

# Meta-analysis of Genome-wide Association Studies Identifies 1q22 as a Susceptibility Locus for Intracerebral Hemorrhage

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Intracerebral hemorrhage (ICH) is the stroke subtype with the worst prognosis and has no established acute treatment. ICH is classified as lobar or nonlobar based on the location of ruptured blood vessels within the brain. These different locations also signal different underlying vascular pathologies. Heritability estimates indicate a substantial genetic contribution to risk of ICH in both locations. We report a genome-wide association study of this condition that meta-analyzed data from six studies that enrolled individuals of European ancestry. Case subjects were ascertained by neurologists blinded to genotype data and classified as lobar or nonlobar based on brain computed tomography. ICH-free control subjects were sampled from ambulatory clinics or random digit dialing. Replication of signals identified in the discovery cohort with  $p < 1 \times 10^{-6}$  was pursued in an independent multiethnic sample utilizing both direct and genome-wide genotyping. The discovery phase included a case cohort of 1,545 individuals (664 lobar and 881 nonlobar cases) and a control cohort of 1,481 individuals and identified two susceptibility loci: for lobar ICH, chromosomal region 12q21.1 (rs11179580, odds ratio [OR] = 1.56,  $p = 7.0 \times 10^{-8}$ ); and for nonlobar ICH, chromosomal region 1q22 (rs2984613, OR = 1.44,  $p = 1.6 \times 10^{-8}$ ).

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The replication included a case cohort of 1,681 individuals (484 lobar and 1,194 nonlobar cases) and a control cohort of 2,261 individuals and corroborated the association for 1q22 ( $p = 6.5 \times 10^{-4}$ ; meta-analysis  $p = 2.2 \times 10^{-10}$ ) but not for 12q21.1 ( $p = 0.55$ ; meta-analysis  $p = 2.6 \times 10^{-5}$ ). These results demonstrate biological heterogeneity across ICH subtypes and highlight the importance of ascertaining ICH cases accordingly.

## Introduction

Stroke is the most devastating manifestation of cerebrovascular disease and the second leading cause of death and acquired disability worldwide.<sup>1,2</sup> Strokes are classified as ischemic or hemorrhagic (85% and 15% in people of European descent, respectively), and spontaneous intracerebral hemorrhage (ICH [MIM 614519]) is by far the most common type of hemorrhagic stroke.<sup>3</sup> Largely a disease of the elderly, ICH occurs when cerebral vessels rupture and is associated with 40%–50% 3-month mortality as well as sustained disability in more than half of survivors.<sup>4,5</sup> The incidence of ICH is expected to rise in coming years because of increases in life expectancy and widespread use of antithrombotic therapy in the elderly.<sup>6,7</sup> Although treatment of hypertension partially reduces the risk of initial or recurrent ICH,<sup>8</sup> there are no established acute treatments for this condition. Therefore, identification of biological pathways that could eventually be targeted by novel therapeutic strategies is vital to reducing the health care burden associated with this disease.

Histopathological observations demonstrate that the underlying cerebral small vessel disease differs according to the location of the ICH within the brain. Lobar ICH originates in the cerebral cortex or cortical-subcortical junction and is most commonly associated with cerebral amyloid angiopathy.<sup>9</sup> Nonlobar ICH originates in deep structures of cerebral hemispheres, brainstem, and cerebellum and tends to be associated with what is typically called hypertensive vasculopathy.<sup>10</sup> This heterogeneity in underlying biological processes leading to different ICH subtypes has been corroborated by epidemiologic,<sup>11</sup> neuroimaging,<sup>12</sup> and genetic studies.<sup>13,14</sup> A large multicenter candidate gene study undertaken by the International Stroke Genetics Consortium in the same populations utilized in the present study established that the epsilon variants of *APOE* (MIM 107741), known to be risk factors for sporadic cerebral amyloid angiopathy, are associated at genome-wide significance levels specifically with lobar ICH.<sup>13</sup> Likewise, it was subsequently found that the burden of risk alleles for high blood pressure associates specifically with nonlobar ICH.<sup>14</sup>

Heritability estimates indicate that common genetic variation plays a substantial role in risk of both ICH subtypes beyond *APOE* and blood-pressure-related variants.<sup>15</sup> Identification of these genetic contributors would have a significant impact on the field of stroke, because it could help uncover specific biological pathways hitherto unsuspected to play a role in this condition that could be targeted by novel therapeutic strategies. In this study we meta-analyzed data from six previously unpublished genome-wide association studies of ICH that enrolled sub-

jects of European ancestry in the United States and Europe under the auspices of the International Stroke Genetics Consortium, with subsequent replication of identified susceptibility loci in an independent study of ICH.

## Subjects and Methods

### Participating Studies

Case and control subjects included in the discovery phase were subjects of European ancestry aged >55 years in the Genetics of Cerebral Hemorrhage with Anticoagulation<sup>13</sup> (GOCHA) study (multicenter study in the US) and aged >18 years in the Genetic and Environmental Risk Factors for Hemorrhagic Stroke<sup>16</sup> (GERFHS) studies I and II in Cincinnati, OH; Hospital del Mar Intracerebral Hemorrhage<sup>17</sup> study and Vall d'Hebron Hospital ICH<sup>18</sup> study in Barcelona, Spain; Jagiellonian University Hemorrhagic Stroke Study<sup>19</sup> in Krakow, Poland; and the Lund Stroke Register<sup>20</sup> study in Lund, Sweden. Because of their limited sample sizes, data from the four European studies (ESs) were analyzed together for the purposes of quality control, imputation, and association testing.

### Subjects

Cases were ascertained across participating studies according to predefined standardized criteria. Spontaneous ICH was defined as a new and acute neurological deficit with compatible brain imaging (computed tomography or magnetic resonance imaging) showing the presence of intraparenchymal bleeding. According to standard research and clinical practice in the field,<sup>3</sup> ICH location was assigned based on admission images by neurologists who were blinded to genotype data. ICH originating at the cerebral cortex or cortical-subcortical junction (with or without involvement of subcortical white matter) was defined as lobar, and ICH originating at the thalamus, internal capsule, basal ganglia, deep periventricular white matter, cerebellum, or brain stem was defined as nonlobar. Exclusion criteria included trauma, brain tumor, hemorrhagic transformation of ischemic stroke, vascular malformation, and any other cause of secondary ICH.

Control subjects were ICH-free individuals enrolled from the same population that gave rise to the case subjects at each participating study site, aged >55 years (GOCHA) and >18 years (GERFHS and ESs). Control subjects were sampled by random digit dialing in GERFHS and from ambulatory clinics in the remainder of the studies.

All studies were approved by the Institutional Review Board or ethics committee at each participating site. Participants provided informed consent; when subjects were not able to communicate, consent was obtained from their legal proxies.

### Genome-wide Genotyping and Quality Control

Case and control subjects were genotyped with Affymetrix 6.0 in GERFHS and with Illumina HumanHap610-Quad in GOCHA and ESs. Case and control subjects from each study were genotyped side-by-side on the same plates with the exception of the replication controls from the Cincinnati Control Cohort (CCC)

and Genomic Control Cohort (GCC), which were genotyped from separate studies. Plate-to-plate variability was assessed by comparison of SNP call and error rates. Standardized prespecified quality-control procedures<sup>21</sup> were implemented separately in GOCHA, GERFHS, and ESs. These filters excluded SNPs with genotype call rate <0.95, significant differential missingness between case and control subjects ( $p < 0.05$ ), deviation from Hardy-Weinberg equilibrium ( $p < 1 \times 10^{-6}$ ), or minor allele frequency (MAF) <0.01. At the subject level, quality control excluded individuals with genotype call rate of <95%; inconsistency between self-reported and genotypic gender; an inferred first- or second-degree relative in the sample identified on the basis of pairwise allele sharing estimates (estimated genome proportion shared identical by descent;  $\pi > 0.1875$ ); and extreme genome-wide heterozygosity  $f$  statistic, defined as >5 times its standard deviation.

### Population Stratification

After quality-control procedures, principal-components analysis<sup>22</sup> was implemented separately in GOCHA, GERFHS, and ESs, incorporating genotype data from 1000 Genomes<sup>23</sup> populations. Population outliers were identified and removed by visual inspection of principal component plots, and the first four principal components were subsequently included in regression models fitted for association testing. Principal-component and identity-by-descent analyses were performed via a pruned subset of independent SNPs (61,325 SNPs in GOCHA, 95,013 in GERFHS, and 64,728 in ESs) to account for potential biases introduced by LD structure.

### Imputation

After quality-control procedures and principal component analysis, imputation was performed separately in GOCHA, GERFHS, and ESs via IMPUTE2 v.2.2<sup>24</sup> and 1000 Genomes<sup>23</sup> integrated reference panels (Phase I interim release in NCBI build 37). The number of SNPs that entered the imputation process were 525,752, 795,240, and 532,149 for GOCHA, GERFHS, and ESs, respectively. Postimputation filters excluded imputed SNPs with MAF <0.01, IMPUTE2 information score <0.7, confidence score <0.9, and missing estimates in association testing for 1 or more studies.

### Genome-wide Association Testing

Given the biological differences in ICH subtypes outlined in the introduction and after a prespecified analysis plan, genome-wide association analyses were computed separately for all ICH (lobar and nonlobar combined), for lobar ICH, and for nonlobar ICH. These analyses were completed separately in GOCHA, GERFHS, and ESs via logistic regression, assuming additive genetic effects (1-degree-of-freedom additive trend test) and adjusting for age, gender, and principal components. In secondary analysis, association testing was carried out separately in each European study. Association  $p$  values obtained in GOCHA, GERFHS, and ESs were meta-analyzed via the inverse normal method weighting by sample size as implemented in METAL,<sup>25</sup> and heterogeneity of pooled estimates was quantified by computing Cochran's  $Q$  and corresponding  $p$  and  $I^2$ . After recent GWAS meta-analysis,<sup>26</sup> only SNPs with available estimates in all three data sets are reported. Quantile-quantile plots were utilized to assess systematic inflation in association results resulting from population stratification or other systematic causes of bias.

Further analyses were undertaken to evaluate the presence of additional independent signals at each locus. Additional indepen-

dent signals at each locus were evaluated by conditional testing completed by adding the dosages of the top SNP at each locus to logistic regression models. Pairwise linkage disequilibrium (LD) between SNPs was assessed and visualized with 1000 Genomes Ensemble-based genome browser.<sup>27</sup> Regional association plots were constructed with LocusZoom software.<sup>28</sup>

### Replication

Replication of associations with  $p < 1 \times 10^{-6}$  in the discovery meta-analysis was pursued in case and control groups from the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH)<sup>29</sup> and GERFHS III<sup>16</sup> studies, in adult control group from the CCC,<sup>16</sup> and GCC.<sup>16</sup> Enrolled ICH cases and controls from ERICH were non-Hispanic whites, African Americans, and Hispanic subjects (based on self-reported race and ethnicity) aged >18 years from multiple study centers across the US. ICH case subjects were ascertained with the same criteria utilized in the discovery phase. ICH-free control subjects were sampled by random digit dialing from the population that gave rise to the case cohort. The CCC and GCC cohorts are population-based cohorts of ICH-free individuals from the Greater Cincinnati area. The CCC cohort was specifically enrolled to approximate the age, sex, and race distribution of ICH subjects, and the GCC was enrolled to match the population and geographic distribution of the metropolitan area. Genotyping was completed with TaqMan assays (ERICH Study) or Affymetrix 6.0 (GERFHS III and CCC-GCC). For the latter, preimputation quality-control procedures, imputation, and postimputation filters were implemented as described for the discovery phase. Association testing was carried out by fitting logistic regression models and implementing a 1-degree-of-freedom trend test, assuming additive effects and including age and gender in all models. Meta-analyses across discovery and replication proceeded as described above for the discovery phase. Replication results were considered significant at  $p < 0.05$  and genome-wide significance was defined as  $p < 5 \times 10^{-8}$ .<sup>30</sup>

### Overlap with Common Variants Related to Blood Pressure

Given the well-established role of hypertension in causing ICH, especially of nonlobar type, we specifically assessed the role in ICH of common genetic variants known to play a role in determining blood pressure. SNPs reported to be related to blood pressure at  $p < 1 \times 10^{-5}$  were identified in the GWAS Catalog.<sup>31</sup> Queried traits included blood pressure; hypertension; and diastolic, systolic, mean, and pulse blood pressures. Association results for these SNPs were identified for all, for lobar, and for nonlobar ICH.

### Overlap with DNase I Hypersensitivity Sites

The positions of SNPs in ICH-associated loci were overlapped with DNase I hotspot regions from the Encyclopedia of DNA Elements (ENCODE) Project that mark generalized chromatin accessibility, mapped for each of 125 diverse cell lines and tissues.<sup>32</sup> The genomic region of interest for each identified loci was defined based on the genomic variants that were in linkage disequilibrium with the top variant at each locus (defined as  $r^2 > 0.5$ ). In addition, ICH-associated SNPs were analyzed for other overlap with ENCODE data, including transcription factor motifs, via RegulomeDB.<sup>33</sup>

**Table 1. Descriptive Characteristics of Participating Studies**

Covariate	Discovery								Replication			
	Multicenter, US				European Studies				Cincinnati, US		Cincinnati, US	
	GOCHA		HM-ICH + VVH-ICH		JUHSS		LSR		GERFHS I & II		ERICH/GERFHS III/CCC-GCC	
	Case Cohort	Control Cohort	Case Cohort	Control Cohort	Case Cohort	Control Cohort	Case Cohort	Control Cohort	Case Cohort	Control Cohort	Case Cohort	Control Cohort
Subjects, n	298	457	212	169	122	163	116	153	797	539	1,681	2,261
Age, mean (SD)	74 (10)	72 (8)	74 (11)	71 (9)	67 (12)	65 (13)	75 (10)	75 (10)	67 (15)	66 (15)	62 (15)	43 <sup>a</sup> (26)
Female, n (%)	134 (45)	231 (51)	103 (49)	77 (46)	69 (57)	93 (57)	49 (42)	69 (45)	383 (48)	243 (45)	701 (42)	1,113 (49)
Hypertension, n (%)	217 (73)	280 (61)	126 (60)	99 (64)	96 (81)	74 (45)	76 (67)	65 (43)	494 (62)	280 (52)	1,009 (60)	738 <sup>b</sup> (51)
Lobar ICH, n (%)	184 (58)	–	88 (40)	–	51 (39)	–	36 (28)	–	327 (41)	–	484 (29)	–
Nonlobar ICH, n (%)	132 (42)	–	133 (60)	–	80 (61)	–	94 (72)	–	470 (59)	–	1,197 (71)	–

Abbreviations are as follows: ICH, intracerebral hemorrhage; GOCHA, Genetics of Cerebral Hemorrhage on Anticoagulation Study; HM-ICH, Hospital del Mar Intracerebral Hemorrhage Study; VVH-ICH, Vall d'Hebron Hospital ICH Study; JUHSS, Jagiellonian University Hemorrhagic Stroke Study; LSR, Lund Stroke Register; GERFHS, Genetic and Environmental Risk Factors for Hemorrhagic Stroke Study; ERICH, Ethnic/Racial Variations of Intracerebral Hemorrhage Study; CCC-GCC, Cincinnati Control Cohort - Genomic Control Cohort.

<sup>a</sup>Includes the 819 GCC pediatric control subjects with ages  $\leq 18$ .

<sup>b</sup>Excludes the 819 GCC pediatric control subjects with no hypertension history.

### eQTL Analyses

Variants within each identified susceptibility locus for ICH were evaluated for gene expression in *cis* via publicly available resources. SNPs with  $p < 1 \times 10^{-5}$  were assessed in four publicly available eQTL databases: SCAN (SNP and CNV Annotation Database), the NCBI and Broad Institute GTEx (Genotype-Tissue Expression) eQTL Browsers,<sup>34</sup> the Pritchard laboratory UChicago eQTL browser,<sup>35</sup> and mRNA by SNP Browser v.1.0.1.<sup>36</sup> Gene expression was assessed in a range of tissue and cell types, including liver, brain, lymphoblastoid cell lines, monocytes, fibroblasts, and T cells. As in previous reports,<sup>37</sup> we defined potential *cis* eQTLs as candidate SNPs associated with gene expression mapping to a 1 Mb window around each locus with  $p < 1 \times 10^{-3}$ .

