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Burden of Risk Alleles for Hypertension Increases Risk of Intracerebral Hemorrhage

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Background and Purpose—Genetic variation influences risk of intracerebral hemorrhage (ICH). Hypertension (HTN) is a potent risk factor for ICH and several common genetic variants (single nucleotide polymorphisms [SNPs]) associated with blood pressure levels have been identified. We sought to determine whether the cumulative burden of blood pressure-related SNPs is associated with risk of ICH and pre-ICH diagnosis of HTN.

Methods—We conducted a prospective multicenter case–control study in 2272 subjects of European ancestry (1025 cases and 1247 control subjects). Thirty-nine SNPs reported to be associated with blood pressure levels were identified from the National Human Genome Research Institute genomewide association study catalog. Single-SNP association analyses were performed for the outcomes ICH and pre-ICH HTN. Subsequently, weighted and unweighted genetic risk scores were constructed using these SNPs and entered as the independent variable in logistic regression models with ICH and pre-ICH HTN as the dependent variables.

Results—No single SNP was associated with either ICH or pre-ICH HTN. The blood pressure-based unweighted genetic risk score was associated with risk of ICH (OR, 1.11; 95% CI, 1.02–1.21; P=0.01) and the subset of ICH in deep regions (OR, 1.18; 95% CI, 1.07–1.30; P=0.001), but not with the subset of lobar ICH. The score was associated with a history of HTN among control subjects (OR, 1.17; 95% CI, 1.04–1.31; P=0.009) and ICH cases (OR, 1.15; 95% CI, 1.01–1.31; P=0.04). Similar results were obtained when using a weighted score.

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Conclusion—Increasing numbers of high blood pressure-related alleles are associated with increased risk of deep ICH as well as with clinically identified HTN. **(*Stroke*. 2012;43:2877-2883.)**

Key Words: genetic risk score ■ genetics ■ hypertension ■ intracerebral hemorrhage

Worldwide stroke is the second leading cause of death and the leading cause of acquired disability.[1] Intracerebral hemorrhage (ICH), the severest form of stroke, accounts for 15% of acute strokes in the United States. Despite advances in neurocritical care, >75% of patients will die or become severely disabled as a result of their ICH.[2] Effective preventive and acute treatments are therefore urgently needed.

Hypertension (HTN) is a potent risk factor for ICH.[3] This effect is strongest for ICH in deep hemispheric locations.[4] HTN has also been associated with increased ICH volumes and worse clinical outcome.[5,6] In recent years, genomewide association studies have identified several common genetic variants (or single nucleotide polymorphisms [SNPs]) associated with blood pressure (BP) levels.[7–9] Each of these common genetics variants, however, exerts only a small effect on BP. Consequently, estimating the combined effect that all these SNPs produced may be the only way to determine whether these variants influence risk of ICH. Genetic risk scores (GRSs) can be implemented to obtain an aggregate measure of the burden of risk alleles related to high BP carried by each individual.[10,11] This approach has already shown that larger burdens of risk alleles for high BP levels are associated with increased risk of stroke.[9]

Within the International Stroke Genetics Consortium's (ISGC) ongoing genomewide association study of ICH, we investigated the role of BP-associated SNPs on both ICH and pre-ICH diagnosis of HTN. We hypothesized that individuals with larger burdens of BP alleles will have an increased risk of ICH, specifically in deep locations of the brain. We also postulated that subjects with ICH carrying greater numbers of risk alleles for high BP should have an increased risk of HTN.

Materials and Methods

Study Design and Patients

We used a multicenter case–control design for the outcomes ICH and pre-ICH HTN in subjects of self-reported European ancestry from the following ISGC studies: Hospital del Mar Intracerebral Hemorrhage study[12] in Barcelona, Spain; the Jagiellonian University Hemorrhagic Stroke Study[13] in Krakow, Poland; the Lund Stroke Register[14] in Lund, Sweden; the Vall d'Hebron Hospital ICH Study[15] in Barcelona, Spain; the Medical University of Graz Intracerebral Hemorrhage study[16] in Graz, Austria; the Genetic and Environmental Risk Factors for Hemorrhagic Stroke[4] at the University of Cincinnati in Cincinnati, Cincinnati, OH; and the Genetics of Cerebral Hemorrhage on Anticoagulation study[17] in the United States (participating sites included Massachusetts General Hospital, Beth Israel Deaconess Medical Center, Mayo Clinic Jacksonville, and the Universities of Michigan, Virginia, Florida at Jacksonville, Washington, and Utah).

All studies were approved by the Institutional Review Board or ethics committee of participating institutions. All participants provided informed consent; when subjects were not able to communicate, written consent was obtained from their legal proxies.

Case Ascertainment

Cases were enrolled according to methods previously described.[18] ICH was defined as a new and acute (<24 hours) neurological deficit with compatible brain imaging showing the presence of intraparenchymal bleeding. Enrolled subjects were primary acute ICH cases that presented to the emergency department of participating institutions (all accredited stroke centers) who provided written consent, were >18 years of age, and had confirmation of primary ICH through neuroimaging (either CT or MRI). Exclusion criteria included: anticoagulation, trauma, brain tumor, hemorrhagic transformation of a cerebral infarction, vascular malformation, or any other cause of secondary ICH. Additional recorded clinical characteristics included pre-ICH exposure to antiplatelet drugs or statins, history of ICH in a first-degree relative, and alcohol or tobacco use.

Ascertainment of ICH cases and assignment of hemorrhage location were performed by stroke neurologists at each ISGC site. ICH located in the cortex (with or without involvement of subcortical white matter) was defined as lobar, whereas ICH selectively involving the thalamus, internal capsule, basal ganglia, or brain stem was defined as deep. Cerebellar hemorrhages were excluded from the study.

Control Ascertainment

Control subjects were >18 years of age and were enrolled from the same population that gave rise to the cases at each participating institution. Control subjects came from the same geographical area as the cases and 2 different sampling techniques were used for enrollment. For the Genetic and Environmental Risk Factors for Hemorrhagic Stroke study, random digit dialing was implemented. For the remainder of the studies, control subjects were enrolled through ambulatory clinics. This last control sampling strategy can sometimes introduce selection bias. To assess this possibility, the distribution of the BP-based GRS was compared between Genetic and Environmental Risk Factors for Hemorrhagic Stroke (that used random digit dialing) and the rest of studies by means of analysis of variance. Control subjects were confirmed to have no history of previous ICH by means of interview and review of medical records. Recorded clinical characteristics were identical to ICH cases.

