

SUPPLEMENTARY INFORMATION

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1. Supplementary Tables

Study	No. Cases AS	No. Cases AIS	No. Cases LAS	No. Cases CES	No. Cases SVS	No. controls	Ethnicity
CHARGE	4,348	3,028		602		80,613	EUR
METASTROKE	10,307	10,307	1,817	1,859	1,349	19,326	EUR
SIGN	7,743	7,743	1,253	2,135	1,534	17,970	EUR
DECODE	5,520	4,483	512	1,346	615	255,213*	EUR
EPIC-CVD	4,347	2,226				7,897	EUR
Young Lacunar DNA	1,403	1,268			1,012	970	EUR
SIFAP	981	981	184	170	104	1,824	EUR
INTERSTROKE EUR	911	826	188	208	243	863	EUR
HVH1	681	577	62	92	175	1,331	EUR
Glasgow	599	599	72	105	137	1,775	EUR
CADISP	555	555	67	211	31	9,259	EUR
Barcelona	520	520	119	215		315	EUR
FINLAND	501	501	99	187	62	1,813	EUR
SAHLSIS	298	298		35	85	596	EUR
MDC	202	202				4,295	EUR
HVH2	124	103		28	39	570	EUR
ICH	1,545					1,481	
Total European	40,585	34,217	4,373	7,193	5,386	406,111	
Biobank Japan	16,256	16,256	1,256	710	4,613	27,294	EAS
HISAYAMA	1,113	1,113	370	137	483	901	EAS
RACE1	1,218	1,218	200	229	192	1,158	SAS
RACE2	1,167	1,167	155	193	122	4,035	SAS
SDS	52	52				1,514	SAS
COMPASS	5,541	5,541				11,664	AFR
SLESS**			102	173	271	868	AFR
SIGN_3**			23	77	78	361	AFR
SIGN_4**			102	118	301	2,022	AFR
INTERSTROKE AFR**			32	46	44	231	AFR
INTERSTROKE ASN	365	222	34	31	134	333	ASN
INTERSTROKE LAT	865	555	41	99	86	692	LAT
TOTAL	67,162	60,341	6,688	9,006	11,710	454,450	

Supplementary Table 1 Overview of studies included in MEGASTROKE. AS, any stroke; AIS, any ischemic stroke; LAS, large artery stroke; CES, cardioembolic stroke; SVS, small vessel stroke. * included differently sized control sets for stroke subtypes. (LAS:146,392 controls, CE:204,570 controls, SVD:192,662 controls) ** subsamples of COMPASS

Supplementary Table 2 Sample overview and genetic information of all studies. Given for each sample are the age distribution, gender distribution and risk factors distribution, if available. Further, information on genotyping platform, technique, imputation parameters and QC parameters are given, if available.