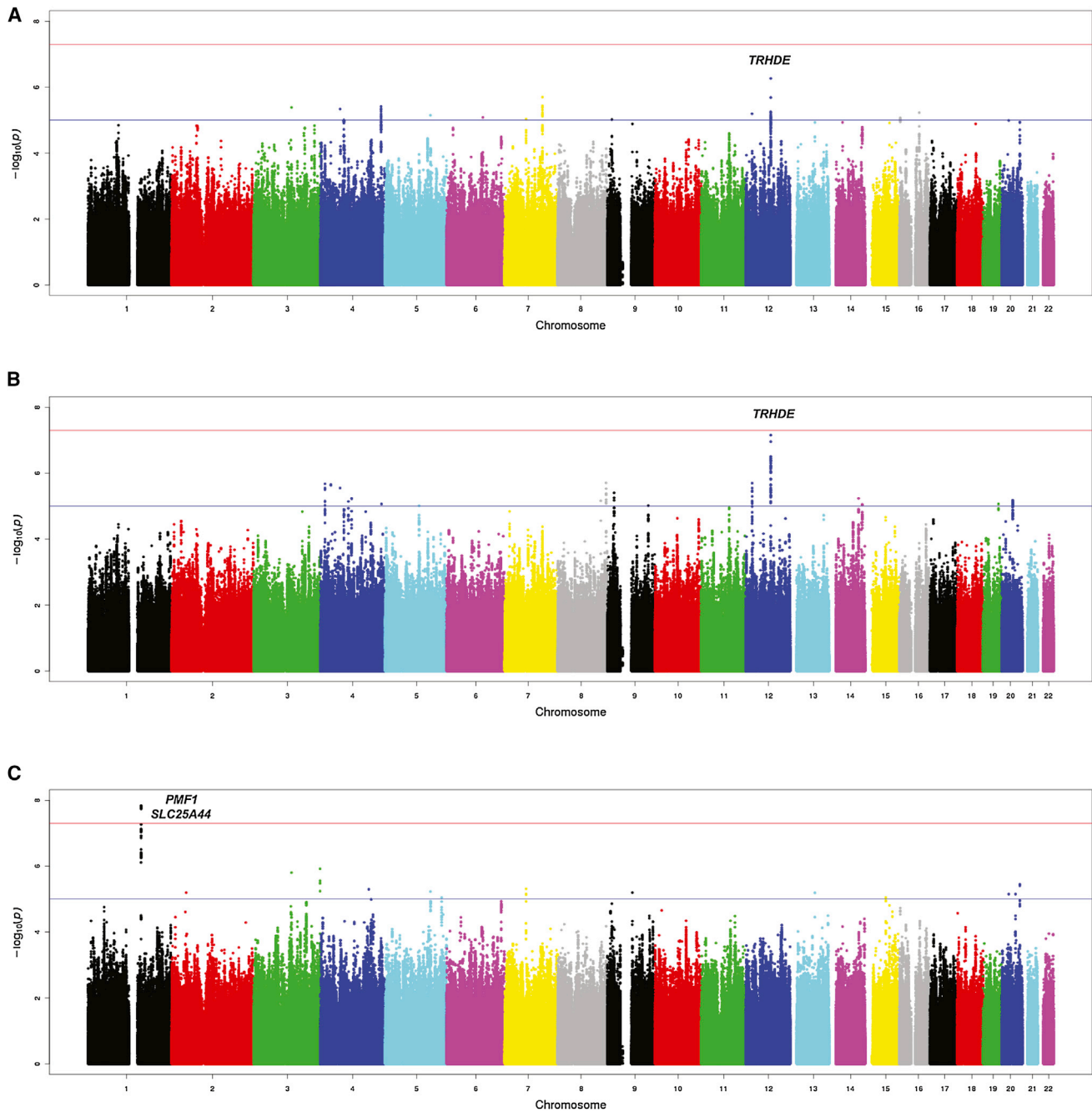
### Results

After excluding subjects based on quality-control procedures ( $n = 23$ ) and principal component analysis ( $n = 93$ ), a case cohort of 1,545 subjects and a control cohort of 1,481 subjects were available for association testing in the discovery analysis (mean age 67 [SD 10], female sex 45%, Table 1). After preimputation quality-control procedures, imputation to 1000 Genomes reference panels, and postimputation quality-control filters, a total of 5,258,103 SNPs were available for association testing across all data sets included in the discovery sample.

Susceptibility loci were identified for lobar and nonlobar ICH, but not for all ICH (lobar and nonlobar combined) (Figures 1A–1C, Tables S1–S3 available online). The estimated inflation factors ( $\lambda$  of 1.039, 1.016, and 1.038 for all, lobar, and nonlobar ICH, respectively) and quantile-quantile plots (Figure S1) indicated absence of inflation resulting from systematic bias caused by population substructure or other artifacts. Several SNPs on chromosomal region 12q21.1, an intergenic region near *TRHDE* (MIM

606950), were associated with lobar ICH, with peak association detected at rs11179580 (MAF = 0.24, per additional major allele [C], odds ratio [OR] 1.56, 95% confidence interval [CI] 1.33–1.84;  $p = 7.0 \times 10^{-8}$ ;  $Q = 0.43$ ,  $I^2 = 0\%$ ; Figure 1B and Table 2). Similar results were obtained when analyzing each European study separately (Figure S2). A similar effect was observed for all ICH (per additional C allele, OR 1.36, 95% CI 1.21–1.54;  $p = 5.4 \times 10^{-8}$ ;  $Q = 0.07$ ,  $I^2 = 62\%$ ; Table 2 and Figure 1A), but the combination of similar effect magnitudes (despite double the sample size) and significant increase in heterogeneity suggests that the observed association is driven by lobar ICH. rs11179580 also showed some effect in nonlobar ICH (OR 1.25, 95% CI 1.09–1.42,  $p = 0.002$ ; Table 2), indicating that the affected biological pathway could impact both types of cerebral hemorrhage. Neither adjustment for the most significant SNPs at this locus (Figure S3A) nor haplotype testing identified additional associations of interest.

For nonlobar ICH, a susceptibility locus was identified on chromosomal region 1q22, a region that contains *PMF1* (MIM 609176) and *SLC25A44* (MIM 610824). The top-associated variant within this locus was the intronic SNP rs2984613 (MAF 0.31; per additional major allele [C] OR 1.44, 95% CI 1.27–1.64;  $p = 1.6 \times 10^{-8}$ ;  $Q = 0.05$ ,  $I^2 = 66\%$ ; Table 2 and Figure 1C). Although some heterogeneity was observed for this specific variant, several SNPs within this locus achieved genome-wide significance with substantially lower heterogeneity (as showed by  $Q > 0.05$ , Table S5). Comparable results were obtained when analyzing each European study separately (Figure S2). rs2984613 also had some effect in all ICH (OR 1.21, 95% CI 1.12–1.38,  $p = 6.0 \times 10^{-4}$ ), probably driven by nonlobar cases, and had no effect on lobar ICH. Neither analysis adjusting for the most significant SNPs (Figure S3B) nor haplotype testing within these loci identified additional associations of interest.



### Figure 1. Genome-wide Association Study Results

Genome-wide association study results of autosomal SNPs: (A) all (lobar ICH and nonlobar ICH combined), (B) lobar ICH, and (C) nonlobar ICH. The plots show  $-\log_{10}$ -transformed p values for genotyped and imputed SNPs with respect to their physical positions. The threshold for association at genome-wide significance ( $p = 5 \times 10^{-8}$ ) is shown by the upper dashed line, and the lower dashed line corresponds to  $p = 1 \times 10^{-5}$ . Landmark genes are indicated for loci that reached the threshold to pursue replication.

Replication of identified associations was pursued in 1,681 case subjects (513 non-Hispanic whites, 634 African Americans, and 534 Hispanics) and 2,261 control subjects (1,552 non-Hispanic whites, 449 African Americans, and 260 Hispanics) (Tables 1 and S4). Genotyping at this stage included both direct genotyping (ERICH study) and genome-wide genotyping (GERFHS III and CCC-GCC studies). Direct genotyping in ERICH included the top SNP at each locus: rs11179580 for 12q21.1 in lobar ICH

and rs2758605 for 1q22 in nonlobar ICH. For technical reasons, rs2758605 (second top SNP) was genotyped in lieu of rs2984613 ( $r^2 = 0.99$ ). The association of chromosomal region 1q22 with nonlobar ICH replicated but that of 12q22.1 with lobar ICH did not. No association was found between rs11179580, the top SNP at 12q21.1, and lobar ICH (OR 1.05, 95% CI 0.89–1.24;  $p = 0.55$ ; meta-analysis  $p = 2.6 \times 10^{-5}$ ; Figure 2A). For rs2758605 (1q22) in nonlobar ICH, each additional C allele was associated

**Table 2. Loci with  $p < 1 \times 10^{-6}$  in at least One Subtype of Intracerebral Hemorrhage**

SNP Characteristics									Meta-analysis Discovery Phase				
SNP	Chr	Position	Locus	Major/Minor Allele	Tested Allele <sup>a</sup>	MAF	Type	Gene Landmarks	Trait	OR	p	Q	I
rs11179580	12	73586579	12q21.1	C/T	C	0.24	intergenic	TRHDE	all ICH	1.36	$7.1 \times 10^{-7}$	0.07	61%
									lobar ICH	1.56	$7.0 \times 10^{-8}$	0.43	0%
									nonlobar ICH	1.25	0.002	0.03	72%
rs2984613	1	156197380	1q22	C/T	C	0.32	intronic	PMF1 SLC25A44	all ICH	1.21	$6.0 \times 10^{-4}$	0.15	48%
									lobar ICH	0.97	0.62	0.7	1%
									nonlobar ICH	1.44	$1.6 \times 10^{-8}$	0.05	66%

Abbreviations are as follows: Chr, chromosome; MAF, minor allele frequency; OR, odds ratio; ICH, intracerebral hemorrhage.

<sup>a</sup>Showing effect estimates when testing the major allele to depict genetic variation associated with increased risk of ICH.

with a 24% increase in risk of hemorrhage (95% CI 1.09–1.40;  $p = 6.5 \times 10^{-4}$ ; meta-analysis  $p = 2.2 \times 10^{-10}$ ; Figure 2B). When considering ethnic-specific analysis (Table S6), the association was significant for non-Hispanic whites ( $p = 0.04$ ) and African Americans ( $p = 1 \times 10^{-4}$ ) but not for Hispanics ( $p = 0.90$ ).

The 1q22 locus contains *PMF1* and *SLC25A44* (Figure 3A), two genes that code polyamine-modulated factor 1 and solute carrier family 25-member 44, respectively. A total of 49 SNPs in this locus achieved  $p < 1 \times 10^{-5}$  (Table S7) and at least one of these was directly genotyped in all participating studies. Although most of these SNPs are intronic, rs1052053 has transcriptional impact, resulting in substitution of glutamine by arginine in position 75 of exon 2 of *PMF1*. The resulting transcript variant (isoform 3) is shorter than isoform 1 and has a distinct C terminus. This variation has benign functional impact according to PolyPhen-2 (score 0) and is well tolerated according to SIFT (score 1). In addition, rs2241107 is located in a promoter region in front of *PMF1*, and this region also corresponds to a DNase I hypersensitivity region in all ENCODE cell types.

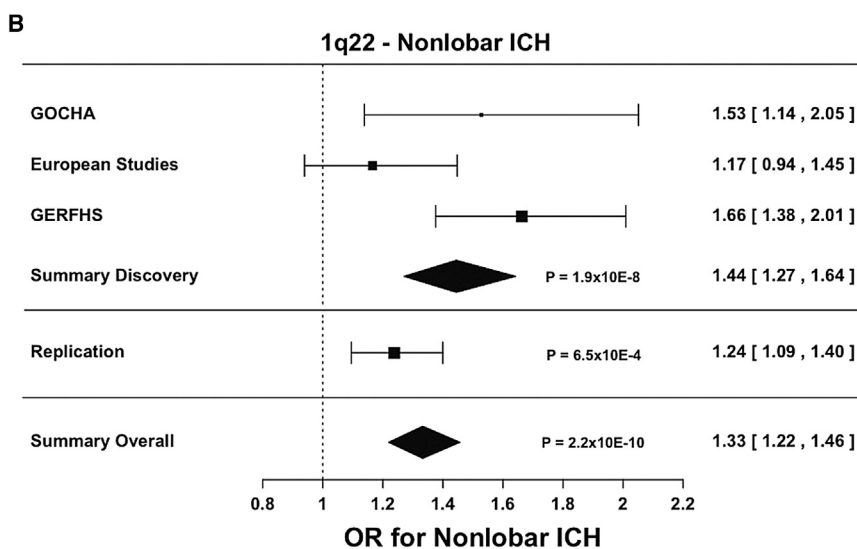
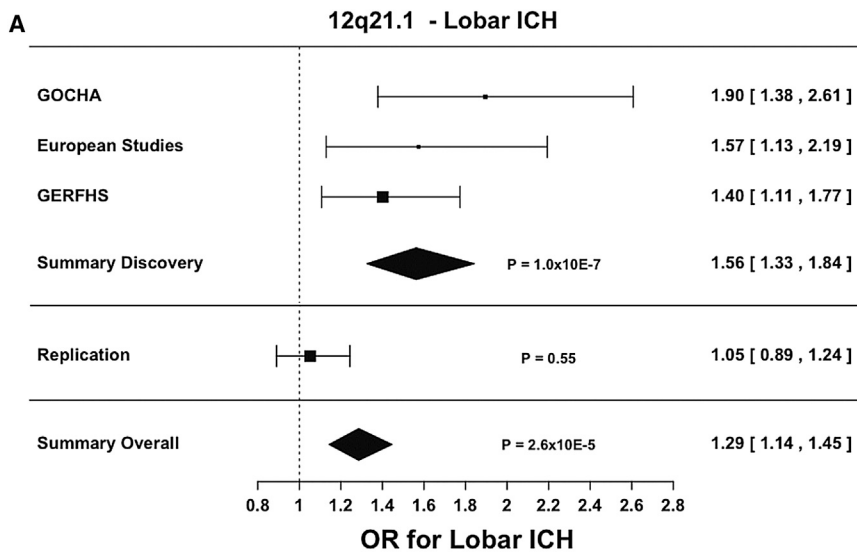
Expression data from GTEx show that gene expression in neural tissues is high for *SLC25A44* (Figure S4) and moderate for *PMF1* (Figure S5). Moreover, eQTL data from this same source raises the possibility of 1q22 exerting its effect by regulating nearby genes, with 27 of the 49 SNPs mentioned above being associated with expression of *SEMA4A* (MIM 607292) in tibial nerve tissue (most significant  $p = 5.3 \times 10^{-6}$  for rs6427304, Table S8). Axons, the main component of peripheral nerves, are extensions of neurons that, together with the blood vessel wall, extracellular matrix, and glia, form the neurovascular unit, a biological compartment suggested to play an important role in cerebrovascular disease.<sup>38</sup> *SEMA4A* is located upstream of *SLC25A44* and codes for semaphorin-4A, a member of the semaphorin family of soluble and transmembrane proteins that is involved in numerous functions, including axon guidance, morphogenesis, carcinogenesis, and immunomodulation. *SEMA4A* has moderate-to-high expression in neural tissues (Figure S6).

Variants known to influence blood pressure did not significantly affect ICH risk. A total of 172 entries related to blood pressure were identified in the GWAS catalog. These corresponded to 72 unique SNPs. None of these SNPs was significantly associated with all, lobar, or nonlobar ICH after adjusting for multiple testing (Bonferroni-corrected threshold  $p < 0.0007$ , Table S9).

## Discussion

In this GWAS of ICH, we meta-analyzed data from 3,223 case subjects and 3,725 control subjects and identified and replicated a susceptibility locus for this condition located at 1q22 (nonlobar ICH). Importantly, the replication spanned European- and African-derived ethnicities. These results confirm previous heritability studies that indicated that common genetic variation may play an important role in the occurrence of this condition.<sup>15</sup> The subtype specificity of the identified susceptibility locus is consistent with the findings of histologic, epidemiologic, and candidate-gene studies that different mechanisms underlie each ICH subtype. Given the absence of an effective treatment and the heavy burden imposed by ICH to society, the present findings inaugurate the possibility of identifying novel biological mechanisms involved in causing this disease that could eventually be targeted by new therapeutic interventions.

Providing important supportive evidence for a role of 1q22 in cerebral small vessel disease, a recent GWAS of cerebral white matter lesions in healthy adults identified 1q22 as a suggestive locus. Cerebral white matter lesions constitute a radiological manifestation of cerebral small vessel disease,<sup>39</sup> and several studies have shown that nonlobar ICH is the most devastating clinical manifestation of this vasculopathy.<sup>40,41</sup> Importantly, several SNPs identified in our study were also listed in the mentioned GWAS (Table 3).<sup>42</sup> This previous study of white matter hyperintensities informs our GWAS of ICH because the former was undertaken in individuals of European ancestry, thus providing crucial support to our findings by confirming



the association between 1q22 and cerebral small disease in whites. Likewise, our study informs the GWAS of white matter hyperintensities, because in the latter 1q22 achieved only sub-genome-wide significance ( $p = 5 \times 10^{-6}$ ).<sup>42</sup> In this setting, our findings represent an important contribution to definitively establishing the role of this locus in cerebrovascular disease by taking the association signal beyond the genome-wide threshold and extending the effect of this genomic region beyond the realm of imaging endophenotypes to meaningful clinical impact.