HTN Status

Cases and control subjects were considered to have HTN when they (or their proxies) reported a medical history of HTN or when receiving anti-HTN medications at the time of admission with ICH. Several validation studies have shown that this approach has acceptable accuracy as compared with direct ascertainment of HTN through BP measurement.[19–22]

Procedures

Peripheral whole blood was collected from cases and control subjects at each participating institution at the time of consent. Blood samples were subsequently shipped to the Massachusetts General Hospital, the coordinating center, and genotyping was carried out at the Broad Institute. DNA was isolated from fresh or frozen blood, quantified with a quantification kit (Qiagen, Valencia, CA), and normalized to a concentration of 30 ng/μL. Genotyping was performed using Affymetrix 6.0 (Santa Clara, CA) in Genetic and Environmental Risk Factors for Hemorrhagic Stroke and Illumina 610k (San Diego, CA) in the rest of the studies. Quality control procedures were implemented as described in online-only Data Supplement

Table 1. Population Characteristics by Center

	Multicenter, US GOCHA		Barcelona, Spain HM-ICH+VHH		Krakow, Poland JUHSS		Lund, Sweden LSR		Cincinnati, OH GERFHS	
	Cases	Control Subjects	Cases	Control Subjects	Cases	Control Subjects	Cases	Control Subjects	Cases	Control Subjects
Subjects, no.	298	457	212	169	122	163	116	153	277	305
Age, mean y (SD)	74 (10)	72 (8)	74 (11)	71 (9)	67 (12)	65 (13)	75 (10)	75 (10)	67 (15)	66 (15)
Sex, no. (%)										
Female	134 (45)	231 (51)	103 (49)	77 (46)	69 (57)	93 (57)	49 (42)	69 (45)	136 (48)	138 (45)
Male	164 (55)	226 (49)	109 (51)	92 (49)	53 (43)	70 (43)	67 (58)	141 (55)	209 (52)	167 (54)
Hypertension, no. (%)										
Yes	217 (73)	280 (61)	126 (60)	99 (64)	96 (81)	74 (45)	76 (67)	65 (43)	169 (62)	157 (52)
No	81 (27)	177 (39)	83 (40)	56 (36)	23 (19)	89 (55)	38 (33)	86 (57)	142 (36)	170 (48)
ICH type, no. (%)										
Lobar	184 (58)	. . .	88 (40)	. . .	51 (39)	. . .	36 (28)	. . .	149 (41)	. . .
Deep	114 (36)	. . .	124 (56)	. . .	71 (54)	. . .	80 (62)	. . .	128 (48)	. . .
Cerebellar	18 (6)	. . .	8 (4)	. . .	9 (7)	. . .	14 (10)	. . .	36 (11)	. . .

GOCHA indicates Genetics of Cerebral Hemorrhage on Anticoagulation Study; HM-ICH, Hospital del Mar Intracerebral Hemorrhage Study; VHH-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; ICH, intracerebral hemorrhage.

Figure I. MACH software[23] was used to impute unobserved SNPs based on reference panels from HapMap[24] and the 1000-genomes project.[25]

Statistical Analysis

Selection of SNPs Associated With BP

SNPs associated with BP levels at $P<1\times10E^{-7}$ were selected from the National Human Genome Research Institute genomewide association study catalog.[26] To ensure that the results of this study reflect independent effects, SNPs in each chromosome were pruned to avoid including variants in linkage disequilibrium ($r^2>0.5$).

Population Stratification

Assessment of the relation between each BP-associated SNP and risk of ICH or HTN was carried out after principal components analysis was implemented to account for population stratification.[27] Principal components were initially applied to identify and remove population outliers and subsequently entered as covariates in the regression models that were fit to test each hypothesis.

Genetic Association Analysis for Individual Variants

Single-SNP genetic association testing was completed within each sample using logistic regression, assuming additive effects for each risk allele present, and including age, sex, and principal components 1 and 2 in the model. Results for individual samples were combined in meta-analysis using inverse variance-weighted, fixed-effects meta-analysis.

GRS Analysis

The main exposure of interest in the present study is the burden of risk alleles for increased BP, as expressed by a GRS. Both weighted GRS (wGRS) and unweighted GRS (uGRS) were calculated. A wGRS is the sum of the products of the risk allele count (0, 1, or 2) at each locus multiplied by the reported effect of that risk allele on BP. An uGRS is simply the sum of the risk alleles for BP across the selected loci. In both instances, for SNPs reported to have minor alleles that reduce BP, the risk allele was set to be the other (major) allele.

Association Analysis for GRS

Multivariate logistic regression was used to model the risk of HTN or ICH using age and sex as covariates. These covariates were included in the model for efficiency. In all models, the GRS was converted to the standard normal distribution and entered as a continuous predictor. In this context, the β for the GRS can be interpreted as the increase in risk of the outcome per 1-SD increase of the GRS.

Additional Analyses

Two additional association analyses involving GRSs were carried out, one excluding brain stem hemorrhages and the other adding principal components 1 and 2 as covariates in the model. To ascertain if the effect of the GRS on ICH was mediated through clinically observed HTN, the multivariate model described for ICH was rerun entering HTN as a covariate. Finally, the same models were also implemented after stratifying by HTN status.

Statistical significance was considered to be Bonferroni-corrected $P<0.001$ and $P<0.017$ for single-SNP association analyses (39 tests) and GRS analyses (3 tests: all, deep, and lobar ICH), respectively, all tests being 2-sided. Genetic association testing for single variants as well as score calculations were performed in PLINK (http://pngu.mgh.harvard.edu/purcell/plink/).[28] All other statistical analyses were performed in SAS 9.2 (SAS Institute, Cary, NC). Post hoc power analysis showed that the study would achieve 90% power to detect a risk increase of 10% per additional SD of the GRS.