Enclosed electronic excel file

rs_ID	Gene(s)	Phenotype	log(BF)	transethnic Fixed effects	European Fixed effects	Het_pval MANTRA	Het_pval Fixed effects	Het_pval European	Mean oevar_imp transethnic	Mean oevar_imp European
rs880315	CASZ1	AS	8.09489	3.62E-10	6.55E-08	0.068	0.577	0.5623	0.9248	0.9990
rs12037987	WNT2B	AS	6.33614	2.73E-08	9.39E-07	0.135	0.6592	0.3841	0.9126	0.9188
rs12124533	TSPAN2	LAS	6.60016	1.22E-08	6.73E-08	0.148	0.757	0.341	0.9111	0.9560
rs1052053	PMF1- SEMA4A	AS	11.92471	2.70E-14	2.25E-12	0.062	0.6419	0.9224	0.9997	0.9997
rs146390073	RGS7	CES	NA	NA	2.20E-08	NA	NA	0.6137	NA	0.8952
rs12476527	KCNK3	AS	6.47247	6.44E-08	3.71E-04	0.755	0.02834	0.006444	0.8816	0.8730
rs7610618	TM4SF4-TM4SF1	LAS	NA	NA	1.44E-08	NA	NA	0.3887	NA	0.9101
rs13143308	PITX2	CES	45.10357	1.86E-47	5.19E-41	0.491	0.0143	0.02133	0.9955	0.9960
rs34311906	ANK2	AIS	5.67196	1.19E-07	1.07E-08	0.135	0.2377	0.2558	0.8613	0.8477
rs17612742	EDNRA	LAS	9.47422	1.46E-11	1.05E-06	0.138	0.3331	0.4329	0.9274	0.9329
rs6825454	FGA	AIS	7.53002	7.43E-10	9.23E-08	0.08	0.3185	0.4575	0.9531	0.9475
rs11957829	LOC100505841	AIS	6.67074	7.51E-09	7.51E-07	0.096	0.4534	0.9846	0.9266	0.9408
rs6891174	NKX2-5	CES	6.9559	5.82E-09	3.19E-07	0.189	0.5987	0.9462	0.9319	0.9259
rs4959130	FOXF2	AS	7.51576	1.42E-09	1.13E-09	0.107	0.6876	0.8494	0.9243	0.9336
rs16896398	SLC22A7- ZNF318	AS	6.59891	1.30E-08	8.62E-06	0.064	0.2401	0.422	0.9889	0.9920
rs2107595	HDAC9-TWIST1	LAS	12.99407	3.65E-15	1.44E-13	0.307	0.1365	0.02756	0.9084	0.9286
rs42039	CDK6	AIS	6.83974	6.55E-09	2.18E-07	0.106	0.6212	0.4498	0.9701	0.9626
rs7859727	Chr9p21	AS	8.01097	4.22E-10	7.18E-08	0.061	0.5571	0.689	0.9920	0.9912
rs10820405	LINC01492	LAS	4.74007	1.86E-06	4.51E-08	0.503	0.03186	0.6144	0.9412	0.9571
rs635634	ABO	AIS	1.24591	6.93E-03	9.18E-09	0.68	0.01488	0.4505	0.9941	0.9925
rs2295786	SH3PXD2A	AS	8.335	1.80E-10	1.43E-07	0.071	0.9895	0.1098	0.9690	0.9794
rs2005108	MMP12	AIS	6.12069	3.33E-08	1.74E-07	0.13	0.3794	0.3116	0.9610	0.9697
rs7304841	PDE3A	AIS	5.87141	4.93E-08	5.80E-04	0.104	0.2739	0.2258	0.9259	0.9271
rs3184504	SH2B3	AIS	12.04062	2.17E-14	1.23E-14	0.085	0.2964	0.4207	0.9956	0.9952
rs35436	TBX3	AS	6.29274	2.87E-08	3.26E-04	0.215	0.1458	0.07261	0.9437	0.9526
rs9526212	LRCH1	AS	7.97154	5.03E-10	1.78E-08	0.08	0.6197	0.912	0.9490	0.9696
rs4932370	FURIN-FES	AIS	6.05016	2.88E-08	6.32E-07	0.049	0.8489	0.08447	0.9123	0.9214

rs12932445	ZFHX3	CES	15.48565	6.86E-18	6.88E-13	0.118	0.5875	0.09736	0.9442	0.9611
rs12445022	ZCCHC14	AS	8.57641	1.05E-10	1.03E-07	0.062	0.6384	0.2271	0.8970	0.9253
rs11867415	PRPF8	AIS	6.05679	4.81E-08	6.58E-07	0.115	0.5156	0.3308	0.9290	0.9476
rs2229383	ILF3-SLC44A2	AIS	6.02123	4.72E-08	3.71E-07	0.055	0.8613	0.7238	0.9719	0.9691
rs8103309	SMARCA4-LDLR	AS	5.85534	3.40E-08	3.70E-07	0.052	0.442	0.6725	0.8970	0.8982

