4783963	0.96	0.10	0.67460	-++	39.7
rs74023632	0.94	0.16	0.67490	+--	0
rs74611520	1.04	0.09	0.67580	-+-	10.9
rs28438857	1.04	0.10	0.67760	++-	50.9
rs34531240	1.04	0.10	0.67760	++-	50.9
rs17369768	1.03	0.07	0.67840	--+	50.2
rs173538	0.97	0.06	0.67850	-++	0
rs6499861	0.97	0.08	0.68360	-+-	0
rs60169561	0.97	0.07	0.68840	--+	64
rs72786781	0.91	0.25	0.69420	-+-	0
rs117199686	0.95	0.14	0.69470	++-	36.2
rs7198642	1.03	0.07	0.69540	-+-	13.1
rs11642606	0.98	0.06	0.69850	--+	0

rs1549670	0.98	0.06	0.69980	--+	22
rs72773119	0.94	0.15	0.70100	+--	0
rs72773120	0.94	0.15	0.70100	+--	0
rs12708967	0.97	0.08	0.70330	-++	0
rs12934632	0.97	0.08	0.70990	---	0
rs8056195	1.02	0.06	0.71110	+-+	25.2
rs9938413	1.03	0.09	0.71190	-+-	0
rs72778395	1.05	0.13	0.71880	-++	0
rs11076175	1.03	0.08	0.72010	-+-	61.6
rs62035546	0.97	0.10	0.72510	++-	59.6
rs62035547	0.97	0.10	0.72510	++-	59.6
rs9931755	1.02	0.06	0.72880	+-+	0
rs55958623	1.03	0.09	0.73290	++-	68.2
rs12444708	1.04	0.11	0.74060	-++	0
rs37028	1.02	0.06	0.74230	+-+	0
rs28439729	0.95	0.14	0.74340	++-	39
rs9938543	0.97	0.10	0.74640	++-	54.9
rs72773124	0.95	0.16	0.75040	+--	0
rs7195863	0.95	0.16	0.75200	+--	0
rs11076174	1.03	0.11	0.75460	-++	61.2
rs12720922	1.02	0.08	0.75480	-+-	62.5
rs176533	1.02	0.06	0.75480	+--	14.1
rs9937834	0.97	0.10	0.75750	++-	57.8
rs56096618	1.04	0.13	0.75850	-++	0
rs34760410	0.97	0.11	0.76310	+-+	20.7
rs289708	0.98	0.08	0.76560	-++	0
rs291040	0.98	0.06	0.76990	+-+	0
rs9923854	0.97	0.11	0.77100	-++	33.9
rs7499892	1.02	0.08	0.77580	-+-	65.5
rs1991515	0.98	0.06	0.79010	-++	27.7
rs9930761	0.97	0.13	0.79220	-++	33
rs11644125	0.98	0.06	0.79850	--+	65.6
rs12445769	1.02	0.06	0.79860	+-+	11.5
rs7499911	0.96	0.14	0.80040	++-	43.8
rs5883	0.97	0.15	0.81220	-++	60.1
rs12149408	1.02	0.06	0.81240	+-+	0
rs28888131	0.98	0.08	0.81300	-+-	0
rs9788873	0.99	0.06	0.81520	+-+	16.7
rs12928552	1.03	0.12	0.81890	-++	0
rs1566439	1.01	0.06	0.81980	--+	0
rs7204290	0.99	0.06	0.82070	+-+	25.2
rs821463	1.01	0.06	0.82460	+--	6.3
rs56315364	1.01	0.06	0.82880	--+	26.8

