SUPPLEMENTAL MATERIAL

Genome wide analysis of blood pressure variability and ischemic stroke

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Section 1: ASCOT cohort

Cohort description

The Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) study is a longitudinal study investigating the impact of a calcium channel blocker against a beta-blocker regime in 19,342 hypertensive individuals at moderate risk of a CV outcome recruited in the United Kingdom, Ireland and Nordic countries[1]. The ASCOT Blood Pressure Lowering Arm (ASCOT-BPLA) is an investigator-led multi-centre trial which included over 19,000 hypertensive patients, aged 40-79 years at baseline, with an average SBP of 140/90 mmHg on-treatment and 160/100 mmHg off-treatment. Patients had no history of CHD but had at least three other risk factors for cardiovascular disease such as LVH, type II diabetes mellitus, peripheral artery disease, previous stroke/TIA, male, ≥ 55 years of age or cigarette smoking. The study tested the impact of a contemporary calcium channel blocker based regimen against an older beta blocker based regime in hypertensives at moderate risk of a CV outcome. The primary objective of the blood pressure-lowering arm was to assess and compare the long-term effects of two blood-pressure-lowering regimens on the combined endpoint of non-fatal myocardial infarction (including silent myocardial infarction) and fatal CHD. Visit-to-visit BP variability measurements were recorded prospectively over 5.5 years and blood pressure was measured in a seated position by a uniform automated device (Omron HEM705CP) in all participants. Genome wide association scan was performed with no a prior hypothesis about mechanism. 3802 individuals from ASCOT (UK or Irish) were genotyped on Illumina 370K array. The Analyse Variance Independent of Mean (VIM) test was performed for significance and Residual Standard Deviation (RSD) for effect size estimates.

A subset of 3,900 individuals from the ASCOT study recruited in Denmark, Finland, Norway and Sweden (ASCOT-DK-FI-NO-SE) for whom DNA was available were utilized for replication analyses. The recruitment criteria for the Scandinavian ASCOT participants were identical to the UK and Irish participants, and all had BP measurements taken at similar time-points to calculate BP variability.

Details of ASCOT-UK-IR study population are tabulated in Table I.

Genotyping and imputation

Genotyping for the ASCOT samples was performed using the Illumina Human CNV370 Bead Array. For the SNPs that were not directly genotyped, genotypes were obtained through imputation.

Single SNP genotyping of rs976683 in 3,900 Scandinavian ASCOT samples was performed using the KASPAR assay at Bart's and the London Genome Centre. Image processing and genotype calling was using SDS (Applied Biosystems) and Autocaller

(Applied Biosystems). Any genotypes discrepant between the two calling algorithms was manually inspected and corrected.

Quality Control

Quality control and imputation of the ASCOT data have been described previously[2]. After stringent quality control and genotype imputation, a total of ~2.5 million SNPs and 3,802 individuals were tested for association.

Section 2: Ischemic stroke cohort

Cohort descriptions

The stroke population included 8,624 cases and 12,722 controls from 7 different cohorts: Australian Stroke Genetics Collaborative (ASGC) [3, 4], Bio-Repository of DNA in Stroke (BRAINS)[5, 6], Genetics of Early Onset Stroke (GEOS) [7, 8], Ischemic Stroke Genetics Study and Siblings with Ischemic Stroke Study (ISGS [9]/ SWISS [10]), Welcome Trust Case Control Consortium 2 United Kingdom (WTCCC2-UK) [11], Welcome Trust Case Control Consortium 2 Germany (WTCCC2-Germany) [11] and Vitamin Intervention for Stroke Prevention trial (VISP) [12]. All participating cohorts received institutional ethical clearance and signed consent from each participating study subject.