Results

A total of 2272 subjects were included in the study: 1025 ICH cases and 1247 ICH-free control subjects (mean [SD] age 71 [±12] years, 48% female). Among cases, 521 (53%) had deep and 462 (47%) had lobar hemorrhages (Table 1). Fifty-two SNPs associated with BP levels were identified from the National Human Genome Research Institute genomewide association study catalog. After pruning to remove genetic variants in high linkage disequilibrium, 38 SNPs remained to be used in the GRS (online-only Data Supplement Table I). Tested independently in meta-analysis, no single SNP was associated with either pre-ICH HTN among controls (online-only Data Supplement Table II) or ICH (online-only Data Supplement Tables III, IV, and V).

The GRS was associated with a diagnosis of pre-ICH HTN among control subjects and among subjects with lobar hemorrhages (Table 2). Within control subjects, each additional SD of the GRS produced an increase in risk of HTN of 22% (OR, 1.22; 95% CI, 1.08–1.37; $P=0.001$) and 17% (OR, 1.17;

Table 2. Multivariate Logistic Regression Results: Odds of Pre-ICH HTN as a Function of Blood Pressure-Based GRS, Age, and Sex

	ICH Control Subjects				ICH Cases							
					All ICH				Deep ICH		Lobar ICH	
	Weighted GRS		Unweighted GRS		Weighted GRS		Unweighted GRS		Weighted GRS		Weighted GRS	Unweighted GRS
	OR	*P* Value	OR	*P* Value	OR	*P* Value	OR	*P* Value	OR	*P* Value	OR	*P* Value	OR	*P* Value	OR	*P* Value	OR	*P* Value	OR	*P* Value
Covariate	(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)	
Score	1.22 (1.08–1.37)	0.001	1.17 (1.04–1.31)	0.009	1.12 (0.98–1.18)	0.09	1.15 (1.01–1.31)	0.04	1.02 (0.84–1.25)	0.83	1.05 (0.86–1.27)	0.66	1.25 (1.03–1.51)	0.02	1.32 (1.08–1.61)	0.006				
Age	1.57 (1.39–1.78)	<0.0001	1.58 (1.39–1.79)	<0.0001	0.99 (0.87–1.11)	0.80	0.98 (0.87–1.11)	0.77	0.89 (0.75–1.08)	0.24	0.89 (0.75–1.08)	0.24	1.20 (0.99–1.45)	0.06	1.20 (0.99–150)	0.06				
Sex	1.04 (0.83–1.31)	0.73	1.05 (0.83–1.32)	0.69	1.40 (1.08–1.81)	0.01	1.41 (1.08–1.82)	0.01	1.45 (0.98–2.20)	0.07	1.15 (0.97–2.2)	0.06	1.27 (0.87–1.85)	0.22	1.28 (0.87–1.86)	0.21				

ICH indicates intracerebral hemorrhage; HTN, hypertension; GRS, genetic risk score.

95% CI, 1.10–1.31; *P*=0.009) for wGRS and uGRS, respectively (Table 2). Within cases with lobar ICH, each additional SD of the GRS produced an increase in risk of HTN of 32% (OR, 1.32; 95% CI, 1.08–1.61; *P*=0.006) and 25% (OR, 1.25; 95% CI, 1.03–1.51; *P*=0.02; Table 2) for wGRS and uGRS, respectively.

The GRS was associated with risk of all (deep and lobar) and deep ICH but not with lobar ICH (Table 3). When considering all (deep and lobar) ICH cases, each additional SD of the GRS produced an increase in risk of ICH of 10% (OR, 1.10; 95% CI, 1.01–1.19; *P*=0.03) and 11% (OR, 1.11; 95% CI, 1.02–1.21; *P*=0.01; Table 3) for wGRS and uGRS, respectively. When including only deep hemorrhages in the analysis, each additional SD of the GRS produced an increase in risk of ICH of 15% (OR, 1.15; 95% CI, 1.04–1.27; *P*=0.008) and 18% (OR, 1.18; 95% CI, 1.07–1.30; *P*=0.001; Table 3) for wGRS and uGRS, respectively. These results remained unchanged when excluding brain stem hemorrhages and when adding principal components 1 and 2 to the model.

The association between the GRS and ICH appears to be stronger in nonhypertensives (Table 4; Figure). When stratifying by HTN status, the effect of the GRS remained present within deep ICH in nonhypertensives (per increase in 1 SD of the uGRS OR, 1.25; 95% CI, 1.06–1.50; *P*=0.007) but not in hypertensives (per increase in 1 SD of the uGRS OR, 1.1; 95% CI, 0.97–1.25; *P*=0.14). No effect was observed within HTN strata for all and lobar ICH. When incorporating HTN into the model, the strength of the association was not substantially modified (online-only Data Supplement Table VI).

Discussion

The present study demonstrates that the burden of risk alleles for BP, as measured by the GRS, is associated with risk of ICH. We also show that, as expected, the GRS is associated with clinically identified pre-ICH HTN. In line with previous findings suggesting differences in underlying biology between deep and lobar ICH,[29] the association between the GRS and risk of ICH appears to be driven by ICH in deep regions of the brain. This association remained significant even when HTN was incorporated into the model, a finding that raises the possibility of misclassification of HTN status given that self-report and medication intake, and not actual BP levels, were used to ascertain this status.

This is the first demonstration that genetic variants for BP also influence risk of ICH. These findings build on previous reports demonstrating the feasibility of applying GRSs to stroke. A mitochondrial genomewide association study of

Table 3. Multivariate Logistic Regression Results: Odds of ICH as a Function of Blood Pressure-Based GRS, Age, and Sex

	All ICH				Deep ICH				Lobar ICH			
	Weighted GRS		Unweighted GRS		Weighted GRS		Unweighted GRS		Weighted GRS		Unweighted GRS	
	OR	*P* Value	OR	*P* Value	OR	*P* Value	OR	*P* Value	OR	*P* Value	OR	*P* Value
Covariate	(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)	
Score	1.10 (1.01–1.19)	0.03	1.11 (1.02–1.21)	0.01	1.15 (1.04–1.27)	0.008	1.18 (1.07–1.30)	0.001	1.05 (0.95–1.17)	0.34	1.05 (0.95–1.17)	0.34
Age	1.09 (1.01–1.19)	0.04	1.09 (1.01–1.19)	0.04	0.97 (0.88–1.07)	0.59	0.97 (0.87–1.07)	0.55	1.27 (1.14–1.43)	<0.001	1.27 (1.14–1.43)	<0.001
Sex	0.99 (0.85–1.18)	0.98	0.99 (0.85–1.18)	0.98	1.05 (0.86–1.28)	0.65	1.05 (0.86–1.28)	0.64	0.91 (0.74–1.12)	0.35	0.91 (0.74–1.11)	0.35

ICH indicates intracerebral hemorrhage; GRS, genetic risk score.