rs72771478	0.95	0.23	0.83030	-+-	0
rs72771479	0.95	0.23	0.83030	-+-	0
rs12708974	1.02	0.10	0.83470	+-+	55.5
rs62035542	0.98	0.10	0.83840	++-	65.5
rs2399597	0.98	0.09	0.84060	-++	0
rs74439742	0.98	0.08	0.84680	--+	9.4
rs117426126	0.97	0.15	0.84760	++-	39.3
rs76691037	0.97	0.16	0.84890	+--	0
rs863706	1.01	0.07	0.85560	++-	35.9
rs80195568	1.03	0.14	0.85600	++-	0
rs75378421	0.97	0.14	0.85750	++-	28.1
rs118146573	1.02	0.09	0.85860	-+-	0
rs1651667	0.99	0.07	0.85910	--+	66.4
rs80327887	0.98	0.14	0.85920	++-	0
rs78459786	0.98	0.14	0.86240	++-	37.2
rs16965070	0.98	0.12	0.86280	-++	0
rs9929488	0.99	0.07	0.86460	-+-	60.2
rs56285233	0.98	0.12	0.86890	-++	0
rs16965037	1.01	0.06	0.87340	--+	58.5
rs62038194	1.01	0.07	0.88320	++-	31.6
rs16965039	1.02	0.12	0.88380	-+-	0
rs62035543	0.99	0.10	0.88690	++-	65.4
rs4544228	1.01	0.07	0.88820	++-	40.5
rs116889966	1.02	0.14	0.89070	++-	0
rs1151265	1.02	0.13	0.89260	-+-	0
rs16965033	0.98	0.12	0.89270	-+-	0
rs80103996	1.02	0.14	0.89800	++-	0
rs36229786	0.99	0.08	0.90440	-++	0
rs17310296	0.98	0.14	0.90770	++-	34.2
rs8044804	0.99	0.06	0.91290	+-+	25.9
rs11861555	1.01	0.06	0.91590	+-+	0
rs62035537	0.99	0.09	0.91610	-++	3.3
rs62035545	1.01	0.10	0.92080	++-	65.8
rs7500979	0.99	0.06	0.92890	+-+	33.7
rs7205692	0.99	0.09	0.93500	-++	0
rs9939318	0.99	0.10	0.94140	++-	63.1
rs11864751	1.00	0.06	0.96150	+-+	28.6
rs74912812	0.99	0.14	0.96220	++-	46.4
rs289737	1.00	0.07	0.96920	++-	0
rs1167513	1.00	0.13	0.97280	-+-	0
rs291042	1.00	0.08	0.97420	-+-	0
rs62035544	1.00	0.10	0.97520	++-	61.3
rs76631084	1.00	0.14	0.97580	++-	0

rs17369578	1.00	0.14	0.97700	++-	57.9
rs289752	1.00	0.06	0.97820	+--	39.6
rs74613568	1.00	0.14	0.98330	++-	0
rs55744249	1.00	0.09	0.98600	++-	72.4
rs56273021	1.00	0.06	0.98790	--+	62.8

OR = odds ratio, SE = standard error, SNP = single nucleotide polymorphism, + = variant increases ICH risk, - = variant decreases ICH risk.

Supplementary Table S5. Discovery phase results for top SNPs within each semi-independent *CETP* locus with ICH risk

Allele information				Meta-analysis results				Study specific odds ratios		
Lead SNP	CHR	BPP	Tested allele	OR	SE	P	I^2	GOCHA	ISGC ICH	GERFHS
rs173539	16	56988044	T	1.25	0.0646	0.00060	0	1.19	1.34	1.22
rs820299	16	57000284	G	0.81	0.0628	0.00075	48	0.82	0.71	0.97
rs158478	16	57007734	A	1.21	0.0611	0.00148	56	1.16	1.43	1.05
rs4784745	16	57014875	G	0.85	0.0635	0.00973	0	0.89	0.80	0.87
rs7187261	16	57031716	T	1.46	0.1588	0.01636	0	1.34	1.67	1.33
rs289751	16	57026775	G	1.50	0.1777	0.02310	19	1.48	1.93	0.96
rs711751	16	56993909	A	0.87	0.0617	0.02725	0	0.88	0.83	0.93
rs4783962	16	56995038	T	0.86	0.0697	0.02749	0	0.89	0.80	0.91
rs891144	16	57011936	T	1.81	0.2872	0.03975	0	1.77	2.09	1.48
rs71387147	16	57010382	G	0.77	0.1269	0.04162	0	0.79	0.77	0.75
rs1800775	16	56995236	A	1.12	0.058	0.04412	0	1.20	1.11	1.05
rs289746	16	57020205	T	1.16	0.0728	0.04637	30	1.38	1.07	1.05