Supplementary Table 3 Heterogeneity and imputation quality metrics for the MEGASTROKE lead SNPs. Shown are the MANTRA transethnic meta-analysis log(BF), the fixed effects transethnic meta-analysis p-value, and the fixed effects Europeans-only p-value. For both the MANTRA meta-analysis and the two fixed-effects meta-analyses, the heterogeneity p-values are shown. For each SNP, the mean imputation quality (oevar_imp) score for both the overall transethnic sample and the Europeans-only sample are shown. BF, Bayes factor; Het_pval, heterogeneity p-value; oevar_imp, imputation quality.

Supplementary Table 4 Detailed description of the genes at novel stroke loci

Chromosomal location, Lead variant, *Gene(s)*: Description of the genes at the locus.

1p36, rs880315, CASZ1: rs880315 is an intronic variant in *CASZ1*. *CASZ1* encodes Castor Zinc Finger 1, a zinc finger transcription factor, which is regulated by *PRRXL1*.(PMID [26913565](#)) *CASZ1* is required for cardiomyocyte G1-to-S phase progression during mammalian cardiac development (PMID [25953344](#)) and promotes vascular assembly and morphogenesis through the direct regulation of an EGFL7/RhoA-mediated pathway.(PMID [23639441](#)) *CASZ1*-depleted human endothelial cells display marked alterations in adhesion, morphology, and sprouting. *CASZ1* is also implicated in several forms of cancer, including neuroblastoma.(PMID [21252912](#))

1p13, rs12037987, WNT2B: rs12037987 is an intronic variant in *WNT2B*. *WNT2B* encodes Wnt Family Member 2B, a member of the wingless-type MMTV integration site (WNT) family. *WNT2B* is implicated in the survival of intestinal stem cells and gut homeostasis.(PMID [27117411](#)) Elevated TGF- β /Smad3 stimulates the secretion of *WNT2B* which in turn enhances vascular smooth muscle proliferation through β -catenin stabilization.(PMID [26912210](#)) Secretion of *WNT2B* and stabilization of β -catenin upon virus infection negatively regulates expression of *IFNB1*, *IFIT1* and *TNF* in a β -catenin-dependent effector mechanism.(PMID [23785285](#))

1q43, rs146390073, RGS7: rs146390073 is located intronic in *RGS7*. *RGS7* encodes Regulator of G-Protein Signaling 7 which regulates G-protein-coupled receptor signaling cascades. It is highly expressed in neurons where it regulates many physiological processes. RGS7 protein contains several distinct domains and forms obligatory dimers with the atypical G β subunit, G β 5. (PMID [10521509](#)) *RGS7* inhibits signal transduction by increasing the GTPase activity of G protein alpha subunits, thereby driving them into their inactive GDP-bound form.(PMID [10521509](#), [10862767](#)) The *RGS7/GNB5* dimer enhances *GNAO1* GTPase activity.(PMID [10521509](#)) *RGS7* may play a role in synaptic vesicle exocytosis.(PMID [12659861](#)) It modulates the activity of potassium channels that are activated by *GNAO1* in response to muscarinic acetylcholine receptor M2/CHRM2 signaling.(PMID [15897264](#))

2p23, rs12476527, KCNK3: rs12476527 is located in the 5'-untranslated region of *KCNK3*. *KCNK3* encodes Potassium Two Pore Domain Channel Subfamily K Member 3, a member of the superfamily of potassium channel proteins that contain two pore-forming P domains. *KCNK3* is a pH-sensitive potassium channel characterized by the presence of four transmembrane domains and two pore domains per sub-unit.(PMID [11053038](#)) *KCNK3*, an important determinant of background K(+) conductance and membrane potential, is regulated by diacylglycerol (PMID [25420509](#)). The *KCNK3* channel, a nonvoltage-dependent outward rectifier potassium channel, participates in the regulation of plasma membrane resting potential (PMID [16574908](#), [11344164](#), [9113366](#)) in several cell types including human pulmonary artery smooth muscle cells.(PMID [19188660](#)) All pathogenic mutations currently identified in *KCNK3* alter conserved residues, and electrophysiological studies demonstrated the loss of function of the potassium channel. (PMID [23883380](#)) The decreased *KCNK3* activities due to mutations cause depolarization of the resting membrane potential, which can lead to vasoconstriction and pulmonary artery remodeling. *Endothelin-1* has been shown to inhibit the *KCNK3* channel in human pulmonary artery smooth muscle cells via rho kinase phosphorylation.(PMID [21838752](#))