Table 4. Increase in Risk of ICH per Additional SD of the Unweighted GRS, Stratifying by HTN

	All ICH			Deep ICH			Lobar ICH		
Stratifying Covariate	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Hypertension no	1.1	(0.96–1.26)	0.16	1.26	(1.06–1.50)	0.007	1.04	(0.89–1.21)	0.59
Hypertension yes	1.08	(0.97–1.22)	0.13	1.1	(0.97–1.25)	0.14	1.07	(0.93–1.25)	0.31

ICH indicates intracerebral hemorrhage; GRS, genetic risk score; HTN, hypertension.

ischemic stroke described a relation between a GRS generated with mitochondrial variants and risk of ischemic stroke.[30] Our results also complement the conclusions of a recent report that specifically looked into the role of the genetics of hypertension in stroke. This report was a subanalysis of a large meta-analysis of genomewide association studies of BP[9] and found an association between the aggregate burden of BP variants and stroke. In that study, however, the effect of the BP-associated GRS was not assessed specifically for ICH or for ICH subtypes.

Deep ICH has been primarily attributed to the effects on the cerebral vessels of long-standing hypertension, whereas a substantial proportion of lobar ICH appears to arise in the setting of amyloid angiopathy. In the present study, the association between the BP-based GRS and ICH was restricted to deep ICH cases. Furthermore, the association for deep ICH was predominantly observed in subjects who had not been labeled as hypertensives. One explanation could be that the GRS captured increases in risk of ICH produced by BP levels that are below those currently used to establish a diagnosis of HTN. Given the limitations of the approach implemented in the study to ascertain HTN, a second possibility is that subjects labeled as nonhypertensives in this population were misclassified.

These data have important implications for risk prediction of ICH. Given the limited impact of acute treatments for this condition, identifying subjects at highest risk of sustaining an ICH is of paramount importance, because it would open the possibility of implementing aggressive preventive strategies in high-risk individuals. Genetic data can aid in this goal, as they are available from birth, long before hypertension is diagnosed, are constant over time, and are not subject to misclassification and can be collected quickly, inexpensively, and painlessly. Importantly, this same approach could be applied to other risk factors and intermediates, and combined genetic data on common variants for these intermediates could be used to build increasingly precise risk prediction models.

With regard to future research directions, our results demonstrate that, considered in isolation, no single variant related to HTN is associated with ICH. Indeed, it is the aggregate burden of these variants that, in the end, increase the risk of sustaining an ICH. Future investigations can leverage this finding and test if genetic variation affecting entire biological pathways known to influence BP influence risk of ICH. Furthermore, this same approach may be applied to other biological processes and risk factors known to play a role in ICH, like hypercholesterolemia, alcohol abuse, smoking, and obesity.

The present study was undertaken within the largest sample assembled of ICH cases with available genomewide data. In addition, the collection of clinical data and biological samples was done following standardized, prespecified guidelines at every participating site, and stroke neurologists and neuroradiologists ascertained the cases and described important phenotypic characteristics, including ICH location. These last 2 features combined greatly decrease the possibility of outcome misclassification. This is particularly important in the field of stroke, where misclassification of stroke subtypes is usually a limitation.

A number of limitations in the study should be addressed. First, the fact that some of the controls were selected in ambulatory clinics introduces the possibility of selection bias. This would be important because the proportion of hypertensive controls could be higher using this sampling scheme, with a consequent increase in the presence of SNPs associated with hypertension among controls. It should be noted, however, that this situation, if anything, would bias the results toward the null. Additionally, the distribution of the GRS among controls enrolled by Genetic and Environmental Risk Factors for Hemorrhagic Stroke, a study that implemented random digit dialing, was similar to that observed in controls enrolled by studies that applied a sampling scheme based on ambulatory

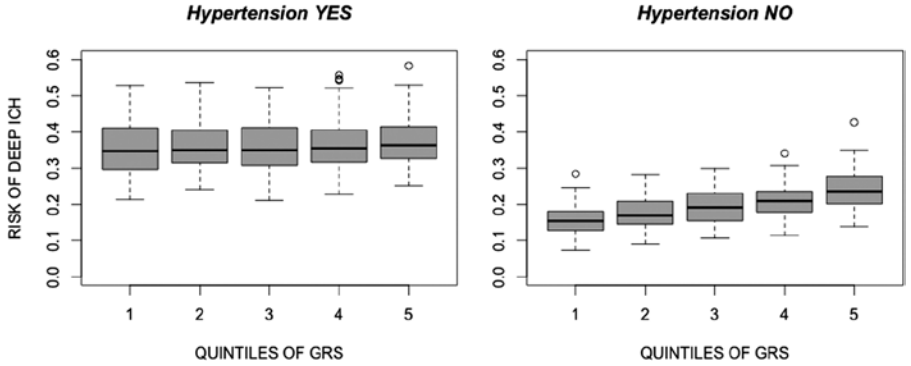

Figure. Predicted probabilities of deep ICH by quintiles of the unweighted GRS, stratifying by HTN status. The x-axis represents predicted probabilities of deep ICH, modeling the score linearly and including age and sex in the model. The y-axis shows categorization based on quintiles of the GRS. **Left**, hypertensives. **Right**, nonhypertensives. ICH indicates intracerebral hemorrhage; GRS, genetic risk score; HTN, hypertension.

clinics (data not shown). Second, selection bias could also be present in the form of survival bias. Patients picked up in the setting of a case–control design would be those who survived the onset of an ICH, thus reaching the hospital and allowing for their enrollment. As has been shown recently, however, simulation results suggest that the effect on risk estimates introduced in this setting would be relatively small.[31]

Summary

In conclusion, we show that an association exists between the burden of risk alleles for elevated BP and the risk of deep ICH. This association is stronger for those individuals labeled as nonhypertensives. Further research is needed to evaluate the clinical value of this genetic risk score.

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Disclosures

None.