ASGC: ASGC stroke cases comprised stroke patients of European ancestry who were admitted to four clinical centers across Australia (The Neurosciences Department at Gosford Hospital, Gosford; the Neurology Department at John Hunter Hospital, Newcastle; The Queen Elizabeth Hospital, Adelaide; and the Royal Perth Hospital, Perth) between 2003 and 2008[4]. Stroke was defined by World Health Organization criteria as a sudden focal neurological deficit of vascular origin, lasting more than 24 h and confirmed by imaging, such as computerized tomography (CT) and/or magnetic resonance imaging (MRI) brain scan. Other investigative tests such as electrocardiogram, carotid doppler and trans-esophageal echocardiogram were conducted to define ischemic stroke mechanism as clinically appropriate. Cases were excluded from participation if they were aged <18 years, were diagnosed with hemorrhagic stroke or had transient ischemic attack rather than ischemic stroke or if they were unable to undergo baseline brain imaging. On the basis of these criteria, a total of 1,230 ischemic stroke cases were included in the current study. Ischemic stroke subtypes were assigned using TOAST criteria on the basis of clinical, imaging and risk factor data. ASGC controls were participants in the Hunter Community Study (HCS), a population-based cohort of individuals aged 55–85 years, predominantly of European ancestry and residing in the Hunter Region in New South Wales, Australia. Detailed recruitment methods for the HCS have been previously described. Briefly, participants were randomly selected from the New South Wales State electoral roll and were contacted by mail between 2004 and 2007. Consenting participants completed five detailed self-report questionnaires and attended the HCS data collection center, at which time a series of clinical measures were obtained. A total of 1,280 HCS participants were genotyped for the current study. All study participants gave informed consent for participation in genetic studies. Approval for the individual studies was obtained from the relevant institutional ethics committees.

BRAINS is an ongoing, multicentre, in-hospital study which recruits consenting acute stroke patients into a highly characterized biobank[5, 6]. All adult (>18 years of age) stroke patients are recruited with either ischemic or haemorrhagic pathology MRI confirmed lesions. Ischemic stroke subtypes are further sub-classified according to TOAST criteria[13].

Known monogenic causes of stroke are excluded. BRAINS has two principal arms. The first arm recruits UK European stroke patients while the second arm recruits South Asian stroke patients from multiple sites in the UK and also from sites in India. Control data for the European arm is provided by the Wellcome Trust Case Control Consortium while control subjects for the South Asian arm are recruited simultaneously as the affected stroke patient and usually is the proband's spouse.

For the BRAINS dataset site-specific quality control was performed in PLINK to remove individuals failing the following filters: (1) Call rate ≤ 95%, (2) Non-European ancestry (ϵ between -1 and 1), (3) Outlying autosomal heterozygosity, and (4) Cryptic relatedness (pi-hat ≥ 0.2). Quality control also removed SNPs failing the following filters: (1) Call frequency ≤ 95%, (2) MAF ≤ 0.01 and (3) HWE ≥ 10^{-6}. Post imputation, SNPs with imputation r^2 <0.3 or MAF ≤ 0.01 were removed.

GEOS is a population-based case-control study designed to identify genes associated with early-onset ischemic stroke and to characterize interactions of identified stroke genes and/or SNPs with environmental risk factors [14]. Participants were recruited from the greater Baltimore-Washington area in 4 different time periods: Stroke Prevention in Young Women-1 (SPYW-1) conducted from 1992-1996, Stroke Prevention in Young Women-2 (SPYW-2) conducted from 2001-2003, Stroke Prevention in Young Men (SPYM) conducted from 2003-2007, and Stroke Prevention in Young Adults (SPYA) conducted in 2008. *Case participants* were hospitalized with a first cerebral infarction identified by discharge surveillance from one of the 59 hospitals in the greater Baltimore-Washington area and direct referral from regional neurologists. The abstracted hospital records of cases were reviewed and adjudicated for ischemic stroke subtype by a pair of neurologists according to previously published procedures with disagreements resolved by a third neurologist. The ischemic stroke subtype classification system retains information on all probable and possible causes, and is reducible to the more widely used TOAST system that assigns each case to a single category. *Control participants* without a history of stroke were identified by random-digit dialing and were balanced to cases by age and region of residence in each recruitment periods. Genomic DNA was isolated from a variety of sample types, including cell line, whole blood, mouth wash and buccal swab. Samples were genotyped at the Johns Hopkins Center for Inherited Disease Research (CIDR) using the Illumina HumanOmni1-Quad_v1-0_B BeadChip (Illumina, San Diego, CA, USA). Individuals were excluded if they were unexpected duplicates, gender discrepancy and unexpected relatedness.