Variants within 1q22 are located in an LD block of 48 kb that contains *PMF1* and *SLC25A44* (Figure 3A). *PMF1* codes for polyamine-modulated factor 1, a nuclear protein regulated by polyamines that is required for normal chromosome alignment and kinetochore formation during mitosis.<sup>43</sup> In conjunction with the transcription factor NFE2L2 (nuclear factor, erythroid 2-like 2; also known as NRF2), *PMF1* also mediates the transcriptional induction of *SAT1*, which codes for an acetyltransferase responsible

## Figure 2. Meta-analysis Results

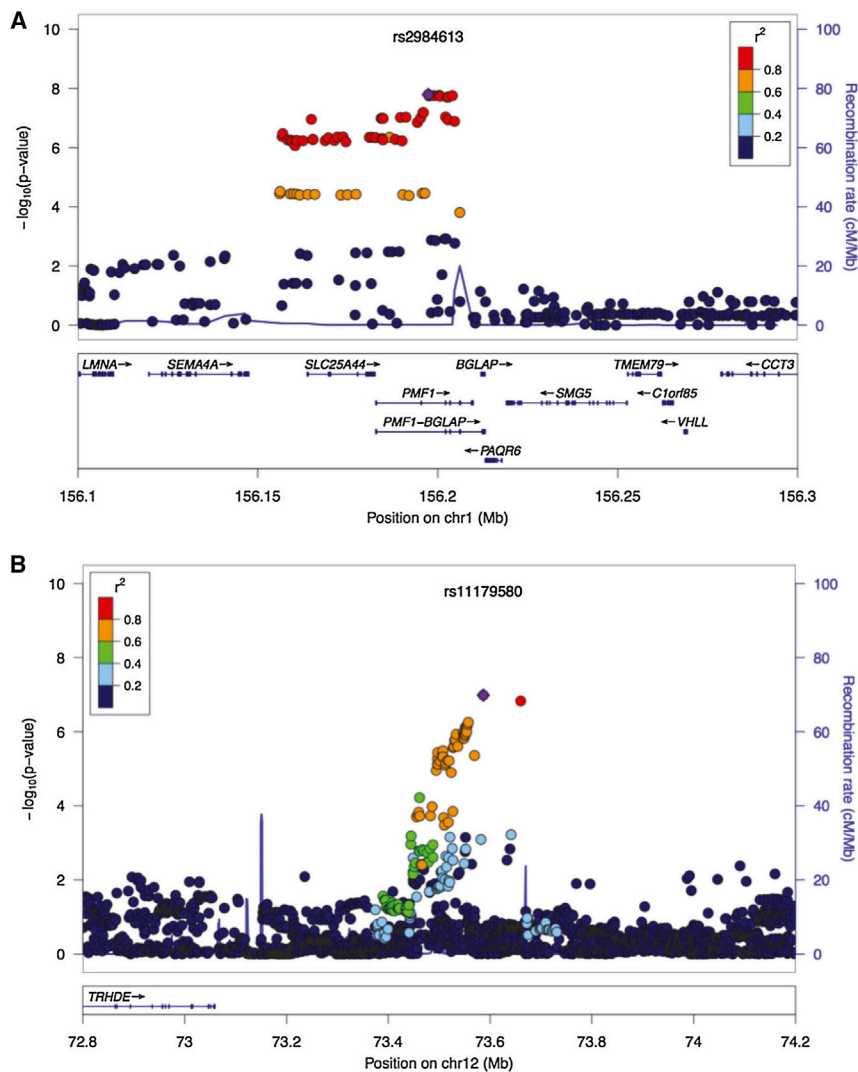
Forest plots describing effect estimates for participating studies, as well as for the replication effort. Pooled estimates for odds ratios and 95% confidence intervals were calculated by fixed effects, inverse variance weighting meta-analysis.

(A) Association results for rs11179580 at chromosomal region 12q21.1 in lobar ICH. (B) Association results for rs2984613 at chromosomal region 1q22 in nonlobar ICH. Results correspond to effect estimates when testing the major allele to depict genetic variation associated with increased risk of ICH.

for the rate-limiting enzyme in the catabolic pathway of polyamine metabolism.<sup>44</sup> Polyamines are proteins with multiple amine groups that have been linked to cerebrovascular disease by several studies. They have been found to be elevated in stroke subjects and to be implicated in breakdown of the blood-brain barrier<sup>45,46</sup> and regulation of the receptor for the excitatory neurotransmitter NMDA through a polyamine-specific binding site.<sup>47</sup> *SLC25A44* encodes solute carrier family 25-member 44, a member of the SLC25 family of mitochondrial carrier proteins,<sup>48</sup> and no pathological consequences have been reported so far for genetic variation within this gene.

Although the lack of replication of 12q21.1 raises the possibility that the result of the discovery phase could be spurious, the consistency in effect estimates across the discovery cohorts suggests that follow-up studies should explore this locus further. Identified SNPs at this locus are located within an intergenic region that lies 400 kb upstream of *TRHDE* (Figure 3B), a gene that codes for thyrotropin-releasing hormone-degrading enzyme. However, this gene is located beyond the adjacent recombination hotspot. Four different publicly available databases on eQTLs were queried with no significant findings. Likewise, data from the ENCODE project were also utilized to evaluate whether this genomic region contains histone modification patterns observed in regulatory regions, also with no significant findings. This locus has not been linked to other clinical traits.

Several additional complementary analyses could enrich the results presented here. In particular, evaluation of gene- and pathway-based association with ICH could allow identification of both genes and relevant biologic pathways involved in causing ICH but that had only sub-GW results of the present analysis. Additionally, now that



**Figure 3. Zoom Plots**

Regional association results.

(A) Chromosomal region 1q22 in nonlobar ICH.

(B) Chromosomal region 12q21.1 in lobar ICH.

The index-associated SNP is labeled with violet color.

could be utilized to account for population structure at that stage.

Importantly, other complex genetic disorders show that there are probably numerous susceptibility loci with small or modest effects that require significant increases in sample size to be discovered.<sup>49,50</sup> In this regard, the overlap of chromosomal region 1q22 with another cerebral-small-vessel-disease-related trait (white matter hyperintensities<sup>42</sup>) points to the interesting opportunity of collaborating with consortia that focus on phenotypes like cognitive decline, late-life depression, and non-parkinsonian gait disturbances, all believed to be mediated to some degree by small vessel diseases of the brain.

We report a GWAS of ICH, the most devastating stroke type that currently has no effective treatment. As has been the case for ischemic stroke,<sup>37,51</sup> careful phenotyping of ICH based on known differences in cerebrovascular histopathology proved essential for successful discovery of susceptibility loci. We identified one susceptibility locus for nonlobar ICH (chromosomal region 1q22), confirmed through independent replication. The results of a prior GWAS report of white matter hyperintensities, an established risk factor for ICH, provide complementary evidence for a role of 1q22 in cerebral small vessel disease. The specific biological mechanisms underlying the described associations remain to be elucidated.

### Supplemental Data

Supplemental Data include six figures and nine tables and can be found with this article online at <http://www.cell.com/ajhg/>.

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GW data become available for ICH, joint genetic contribution to ischemic and hemorrhagic stroke can be assessed, as well as joint genetic contribution to ICH and white matter hyperintensities, a widely studied endophenotype for cerebral small vessel disease.

Our study has limitations. Although we strived to reduce possible misclassification of cases when assigning lobar and nonlobar categories, some residual misclassification may still have occurred. However, it is reasonable to assume that, if present, this misclassification was independent and nondifferential, thus biasing our results toward the null. A second limitation is sample size: although the discovery cohort was large, additional samples will be critical to further depict the genetic architecture of ICH and its subtypes and to better understand how genetic effects vary by race and ethnicity. Although the null result obtained in replication for 1q22 in Hispanics could be truly negative—reflecting heterogeneity of effects across ethnic groups—power limitations could also account for it. Finally, because direct genotyping was performed in the majority of samples included in replication, only self-reported ancestry



**Table 3. Overlapping Results: GWAS of Nonlobar ICH and White Matter Hyperintensities**

SNP	Minor Allele	Other Allele	MAF	Landmark Gene	p Value Nonlobar ICH	p Value White Matter Hyperintensities
rs2758605	c	g	0.36	<i>PMF1;BGLAP</i>	$1.5 \times 10^{-8}$	$9.4 \times 10^{-6}$
rs2251847	a	g	0.36	<i>PMF1;BGLAP</i>	$1.6 \times 10^{-8}$	$1.0 \times 10^{-5}$
rs887953	c	t	0.34	<i>PMF1;BGLAP</i>	$7.5 \times 10^{-8}$	$8.2 \times 10^{-5}$
rs2244144	a	g	0.34	<i>PMF1;BGLAP</i>	$8.2 \times 10^{-8}$	$8.2 \times 10^{-5}$
rs1052053	g	a	0.38	<i>PMF1;BGLAP</i>	$9.2 \times 10^{-8}$	$5.0 \times 10^{-6}$
rs2842873	t	c	0.38	<i>PMF1;BGLAP</i>	$1.4 \times 10^{-7}$	$6.4 \times 10^{-6}$
rs6427304	g	a	0.36	<i>SLC25A44</i>	$4.0 \times 10^{-7}$	$6.8 \times 10^{-5}$
rs2853641	g	a	0.35	<i>SLC25A44</i>	$4.2 \times 10^{-7}$	$5.3 \times 10^{-5}$
rs2241108	g	c	0.35	<i>SLC25A44</i>	$4.2 \times 10^{-7}$	$5.2 \times 10^{-5}$
rs2241107	c	t	0.35	<i>PMF1;BGLAP</i>	$4.2 \times 10^{-7}$	$5.4 \times 10^{-5}$

Abbreviations are as follows: PMF1, Polyamine Modulating Factor 1; BGLAP, bone gamma-carboxyglutamate protein; SLC25A44, solute carrier family 25, member 44. See also Fornage et al.<sup>42</sup>

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### Web Resources

The URLs for data presented herein are as follows:

dbGaP, <http://www.ncbi.nlm.nih.gov/gap>

eqtl.uchicago.edu, <http://eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl>

Haploview, <http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview/>

IMPUTE2, [http://mathgen.stats.ox.ac.uk/impute/impute\\_v2.html](http://mathgen.stats.ox.ac.uk/impute/impute_v2.html)

LocusZoom, <http://csg.sph.umich.edu/locuszoom/>

METAL, <http://www.sph.umich.edu/csg/abecasis/metal/>

mRNA by SNP Browser, <http://www.sph.umich.edu/csg/liang/asthma/>

NCBI GTEx (Genotype-Tissue Expression) eQTL Browser, <http://www.ncbi.nlm.nih.gov/gtex/GTEX2/gtex.cgi>

Online Mendelian Inheritance in Man (OMIM), <http://www.omim.org/>

PLINK, <http://pngu.mgh.harvard.edu/~purcell/plink/>

SCAN: SNP and CNV Annotation Database, <http://www.scandb.org/newinterface/about.html>

SNP Annotation and Proxy Search (SNAP), <http://www.broadinstitute.org/mpg/snap/>

SNPDoc, <https://www.phs.wakehealth.edu/public/bios/gene/downloads.cfm>

SNPLASH, <https://www.phs.wakehealth.edu/public/bios/gene/downloads.cfm>

UNPHASED, <https://sites.google.com/site/fdudbridge/software/>

### Accession Numbers

The dbGaP accession number for data reported in this paper is phs000416.v1.p1.

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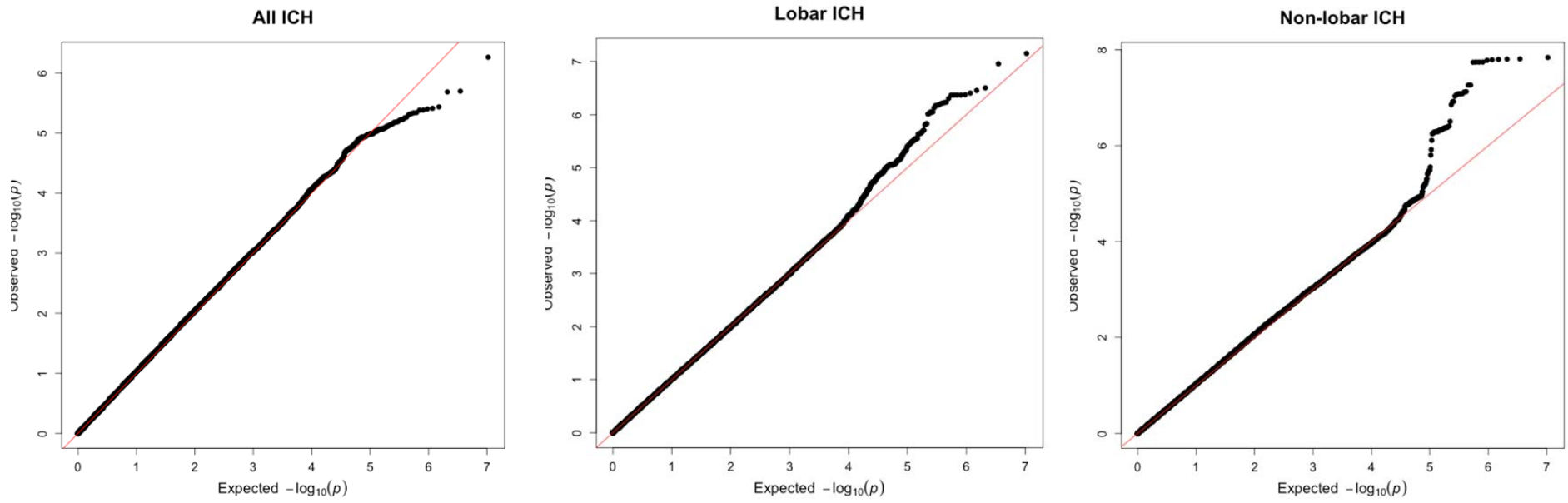
The American Journal of Human Genetics, Volume 94

Supplemental Data

# **Meta-Analysis of Genome-Wide Association Studies Identifies 1q22 as a Susceptibility Locus for Intracerebral Hemorrhage**

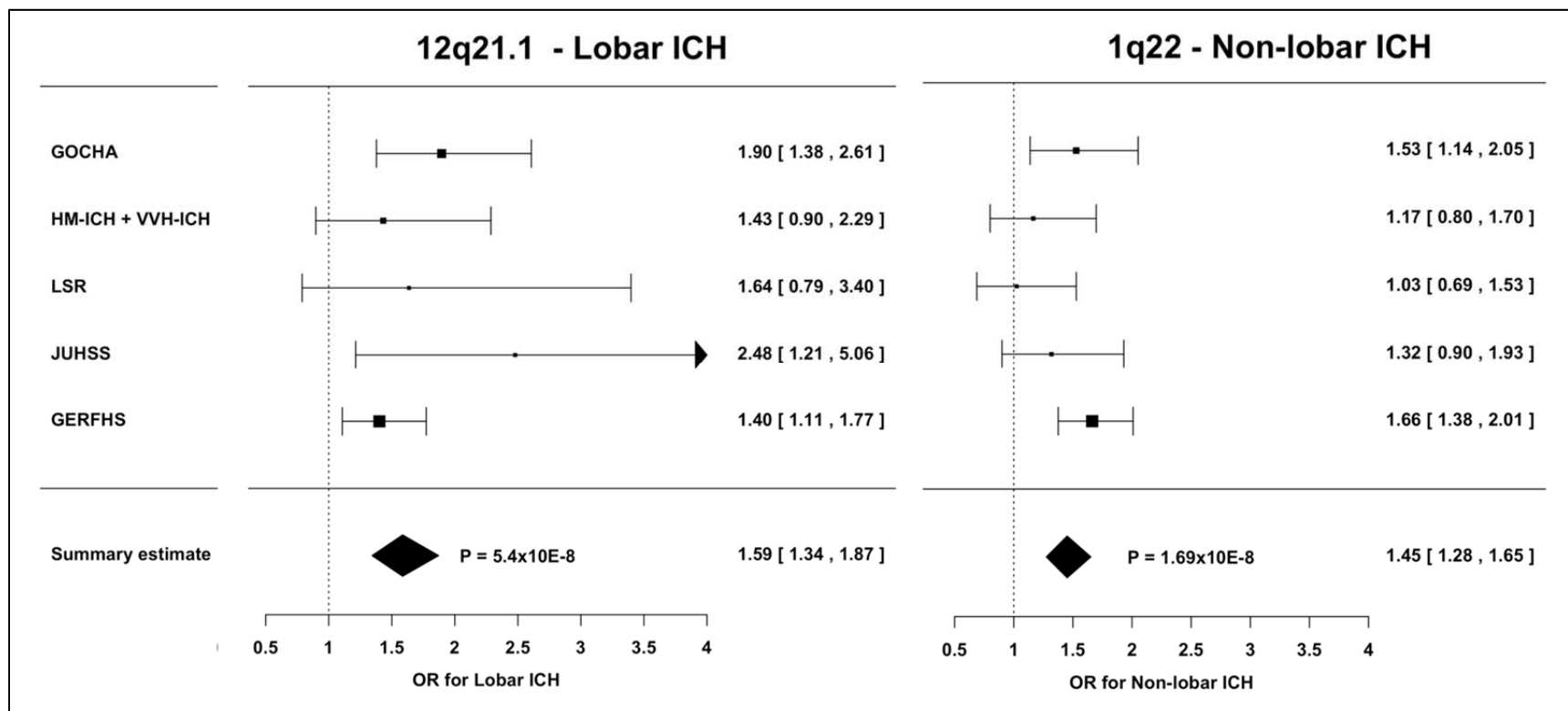
**Daniel Woo, Guido J. Falcone, William J. Devan, W. Mark Brown, Alessandro Biffi, Timothy D. Howard, Christopher D. Anderson, H. Bart Brouwers, Valerie Valant, Thomas W.K. Battey, Farid Radmanesh, Miriam R. Raffeld, Sylvia Baedorf Kassis, Ranjan Deka, Jessica G. Woo, Lisa J. Martin, Mary Haverbusch, Charles J. Moomaw, Guangyun Sun, Joseph P. Broderick, Matthew L. Flaherty, Sharyl R. Martini, Dawn O. Kleindorfer, Brett Kissela, Mary E. Comeau, Jeremiasz M. Jagiella, Helena Schmidt, Paul Freudenberger, Alexander Pichler, Christian Enzinger, Björn M. Hansen, Bo Norrving, Jordi Jimenez-Conde, Eva Giralt-Steinhauer, Roberto Elosua, Elisa Cuadrado-Godia, Carolina Soriano, Jaume Roquer, Peter Kraft, Alison M. Ayres, Kristin Schwab, Jacob L. McCauley, Joanna Pera, Andrzej Urbanik, Natalia S. Rost, Joshua N. Goldstein, Anand Viswanathan, Eva-Maria Stögerer, David L. Tirschwell, Magdy Selim, Devin L. Brown, Scott L. Silliman, Bradford B. Worrall, James F. Meschia, Chelsea S. Kidwell, Joan Montaner, Israel Fernandez-Cadenas, Pilar Delgado, Rainer Malik, Martin Dichgans, Steven M. Greenberg, Peter M. Rothwell, Arne Lindgren, Agnieszka Slowik, Reinhold Schmidt, Carl D. Langefeld, and Jonathan Rosand on behalf of the International Stroke Genetics Consortium**

Figure S1. Distribution of association results.