References

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet*. 2009;373:1632–1644.
2. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol*. 2010;9:167–176.
3. Brott T, Thalinger K, Hertzberg V. Hypertension as a risk factor for spontaneous intracerebral hemorrhage. *Stroke*. 1986;17:1078–1083.
4. Woo D, Sauerbeck LR, Kissela BM, Khoury JC, Szaflarski JP, Gebel J, et al. Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. *Stroke*. 2002;33:1190–1195.
5. Qureshi AI. Acute hypertensive response in patients with stroke: pathophysiology and management. *Circulation*. 2008;118:176–187.
6. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med*. 2004;255:257–265.
7. Hiura Y, Tabara Y, Kokubo Y, Okamura T, Miki T, Tomoike H, et al. A genome-wide association study of hypertension-related phenotypes in a Japanese population. *Circ J*. 2010;74:2353–2359.
8. Ehret GB. Genome-wide association studies: contribution of genomics to understanding blood pressure and essential hypertension. *Curr Hypertens Rep*. 2010;12:17–25.
9. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*. 2011;478:103–109.
10. Morrison AC, Bare LA, Chambless LE, Ellis SG, Malloy M, Kane JP, et al. Prediction of coronary heart disease risk using a genetic risk score: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2007;166:28–35.
11. Hivert M-F, Jablonski KA, Perreault L, Saxena R, McAteer JB, Franks PW, et al. Updated genetic score based on 34 confirmed type 2 diabetes loci is associated with diabetes incidence and regression to normoglycemia in the diabetes prevention program. *Diabetes*. 2011;60:1340–1348.
12. Gomis M, Ois A, Rodríguez-Campello A, Cuadrado-Godia E, Jiménez-Conde J, Subirana I, et al. Outcome of intracerebral haemorrhage patients pre-treated with statins. *Eur J Neurol*. 2010;17:443–448.
13. Pera J, Slowik A, Dziedzic T, Pulyk R, Wloch D, Szczudlik A. Glutathione peroxidase 1 C593T polymorphism is associated with lobar intracerebral hemorrhage. *Cerebrovasc Dis*. 2008;25:445–449.
14. Hallström B, Jönsson A-C, Nerbrand C, Norrving B, Lindgren A. Stroke incidence and survival in the beginning of the 21st century in southern Sweden: comparisons with the late 20th century and projections into the future. *Stroke*. 2008;39:10–15.
15. Domingues-Montanari S, Hernandez-Guillamon M, Fernandez-Cadenas I, Mendioroz M, Boada M, Munuera J, et al. ACE variants and risk of intracerebral hemorrhage recurrence in amyloid angiopathy. *Neurobiol Aging*. 2011;32:551.e13–22.
16. Seifert T, Lechner A, Flooh E, Schmidt H, Schmidt R, Fazekas F. Lack of association of lobar intracerebral hemorrhage with apolipoprotein E genotype in an unselected population. *Cerebrovasc Dis*. 2006;21:266–270.
17. Genes for Cerebral Hemorrhage on Anticoagulation (GOCHA) Collaborative Group. Exploiting common genetic variation to make anticoagulation safer. *Stroke*. 2009;40:S64–S66.
18. Biffi A, Sonni A, Anderson CD, Kissela B, Jagiella JM, Schmidt H, et al. Variants at APOE influence risk of deep and lobar intracerebral hemorrhage. *Ann Neurol*. 2010;68:934–943.
19. Wada K, Yatsuya H, Ouyang P, Otsuka R, Mitsuhashi H, Takefuji S, et al. Self-reported medical history was generally accurate among Japanese workplace population. *J Clin Epidemiol*. 2009;62:306–313.
20. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol*. 1986;123:894–900.
21. Alonso A, Beunza JJ, Delgado-Rodríguez M, Martínez-González MA. Validation of self reported diagnosis of hypertension in a cohort of university graduates in Spain. *BMC Public Health*. 2005;5:94.
22. Vargas CM, Burt VL, Gillum RF, Pamuk ER. Validity of self-reported hypertension in the National Health and Nutrition Examination Survey III, 1988–1991. *Prev Med*. 1997;26:678–685.
23. Li Y, Willer CJ, Ding J, Scheet P, Abecasis GR. MaCH: using sequence and genotype data to estimate haplotypes and unobserved genotypes. *Genetic Epidemiology*. 2010;34:816–834.
24. The International HapMap Consortium. A haplotype map of the human genome. *Nature*. 2005;437:1299–1320.

25. Consortium T1000 GP. A map of human genome variation from population-scale sequencing. *Nature*. 2010;467:1061–1073.
26. Hindorff LA, MacArthur J, Wise A, Junkins HA, Hall PN, Klemm AK, et al. A Catalog of Published Genome-Wide Association Studies. Available at: www.genome.gov/gwastudies. Accessed January 25, 2012.
27. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet*. 2006;38:904–909.
28. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81:559–575.
29. Burns JD, Manno EM. Primary intracerebral hemorrhage: update on epidemiology, pathophysiology, and treatment strategies. *Compr Ther*. 2008;34:183–195.
30. Anderson CD, Biffi A, Rahman R, Ross OA, Jagiella JM, Kissela B, et al. Common mitochondrial sequence variants in ischemic stroke. *Ann Neurol*. 2011;69:471–480.
31. Anderson CD, Nalls MA, Biffi A, Rost NS, Greenberg SM, Singleton AB, et al. The effect of survival bias on case–control genetic association studies of highly lethal diseases. *Circ Cardiovasc Genet*. 2011;4:188–196.

SUPPLEMENTAL MATERIAL

Burden of risk alleles for Hypertension Increases Risk of Intracerebral Hemorrhage

Content

Supplementary table 1. SNPs associated with blood pressure levels selected for the score.