ISGS/SWISS: ISGS is a multicenter inception cohort study of first-ever ischemic stroke in adult men and women[9]. Cases were recruited from inpatient stroke services at five academic medical centers in Florida, Georgia, Virginia and Minnesota. The diagnosis of ischemic stroke was confirmed by a study neurologist on the basis of medical history, physical examination and CT or MR imaging of the brain. Cases had to be enrolled within

30 days of onset of stroke symptoms. Cases were excluded if they had a mechanical aortic or mitral valve, central nervous system vasculitis, or bacterial endocarditis at the time of the stroke. They were also excluded if they were known to have: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Fabry disease, homocystinuria, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), or sickle cell anemia. Stroke severity at enrollment was assessed using the NIH Stroke Scale (NIHSS) and outcomes at 90-days were assessed by telephone using the Barthel Index, Glasgow Outcome Scale, and the modified Rankin scale [15]. Diagnostic evaluation included: head CT (95% of individuals enrolled) or MRI (83%), electrocardiography (92%), cervical arterial imaging (86%), and echocardiography (74%). A vascular neurology committee reviewed the medical records of every case and assigned ischemic stroke subtype diagnoses according to criteria from the Trial of ORG10172 (TOAST) [13], the Oxfordshire Community Stroke Project [16], and the Baltimore-Washington Young Stroke Study [17]. DNA was donated to the NINDS DNA Repository (Coriell Institute, Camden, NJ) for eligible samples with appropriate written informed consent. A separate certified neurologist adjudicator additionally assigned a subtype diagnosis using the standardized Causative Classification of Stroke web-based algorithm[18].

SWISS is a multicenter affected sibling pair study[19]. Probands with ischemic stroke were enrolled at 66 US medical centers and 4 Canadian medical centers. Probands are adult men and women over the age of 18 years diagnosed with ischemic stroke confirmed by a study neurologist on the basis of history, physical examination and CT or MR imaging of the brain. Probands were required to have a history of at least one living sibling with a history of stroke. Probands were excluded if they had a mechanical aortic or mitral valve, central nervous system vasculitis, or bacterial endocarditis at the time of the index ischemic stroke. Probands were also excluded if they were known to have cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Fabry disease, homocystinuria, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), or sickle cell anemia. Siblings were enrolled using proband-initiated contact [20] or direct contact when permitted by Institutional Review Boards. Concordant (affected) siblings had their diagnosis of ischemic stroke confirmed by review of medical records by a vascular neurology committee. Concordant siblings had the same eligibility criteria as probands. Subtype diagnoses were assigned to the index strokes of probands and concordant siblings according to TOAST criteria[13]. Discordant siblings of the proband were confirmed to be stroke-free using the Questionnaire for Verifying Stroke-free Status [21]. Lymphoblastoid cell lines were created on all subjects. A certified neurologist adjudicator additionally assigned a subtype diagnosis using the standardized Causative Classification of Stroke web-based algorithm to all concordant siblings and a subset of probands for whom medical records were available[18].

VISP: The VISP trial (P.I. James Toole, MD, Wake Forest University School of Medicine (WFU); R01 NS34447) was a multi-center, double-blind, randomized, controlled clinical