3q25, rs7610618, TM4SF4-TM4SF1: rs7610618 is located in an intergenic region between *TM4SF1* and *TM4SF4*. *TM4SF1* and *TM4SF4* encode Transmembrane 4 L Six Family Member 1 and Transmembrane 4 L Six Family Member 4 respectively. Both are members of the transmembrane 4 superfamily, also known as the tetraspanin family. *TM4SF1* is a paralog of *TM4SF4*. *TM4SF1* is a small plasma membrane glycoprotein that regulates cell motility and proliferation. It is highly expressed in tumor cells and in activated endothelial cells (EC), including cultured ECs and in cells lining the blood vessels supplying several human cancers.(PMID [24986520](#)) *TM4SF4* is a transcriptional target of *Nkx2.2*, which is upregulated during pancreas development.(PMID [21750032](#))

4q25, rs34311906, ANK2: rs34311906 is situated in an intergenic region upstream of *ANK2*. *ANK2* encodes *Ankyrin 2* or *Ankyrin-b*, a member of the ankyrin family of proteins that link the integral membrane proteins to the underlying spectrin-actin cytoskeleton. *ANK2* is ubiquitously expressed, but shows high expression in cardiac muscle. The death/C-terminal domain of *ANK2* determines both the subcellular localization as well as the activity in restoring normal inositol trisphosphate receptor (*ITR*) and ryanodine receptor (*RR*) localization and cardiomyocyte contractility.(PMID [11781319](#)) Further studies have shown that the beta-hairpin loops within the ankyrin repeat domain of *ANK2* are required for the interaction with the *ITR*, and a reduction of *ANK2* in neonatal cardiomyocytes reduces the half-life of the *ITR* receptor by 3-fold and destabilizes its proper localization; all of these effects were rescued by reintroducing *ANK2*.(PMID [14722080](#)) *Ank2* deficient mice display several electrophysiological abnormalities, including bradycardia, variable heart rate, long QT intervals, catecholaminergic polymorphic ventricular tachycardia, syncope, and sudden cardiac death.(PMID [12571597](#)) Effects on ryanodine receptors specifically were also rescued by a potent Ca²⁺/calmodulin-dependent protein kinase II inhibitor, suggesting that inhibition of Ca²⁺/calmodulin-dependent protein kinase II may also be a potential treatment strategy.

4q31, rs17612742, EDNRA: rs17612742 is located intronic in *EDNRA*. *EDNRA* encodes Endothelin Receptor Type A, the receptor for endothelin-1, a peptide that plays a role in potent and long-lasting vasoconstriction.(PMID [8581282](#)) Signaling via both *EDNRA* and *EDNRB* in smooth muscle cells has potent vasoconstrictive effects. *EDNRA* knockout mice share defects of the cardiac outflow tract and large vessels.(PMID [2407710](#)) It has been shown that *EDNRA*-dependent mast cell activation can diminish both endothelin-1 levels and endothelin-1-induced pathology in vivo.(PMID [15543132](#))