Association results by locus for variants displaying association with ICH with $p<0.05$, clumped into regions with $r^2>0.5$. BPP = base pair position, CHR = chromosome, GERFHS = Genetic and Environmental Risk Factors for Hemorrhagic Stroke study, GOCHA = Genes and Outcomes of Cerebral Hemorrhage on Anticoagulation study, ISGC = International Stroke Genetics Consortium, OR = odds ratio, SE = standard error, SNP = single nucleotide polymorphism

Supplementary Table S6. Discovery phase association results for top SNPs within each semi-independent *CETP* locus, stratified by ICH location

Allele information			All ICH				Lobar ICH				Non-lobar ICH			
SNP	CHR	Tested allele	OR	SE	p	I^2	OR	SE	p	I^2	OR	SE	p	I^2
rs173539	16	T	1.25	0.06	0.00060	0	1.27	0.08	0.00309	0	1.22	0.08	0.01151	0
rs820299	16	G	0.81	0.06	0.00075	48	0.83	0.08	0.02348	0	0.80	0.08	0.00348	55
rs158478	16	A	1.21	0.06	0.00148	56	1.12	0.08	0.12610	0	1.28	0.07	0.00067	70
rs4784745	16	G	0.85	0.06	0.00973	0	0.81	0.08	0.01099	0	0.86	0.08	0.05479	0
rs7187261	16	T	1.46	0.16	0.01636	0	1.49	0.20	0.04468	0	1.40	0.19	0.08000	17
rs289751	16	G	1.50	0.18	0.02310	19	1.16	0.24	0.53900	0	1.71	0.20	0.00761	45
rs711751	16	A	0.87	0.06	0.02725	0	0.83	0.08	0.02132	0	0.92	0.07	0.27480	0
rs4783962	16	T	0.86	0.07	0.02749	0	0.88	0.09	0.16880	0	0.83	0.08	0.02928	8
rs891144	16	T	1.81	0.29	0.03975	0	2.02	0.53	0.18860	0	2.45	0.49	0.06926	0
rs71387147	16	G	0.77	0.13	0.04162	0	0.75	0.17	0.08241	0	0.81	0.15	0.16250	0
rs1800775	16	A	1.12	0.06	0.04412	0	1.14	0.07	0.06925	0	1.13	0.07	0.08727	0
rs289746	16	T	1.16	0.07	0.04637	30	1.17	0.09	0.08431	60	1.15	0.09	0.09409	0

CHR = chromosome, OR = odds ratio, SE = standard error, SNP = single nucleotide polymorphism

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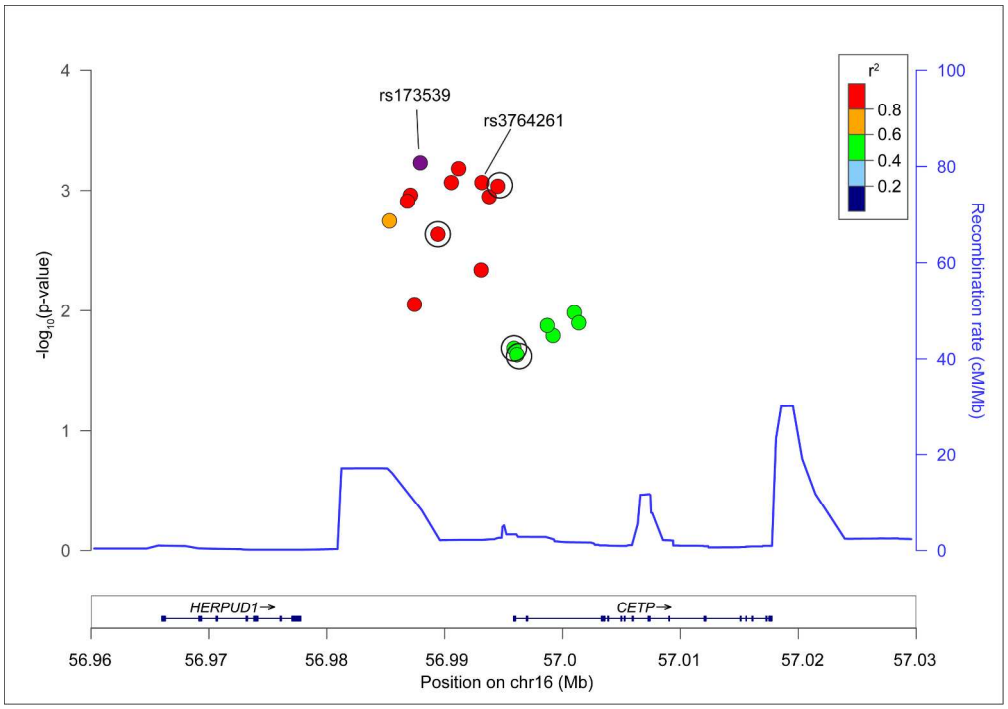