trial that enrolled patients aged 35 or older with Homocysteine levels above the 25th percentile at screening and a non-disabling cerebral infarction (NDCI) within 120 days of randomization.34,35 NDCI was defined as an ischemic brain infarction not due to embolism from a cardiac source, characterized by the sudden onset of a neurological deficit. The deficit must have persisted for at least 24 hours, or if not, an infarction in the part of the brain corresponding to the symptoms must have been demonstrated by CT or MRI imaging. The trial was designed to determine if daily intake of a multivitamin tablet with high dose folic acid, vitamin B6 and vitamin B12 reduced recurrent cerebral infarction (1° endpoint), and nonfatal myocardial infarction (MI) or mortality (2° endpoints). Subjects were randomly assigned to receive daily doses of the high-dose formulation (n=1,827), containing 25mg pyridoxine (B6), 0.4mg cobalamin (B12), and 2.5mg folic acid; or the low-dose formulation (n=1,853), containing 200µg pyridoxine, 6µg cobalamin and 20µg folic acid. Enrollment in VISP began in August 1997, and was completed in December 2001, with 3,680 participants enrolled, from 55 clinic sites across the US and Canada and one site in Scotland.

A subset of VISP participants gave consent and were included in the GWAS component of VISP, supported by the National Human Genome Research Institute (NHGRI), Grant U01 HG005160, as part of the Genomics and Randomized Trials Network (GARNET). Samples were genotyped at the Johns Hopkins Center for Inherited Disease Research (CIDR), and genotyping was performed using the Illumina HumanOmni1-Quad_v1-0_B BeadChip (Illumina, San Diego, CA, USA). Individuals were excluded if they were unexpected duplicates or had gender discrepancies. All VISP participants are stroke cases, therefore we obtained GWAS data (dbGAP) for 1047 external controls from the High Density SNP Association Analysis of Melanoma: Case-Control and Outcomes Investigation (Study Accession: phs000187.v1.p1). These samples were also genotyped on the Illumina HumanOmni1-Quad.

WTCCC2- United Kingdom and WTCCC2-Germany

The WTCCC2 samples were genotyped as part of the WTCCC 2 ischemic stroke study[11]. Stroke cases included samples recruited by investigators at St. George's University London (SGUL), University of Oxford and Edinburgh Stroke Study in the UK and the Department of Neurology, Klinikum Großhadern, Ludwig-Maximilians-University, Munich. The SGUL collection comprised 1224 ischemic stroke samples from a hospital based setting. All cases were of self-reported Caucasian ancestry. Ischemic stroke subtypes were determined according to TOAST criteria based on relevant clinical imaging and available information on cardiovascular risk factors. The University of Oxford collection comprised 896 ischemic stroke cases, consecutively collected as part of the Oxford vascular study (OXVASC). Cases were of self-reported Caucasian ancestry, and ischemic stroke subtypes were determined according to TOAST criteria based on relevant clinical imaging. For the Edinburgh Stroke Study, consecutive consenting patients with stroke who were admitted to or seen as outpatients at the Western General Hospital, Edinburgh were prospectively recruited between 2002 and 2005.

Cases in this study were those with a clinically evident stroke, demonstrated by brain imaging (CT or MRI) to be ischemic. An experienced stroke physician assessed each patient as soon as possible after the stroke, prospectively recording demographic and clinical details, including vascular risk factors and results of brain imaging and other investigations. The Munich samples included 1383 ischemic stroke cases. Cases were consecutive European Caucasians recruited from a single dedicated Stroke Unit at the Department of Neurology, Klinikum Großhadern, Ludwig-Maximilians-University, Munich. Ischemic stroke subtypes were determined according to TOAST criteria based on relevant clinical and imaging data. Controls for the UK samples were drawn from shared WTCCC controls obtained from the 1958 Birth Cohort. This is a prospectively collected cohort of individuals born in 1958 (http://www.b58cgene.sgul.ac.uk/), and ascertained as part of the national child development study (http://www.cls.ioe.ac.uk/studies.asp). Data from this cohort are available as a common control set for a number of genetic and epidemiological studies. For the German samples controls were Caucasians of German origin participating into the population KORAgen study (www.gsf.de/kora). This survey represents a gender- and age stratified random sample of all German residents of the Augsburg area and consists of individuals 25 to 74 years of age, with about 300 subjects for each 10-year increment. All controls were free of a history of stroke or transient ischemic attack.