SNP	Ref. All.	Weight	Chr.	Chr. Position	Context	P	PubMed ID	1st Author	Journal
rs1918974	T	0.27	3	169165888	intron	8E-8	19430483	Newton-Cheh C	Nat Genet
rs13082711	C	0.28	3	27537909	Intergenic	4E-9	21909115	Ehret GB	Nature
rs13139571	C	0.29	4	156645513	intron	2E-10	21909115	Ehret GB	Nature
rs4373814	C	0.30	10	18419972	Intergenic	4E-10	21909115	Ehret GB	Nature
rs805303	G	0.30	6	31616366	intron	3E-11	21909115	Ehret GB	Nature
rs16948048	G	0.31	17	47440466	nearGene-5	5E-9	19430483	Newton-Cheh C	Nat Genet
rs2932538	G	0.31	1	113216543	nearGene-5	1E-9	21909115	Ehret GB	Nature
rs17477177	C	0.32	7	106411858	Intergenic	2E-13	21909110	Wain LV	Nat Genet
rs1327235	G	0.32	20	10969030	Intergenic	1E-15	21909115	Ehret GB	Nature
rs932764	G	0.33	10	95895940	intron	7E-16	21909115	Ehret GB	Nature
rs17608766	C	0.34	17	45013271	intron	1E-10	21909115	Ehret GB	Nature
rs2782980	C	0.35	10	115781527	Intergenic	2E-9	21909110	Wain LV	Nat Genet
rs11953630	C	0.35	5	157845402	Intergenic	4E-13	21909115	Ehret GB	Nature
rs2384550	A	0.35	12	115352731	Intergenic	4E-8	21909110	Wain LV	Nat Genet
rs1446468	C	0.38	2	164963486	Intergenic	6E-12	21909110	Wain LV	Nat Genet
rs1530440	T	0.39	10	63524591	intron	1E-9	19430483	Newton-Cheh C	Nat Genet
rs633185	C	0.45	11	100593538	intron	2E-15	21909115	Ehret GB	Nature
rs7129220	A	0.46	11	10350538	Intergenic	6E-8	21909115	Ehret GB	Nature
rs653178	T	0.46	12	112007756	intron	7E-20	21909110	Wain LV	Nat Genet
rs381815	T	0.46	11	16902268	intron	3E-8	21909110	Wain LV	Nat Genet
rs9815354	A	0.49	3	41912651	intron	3E-9	19430479	Levy D	Nat Genet
rs11014166	A	0.50	10	18708798	intron	1E-8	19430479	Levy D	Nat Genet
rs2521501	T	0.50	15	91437388	intron	2E-15	21909115	Ehret GB	Nature
rs1378942	C	0.51	15	75077367	intron	3E-26	21909115	Ehret GB	Nature
rs4590817	G	0.53	10	63467553	intron	2E-18	21909110	Wain LV	Nat Genet
rs1799945	G	0.54	6	26091179	missense	2E-15	21909115	Ehret GB	Nature
rs12946454	T	0.57	17	43208121	intron;nearG	1E-8	19430483	Newton-Cheh C	Nat Genet
rs1458038	T	0.58	4	81164723	Intergenic	9E-25	21909115	Ehret GB	Nature
rs6825911	C	0.60	4	111381638	Intergenic	7E-8	21572416	Kato N	Nat Genet
rs1173766	C	0.63	5	32804528	Intergenic	2E-8	21572416	Kato N	Nat Genet
rs35444	A	0.63	12	115552437	Intergenic	8E-10	21572416	Kato N	Nat Genet
rs6015450	G	0.73	20	57751117	Intergenic	6E-23	21909115	Ehret GB	Nature
rs880315	C	0.74	1	10796866	intron	3E-10	21572416	Kato N	Nat Genet
rs16849225	C	0.75	2	164906820	Intergenic	4E-11	21572416	Kato N	Nat Genet
rs2681492	T	0.85	12	90013089	intron	4E-11	19430479	Levy D	Nat Genet
rs1004467	A	1.05	10	104594507	intron	1E-10	19430479	Levy D	Nat Genet
rs13333226	A	1.15	16	20365654	nearGene-5	4E-11	21082022	Padmanabhan S	PLoS Genet
rs11066280	T	1.56	12	112817783	intron	3E-63	21909109	Kim YJ	Nat Genet

Supplementary table 2. Single-SNP association meta-analysis within CASES - Outcome: Hypertension.

SNP	P	P(R)	OR	OR(R)	Q	I
rs13333226	0.03678	0.03678	0.7952	0.7952	0.6041	0
rs633185	0.03806	0.03806	0.8251	0.8251	0.4685	0
rs932764	0.06485	0.06485	1.1747	1.1747	0.819	0
rs1918974	0.06532	0.06532	1.1783	1.1783	0.3278	0
rs880315	0.09381	0.09381	1.1708	1.1708	0.6548	0
rs6825911	0.09534	0.1584	1.1822	1.2167	0.2171	34.35
rs10850411	0.1175	0.1719	0.8683	0.8499	0.2348	29.16
rs16849225	0.07291	0.1869	0.8319	0.7802	0.1203	58.57
rs1446468	0.1967	0.245	0.8908	0.8743	0.2359	28.81
rs11014166	0.2019	0.2578	0.8945	0.8748	0.219	33.83
rs11953630	0.2811	0.2811	0.912	0.912	0.9212	0
rs6015450	0.3206	0.3206	1.1515	1.1515	0.382	0
rs2384550	0.3807	0.4018	0.925	0.9019	0.2159	34.69
rs17477177	0.2903	0.4092	0.8939	0.7847	0.0191	81.78
rs2521501	0.4039	0.4579	1.0989	1.1557	0.1129	60.22
rs16948048	0.4245	0.4609	1.0717	1.1296	0.0903	65.15
rs1173766	0.5086	0.4976	0.9446	0.915	0.1738	45.93
rs805303	0.2174	0.5005	0.8981	0.9212	0.2095	36.51
rs1799945	0.3296	0.5041	1.1267	1.1047	0.2613	20.75
rs1004467	0.5229	0.5229	0.914	0.914	0.6202	0
rs35444	0.5417	0.5417	1.0538	1.0538	0.808	0
rs381815	0.564	0.564	1.0546	1.0546	0.8367	0
rs2681492	0.6576	0.5781	0.9518	0.9057	0.1648	48.18
rs1327235	0.6136	0.6136	0.9583	0.9583	0.4431	0
rs9815354	0.6496	0.6496	0.9507	0.9507	0.9681	0
rs4373814	0.7435	0.7189	0.9724	0.9668	0.2888	11.11
rs12946454	0.4269	0.7218	1.0798	1.0494	0.2104	36.25
rs13139571	0.7833	0.7833	0.9742	0.9742	0.7193	0
rs2782980	0.8113	0.8113	0.9781	0.9781	0.6346	0
rs13082711	0.8501	0.8501	0.9809	0.9809	0.7101	0
rs653178	0.7982	0.8546	1.0217	0.9707	0.0834	66.63
rs1458038	0.4174	0.8719	1.0827	1.0269	0.1752	45.58
rs4590817	0.8972	0.8972	0.985	0.985	0.7875	0
rs2932538	0.9166	0.9166	0.9899	0.9899	0.4857	0
rs1378942	0.5061	0.9315	1.0607	1.0131	0.1356	55.1
rs7129220	0.5381	0.9499	0.9158	1.0184	0.0816	67.02
rs1530440	0.9526	0.9526	0.9933	0.9933	0.4132	0
rs2820037	0.669	0.9861	0.9524	0.9969	0.1676	47.49
rs17608766	0.812	0.9998	1.0317	1	0.243	26.65

Supplementary table 3 - Single-SNP association meta-analysis - Outcome: ICH (all types).