Left panel: All ICH (lobar and non-lobar combined),  $\lambda = 1.039$ . Central panel: Lobar ICH,  $\lambda = 1.016$ . Right panel: Non-lobar ICH,  $\lambda = 1.038$ .

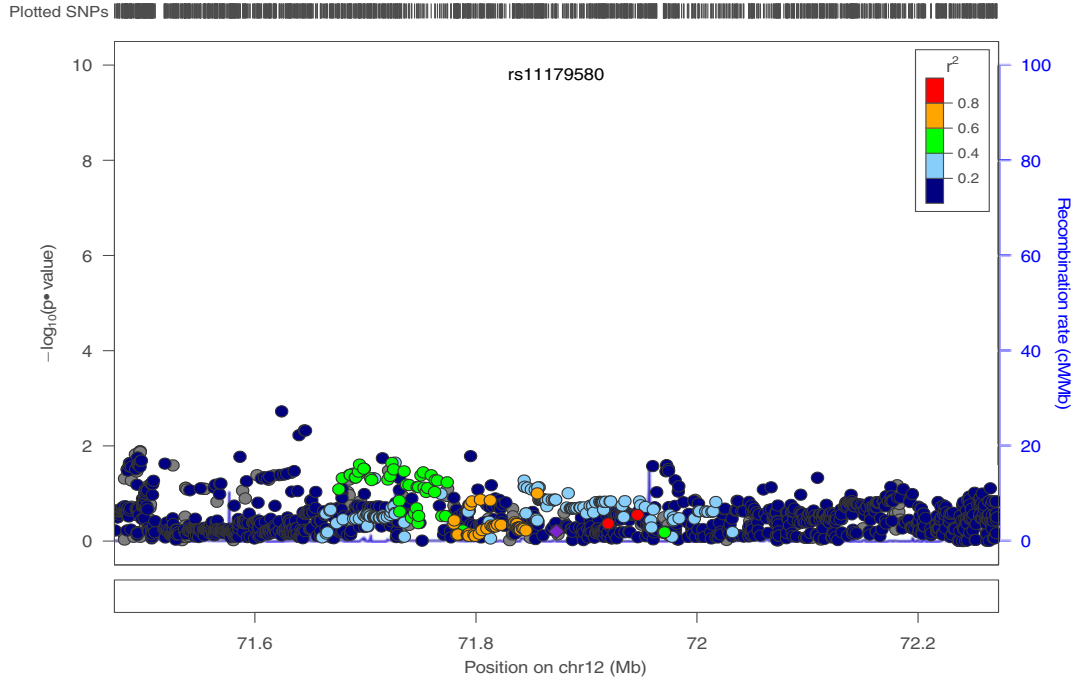
**Figure S2. Meta-analysis of association tests for each separate European study.**



Forest plots describing effect estimates for participating studies in the discovery phase. Pooled estimates for odds ratios and 95% confidence intervals were calculated using fixed effects, inverse variance weighting meta-analysis. Left) Association results for rs11179580 at chromosome 12q21.1 in lobar ICH. Right) Association results for rs2984613 at chromosome 1q22 in non-lobar ICH. Results correspond to effect estimates when testing the major allele to depict genetic variation associated with increased risk of ICH. ICH = Intracerebral hemorrhage, GOCHA = Genetics of Cerebral Hemorrhage on Anticoagulation Study, HM-ICH = Hospital del Mar Intracerebral Hemorrhage Study, VVH-ICH = Vall d’Hebron Hospital ICH Study, JUHSS = Jagiellonian University Hemorrhagic Stroke Study, LSR = Lund Stroke Register, GERFHS = Genetic and Environmental Risk Factors for Hemorrhagic Stroke Study.

Figure S3. Regional association results after adjusting for top associated SNP.

### 3A– rs11179580 and risk of lobar ICH



### 3B – rs2758605 and risk of non-lobar ICH

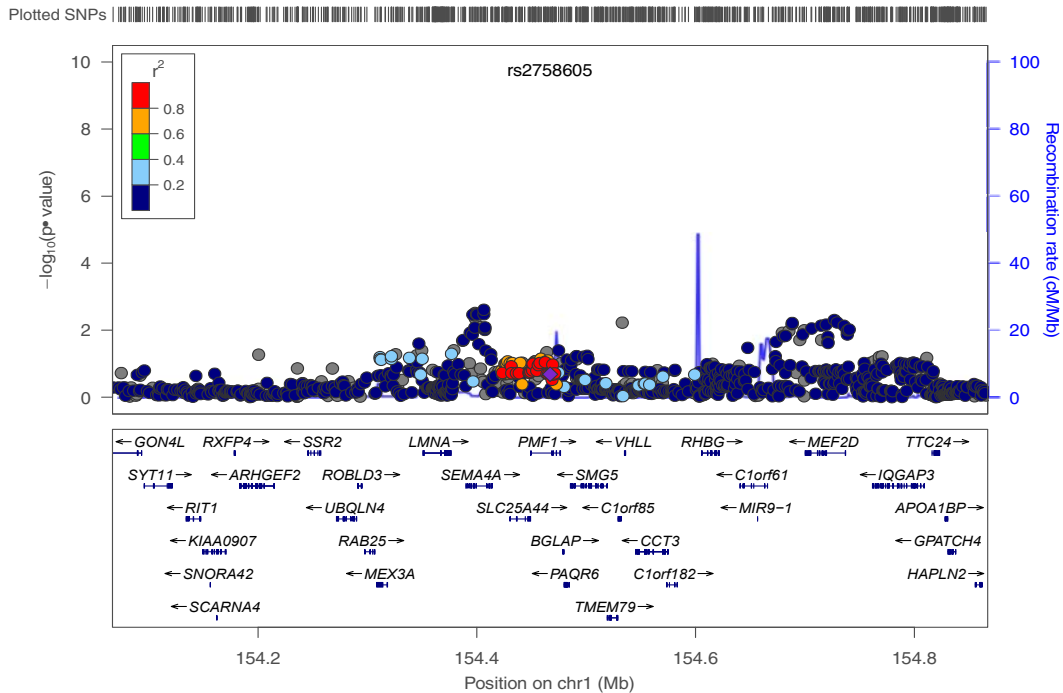


Figure S4. Box-and-whisker plot showing tissue-specific gene expression of *SLC25A44* (Broad Institute's Genotype-Tissue Expression Portal).

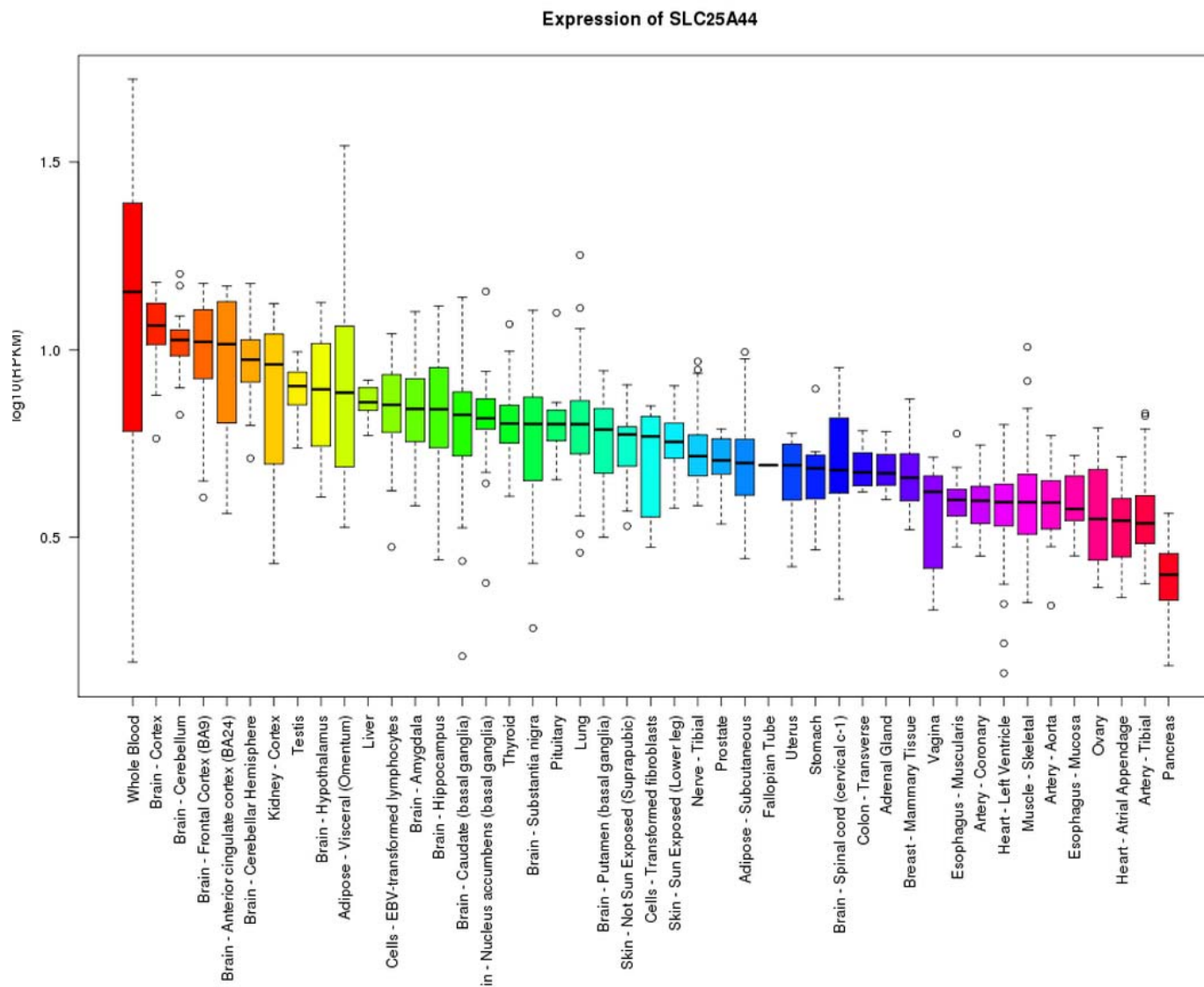




Figure S5. Box-and-whisker plot showing tissue-specific gene expression of *PMF1* (Broad Institute's Genotype-Tissue Expression Portal).

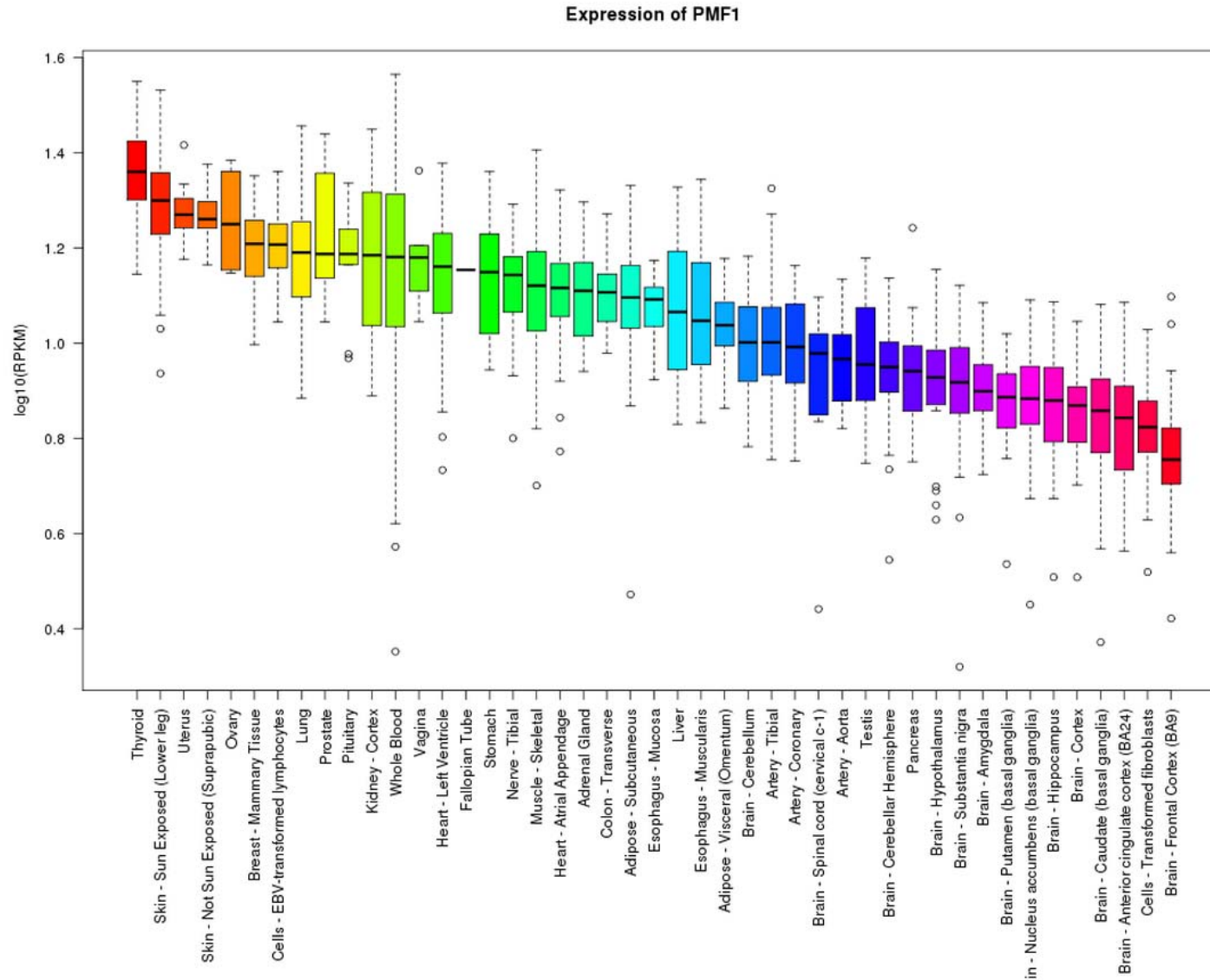
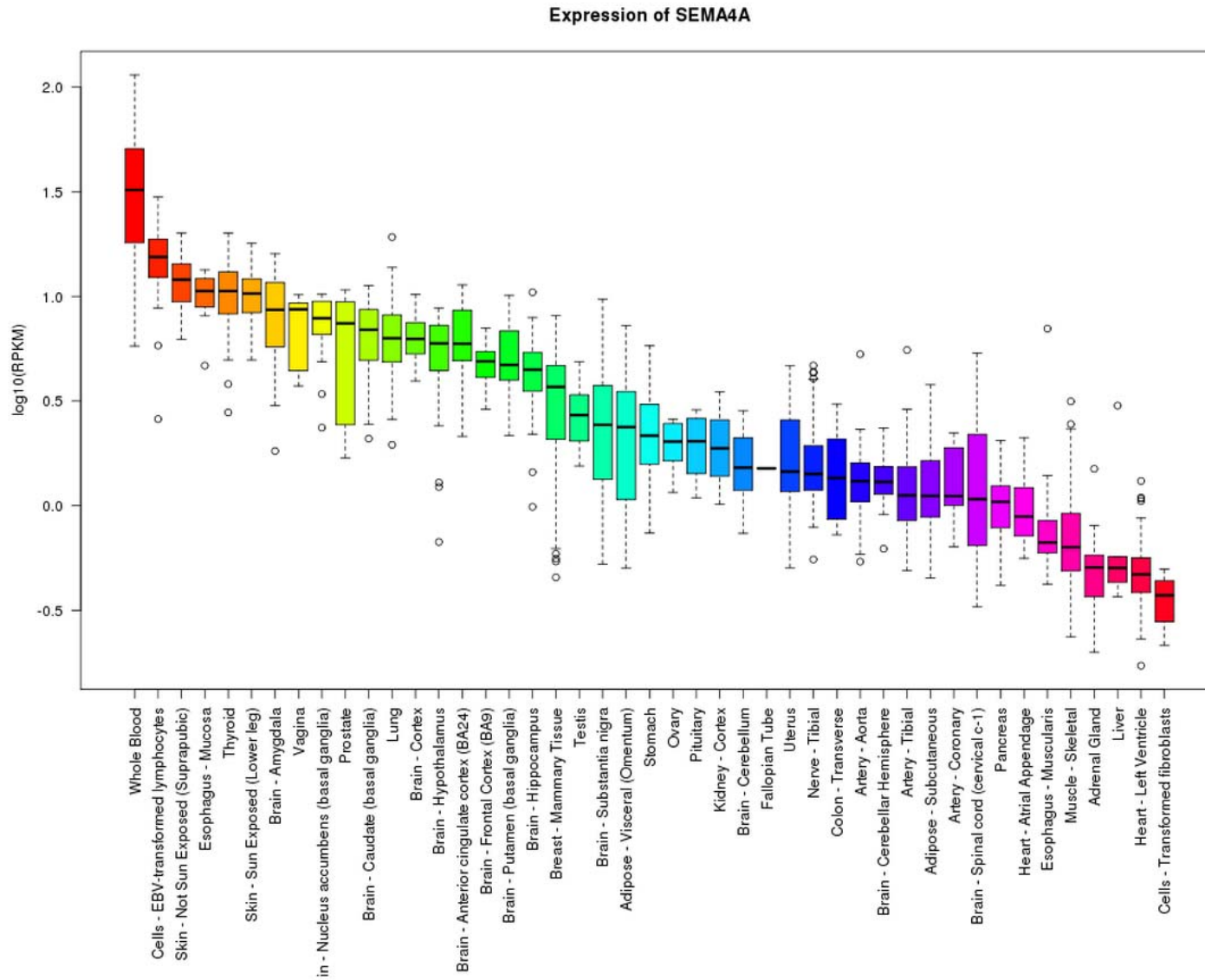


Figure S6. Box-and-whisker plot showing tissue-specific gene expression of *SEMA4A* (Broad Institute's Genotype-Tissue Expression Portal).