Wellcome Trust Case-Control Consortium 2 (WTCCC2) - Genotyping

All WTCCC2 cases were genotyped as part of the WTCCC2 Ischemic Stroke study using the Illumina Human660W-Quad array. British controls were genotyped using the Illumina Human1.2M-Duo. German controls were genotyped on the Illumina Human 550k platform. Quality control procedures in the WTCCC2 excluded SNPs not genotyped on all case and control collections and SNPs with Fisher information measure <0.98, genotype call rate <0.95, MAF <0.01 or Hardy-Weinberg P-value <1×10-20 in either the case or control collections. Samples were excluded if identified as outliers on call rate, heterozygosity, ancestry and average probe intensity based on a Bayesian clustering algorithm. Samples were also removed if they exhibited discrepancies between inferred and recorded gender or cryptic relatedness with other WTCCC2 samples (pairwise identity-by-descent >0.05). Autosomal genotype imputation was performed using MACH based on HapMap Phase 2 European (CEU) reference data.

Supplemental Tables

Table I. ASCOT-UK-IR stroke cohort population demographics

Clinical Phenotype	
N	3802
Age (mean ± SD)	63.7 ± 8.1
Males, N (%)	3131 (82%)
SBP baseline (Mean ± SD)	161.6 ± 17.6
DBP baseline (Mean ± SD)	92.4 ± 9.9
VIM (Mean ± SD)	0.004 (±0.001)

Table II. Ischemic stroke cohort population demographics

	ASGS		BRAINS		GEOS		ISGS-SWISS	
	Case	**Control**	**Case**	**Control**	**Case**	**Control**	**Case**	**Control**
N	1162	1244	342	2473	448	498	1070	1488
Age in years (mean±SD)	72.87 ± 13.16	66.28 ± 7.54	71.43 ± 14.02	45 ± 0	41.0 (7.0)	39.5 (6.7)	66.62 ± 13.63	64.12 ± 17.29
Male n (%)	688 (59.21)	625 (50.24)	191 (56)	1292 (52)	275 (61.4)	282 (56.6)	607 (57%)	715 (48%)
IS stroke subtype,n (%)								
-Cardioembolic	240	---	79	---	90	---	247	---
-Large Artery	421	---	42	---	37	---	229	---
-Small Vessel	310	---	30	---	54	---	201	---
Hypertension, n (%)	732 (63.99)	809 (65.08)	240 (71)	---	137 (30.6)	79 (15.9)	691 (65)	518 (35)
Diabetes, n (%)	249 (21.75)	126 (10.52)	46 (14)	---	52 (11.6)	12 (2.4)	220 (20)	163 (11)
Hypercholestrimemia, n (%)	435 (42.48)	513 (41.24)	145 (44)	---	126 (28.1)	117 (23.5)	NA	NA
Smoking, n (%)	207 (18.45)	80 (6.67)	69(21)	---	187 (41.7)	117 (23.5)	196 (18)	716 (48)

Table II. Ischemic stroke cohort population demographics continued

	VISP		WTCCC2-UK		WTCCC2-Ger	
	Case	**Control**	**Case**	**Control**	**Case**	**Control**
N	1726	1047	2702	5175	1174	797
Age in years (mean±SD)	67.99 ± 10.66	51.22 ± 12.57	72.1 ± 12.5	---	66.7 ± 12.9	62.7 ± 10.9
Male n (%)	1121 (65)	622 (59)	1468 (54.3)	---	727 (62)	410 (51)
IS stroke subtype,n (%)						
-Cardioembolic	---	---	537	---	330	---
-Large Artery	---	---	564	---	346	---
-Small Vessel	---	---	553	---	106	---
Hypertension, n (%)	1203 (70)	---	1936 (71.1)	---	751 (64)	---
Diabetes, n (%)	429 (25)	---	403 (14.0)	---	270 (23)	---
Hypercholestrimemia, n (%)	140 (8)	---	1280 (47.4)	---	479 (41)	---
Smoking, n(%)	860 (53)	---	1785 (66.1)	---	366 (31)	---

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Table III. Ischemic stroke cohort genotyping and imputation