4q31, rs6825454, FGA: rs6825454 is located in an intergenic region between *FGA* and *FGB*. *FGA*, *FGB* and *FGG* encode Fibrinogen Alpha, Beta and Gamma Chain, respectively. Fibrinogen is a hexameric protein composed of two copies of these three peptide chains. The latter are expressed and secreted as an assembled hexamer ($\alpha\alpha\beta\beta\gamma$)₂ from hepatocytes. Next to its well-described role in clotting, physiological functions of fibrinogen also include platelet crosslinking as part of primary haemostasis, as contribution to blood viscosity, as a binding surface for a number of proteins involved in various aspects of vascular physiology (PMID [11090059](#), [9516457](#)) and as an extracellular matrix component.(PMID [6752288](#), [2613766](#)) *IL-6* stimulates a coordinated increase in fibrinogen mRNA and protein expression via *STAT3* activation (phosphorylation) and interaction with *IL-6*-responsive elements. This is potentiated by *IL-6*-induced miR-18a that targets *PIAS3*, a negative regulator of *STAT3*.(PMID [7592638](#))

5q23, rs11957829, LOC100505841: rs11957829 is located intronic in *LOC100505841*. *LOC100505841* is annotated as Zinc Finger Protein 474-like due to its vicinity to *ZNF474*. The upstream *ZNF474* gene encodes Zinc Finger Protein 474, which due to its domain structure is likely involved in transcription. *ZNF474* is ubiquitously expressed, but nothing is known about its function.

5q35, rs6891174, NKX2-5: rs6891174 is located in an intergenic region between *BNIP1* and *NKX2-5*. *NKX2-5* encodes NK2 Homeobox 5, a transcription factor involved in cardiac development. The in vitro characterization of *NKX2-5* as a master regulator of the transcriptional activity of cardiac-specific genes like Natriuretic Peptide A (*NPPA*), and the early and broad expression of the gene in the heart suggests a role in cardiogenesis.(PMID [16510504](#)) This is further supported by a *NKX2-5*^{-/-} knock-out mouse model, which shows abnormal heart morphogenesis, growth retardation and embryonic lethality at embryonic stage 10.5.(PMID [7628699](#)) Additional studies have shown a regulatory role of this gene in controlling cardiac cell specification, and chamber formation.(PMID [17604724](#), [21357845](#))

6p21, rs16896398, SLC22A7-ZNF318: rs16896398 is located in an intergenic region upstream of *SLC22A7*.

SLC22A7 encodes Solute Carrier Family 22 Member 7, which belongs to the solute carrier group of membrane transport proteins that mediate cellular uptake of numerous organic ions, including xenobiotics and endogenous substrates. *SLC22A7* expression appears to be comparable in human kidney and liver and it is a facilitative transporter for cGMP and other guanine nucleotides.(PMID [18216183](#))

ZNF318 encodes zinc finger protein 318, a nuclear protein with two U1-type zinc fingers found in RNA-binding proteins. *ZNF318* is essential for expression of Immunglobulin D, the alternatively spliced Immunglobulin H product made by mature B lymphocytes.(PMID [24616512](#))

7q21, rs42039, CDK6: rs42039 is located in the 3'-untranslated region of *CDK6*. *CDK6* encodes Cell division protein kinase 6. It is regulated by cyclins, more specifically by Cyclin D proteins and cyclin-dependent kinase inhibitor proteins. *CDK6* is a catalytic subunit of the protein kinase complex important for the G1 phase progression and G1/S transition of the cell cycle. Another important component of this complex is the activating sub-unit *cyclin D*.(PMID [23861057](#)) In mutant knockout mice of *CDK6*, the hematopoietic function is impaired with otherwise organism normal development. This might hint at additional roles of *CDK6* in the development of blood components.(PMID [15315761](#)) There are additional functions of *CDK6* not associated with its kinase activity. For example, *CDK6* is involved in the differentiation of T cells, acting as an inhibitor of differentiation. Even though *CDK6* and *CDK4* share 71% amino acid identity, this role in differentiation is unique to *CDK6*.(PMID [26500059](#)) *CDK6* has further been found to be important in the development of other cultured cells, including astrocytes.(PMID [12861051](#))