**Table S1. Top results for all (lobar + non-lobar ICH) -  $p < 5 \times 10^{-5}$ .**

SNP	CHR	Base Pair Position	A1	A2	P	Effect Direction
rs11179580	12	73586579	t	c	5.42E-07	---
rs12705741	7	110513744	a	c	2.00E-06	+++
rs1606958	12	73659931	a	c	2.06E-06	---
rs2190529	7	110516563	a	g	3.65E-06	+++
rs17665526	4	178031539	a	g	3.86E-06	---
rs799642	7	110499232	a	g	3.96E-06	---
rs4682240	3	110892394	a	g	4.12E-06	---
rs799626	7	110513423	t	g	4.14E-06	---
rs1898856	4	178045296	t	c	4.55E-06	+++
rs13147707	4	58108131	t	c	4.59E-06	+++
rs57486023	4	178025392	a	g	4.75E-06	---
rs764864	7	110499965	t	c	4.89E-06	+++
rs17722524	4	178047394	c	g	5.41E-06	---
rs2090315	12	73461400	t	c	5.55E-06	+++
rs1895522	16	58459038	a	g	5.92E-06	---
rs799643	7	110501952	a	t	5.92E-06	---
rs7302852	12	73557168	a	c	6.09E-06	---
rs60685745	12	18668253	a	t	6.42E-06	+++
rs62345687	4	178092434	c	g	6.49E-06	---
rs6973561	7	110495290	t	g	6.56E-06	---
rs6944312	7	110494098	a	g	6.61E-06	+++
rs12826112	12	73555900	t	c	6.91E-06	+++
rs114491858	5	132656091	a	g	7.11E-06	+++
rs1406049	7	110505179	t	c	7.19E-06	+++
rs62345686	4	178087578	t	c	7.32E-06	---
rs740341	7	110497173	a	g	7.57E-06	---
rs7299264	12	73553337	a	c	7.66E-06	+++
rs61277341	4	178036752	t	c	7.68E-06	+++
rs12813018	12	73553998	a	t	8.06E-06	---
rs62342386	4	178093529	t	g	8.11E-06	---
rs2202768	6	106149846	a	g	8.26E-06	---
rs11107581	12	94934162	t	c	8.29E-06	+++
rs12811378	12	73553914	c	g	8.44E-06	+++
rs1976730	12	73553182	a	g	8.49E-06	+++
rs2176205	12	73553218	t	c	8.49E-06	---
rs10785010	12	73551267	t	c	8.52E-06	+++
rs10879572	12	73551571	t	c	8.52E-06	---
rs8044279	16	2944857	a	g	8.55E-06	+++
rs9926873	16	2939566	a	t	8.70E-06	---
rs58534500	4	178093573	t	g	9.00E-06	---
rs1400059	12	73486199	t	c	9.14E-06	---
rs7960698	12	73552114	c	g	9.23E-06	+++
rs8056903	16	2942154	t	c	9.27E-06	---
rs4628161	7	62535681	a	g	9.32E-06	+++
rs4786348	16	2943106	t	c	9.40E-06	+++
rs2382400	9	13594673	c	g	9.57E-06	+++
rs7691074	4	69138386	a	g	9.85E-06	+++
rs10008769	4	69136174	a	g	1.01E-05	+++
rs28812606	4	69136747	a	g	1.02E-05	+++
rs1976729	12	73553089	a	g	1.02E-05	---
rs28412553	4	69137137	a	c	1.02E-05	+++
rs28451838	4	69137007	a	t	1.02E-05	+++
rs6046712	20	20167347	t	c	1.02E-05	---
rs7692218	4	69129457	a	g	1.03E-05	---
rs8048325	16	2944912	a	t	1.03E-05	---
rs72856446	4	69137905	a	g	1.03E-05	---
rs9673454	16	2944762	t	g	1.05E-05	---
rs10032194	4	69136631	t	c	1.05E-05	+++
rs10009194	4	69136630	c	g	1.05E-05	+++
rs7674768	4	69138292	t	c	1.05E-05	---
rs28715439	16	2945671	a	g	1.08E-05	+++

rs10005430	4	178092923	a	g	1.09E-05	---
rs77738469	4	69136926	a	g	1.10E-05	---
rs10879561	12	73533327	a	t	1.12E-05	+++
rs8048185	16	2942214	a	g	1.14E-05	+++
rs7665069	4	69135773	a	g	1.14E-05	+++
rs28587349	4	178096526	t	c	1.15E-05	+++
rs6512935	20	52691156	a	g	1.15E-05	---
rs7660618	4	69135223	t	c	1.16E-05	+++
rs77820753	4	69134905	a	g	1.16E-05	+++
rs72700535	4	178051270	t	c	1.16E-05	---
rs10879568	12	73550277	t	c	1.17E-05	---
rs10150709	14	39440106	t	c	1.17E-05	+++
rs17088724	13	72610915	a	g	1.17E-05	+++
rs9668887	12	73459976	a	c	1.18E-05	---
rs10879569	12	73550881	a	g	1.18E-05	+++
rs6064043	20	52690458	t	g	1.18E-05	---
rs11179569	12	73547054	c	g	1.20E-05	---
rs4777345	15	71522857	c	g	1.22E-05	+++
rs10879567	12	73550092	c	g	1.22E-05	---
rs7311904	12	73548743	t	c	1.24E-05	---
rs7661368	4	69135567	c	g	1.24E-05	---
rs34144381	12	73547558	a	t	1.25E-05	+++
rs34661740	12	73547492	t	c	1.25E-05	---
rs28821242	4	178077865	a	g	1.29E-05	---
rs2588476	18	53630757	a	g	1.30E-05	+++
rs11142708	9	73778502	a	g	1.30E-05	+++
rs7312029	12	73548826	t	c	1.37E-05	---
rs72700536	4	178052721	a	g	1.40E-05	---
rs28711479	4	178075396	t	c	1.42E-05	---
rs1516058	12	73531669	t	c	1.42E-05	+++
rs799628	7	110513735	a	c	1.42E-05	---
rs17721806	4	178022268	t	c	1.43E-05	+++
rs72953868	1	89896790	a	g	1.43E-05	---
rs10013076	4	178085467	a	g	1.47E-05	---
rs2575992	3	178030432	a	t	1.47E-05	---
rs10174010	2	72387539	t	c	1.48E-05	---
rs35951645	2	75838889	a	t	1.52E-05	---
rs799624	7	110511038	t	c	1.54E-05	+++
rs3890512	16	58470046	c	g	1.54E-05	+++
rs6811719	4	178051454	a	g	1.57E-05	---
rs799616	7	110520903	t	c	1.59E-05	---
rs10161441	12	73530269	t	c	1.62E-05	---
rs34997848	12	73455475	t	c	1.63E-05	+++
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rs10879563	12	73536503	a	g	1.66E-05	---
rs258979	7	110530334	t	c	1.68E-05	---
rs10879543	12	73461910	t	c	1.69E-05	---
rs7562242	2	75832989	a	g	1.70E-05	---
rs7632916	3	149777563	a	c	1.71E-05	---
rs17654008	6	18816027	a	g	1.73E-05	+++
rs258978	7	110530288	t	c	1.75E-05	+++
rs185441	7	110534429	t	c	1.76E-05	---
rs7967256	12	73528954	t	c	1.77E-05	---
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rs12319470	12	73482915	a	g	1.78E-05	+++
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rs740270	2	75837011	t	g	1.79E-05	---
rs4681564	3	149777272	t	c	1.79E-05	+++
rs7562126	2	75832877	c	g	1.81E-05	---
rs11160357	14	97145352	t	c	1.83E-05	---
rs799623	7	110509136	t	c	1.88E-05	+++
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rs58865616	4	178085158	t	c	1.88E-05	+++
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rs7115314	11	82028616	a	g	2.73E-05	---
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rs61973227	13	72593126	a	g	3.17E-05	---
rs10897959	11	82038385	a	g	3.18E-05	---

rs10961163	9	13594084	a	c	3.21E-05	+++
rs56366023	6	159900835	a	g	3.22E-05	---
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rs78717763	13	72588224	t	c	3.31E-05	+++
rs666320	11	81974862	a	g	3.46E-05	+++
rs80276229	6	159924294	t	g	3.56E-05	+++
rs117222503	7	62191737	a	t	3.57E-05	---
rs11160359	14	97147660	a	g	3.60E-05	---
rs12654041	5	124242910	c	g	3.60E-05	+++
rs12098051	1	89890973	t	g	3.60E-05	---
rs6499956	16	58458445	t	c	3.67E-05	+++
rs56110557	5	124254061	a	c	3.72E-05	+++
rs10078386	5	124253737	t	g	3.74E-05	+++
rs11241777	5	124250896	a	c	3.76E-05	+++
rs1026010	5	124256262	a	g	3.82E-05	+++
rs6575597	14	97149309	t	c	3.84E-05	---
rs61288415	10	98470969	t	c	3.88E-05	---
rs11699339	20	52688306	t	c	3.89E-05	+++
rs3907999	11	82027114	a	g	3.91E-05	---
rs3908000	11	82027104	a	g	3.91E-05	---
rs7655685	4	149887051	a	g	4.00E-05	---
rs12652881	5	124258221	a	g	4.01E-05	+++
rs61856809	10	98469854	a	g	4.03E-05	---
rs12652885	5	124258259	a	g	4.03E-05	+++
rs12495109	3	109074136	c	g	4.04E-05	+++
rs4474359	10	128072363	t	c	4.06E-05	+++
rs75966668	6	159892086	c	g	4.06E-05	---
rs1022331	12	73569295	a	t	4.07E-05	+++
rs9874505	3	149777163	a	g	4.09E-05	+++
rs77811151	6	159905776	t	c	4.12E-05	+++
rs77865018	7	62497888	a	g	4.18E-05	+++
rs61856814	10	98471805	t	c	4.26E-05	---
rs2731553	2	144373941	a	c	4.26E-05	---
rs9323947	14	97136353	a	g	4.26E-05	---
rs6808737	3	178014562	c	g	4.26E-05	+++
rs76770958	17	5794250	t	c	4.27E-05	---
rs73585061	6	159914043	a	g	4.28E-05	---
rs4709340	6	159912782	t	c	4.29E-05	+++
rs2794217	1	84962577	t	c	4.30E-05	+++
rs76959746	6	159911213	t	c	4.31E-05	+++
rs77854375	6	159913356	t	c	4.32E-05	+++
rs73586921	6	159920510	t	c	4.33E-05	---
rs115902257	4	69201180	a	g	4.34E-05	---
rs115010520	4	69199195	t	c	4.34E-05	---
rs61973246	13	72596058	a	g	4.36E-05	+++
rs6808895	3	178014909	t	c	4.37E-05	+++
rs78717299	12	104476255	c	g	4.38E-05	---
rs114053807	5	124262201	a	g	4.41E-05	+++
rs28727366	12	73444812	a	c	4.42E-05	---
rs17186366	6	159898261	t	c	4.43E-05	+++
rs59722191	6	159906395	a	g	4.44E-05	+++
rs75445591	6	159900715	t	c	4.44E-05	---
rs9884610	4	147994958	t	c	4.44E-05	---
rs8057901	16	58470427	a	g	4.45E-05	---
rs17112076	10	98469693	t	c	4.46E-05	---
rs73585056	6	159907069	t	c	4.46E-05	---
rs4835373	4	147992074	a	c	4.47E-05	+++
rs12230898	12	73516804	a	t	4.47E-05	+++
rs73585064	6	159917210	a	c	4.48E-05	---
rs73586917	6	159917621	t	c	4.50E-05	---
rs73177977	12	104489662	c	g	4.51E-05	+++
rs7001084	8	104226946	a	g	4.54E-05	---
rs73586920	6	159919436	t	c	4.56E-05	+++
rs62329208	4	178071440	t	c	4.58E-05	---

rs6898265	5	124255135	a	t	4.64E-05	---
rs1876422	4	147997109	c	g	4.64E-05	+++
rs73586930	6	159921535	c	g	4.64E-05	---
rs59343228	10	98470886	c	g	4.65E-05	+++
rs57710486	10	98470865	t	c	4.65E-05	+++
rs16890441	6	159912117	t	c	4.67E-05	---
rs12572297	10	98470371	t	c	4.67E-05	+++
rs1435767	2	174299698	a	g	4.68E-05	+ +
rs12573330	10	98470341	a	c	4.68E-05	+++
rs111567587	4	30840803	a	c	4.68E-05	---
rs6895765	5	124253140	a	c	4.69E-05	---
rs7927545	11	11446464	a	t	4.69E-05	+++
rs4630205	10	91092706	t	c	4.71E-05	+++
rs7742825	6	159891058	t	c	4.72E-05	+++
rs6535647	4	149871703	t	c	4.76E-05	---
rs79967188	17	5785093	t	c	4.76E-05	---
rs10041713	5	124252550	t	c	4.76E-05	---
rs2659173	1	84981405	a	t	4.78E-05	---
rs6068772	20	52696990	t	c	4.78E-05	+++
rs11822884	11	82032136	c	g	4.82E-05	---
rs12129647	1	82182566	a	g	4.83E-05	+++
rs8041622	15	90352069	a	g	4.85E-05	---
rs2100338	6	159911058	a	t	4.86E-05	+++
rs10793807	5	124252542	t	c	4.86E-05	---
rs34163500	4	2998674	t	c	4.87E-05	+++
rs112645808	7	62555084	t	c	4.92E-05	+++
rs6546748	2	72383868	t	c	4.92E-05	+++
rs12308109	12	73507117	a	g	4.95E-05	+++
rs2583482	3	178083676	t	g	4.95E-05	+++
rs11179552	12	73506220	t	c	4.95E-05	+++
rs4709336	6	159898784	t	c	4.96E-05	---
rs11179553	12	73507345	a	t	4.96E-05	+++
rs6068774	20	52697624	t	g	4.97E-05	+++