	ASGS	BRAINS	GEOS	ISGS-SWISS	VISP	WTCCC2-UK	WTCCC2-Ger
Genotyping Platform	Illumina Human 610 Quad	Illumina Human 610 Quad	HumanOmni 1-Quad_v1-0_B BeadChip	Illumina HumanHap 550k	Illumina HumanOmni1-Quad v1-0 B	Illumina 660	Human660W-Quad (cases) and Illumina Human 550k (controls)
Genotyping calling algorithm	Genome studio	Genome studio V2010.1 Genotyping module	Illumina BeadStudio version3.3.7	Illumina BeadStudio	GenomeStudio V 2010.2 Genotyping Module version 1.7.4 GenTrain version 1.0	Gencall	Illuminus
Call rate threshold (individuals)	≥ 0.95	≥ 0.95	>0.98	≥ 0.95	≥ 0.95	0.95	Bayesian clustering
Call frequency threshold (SNPs)	≥ 0.95	≥ 0.95	>0.95	≥ 0.95	≥ 0.95	0.95	0.95
Imputation software	MACH 1.0.16	MACH 1.0	BEAGLE V3.3	MACH 1.0	MACH 1.0	MACH	MACH

Imputation build	HapMap build 36 release 24	HapMap build 36 release 22	Build 36 (reference panel HapMap Phase 3 release 2)	1000 genomes (06_2010)	HapMap build 36 release 22	HapMap II	HapMap 2
LD threshold (r^2) for surrogate markers	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Imputed Quality score threshold for imputed SNP	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Table IV. Ischemic stroke cohort statistical analysis

	ASGS	BRAINS	GEOS	ISGS-SWISS	VISP	WTCCC2-UK	WTCCC2-Ger
Model	Logistic regression	Logistic regression	Logistic Regression	Logistic Regression	Logistic regression	Logistic Regression	Additive model, Bayesian hierarchical model.
Adjustment covariates	Sex and age	Sex and age	age, study recruitment stages and MDS (component 1)	Sex, age, principal components 1 & 2	Sex, age, PC1, PC2	None	none
Statistical software	Plink, mach2dat, SAS	Plink v1.07 , STATA v11, SPSS v20, METAL	PLINK v1.07	PLINK v1.07 for data cleaning, MACH for imputation, R and MACH2DAT for generation of summary statistics	Plink v1.07	Plink & METAL	SNPTEST, own software

Table V: Association results from the ASCOT GWAS identifying 17 correlated SNPs within the NLGN1 gene on chromosome 3 ($p<5 \times 10^{-7}$).

SNP	Position	A1/A2	RAF	r^2	β	SE	p
rs976683*	174968065	C/T	0.24	0.95	0.0001786	3.15E-05	1.44E-08
rs12635897*	174967790	C/G	0.24	0.95	0.0001784	3.15E-05	1.49E-08
rs9830510	174976996	A/G	0.86	1.00	-0.000215	3.81E-05	1.72E-08
rs9882520	174977714	A/G	0.87	0.99	-0.000217	3.86E-05	1.88E-08
rs12495045	174981764	A/C	0.13	0.99	0.0002175	3.87E-05	1.91E-08
rs6776924	174980201	A/T	0.87	0.99	-0.000216	3.85E-05	2.12E-08
rs1948161*	174974090	C/T	0.81	0.96	-0.000189	3.43E-05	3.55E-08
rs4377507	174982953	A/G	0.89	0.99	-0.000215	4.16E-05	2.49E-07
rs6779230*	174970831	A/C	0.72	0.96	-0.000153	2.96E-05	2.55E-07
rs6779246*	174970869	C/G	0.29	0.96	0.0001521	2.96E-05	2.77E-07
rs9868353	174977376	A/G	0.12	0.99	0.0002028	3.97E-05	3.27E-07
rs7428277	174979295	A/G	0.12	0.99	0.0002035	3.99E-05	3.37E-07
rs9876713	174983921	A/G	0.11	0.99	0.0002117	4.15E-05	3.38E-07
rs1488549	174984586	C/T	0.11	0.99	0.0002116	4.15E-05	3.43E-07
rs4568169	174978999	A/T	0.88	0.99	-0.000202	3.97E-05	3.66E-07
rs6774109	174980026	A/G	0.12	0.99	0.0002015	3.97E-05	3.85E-07
rs7629797	174992286	C/T	0.89	1.00	-0.000208	4.14E-05	5.10E-07