Figure 1. Regional association plot of rs173539 and SNPs exhibiting r2>0.5 in association with ICH. SNPs available for replication are circled. Mean recombination rate across the locus is represented by the continuous blue line. The rs3764261 variant identified was the leading SNP in prior genome-wide association studies of HDL-C. Chr = chromosome, cMMb = centimorgans per megabase, Mb = megabase.

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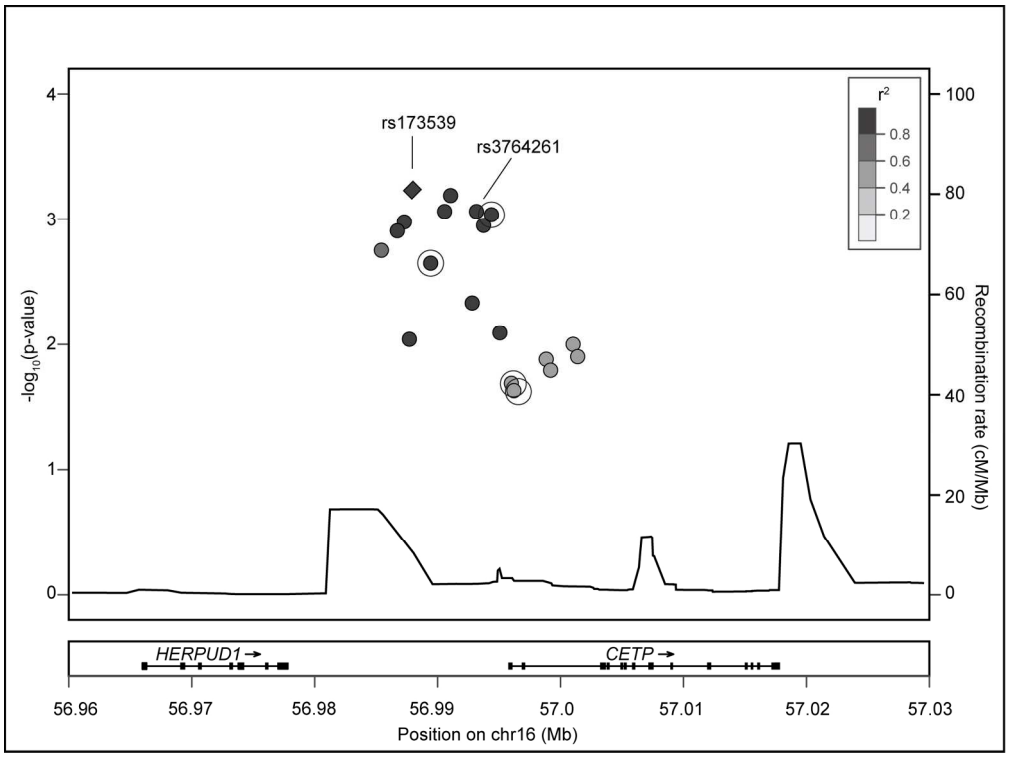

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