**Table S2. Top results for lobar ICH -  $p < 5 \times 10^{-5}$ .**

SNP	CHR	Base Pair Position	A1	A2	P	Effect Direction
rs11179580	12	73586579	t	c	7.01E-08	---
rs1606958	12	73659931	a	c	1.10E-07	---
rs7302852	12	73557168	a	c	3.12E-07	---
rs12826112	12	73555900	t	c	3.50E-07	+++
rs7299264	12	73553337	a	c	3.91E-07	+++
rs12811378	12	73553914	c	g	4.21E-07	+++
rs1976730	12	73553182	a	g	4.26E-07	+++
rs2176205	12	73553218	t	c	4.27E-07	---
rs10785010	12	73551267	t	c	4.27E-07	+++
rs10879572	12	73551571	t	c	4.28E-07	---
rs1976729	12	73553089	a	g	4.95E-07	---
rs11179569	12	73547054	c	g	5.84E-07	---
rs12813018	12	73553998	a	t	5.94E-07	---
rs10879569	12	73550881	a	g	6.07E-07	+++
rs10879561	12	73533327	a	t	6.30E-07	+++
rs7312029	12	73548826	t	c	6.58E-07	---
rs10879567	12	73550092	c	g	6.67E-07	---
rs7960698	12	73552114	c	g	6.75E-07	+++
rs10879568	12	73550277	t	c	7.44E-07	---
rs7311904	12	73548743	t	c	8.93E-07	---
rs34144381	12	73547558	a	t	8.97E-07	+++
rs34661740	12	73547492	t	c	8.97E-07	---
rs10161441	12	73530269	t	c	9.58E-07	---
rs1516058	12	73531669	t	c	9.72E-07	+++
rs11179560	12	73527424	a	t	1.48E-06	---
rs7967256	12	73528954	t	c	1.50E-06	---
rs10879563	12	73536503	a	g	1.56E-06	---
rs7009780	8	142137634	t	c	1.97E-06	---
rs16914908	12	19104435	a	g	2.01E-06	---
rs767111	4	13733778	a	g	2.10E-06	---
rs115278829	4	31093239	a	g	2.21E-06	---
rs12321835	12	73507288	t	g	2.24E-06	---
rs1022331	12	73569295	a	t	2.27E-06	+++
rs11179548	12	73497059	a	c	2.31E-06	+++
rs11933239	4	31095861	t	c	2.33E-06	+++
rs11179552	12	73506220	t	c	2.82E-06	+++
rs13147707	4	58108131	t	c	2.82E-06	+++
rs6823414	4	13731092	t	c	2.83E-06	+++
rs17493417	12	19099613	a	g	2.84E-06	+++
rs6988905	8	142137704	a	g	2.95E-06	+++
rs56282218	4	13732225	c	g	2.98E-06	+++
rs16889082	4	13728706	a	t	3.14E-06	---
rs7301921	12	73506025	a	c	3.16E-06	+++
rs12308109	12	73507117	a	g	3.20E-06	+++
rs11179553	12	73507345	a	t	3.22E-06	+++
rs11179547	12	73496626	t	c	3.33E-06	---
rs17493333	12	19098939	t	c	3.46E-06	---
rs74779214	12	19099084	a	t	3.56E-06	---
rs16914899	12	19098892	t	g	3.62E-06	---
rs10879559	12	73519415	a	g	3.74E-06	+++
rs12230898	12	73516804	a	t	3.83E-06	+++
rs10879548	12	73501855	a	g	3.92E-06	+++
rs12345147	9	20262063	a	c	3.94E-06	+++
rs3739232	8	142138860	c	g	4.12E-06	---
rs3739231	8	142139187	t	c	4.56E-06	+++
rs10879555	12	73512998	a	t	4.70E-06	---
rs10879556	12	73513001	a	t	4.70E-06	---
rs10879547	12	73497463	t	c	4.93E-06	---
rs10785006	12	73497131	a	g	4.96E-06	+++
rs11179546	12	73496604	c	g	4.99E-06	+++



rs1027076	12	19097205	a	g	5.07E-06	---
rs10879554	12	73511933	t	c	5.38E-06	---
rs12342261	9	20263333	t	c	5.56E-06	+++
rs72695296	14	86340774	a	t	5.84E-06	+++
rs34386665	4	92030178	t	c	5.91E-06	+++
rs35946853	4	92030223	t	c	5.91E-06	+++
rs6578152	8	142139251	t	c	6.33E-06	---
rs6141897	20	31824665	t	g	6.62E-06	---
rs12342192	9	20263142	t	c	6.68E-06	+++
rs74736238	8	126465108	a	g	6.85E-06	---
rs76885577	12	19098603	t	g	7.05E-06	---
rs2752902	20	31823024	t	c	7.06E-06	---
rs7976015	12	19098569	t	c	7.06E-06	+++
rs2867535	4	13714273	a	g	7.06E-06	---
rs1474010	12	73494161	t	c	7.15E-06	+++
rs748436	4	82381627	t	c	7.22E-06	+++
rs6059204	20	31841671	a	g	7.27E-06	+++
rs7687430	4	13723887	t	c	7.34E-06	+++
rs7816501	8	142136964	t	c	7.40E-06	+++
rs6057786	20	31840452	a	g	7.77E-06	---
rs1027077	12	19096972	t	g	7.86E-06	+++
rs3746392	20	31827330	a	g	7.96E-06	+++
rs7300179	12	73523691	t	g	8.00E-06	---
rs76048058	8	142136963	c	g	8.33E-06	+++
rs6059171	20	31818704	a	g	8.35E-06	+++
rs1027075	12	19097281	a	g	8.36E-06	+++
rs6059197	20	31838520	a	g	8.47E-06	---
rs6059191	20	31833188	a	c	8.48E-06	---
rs6120186	20	31831745	a	g	8.54E-06	---
rs7259620	19	45407788	a	g	8.60E-06	---
rs2702414	4	179399523	a	g	8.63E-06	---
rs1998149	20	31822170	a	c	8.72E-06	+++
rs12480799	20	31830712	t	c	8.77E-06	---
rs6059186	20	31828254	t	c	8.78E-06	---
rs2295575	20	31831108	a	c	8.78E-06	+++
rs6059185	20	31826732	t	c	8.78E-06	---
rs6141899	20	31827439	a	g	8.78E-06	---
rs6059183	20	31826027	t	c	8.79E-06	---
rs6059184	20	31826465	t	c	8.79E-06	+++
rs6141898	20	31826130	t	g	8.79E-06	+++
rs1407019	20	31825797	a	g	8.79E-06	+++
rs6059181	20	31825373	a	g	8.79E-06	---
rs9323947	14	97136353	a	g	8.85E-06	---
rs6059177	20	31822420	a	c	8.85E-06	---
rs6059178	20	31822547	c	g	8.85E-06	+++
rs6057778	20	31821770	c	g	8.90E-06	+++
rs6059173	20	31821543	a	g	8.94E-06	+++
rs6575594	14	97130612	a	g	9.06E-06	+++
rs1047595	20	31830955	t	c	9.23E-06	---
rs1957819	14	97131992	t	c	9.27E-06	---
rs912339	14	97133001	a	g	9.33E-06	+++
rs6057776	20	31819650	a	g	9.37E-06	---
rs2752903	20	31823390	t	c	9.37E-06	---
rs16889096	4	13730002	c	g	9.55E-06	---
rs6057775	20	31819628	t	g	9.56E-06	---
rs7029721	9	120219553	t	c	9.66E-06	+++
rs6057798	20	31848114	t	c	9.79E-06	---
rs59014024	5	99405223	t	c	9.79E-06	+++
rs750065	20	31822887	a	t	9.91E-06	+++
rs2377864	20	31844770	t	c	9.96E-06	+++
rs3787145	20	31824852	t	c	9.98E-06	+++
rs6057793	20	31845481	t	c	1.00E-05	---
rs6059211	20	31846053	a	g	1.01E-05	+++
rs911137	20	31838820	a	g	1.02E-05	+++

rs6059214	20	31848471	a	c	1.02E-05	---
rs7975626	12	19098035	a	g	1.03E-05	+++
rs6059216	20	31848838	a	g	1.04E-05	---
rs1321417	20	31815973	t	c	1.07E-05	+++
rs10811340	9	20283406	a	g	1.12E-05	+++
rs10897959	11	82038385	a	g	1.12E-05	---
rs10811336	9	20242344	a	c	1.14E-05	+++
rs1562138	4	82372610	t	c	1.17E-05	---
rs1160985	19	45403412	t	c	1.19E-05	---
rs1038025	19	45404972	t	c	1.21E-05	+++
rs12146612	11	82037823	a	g	1.21E-05	+++
rs741780	19	45404431	t	c	1.23E-05	+++
rs10939503	4	13733950	a	g	1.24E-05	---
rs1038026	19	45405062	a	g	1.24E-05	+++
rs7145800	14	86337346	t	c	1.25E-05	---
rs7144499	14	86337292	a	c	1.25E-05	+++
rs116478185	4	69193120	a	g	1.26E-05	---
rs115347518	4	69175447	t	c	1.26E-05	+++
rs116267995	4	69189307	t	c	1.26E-05	+++
rs115252578	4	69196477	t	c	1.26E-05	---
rs115459611	4	69197019	t	g	1.26E-05	---
rs116786722	4	69197381	a	t	1.26E-05	+++
rs115207011	4	69180171	t	c	1.26E-05	+++
rs2888474	14	86336017	t	c	1.28E-05	+++
rs760136	19	45403858	a	g	1.30E-05	+++
rs1157386	4	13730821	t	c	1.31E-05	+++
rs8017965	14	86335746	t	c	1.32E-05	---
rs6059219	20	31851118	a	t	1.32E-05	+++
rs6119356	20	31851429	t	c	1.33E-05	---
rs1558595	4	13727637	a	c	1.33E-05	+++
rs114232966	4	69214382	a	t	1.34E-05	+++
rs61991282	14	86334519	t	c	1.36E-05	+++
rs6059169	20	31817604	a	c	1.36E-05	---
rs10489085	4	13717262	a	g	1.37E-05	+++
rs115010520	4	69199195	t	c	1.38E-05	---
rs115902257	4	69201180	a	g	1.38E-05	---
rs1959456	14	86333800	a	g	1.38E-05	---
rs35878191	4	91802628	t	c	1.43E-05	---
rs34375703	4	91822395	a	g	1.43E-05	+++
rs10757128	9	20267576	a	g	1.44E-05	---
rs61991283	14	86335280	t	c	1.44E-05	+++
rs12504648	4	13728186	t	c	1.44E-05	+++
rs13438266	7	14195661	a	c	1.45E-05	---
rs17796903	14	86334948	a	g	1.46E-05	---
rs16852641	3	142541514	a	c	1.47E-05	---
rs116985522	4	133068157	a	g	1.48E-05	---
rs61991281	14	86334062	a	g	1.49E-05	+++
rs72695288	14	86330884	a	g	1.50E-05	+++
rs7154628	14	97161505	t	c	1.53E-05	+++
rs2373035	14	86336203	t	c	1.54E-05	+++
rs12308333	12	19099838	t	g	1.54E-05	---
rs10811338	9	20248945	a	g	1.58E-05	---
rs72699916	9	20267021	t	c	1.58E-05	---
rs6141900	20	31837363	a	c	1.62E-05	+++
rs55740084	4	13723227	t	g	1.62E-05	+++
rs10964496	9	20248264	a	g	1.63E-05	---
rs10875488	20	31830773	a	g	1.64E-05	---
rs55669100	4	13723103	a	g	1.65E-05	---
rs2752901	20	31822999	a	g	1.65E-05	+++
rs12341270	9	20266189	a	g	1.69E-05	---
rs12641662	4	13734458	t	c	1.70E-05	---
rs7692218	4	69129457	a	g	1.71E-05	---
rs6057794	20	31846600	a	g	1.71E-05	---
rs115736932	4	69183696	t	c	1.78E-05	---

rs1957828	14	97160567	a	c	1.78E-05	---
rs6057800	20	31849506	a	g	1.81E-05	---
rs7025237	9	120225715	t	g	1.83E-05	+++
rs10008769	4	69136174	a	g	1.84E-05	+++
rs4698441	4	13729419	t	c	1.84E-05	+++
rs2120817	4	82376938	a	c	1.85E-05	+++
rs77820753	4	69134905	a	g	1.85E-05	+++
rs3908000	11	82027104	a	g	1.85E-05	---
rs3907999	11	82027114	a	g	1.85E-05	---
rs10032194	4	69136631	t	c	1.86E-05	+++
rs10009194	4	69136630	c	g	1.86E-05	+++
rs7660618	4	69135223	t	c	1.86E-05	+++
rs7665069	4	69135773	a	g	1.87E-05	+++
rs28812606	4	69136747	a	g	1.87E-05	+++
rs10079213	5	99292308	t	g	1.88E-05	---
rs28451838	4	69137007	a	t	1.88E-05	+++
rs884415	13	98411113	a	g	1.89E-05	+++
rs28412553	4	69137137	a	c	1.89E-05	+++
rs77738469	4	69136926	a	g	1.90E-05	---
rs6141902	20	31845531	t	c	1.91E-05	+++
rs72856446	4	69137905	a	g	1.91E-05	---
rs2792969	13	98409719	t	g	1.92E-05	---
rs11160357	14	97145352	t	c	1.92E-05	---
rs11697797	20	31846011	a	g	1.93E-05	---
rs7674768	4	69138292	t	c	1.94E-05	---
rs6141901	20	31839058	t	g	1.96E-05	+++
rs12353526	9	20286678	t	c	1.97E-05	---
rs7021038	9	120224826	t	c	2.00E-05	+++
rs755527	4	82368236	t	c	2.03E-05	---
rs11696598	20	31847816	c	g	2.06E-05	+++
rs74560932	12	19102596	a	g	2.07E-05	---
rs6141903	20	31849421	a	g	2.07E-05	+++
rs7141431	14	97157621	a	g	2.09E-05	+++
rs11696793	20	31848154	t	c	2.09E-05	+++
rs7140622	14	97157452	a	g	2.10E-05	---
rs7661368	4	69135567	c	g	2.13E-05	---
rs67389830	15	60214343	a	g	2.16E-05	+++
rs16914904	12	19100102	t	c	2.18E-05	---
rs11160358	14	97145420	a	g	2.26E-05	---
rs13359551	5	99292103	c	g	2.32E-05	---
rs6479911	10	65351581	a	g	2.35E-05	---
rs7044380	9	120219813	a	g	2.36E-05	+++
rs6141904	20	31850339	t	c	2.37E-05	---
rs10850625	12	116840200	t	g	2.39E-05	+++
rs2025364	14	97147270	t	c	2.47E-05	---
rs1957817	14	97146057	a	g	2.50E-05	---
rs6141378	20	31850648	a	g	2.50E-05	+++
rs7040495	9	120219151	a	t	2.51E-05	+++
rs2025362	14	97147386	c	g	2.53E-05	---
rs9307783	4	82374847	a	g	2.54E-05	---
rs71597222	4	91957156	t	c	2.54E-05	---
rs12364945	11	82031434	a	g	2.54E-05	---
rs12298536	12	19103160	t	g	2.55E-05	+++
rs77465468	10	127983434	c	g	2.55E-05	+++
rs34723702	17	10096877	t	c	2.55E-05	+++
rs12571178	10	127985372	t	g	2.55E-05	---
rs2793710	13	98412848	t	g	2.57E-05	+++
rs1339923	9	120217688	a	g	2.58E-05	---
rs72766168	9	120236853	a	g	2.60E-05	+++
rs7694205	4	91461106	c	g	2.62E-05	+++
rs28409763	4	82369494	t	g	2.67E-05	+++
rs16941938	15	60214234	c	g	2.70E-05	---
rs1077803	4	82369205	a	t	2.73E-05	+++
rs1077802	4	82369160	t	c	2.73E-05	+++

rs9326957	5	99290038	a	g	2.76E-05	---
rs10109137	8	126462698	t	c	2.78E-05	+++
rs62131871	2	27667184	a	g	2.83E-05	+++
rs6734392	2	27677778	t	c	2.83E-05	+++
rs1337216	9	120232342	t	c	2.85E-05	---
rs12303068	12	19100761	a	c	2.87E-05	+++
rs12950553	17	10089563	t	c	2.87E-05	+++
rs7115314	11	82028616	a	g	2.88E-05	---
rs62193988	20	11360517	a	c	2.93E-05	+++
rs62131877	2	27740328	t	c	2.95E-05	+++
rs13360055	5	99444898	a	g	2.96E-05	---
rs7691074	4	69138386	a	g	2.98E-05	+++
rs73775963	5	99289169	a	c	3.00E-05	+++
rs12218815	10	127960395	t	c	3.08E-05	---
rs6575597	14	97149309	t	c	3.09E-05	---
rs11625932	14	70219842	t	c	3.13E-05	---
rs10038187	5	99447747	a	c	3.16E-05	+++
rs57492222	14	70223987	a	g	3.16E-05	+++
rs1953399	14	70223570	t	g	3.17E-05	+++
rs3809399	14	70233632	t	c	3.21E-05	+++
rs11624088	14	94445201	a	g	3.22E-05	---
rs1873519	4	13708154	a	t	3.22E-05	---
rs9884610	4	147994958	t	c	3.23E-05	---
rs56074637	14	70222722	c	g	3.23E-05	---
rs72725724	14	70226387	t	c	3.24E-05	+++
rs9326958	5	99290311	a	g	3.25E-05	---
rs12948698	17	10089663	a	g	3.28E-05	+++
rs55724465	14	70246412	a	g	3.29E-05	+++
rs28437822	14	70246718	a	g	3.30E-05	---
rs10038494	5	99287783	c	g	3.30E-05	---
rs11244927	10	127957086	t	c	3.32E-05	---
rs17488451	12	18900373	t	c	3.38E-05	+++
rs7503909	17	10090019	a	g	3.39E-05	+++
rs75597508	7	14192330	a	g	3.42E-05	---
rs12005027	9	20271277	a	g	3.50E-05	+++
rs75316572	10	127967532	t	c	3.53E-05	+++
rs10071953	5	99286674	a	g	3.54E-05	+++
rs113470953	2	6976394	t	c	3.57E-05	---
rs72953868	1	89896790	a	g	3.57E-05	---
rs72725740	14	70252100	a	g	3.57E-05	---
rs3912083	5	99275788	a	c	3.57E-05	---
rs4899313	14	70230771	a	g	3.58E-05	+++
rs9931636	16	78512088	a	c	3.60E-05	+++
rs1876422	4	147997109	c	g	3.63E-05	+++
rs13104288	4	91794069	a	t	3.66E-05	+++
rs58915059	14	86329630	a	g	3.67E-05	---
rs62131868	2	27631558	t	c	3.72E-05	---
rs58582364	14	70256407	t	g	3.73E-05	+++
rs11160359	14	97147660	a	g	3.74E-05	---
rs72725743	14	70257099	t	g	3.74E-05	---
rs6717803	2	27634511	a	g	3.75E-05	---
rs72725745	14	70258001	a	g	3.76E-05	+++
rs11621916	14	70255617	a	g	3.79E-05	---
rs4835373	4	147992074	a	c	3.83E-05	+++
rs6475175	9	17829896	a	g	3.84E-05	+++
rs11624532	14	70257661	t	c	3.84E-05	+++
rs12571269	10	127982738	a	g	3.85E-05	+++
rs11622925	14	70261665	t	c	3.85E-05	+++
rs4646285	14	70263648	t	c	3.86E-05	+++
rs72695282	14	86328096	a	g	3.87E-05	---
rs62131866	2	27627704	a	g	3.87E-05	+++
rs2090315	12	73461400	t	c	3.89E-05	+++
rs7153985	14	70226487	t	c	3.92E-05	---
rs61356864	14	70266371	a	g	3.94E-05	+++