SNP	P	P(R)	OR	OR(R)	Q	I
rs932764	0.007406	0.02916	1.1795	1.1966	0.2182	34.05
rs880315	0.09533	0.09533	1.1181	1.1181	0.3851	0
rs6825911	0.08394	0.09685	0.8807	0.8774	0.2989	7.34
rs633185	0.1523	0.1523	0.908	0.908	0.565	0
rs1327235	0.154	0.1735	1.0901	1.0945	0.2884	11.29
rs11014166	0.06494	0.2015	0.8902	0.852	0.0838	66.54
rs1004467	0.2033	0.2033	0.8772	0.8772	0.9927	0
rs805303	0.2219	0.2219	0.9264	0.9264	0.7849	0
rs6015450	0.2711	0.2711	1.1152	1.1152	0.3245	0
rs1378942	0.3408	0.3408	0.9423	0.9423	0.331	0
rs381815	0.3511	0.3511	0.94	0.94	0.6219	0
rs9815354	0.2048	0.3771	0.9032	0.7972	0.0082	85.69
rs2932538	0.3405	0.3848	0.9352	0.9142	0.1813	44.05
rs16948048	0.04734	0.445	1.1314	1.0932	0.0894	65.33
rs7129220	0.4807	0.4875	1.0736	1.111	0.1692	47.09
rs2384550	0.5041	0.5041	1.0433	1.0433	0.5357	0
rs13082711	0.5166	0.5166	0.9532	0.9532	0.6952	0
rs13139571	0.5567	0.5567	0.9605	0.9605	0.5285	0
rs1530440	0.6145	0.5623	0.9601	0.9101	0.0733	68.82
rs1458038	0.5679	0.5679	0.9608	0.9608	0.9134	0
rs653178	0.4155	0.5734	0.9524	0.9603	0.2542	23.07
rs17608766	0.5798	0.5798	1.053	1.053	0.9353	0
rs2782980	0.6195	0.6013	1.0336	1.04	0.2852	12.43
rs16849225	0.6076	0.6076	0.963	0.963	0.6644	0
rs4590817	0.6747	0.669	0.9654	0.9637	0.308	3.78
rs4373814	0.9283	0.6778	0.9944	0.9401	0.0355	77.39
rs35444	0.7047	0.7047	0.9768	0.9768	0.4644	0
rs1173766	0.7248	0.7248	1.0219	1.0219	0.5046	0
rs1799945	0.731	0.731	1.0302	1.0302	0.3233	0
rs17477177	0.733	0.733	0.9744	0.9744	0.6582	0
rs2681492	0.2154	0.7401	0.9049	0.9506	0.0946	64.22
rs11953630	0.7562	0.7562	0.9809	0.9809	0.8429	0
rs2521501	0.7998	0.7998	0.9803	0.9803	0.6814	0
rs1918974	0.04519	0.8257	0.8792	0.9565	0.0057	86.92
rs1446468	0.8382	0.8382	1.0133	1.0133	0.5336	0
rs10850411	0.9043	0.9043	1.0079	1.0079	0.7316	0
rs13333226	0.9344	0.9344	1.0064	1.0064	0.4852	0
rs2820037	0.4508	0.9637	1.0626	1.0072	0.0863	66
rs12946454	0.4949	0.999	1.0477	1.0002	0.0981	63.46

Supplementary table 4 - Single-SNP association meta-analysis - Outcome: ICH (Deep hemorrhages).

SNP	P	P(R)	OR	OR(R)	Q	I
rs633185	0.03904	0.03904	0.8384	0.8384	0.3207	0
rs805303	0.03988	0.03988	0.8515	0.8515	0.9501	0
rs880315	0.04166	0.04166	1.1814	1.1814	0.4447	0
rs932764	0.005186	0.04882	1.2378	1.2773	0.1384	54.47
rs35444	0.08042	0.08042	0.8725	0.8725	0.7948	0
rs6015450	0.07405	0.112	1.237	1.2541	0.247	25.38
rs1446468	0.1251	0.1251	0.8831	0.8831	0.3622	0
rs1004467	0.1768	0.1768	0.8377	0.8377	0.5378	0
rs16948048	0.03247	0.2076	1.1771	1.1514	0.1709	46.66
rs381815	0.2615	0.2955	0.9114	0.9137	0.3037	5.47
rs1173766	0.2972	0.3228	1.0823	1.0926	0.2622	20.46
rs16849225	0.3686	0.3686	0.9207	0.9207	0.7285	0
rs9815354	0.28	0.3881	0.8961	0.8076	0.0391	76.5
rs7129220	0.2287	0.3995	1.1619	1.2613	0.0409	76.08
rs1378942	0.4318	0.4318	0.9407	0.9407	0.8202	0
rs2681492	0.09006	0.4414	0.8398	0.8779	0.1376	54.63
rs17477177	0.4557	0.4557	1.0712	1.0712	0.9571	0
rs11953630	0.4601	0.4601	1.0583	1.0583	0.9646	0
rs11014166	0.4167	0.4703	0.9383	0.8589	0.0207	81.31
rs2782980	0.4945	0.4898	1.0576	1.0696	0.2687	18.25
rs1327235	0.6777	0.5824	1.0318	1.1068	0.0308	78.56
rs6825911	0.6157	0.6157	0.956	0.956	0.5863	0
rs17608766	0.6304	0.6304	1.057	1.057	0.8722	0
rs2932538	0.6605	0.6605	0.9625	0.9625	0.4008	0
rs1458038	0.6805	0.6805	0.9647	0.9647	0.78	0
rs4590817	0.7264	0.6878	0.9644	0.952	0.2612	20.77
rs13333226	0.7263	0.7263	1.0341	1.0341	0.9439	0
rs12946454	0.9423	0.7445	1.0062	0.9452	0.0833	66.66
rs4373814	0.7678	0.7678	0.9776	0.9776	0.3419	0
rs10850411	0.8075	0.8075	0.9804	0.9804	0.6794	0
rs2384550	0.8195	0.8195	0.9822	0.9822	0.71	0
rs1799945	0.6679	0.8424	1.0473	1.027	0.253	23.46
rs2521501	0.8426	0.8426	0.9813	0.9813	0.4982	0
rs2820037	0.8549	0.8549	0.9815	0.9815	0.9193	0
rs653178	0.5924	0.8642	0.9611	0.9818	0.1796	44.47
rs13082711	0.9116	0.9116	0.9899	0.9899	0.7301	0
rs1530440	0.6475	0.9413	1.0461	0.9862	0.0866	65.94
rs13139571	0.9842	0.9842	0.9983	0.9983	0.739	0
rs1918974	0.1108	0.9936	0.8794	1.0025	0.0006	91.54