Effect sizes are shown as a unit or percentage change in BP variability per copy of the risk allele. Acronyms are as follows: SNP (Single Nucleotide Polymorphism), A1 (Risk Allele), A2 (Non Risk Allele), RAF (Risk Allele Frequency), r^2 (imputation metric), β (Beta regression coefficient), SE (Standard Error), p (probability value). * represents imputed SNPs. The sentinel SNP rs976683 and top genotyped SNP rs9830510 are in bold.

Table VI. SNPs rs976683 and rs9830510 characteristics in the ischemic stroke meta-analysis cohorts.

	rs976683			rs9830510			
Cohorts	**Minor Allele**	**Major Allele**	**MAF**	**Minor Allele**	**Major Allele**	**MAF**	**Imputed/Genotyped**
ASGC	C	T	0.28	G	A	0.15	Genotyped
BRAINS	C	T	0.24	G	A	0.16	Genotyped
GEOS	C	T	0.25	G	A	0.15	Genotyped
ISGS-SWISS	C	T	0.28	G	A	0.17	Genotyped
VISP	C	T	0.28	G	A	0.17	Genotyped
WTCCC-UK	C	T	0.25	G	A	0.15	Genotyped
WTCCC-Ger	C	T	0.25	G	A	0.16	Genotyped

SNP (Single Nucleotide Polymorphism), MAF (Minor Allele Frequency).

Table VII. Association results for SNP rs976683 with overall ischemic stroke and its subtypes

				Effect	Association		Heterogeneity	
Stroke	**Cohorts**	**N**	**A1/A2**	**direction**	**OR (95% CI)**	**p**	**Q (p)**	**I^2**
All stroke	7	8624	t/c	+--+++-	1.02 (0.97-1.07)	0.52	4.85 (0.56)	0
CE	6	1523	t/c	-+-+++	1.07 (0.97-1.16)	0.17	3.31 (0.65)	0
LVD	6	1639	t/c	--+--+	0.98 (0.89-1.07)	0.60	5.41 (0.37)	7.6
SVD	6	1254	t/c	++-+++	1.07 (0.97-1.17)	0.19	2.92 (0.71)	0

Effect sizes are shown as odds ratios for the % increase or decrease per copy of the risk allele. N (number of individuals) Q (Chi square statistics), I^2 (Index test quantifies extent of variation across studies in a meta-analysis), OR (Odds Ratio), CI (confidence interval), p (probability value), CE (Cardio-embolic stroke), LVD (Large Vessel Disease), SVD (Small Vessel Disease)

Table VIII. Association results for SNP rs9830510 with overall ischemic stroke and its subtypes

				Effect	Association		Heterogeneity	
Stroke	**Cohorts**	**N**	**A1/A2**	**direction**	**OR (95% CI)**	**p**	**Q (p)**	**I^2**
All stroke	7	8624	a/g	---+++-	0.96 (0.90-1.02)	0.54	2.37 (0.88)	0
CE	6	1523	a/g	---+++	1.03 (0.91-1.15)	0.83	4.43 (0.49)	0
LVD	6	1639	a/g	------	0.76 (0.66-0.87)	0.03	1.43 (0.92)	0
SVD	6	1254	a/g	---+-+	1.01 (0.89-1.14)	0.92	5.28 (0.38)	5.4

Effect sizes are shown as odds ratios for the % increase or decrease per copy of the risk allele. N (number of individuals) Q (Chi square statistics), I^2 (Index test quantifies extent of variation across studies in a meta-analysis), OR (Odds Ratio), CI (confidence interval), p (probability value), CE (Cardio-embolic stroke), LVD (Large Vessel Disease), SVD (Small Vessel Disease)

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