rs11905745	20	46361490	a	g	3.94E-05	+++
rs10008755	4	69136133	a	g	3.97E-05	+++
rs114940462	2	27861618	t	g	3.98E-05	+++
rs61551917	9	17792927	t	c	4.05E-05	+++
rs73645334	9	17793759	a	g	4.07E-05	+++
rs12705741	7	110513744	a	c	4.21E-05	+++
rs17646325	15	87415658	c	g	4.21E-05	+++
rs9290132	3	162400620	a	g	4.23E-05	---
rs76681193	7	14196909	a	g	4.23E-05	---
rs56402945	2	27591708	a	g	4.37E-05	+++
rs62131869	2	27647453	a	g	4.37E-05	+++
rs4356896	4	147999338	a	g	4.39E-05	+++
rs55987626	14	70206808	a	g	4.44E-05	+++
rs11577456	1	89899019	a	g	4.46E-05	---
rs11822884	11	82032136	c	g	4.46E-05	---
rs55795546	2	27580983	a	g	4.51E-05	---
rs56047188	2	27699789	t	c	4.56E-05	+++
rs11625731	14	70221010	a	g	4.59E-05	+++
rs8009263	14	97149701	c	g	4.64E-05	+++
rs1027362	5	3232868	t	c	4.65E-05	+++
rs34846042	4	91763006	t	c	4.65E-05	+++
rs79222073	10	127988202	t	c	4.66E-05	+++
rs7583698	2	27712408	t	c	4.72E-05	+++
rs2888473	14	86333289	a	t	4.73E-05	---
rs11891554	2	27613617	a	g	4.77E-05	+++
rs116950250	14	86314568	a	c	4.78E-05	---
rs2667557	16	78513191	t	c	4.82E-05	---
rs76823937	2	27611154	t	c	4.83E-05	---
rs8179219	2	27730817	a	g	4.87E-05	+++
rs58979173	2	27711157	a	c	4.88E-05	---
rs11233081	11	82034725	t	c	4.90E-05	---
rs10963299	9	17833057	t	c	4.90E-05	---
rs79435014	10	127988911	a	g	4.95E-05	+++

Table S3. Top results for non-lobar ICH -  $P < 5 \times 10^{-5}$ .

SNP	CHR	Base Pair Position	A1	A2	P	Effect Direction
rs2984613	1	156197380	t	c	1.44E-08	---
rs2758605	1	156200445	c	g	1.55E-08	---
rs2758603	1	156198994	t	c	1.56E-08	+++
rs3001789	1	156197614	t	g	1.59E-08	+++
rs2251847	1	156204047	a	g	1.62E-08	---
rs2842870	1	156200671	t	c	1.65E-08	+++
rs2758607	1	156202759	a	g	1.80E-08	---
rs2758608	1	156202860	a	t	1.80E-08	+++
rs2758609	1	156202868	a	g	1.80E-08	---
rs2736609	1	156202640	t	c	1.82E-08	---
rs2736613	1	156196016	t	c	5.43E-08	+++
rs2248074	1	156195888	t	c	5.44E-08	---
rs2853646	1	156189626	t	c	7.44E-08	---
rs887953	1	156191149	t	c	7.55E-08	+++
rs2244144	1	156184598	a	g	8.22E-08	---
rs1060604	1	156184268	t	c	8.29E-08	+++
rs2853643	1	156184831	a	g	8.29E-08	---
rs2758600	1	156195205	t	c	8.32E-08	---
rs2540183	1	156164885	c	g	8.65E-08	+++
rs1052053	1	156202173	a	g	9.24E-08	+++
rs2758598	1	156194339	a	g	1.20E-07	---
rs2251636	1	156202809	c	g	1.21E-07	---
rs2842873	1	156204653	t	c	1.40E-07	---
rs11587860	1	156156951	c	g	3.10E-07	---
rs2266514	1	156173685	t	c	3.86E-07	+++
rs6427304	1	156156789	a	g	4.02E-07	+++
rs2253809	1	156172125	t	c	4.14E-07	+++
rs2853641	1	156181770	a	g	4.20E-07	+++
rs2241108	1	156181007	c	g	4.20E-07	+++
rs2241107	1	156182710	t	c	4.27E-07	+++
rs2072499	1	156169610	a	g	4.37E-07	+++
rs1137703	1	156184458	t	c	4.47E-07	+++
rs7534434	1	156186615	a	g	4.62E-07	+++
rs2842882	1	156165342	t	g	4.70E-07	+++
rs2984615	1	156165317	c	g	4.71E-07	---
rs3001790	1	156165290	t	g	4.71E-07	+++
rs2540173	1	156188214	a	g	4.85E-07	+++
rs2842857	1	156168736	t	c	5.01E-07	+++
rs2253677	1	156171296	c	g	5.02E-07	+++
rs2540175	1	156184747	t	c	5.08E-07	+++
rs2758615	1	156158367	t	c	5.08E-07	+++
rs2842864	1	156159217	a	g	5.09E-07	---
rs2758618	1	156160892	t	c	5.16E-07	+++
rs2842869	1	156160696	a	g	5.16E-07	+++
rs2758619	1	156162559	a	g	5.27E-07	+++
rs6427307	1	156190083	a	g	5.34E-07	+++
rs2736605	1	156174475	t	c	5.46E-07	+++
rs2842865	1	156159532	a	g	5.64E-07	---
rs2758616	1	156160358	t	c	7.73E-07	+++
rs1773225	3	194403578	a	g	1.20E-06	+++
rs4682240	3	110892394	a	g	1.57E-06	---
rs812583	3	194406505	c	g	2.77E-06	+++
rs789859	3	194405888	t	g	3.25E-06	---
rs789858	3	194405966	t	c	3.25E-06	---
rs789860	3	194405630	a	t	3.34E-06	+++
rs6064043	20	52690458	t	g	3.56E-06	---
rs6068773	20	52697270	t	c	3.66E-06	+++
rs6512935	20	52691156	a	g	3.93E-06	---
rs113853629	7	62550364	t	g	4.88E-06	+++
rs241867	4	142068023	t	c	5.04E-06	+++

rs789862	3	194404522	a	g	5.73E-06	+++
rs114491858	5	132656091	a	g	5.89E-06	+++
rs2909292	9	73615374	t	c	6.35E-06	+++
rs13412252	2	42373747	t	c	6.37E-06	---
rs17088724	13	72610915	a	g	6.44E-06	+++
rs75046180	7	62548420	t	c	6.97E-06	---
rs75209388	20	40001041	a	g	7.05E-06	---
rs6046712	20	20167347	t	c	7.06E-06	---
rs77865018	7	62497888	a	g	7.29E-06	+++
rs4774359	15	60669311	a	g	8.98E-06	+++
rs17066228	5	165454800	t	g	9.05E-06	+++
rs111780107	4	149063161	a	g	1.03E-05	+++
rs6068774	20	52697624	t	g	1.11E-05	+++
rs12595605	15	60668472	t	g	1.12E-05	---
rs13037207	20	52688797	c	g	1.12E-05	+++
rs12593075	15	60668587	a	g	1.15E-05	---
rs10515463	5	133032214	t	c	1.16E-05	+++
rs7703486	5	133029003	t	g	1.16E-05	+++
rs80276229	6	159924294	t	g	1.16E-05	+++
rs10065792	5	133038091	t	c	1.18E-05	+++
rs112645808	7	62555084	t	c	1.18E-05	+++
rs17066233	5	165457156	a	t	1.19E-05	+++
rs62373493	5	133030698	t	c	1.19E-05	+++
rs62373494	5	133030745	t	c	1.19E-05	+++
rs11242172	5	133030002	a	g	1.21E-05	+++
rs10065215	5	133029538	a	g	1.22E-05	+++
rs7721131	5	133029010	a	c	1.23E-05	---
rs55927312	3	154500310	a	c	1.25E-05	+++
rs55811364	3	154500441	t	c	1.25E-05	+++
rs12188071	5	133035435	a	g	1.29E-05	+++
rs12629156	3	154503522	a	t	1.29E-05	+++
rs12109241	5	133027986	a	g	1.30E-05	+++
rs12110187	5	133028032	c	g	1.30E-05	---
rs6596146	5	133028493	a	g	1.30E-05	+++
rs60036598	5	133032032	t	c	1.30E-05	+++
rs4958147	5	133036637	a	g	1.36E-05	---
rs2382400	9	13594673	c	g	1.38E-05	+++
rs56366023	6	159900835	a	g	1.38E-05	---
rs10039028	5	133034752	c	g	1.38E-05	+++
rs6876108	5	133028324	a	g	1.39E-05	+++
rs73585061	6	159914043	a	g	1.40E-05	---
rs7636681	3	154502582	a	t	1.40E-05	---
rs4709340	6	159912782	t	c	1.40E-05	+++
rs59722191	6	159906395	a	g	1.41E-05	+++
rs73586921	6	159920510	t	c	1.41E-05	---
rs6068772	20	52696990	t	c	1.42E-05	+++
rs73585056	6	159907069	t	c	1.42E-05	---
rs73585064	6	159917210	a	c	1.47E-05	---
rs55875257	6	159923470	a	c	1.47E-05	---
rs73586917	6	159917621	t	c	1.47E-05	---
rs73586920	6	159919436	t	c	1.50E-05	+++
rs73586930	6	159921535	c	g	1.52E-05	---
rs16890441	6	159912117	t	c	1.52E-05	---
rs7742825	6	159891058	t	c	1.53E-05	+++
rs77811151	6	159905776	t	c	1.54E-05	+++
rs997183	3	154511264	a	g	1.54E-05	+++
rs4777345	15	71522857	c	g	1.55E-05	+++
rs11699339	20	52688306	t	c	1.56E-05	+++
rs4709336	6	159898784	t	c	1.60E-05	---
rs77854375	6	159913356	t	c	1.63E-05	+++
rs290396	20	52689838	a	c	1.64E-05	+++
rs76959746	6	159911213	t	c	1.65E-05	+++
rs73586931	6	159921935	c	g	1.65E-05	+++
rs4958096	5	133034165	t	c	1.66E-05	+++

rs75966668	6	159892086	c	g	1.66E-05	---
rs73586936	6	159922820	c	g	1.66E-05	+++
rs12495109	3	109074136	c	g	1.67E-05	+++
rs4958146	5	133036287	a	g	1.69E-05	---
rs12186474	5	133035344	a	g	1.70E-05	---
rs11242174	5	133035170	a	g	1.70E-05	---
rs10039095	5	133034874	a	g	1.71E-05	---
rs73586928	6	159920952	a	c	1.71E-05	+++
rs17186366	6	159898261	t	c	1.72E-05	+++
rs75445591	6	159900715	t	c	1.72E-05	---
rs6673934	1	47870564	c	g	1.75E-05	---
rs115715570	5	165444892	t	c	1.77E-05	---
rs73586924	6	159920582	a	g	1.80E-05	---
rs73586925	6	159920607	t	c	1.80E-05	---
rs8044279	16	2944857	a	g	1.86E-05	+++
rs76681056	6	159922039	a	g	1.88E-05	+++
rs4958097	5	133034195	a	t	2.13E-05	+++
rs73354945	5	165442356	a	g	2.13E-05	+++
rs7743711	6	159925359	a	g	2.16E-05	+++
rs116994217	10	19490381	a	g	2.21E-05	+++
rs9926873	16	2939566	a	t	2.25E-05	---
rs2100338	6	159911058	a	t	2.25E-05	+++
rs4786348	16	2943106	t	c	2.30E-05	+++
rs62373491	5	133027267	t	c	2.30E-05	---
rs8056903	16	2942154	t	c	2.31E-05	---
rs4391483	9	9711904	a	g	2.32E-05	+++
rs55718554	1	47871581	c	g	2.35E-05	+++
rs8048325	16	2944912	a	t	2.36E-05	---
rs9673454	16	2944762	t	g	2.36E-05	---
rs28715439	16	2945671	a	g	2.40E-05	+++
rs1473406	15	80061726	t	c	2.42E-05	---
rs4378017	9	9713959	t	g	2.46E-05	+++
rs75820127	2	40013335	a	g	2.46E-05	---
rs7760303	6	159924923	c	g	2.50E-05	---
rs16855581	3	109072016	a	t	2.52E-05	---
rs73354940	5	165440158	t	c	2.58E-05	+++
rs12497535	3	109073022	a	t	2.61E-05	+++
rs1523397	18	963538	a	g	2.69E-05	+++
rs7031298	9	9716531	t	g	2.70E-05	+++
rs34174758	3	154500154	t	c	2.84E-05	+++
rs16855573	3	109070168	a	g	2.86E-05	+++
rs8048185	16	2942214	a	g	2.92E-05	+++
rs115329309	5	169851043	t	c	2.94E-05	+++
rs59530858	4	154414675	a	g	2.97E-05	---
rs1462807	3	110645112	a	c	2.97E-05	---
rs6787921	3	110643763	a	g	3.00E-05	+++
rs7534339	1	156156219	t	c	3.14E-05	+++
rs9521733	13	111034542	t	c	3.18E-05	---
rs6072351	20	39988139	c	g	3.19E-05	---
rs80112840	9	123454085	t	g	3.20E-05	+++
rs17066274	5	165482802	a	g	3.21E-05	+++
rs12633900	3	154499514	t	c	3.24E-05	+++
rs2100832	11	99060807	a	g	3.28E-05	+++
rs10515915	5	165472605	c	g	3.33E-05	+++
rs1473407	15	80062044	t	c	3.35E-05	---
rs7176846	15	80061250	t	c	3.43E-05	---
rs6440958	3	154497361	a	t	3.45E-05	---
rs1402731	3	154501571	t	c	3.46E-05	---
rs59045097	4	154415272	a	c	3.47E-05	+++
rs61973246	13	72596058	a	g	3.52E-05	+++
rs12476937	2	10761985	t	c	3.53E-05	+++
rs2540171	1	156195682	a	g	3.54E-05	---
rs2842868	1	156196407	t	g	3.55E-05	+++
rs55910626	1	156159909	c	g	3.57E-05	+++



rs3747751	6	41758583	a	g	3.59E-05	+++
rs4682215	3	110642634	t	g	3.60E-05	+++
rs2399368	3	110642384	c	g	3.60E-05	---
rs112223391	1	156156094	a	g	3.61E-05	---
rs57056972	1	156159064	a	c	3.61E-05	---
rs10159384	1	156160822	t	c	3.61E-05	---
rs55675376	1	156165881	t	c	3.62E-05	---
rs41265025	1	156163906	t	c	3.64E-05	---
rs2399367	3	110641021	a	g	3.64E-05	---
rs60168053	5	165472696	t	g	3.65E-05	---
rs72708291	1	156177285	a	t	3.70E-05	+++
rs2736607	1	156174930	t	g	3.71E-05	---
rs3846429	4	7307727	t	g	3.75E-05	---
rs12629856	3	154532713	a	t	3.77E-05	+++
rs61462713	1	156161682	t	c	3.78E-05	---
rs4689694	4	7309659	a	g	3.78E-05	+++
rs34168071	4	7308268	a	g	3.79E-05	+++
rs2241109	1	156173082	t	c	3.80E-05	---
rs78876922	9	123453605	t	g	3.81E-05	---
rs2247476	1	156190280	a	c	3.86E-05	---
rs2285014	14	103443232	a	g	3.96E-05	+++
rs6789924	3	154492161	a	c	4.01E-05	---
rs12625565	20	39986085	a	c	4.02E-05	+++
rs909269	1	156192028	t	c	4.16E-05	---
rs7645606	3	154518276	t	c	4.17E-05	+++
rs13133607	4	149877309	t	c	4.22E-05	---
rs7717411	5	165472108	t	g	4.23E-05	+++
rs6535647	4	149871703	t	c	4.28E-05	---
rs4926854	1	47870661	t	c	4.31E-05	---
rs16824293	3	154508800	a	c	4.43E-05	+++
rs1852217	3	154532079	a	g	4.44E-05	---
rs34758654	3	154536231	a	g	4.46E-05	+++
rs58859735	3	154536725	a	c	4.46E-05	+++
rs6783876	3	154542763	a	c	4.47E-05	+++
rs7652581	3	154537891	a	g	4.47E-05	---
rs7651145	3	154519470	t	c	4.48E-05	+++
rs629343	11	85811138	a	g	4.55E-05	---
rs4630205	10	91092706	t	c	4.57E-05	+++
rs11121464	1	9695888	t	c	4.60E-05	+++
rs75749637	16	60395316	c	g	4.64E-05	---
rs11142708	9	73778502	a	g	4.67E-05	+++
rs6440959	3	154522673	t	c	4.71E-05	---
rs7635271	3	154541218	a	t	4.72E-05	+++
rs114576575	4	71258171	a	c	4.72E-05	---
rs73568432	16	60395552	a	g	4.73E-05	+++
rs6494194	15	60660750	a	t	4.74E-05	+++
rs10961150	9	13573724	t	c	4.81E-05	+++
rs4857894	3	128168037	c	g	4.82E-05	+++
rs4501171	4	156996991	a	t	4.83E-05	---
rs7045998	9	133960777	t	c	4.87E-05	---
rs36035484	9	133960773	t	c	4.87E-05	+++
rs7045991	9	133960768	t	c	4.88E-05	---
rs10901343	9	133945955	a	g	4.90E-05	---
rs7746198	6	41881073	t	c	4.90E-05	---
rs1286328	14	91267866	a	g	4.98E-05	---
rs6455651	6	159926784	a	g	4.98E-05	---
rs28463044	4	99723760	t	c	5.00E-05	---