Supplementary table 5 - Single-SNP association meta-analysis - Outcome: ICH (Lobar hemorrhages).

SNP	P	P(R)	OR	OR(R)	Q	I
rs1004467	0.6628	0.6628	0.9441	0.9441	0.5787	0
rs10850411	0.4202	0.4206	1.0695	1.0695	0.3172	0.04
rs11014166	0.02895	0.02895	0.8347	0.8347	0.7764	0
rs1173766	0.3435	0.3435	0.9265	0.9265	0.7732	0
rs11953630	0.1731	0.1731	0.896	0.896	0.7034	0
rs12946454	0.2554	0.3283	1.1047	1.0982	0.2911	10.27
rs13082711	0.276	0.3675	0.8982	0.905	0.2747	16.17
rs13139571	0.4133	0.4133	0.9295	0.9295	0.3667	0
rs1327235	0.04162	0.04162	1.1728	1.1728	0.5405	0
rs13333226	0.4319	0.4319	0.9208	0.9208	0.3322	0
rs1378942	0.255	0.7004	0.911	0.9475	0.1236	57.83
rs1446468	0.1362	0.1362	1.1332	1.1332	0.6538	0
rs1458038	0.3721	0.3721	0.9213	0.9213	0.6351	0
rs1530440	0.2164	0.2397	0.8752	0.8679	0.2788	14.75
rs16849225	0.942	0.942	1.007	1.007	0.6909	0
rs16948048	0.3637	0.7268	1.0761	1.045	0.1525	51.14
rs17477177	0.3963	0.3963	0.9182	0.9182	0.7426	0
rs17608766	0.6411	0.6411	1.0581	1.0581	0.7578	0
rs1799945	0.7869	0.7869	0.97	0.97	0.7015	0
rs1918974	0.2228	0.2228	0.9034	0.9034	0.4558	0
rs2384550	0.1608	0.1608	1.1225	1.1225	0.5979	0
rs2521501	0.9772	0.8787	1.003	1.0233	0.1601	49.31
rs2681492	0.9698	0.8525	1.0039	1.0255	0.2183	34.01
rs2782980	0.8463	0.8463	0.9832	0.9832	0.4797	0
rs2820037	0.1364	0.9412	1.1654	0.9742	0.0048	87.43
rs2932538	0.272	0.3373	0.9041	0.8754	0.1705	46.77
rs35444	0.1249	0.1249	1.1295	1.1295	0.376	0
rs381815	0.8692	0.8692	0.9858	0.9858	0.8372	0
rs4373814	0.9196	0.663	0.9919	0.9103	0.019	81.82
rs4590817	0.7755	0.7755	0.9694	0.9694	0.6674	0
rs6015450	0.8459	0.8459	0.9746	0.9746	0.8469	0
rs633185	0.9243	0.9243	1.0083	1.0083	0.7642	0
rs653178	0.321	0.321	0.9255	0.9255	0.6211	0
rs6825911	0.01803	0.0445	0.7918	0.7758	0.2445	26.16
rs7129220	0.9268	0.9268	0.9879	0.9879	0.7781	0
rs805303	0.9705	0.9705	1.003	1.003	0.8389	0
rs880315	0.9136	0.9136	1.0097	1.0097	0.4793	0
rs932764	0.2892	0.2892	1.0888	1.0888	0.4992	0
rs9815354	0.3361	0.4122	0.9048	0.8024	0.0323	78.18

Supplementary table 6. Multivariate logistic regression: Modeling the Risk of ICH as a function of the blood-pressure-based GRS, age, gender and HTN.

	All ICH				Deep ICH				Lobar ICH			
	Weigthed GRS		Unweighted GRS		Weigthed GRS		Unweighted GRS		Weigthed GRS		Unweighted GRS	
	OR	p	OR	p	OR	p	OR	p	OR	p	OR	p
Covariate	(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)	
Score	1.08	0.07	1.09	0.03	1.20	0.03	1.16	0.004	1.06	0.26	1.06	0.27
	(0.99-1.18)		(1.01-1.20)		(1.01-1.24)		(1.05-1.29)		(0.96-1.18)		(0.95-1.18)	
Age	1.07	0.09	1.07	0.10	0.94	0.26	0.93	0.23	1.30	<0.001	1.30	<0.001
	(0.99-1.17)		(0.99-1.17)		(0.85-1.05)		(0.85-1.04)		(1.16-1.16)		(1.16-1.46)	
Gender	0.99	0.91	0.99	0.92	1.05	0.65	1.05	0.63	0.91	0.41	0.92	0.41
	(0.84-1.17)		(0.84-1.17)		(0.85-1.28)		(0.86-1.29)		(0.74-1.13)		(0.74-1.13)	
HTN	1.43	<0.001	1.43	<0.001	1.82	<0.001	1.81	<0.001	0.86	0.19	0.87	0.19
	(1.21-1.70)		(1.20-1.70)		(1.47-2.26)		(1.47-2.26)		(0.69-1.073)		(0.70-1.08)	

GRS = genetic risk score, OR = odds ratio, CI = confidence interval, HTN: hypertension.

Supplementary Figure 1. Quality control procedures for GWAS data.