**Table S4**

**Descriptive characteristics of the replication stage  
(ERICH, GERFHS III and CCC-GCC studies).**

<b>Covariate</b>	<b>White</b>		<b>Black</b>		<b>Hispanic</b>	
	<b>Cases</b>	<b>Controls</b>	<b>Cases</b>	<b>Controls</b>	<b>Cases</b>	<b>Controls</b>
<b>N</b>	513	1552	634	449	534	260
<b>Age, mean (SD)</b>	70 (14)	37 (29)	58 (13)	57 (11)	60 (14)	57 (12)
<b>Female, n (%)</b>	246 (48)	783 (50)	259 (41)	209 (47)	198 (37)	121 (47)

**Table S5****Heterogeneity statistics for associations at chromosome 1q22**

SNP	P	I <sup>2</sup>	Q
rs2984613	1.44E-08	68	0.05
rs2758605	1.55E-08	65	0.06
rs2758603	1.56E-08	66	0.06
rs3001789	1.59E-08	66	0.05
rs2251847	1.62E-08	65	0.06
rs2842870	1.65E-08	58	0.09
rs2758607	1.80E-08	56	0.10
rs2758608	1.80E-08	56	0.10
rs2758609	1.80E-08	56	0.10
rs2736609	1.82E-08	56	0.10
rs2736613	5.43E-08	43	0.17
rs2248074	5.44E-08	44	0.17
rs2853646	7.44E-08	60	0.08
rs887953	7.55E-08	50	0.14
rs2244144	8.22E-08	52	0.12
rs1060604	8.29E-08	52	0.12
rs2853643	8.29E-08	52	0.12
rs2758600	8.32E-08	45	0.16
rs2540183	8.65E-08	62	0.07
rs1052053	9.24E-08	61	0.08
rs2758598	1.20E-07	46	0.16
rs2251636	1.21E-07	71	0.03
rs2842873	1.40E-07	70	0.04
rs11587860	3.10E-07	59	0.09
rs2266514	3.86E-07	65	0.06
rs6427304	4.02E-07	59	0.09
rs2253809	4.14E-07	59	0.09
rs2853641	4.20E-07	59	0.09
rs2241108	4.20E-07	59	0.09
rs2241107	4.27E-07	58	0.09
rs2072499	4.37E-07	58	0.09
rs1137703	4.47E-07	58	0.09
rs7534434	4.62E-07	46	0.16
rs2842882	4.70E-07	64	0.06
rs2984615	4.71E-07	64	0.06
rs3001790	4.71E-07	64	0.06
rs2540173	4.85E-07	57	0.10
rs2842857	5.01E-07	65	0.06
rs2253677	5.02E-07	64	0.06
rs2540175	5.08E-07	59	0.09
rs2758615	5.08E-07	64	0.06
rs2842864	5.09E-07	64	0.06
rs2758618	5.16E-07	64	0.06
rs2842869	5.16E-07	64	0.06
rs2758619	5.27E-07	64	0.06
rs6427307	5.34E-07	57	0.10
rs2736605	5.46E-07	63	0.07
rs2842865	5.64E-07	63	0.07
rs2758616	7.73E-07	61	0.08

**Table S6. Replication results for ERICH/GERFS IV/CCC**

<b>Ethnicity</b>	<b>Beta</b>	<b>Standard error</b>	<b>P</b>
<b>Non-lobar ICH - rs2758605 (1q22)</b>			
<b>Whites (MAF 37%)</b>	0.17	0.11	0.04
<b>African Americans (MAF 42%)</b>	0.38	0.10	0.0001
<b>Hispanics (MAF 30%)</b>	0.01	0.12	0.9015
<b>Meta-analysis</b>	0.29	0.05	7x10E-4
<b>Lobar ICH - rs11179580 (12q21.1)</b>			
<b>Whites (MAF 25%)</b>	0.17	0.13	0.21
<b>African Americans (MAF 32%)</b>	0.01	0.14	0.97
<b>Hispanics (MAF 27%)</b>	-0.09	0.19	0.61
<b>Meta-analysis</b>	0.05	0.09	0.55

**Table S7. SNPs on 1q22 with  $P < 1 \times 10^{-5}$ .**

SNP	CH R	BP	Alleles	Minor allele	1000 genomes MAF	Consequence to transcript
rs1052053	1	156202173	A/G	G	0.4382	missense_variant
rs1060604	1	156184268	T/C	C	0.255	intron_variant
rs1137703	1	156184458	T/C	C	0.3704	intron_variant
rs11587860	1	156156951	G/C	C	0.3672	downstream_gene_variant
rs2072499	1	156169610	A/G	G	0.3718	intron_variant
rs2241107	1	156182710	T/C	C	0.3713	downstream_gene_variant
rs2241108	1	156181007	C/G	G	0.3718	downstream_gene_variant
rs2244144	1	156184598	G/A	A	0.2541	intron_variant
rs2248074	1	156195888	C/T	T	0.3008	intron_variant
rs2251636	1	156202809	G/C	C	0.3791	intron_variant
rs2251847	1	156204047	G/A	A	0.37	intron_variant
rs2253677	1	156171296	C/G	G	0.3668	intron_variant
rs2253809	1	156172125	T/C	C	0.3709	intron_variant
rs2266514	1	156173685	T/C	C	0.3668	intron_variant
rs2540173	1	156188214	A/G	G	0.3713	intron_variant
rs2540175	1	156184747	T/C	C	0.3558	intron_variant
rs2540183	1	156164885	C/G	G	0.2473	upstream_gene_variant
rs2736605	1	156174475	T/C	C	0.3599	downstream_gene_variant
rs2736609	1	156202640	C/T	T	0.3251	nc_transcript_variant
rs2736613	1	156196016	T/C	C	0.3063	intron_variant
rs2758598	1	156194339	G/A	A	0.25	intron_variant
rs2758600	1	156195205	C/T	T	0.2505	nc_transcript_variant
rs2758603	1	156198994	T/C	C	0.3622	intron_variant
rs2758605	1	156200445	G/C	C	0.3626	intron_variant
rs2758607	1	156202759	G/A	A	0.3233	intron_variant
rs2758608	1	156202860	A/T	T	0.3233	intron_variant
rs2758609	1	156202868	G/A	A	0.3233	intron_variant

rs2758615	1	156158367	T/C	C	0.3736	downstream_gene_variant
rs2758616	1	156160358	T/C	C	0.3663	upstream_gene_variant
rs2758618	1	156160892	T/C	C	0.3599	upstream_gene_variant
rs2758619	1	156162559	A/G	G	0.3663	upstream_gene_variant
rs2842857	1	156168736	T/C	C	0.3709	intron_variant
rs2842864	1	156159217	G/A	A	0.3654	downstream_gene_variant
rs2842865	1	156159532	G/A	A	0.3576	downstream_gene_variant
rs2842869	1	156160696	A/G	G	0.3617	downstream_gene_variant
rs2842870	1	156200671	T/C	C	0.3897	intron_variant
rs2842873	1	156204653	C/T	T	0.4304	intron_variant
rs2842882	1	156165342	T/G	G	0.3668	intron_variant
rs2853641	1	156181770	A/G	G	0.3713	upstream_gene_variant
rs2853643	1	156184831	G/A	A	0.2541	intron_variant
rs2853646	1	156189626	C/T	T	0.2495	intron_variant
rs2984613	1	156197380	C/T	T	0.3104	intron_variant
rs2984615	1	156165317	G/C	C	0.3668	intron_variant
rs3001789	1	156197614	T/G	G	0.3631	intron_variant
rs3001790	1	156165290	T/G	G	0.3658	intron_variant
rs6427304	1	156156789	A/G	G	0.3764	intron_variant
rs6427307	1	156190083	A/G	G	0.3755	nc_transcript_variant
rs7534434	1	156186615	A/G	G	0.3562	intron_variant
rs887953	1	156191149	T/C	C	0.3182	intron_variant

**Table S8. eQTL data - Broad Institute genotype-tissue (GTEx) expression portal.**

SNP	Gene ID	Gene Symbol	eQTL P-Value	Tissue
rs6427304	ENSG00000196189.6	SEMA4A	5.3E-06	Nerve_Tibial
rs11587860	ENSG00000196189.6	SEMA4A	1.5E-05	Nerve_Tibial
rs2758615	ENSG00000196189.6	SEMA4A	2.9E-05	Nerve_Tibial
rs2842865	ENSG00000196189.6	SEMA4A	4.6E-05	Nerve_Tibial
rs6427307	ENSG00000196189.6	SEMA4A	5.9E-05	Nerve_Tibial
rs2072499	ENSG00000196189.6	SEMA4A	6.0E-05	Nerve_Tibial
rs2241107	ENSG00000196189.6	SEMA4A	6.0E-05	Nerve_Tibial
rs2241107	ENSG00000196189.6	SEMA4A	6.0E-05	Nerve_Tibial
rs2241108	ENSG00000196189.6	SEMA4A	6.0E-05	Nerve_Tibial
rs2253809	ENSG00000196189.6	SEMA4A	6.0E-05	Nerve_Tibial
rs2540173	ENSG00000196189.6	SEMA4A	6.0E-05	Nerve_Tibial
rs2853641	ENSG00000196189.6	SEMA4A	6.0E-05	Nerve_Tibial
rs2251636	ENSG00000196189.6	SEMA4A	6.2E-05	Artery_Tibial
rs1137703	ENSG00000196189.6	SEMA4A	6.7E-05	Nerve_Tibial
rs1052053	ENSG00000196189.6	SEMA4A	7.3E-05	Artery_Tibial
rs2842873	ENSG00000196189.6	SEMA4A	7.5E-05	Artery_Tibial
rs2842869	ENSG00000196189.6	SEMA4A	7.7E-05	Nerve_Tibial
rs2842864	ENSG00000196189.6	SEMA4A	7.8E-05	Nerve_Tibial
rs2758618	ENSG00000196189.6	SEMA4A	7.9E-05	Nerve_Tibial
rs2842857	ENSG00000196189.6	SEMA4A	7.9E-05	Nerve_Tibial
rs2758619	ENSG00000196189.6	SEMA4A	8.0E-05	Nerve_Tibial
rs2253677	ENSG00000196189.6	SEMA4A	8.3E-05	Nerve_Tibial
rs2266514	ENSG00000196189.6	SEMA4A	8.3E-05	Nerve_Tibial
rs2736605	ENSG00000196189.6	SEMA4A	8.3E-05	Nerve_Tibial
rs2842882	ENSG00000196189.6	SEMA4A	8.3E-05	Nerve_Tibial
rs2984615	ENSG00000196189.6	SEMA4A	8.3E-05	Nerve_Tibial
rs3001790	ENSG00000196189.6	SEMA4A	8.3E-05	Nerve_Tibial

**Table S9. Association results for SNPs listed in the GWAS catalog as associated with blood pressure traits at  $p < 1 \times 10^{-5}$ .**

SNPs	Chr	BPP	All ICH P	Lobar ICH P	Non-lobar ICH P
rs12046278	1	10799577	-	-	-
rs17367504	1	11862778	0.915	0.9603	0.6765
rs10493340	1	63591129	0.09383	0.9868	0.05293
rs2932538	1	113216543	0.3697	0.4606	0.3262
rs2820037	1	239436542	0.3308	0.1535	0.9813
rs13002573	2	164915208	0.6926	0.4935	0.9453
rs1446468	2	164963486	0.4292	0.1661	-
rs7591163	2	228715375	0.1182	0.1117	0.4338
rs4370013	3	2654691	0.444	0.8031	0.5737
rs13082711	3	27537909	0.616	0.8581	0.2671
rs3774372	3	41877414	0.2474	0.07099	0.4149
rs9815354	3	41912651	0.2655	0.07545	0.4368
rs319690	3	47927484	0.3941	0.542	0.0635
rs419076	3	169100886	-	0.2273	-
rs448378	3	169100899	-	0.2442	-
rs1918974	3	169165888	-	0.2045	-
rs871606	4	54799245	0.4652	0.3419	0.7139
rs1458038	4	81164723	-	-	-
rs16998073	4	81184341	-	-	-
rs13107325	4	103188709	-	-	-
rs13139571	4	156645513	0.1183	0.1458	0.4237
rs1173771	5	32815028	0.5012	0.6737	0.1536
rs10491334	5	110772404	0.8193	-	0.37
rs9313772	5	157804457	0.4504	0.5586	0.03801
rs11953630	5	157845402	0.4491	0.5482	0.03552
rs1799945	6	26091179	0.3933	0.8019	0.3191
rs198846	6	26107463	0.3921	0.7786	0.3412
rs805303	6	31616366	-	-	-
rs2509458	6	88652580	0.6022	0.9504	0.3868
rs17477177	7	106411858	0.9556	0.3379	0.6239
rs11775334	8	10071620	0.2036	0.4287	0.1793
rs1963982	8	73106916	0.975	0.6381	0.8006
rs2071518	8	120435812	0.7123	0.9514	0.2833
rs4373814	10	18419972	0.4229	0.7735	0.4654
rs11014166	10	18708798	0.7473	0.5718	0.9496
rs12258967	10	18727959	-	-	-
rs4590817	10	63467553	0.739	0.588	0.7154



rs1530440	10	63524591	0.9082	0.4238	0.9076
rs9663362	10	95895177	0.008207	0.1396	0.00928
rs932764	10	95895940	0.001835	0.02743	0.003516
rs1004467	10	104594507	0.3033	0.787	0.04323
rs11191548	10	104846178	0.2996	0.832	0.03339
rs11191593	10	104939215	0.3013	0.8869	0.03701
rs2782980	10	115781527	-	-	-
rs7129220	11	10350538	0.8686	0.5285	0.4665
rs381815	11	16902268	0.454	0.8629	0.2925
rs11024074	11	16917219	0.2401	0.9805	0.06906
rs633185	11	100593538	0.2415	0.8981	0.07541
rs11222084	11	130273230	-	-	-
rs2681472	12	90008959	0.2962	0.6938	0.19
rs2681492	12	90013089	0.2839	0.6808	0.1826
rs17249754	12	90060586	0.3488	0.747	0.2258
rs3184504	12	111884608	-	-	-
rs653178	12	112007756	0.9562	0.5991	0.7974
rs2384550	12	115352731	0.8753	0.5813	0.8399
rs935334	14	76613678	0.9325	0.8134	0.4631
rs2121070	14	76650764	0.7156	0.8483	0.2692
rs1378942	15	75077367	0.5583	0.1964	0.6607
rs6495122	15	75125645	-	-	0.6741
rs2521501	15	91437388	0.6366	0.815	0.9137
rs2398162	15	96830550	0.9131	0.705	0.9852
rs13333226	16	20365654	0.3757	0.6352	0.1307
rs11646213	16	82642651	0.9917	0.8118	0.6125
rs3096277	16	83764204	0.5141	0.9753	0.4448
rs12946454	17	43208121	0.3856	0.7	0.272
rs17608766	17	45013271	-	-	-
rs12940887	17	47402807	-	0.6174	0.2921
rs16948048	17	47440466	-	0.4872	-
rs1327235	20	10969030	0.5739	0.3039	0.8384
rs6015450	20	57751117	0.1469	0.6284	0.2723
rs16982520	20	57758720	0.1244	0.4719	0.3595