9p21, rs7859727, Chr9p21: rs7859727 is located in a non-coding RNA *CDKN2B-AS1*, also known as ANRIL. Multiple linear as well as circular isoforms of ANRIL have been identified. It has been proposed that ANRIL influences gene expression in cis by recruiting chromatin-modifying multiprotein complexes, such as Polycomb repressive complexes (PRCs), to the Chr9p21 region. ANRIL associates with the Polycomb-group protein *CBX7*, which is part of the *PRC1* complex, and together they repress expression of *p16INK4*.(PMID [20541999](#)) Modulation of ANRIL expression leads to the epigenetic regulation of target genes expression in both cis (PMID [21151178](#)) and trans. (PMID [23861667](#), [22382030](#), [20664976](#)) Trans-regulation has recently been shown to be dependent on an Alu-DEIN motif (PMID [23861667](#)) which marks the promoters of ANRIL target genes and is mirrored in ANRIL RNA transcripts.

9q31, rs10820405, LINC01492: rs10820405 is located in a non-coding RNA *LINC01492*. The status of this long intergenic non-protein coding RNA is verified, but there is nothing known about its function.

10q24, rs2295786, SH3PXD2A: rs2295786 is located intergenic between *SH3PXD2A* and *OBCF1*. *SH3PXD2A* encodes the SH3 and PX domain-containing protein 2A or Adapter protein *TKS5*, and has been shown to play an essential role in various malignancies including schwannomas.(PMID [27723760](#)) *TKS5* interacts with Src tyrosine kinase to promote tumor growth and the formation of invadopodia resulting in degradation of extracellular matrix and invasion of cancer cells into surrounding tissue in malignancies including glioma.(PMID [26446840](#), [27802184](#), [27789576](#)) *SH3PXD2A* has further been implicated in axonal guidance by growth cone invadosomes (PMID [25564649](#)), neural crest migration (PMID [25259869](#)), macrophage invasion (PMID [22021214](#)), and the migration of microglia.(PMID [22873355](#))

12p12, rs7304841, PDE3A: rs7304841 is located in an intron of *PDE3A*. *PDE3A* encodes Phosphodiesterase 3A, a member of the cGMP-inhibited cyclic nucleotide phosphodiesterase family. *PDE3A* mRNA is enriched in blood vessels, heart, megakaryocytes, and oocytes.(PMID [7706458](#)) *PDE3A* is activated by *PKC* phosphorylation on Ser(312), Ser(428), Ser(438), Ser(465), and Ser(492).(PMID [19261611](#)) *PDE3A* is a component of the thrombin signaling pathway in platelets. Thrombin raises *PDE3A* activity through phosphorylation/activation of *PDE3A* and activated *PDE3A* participates in regulating intracellular cAMP contents through acceleration of cAMP hydrolysis.(PMID [17392505](#)) In addition to being subject to phosphorylation-induced activation, *PDE3A* is also directly inhibited by cGMP-mediated competition for cAMP binding to the active site. This effect of cGMP can represent a significant mode of regulation of *PDE3A* in cells expressing this enzyme.(PMID [10605731](#)) For example, incubation of *PDE3A*-expressing cells with guanylyl cyclase-activating organic nitrates, nitric oxide donors, or natriuretic peptides, results in a significant increase in both cGMP and cAMP and a synergistic increase in cAMP when these agents are combined with activators of adenylyl cyclases.(PMID [1964912](#), [1851703](#))

12q24, rs35436, TBX3: rs35436 is located in an intergenic region upstream of *TBX3*. *TBX3* encodes T-box transcription factor 3. *TBX3* is a transcriptional repressor and is thought to play a role in the

anterior/posterior axis of the tetrapod forelimb. Recently, heart and conduction system defects have also been described in mice and humans with abnormal *Tbx3* (mice) and *TBX3* (humans) function.(PMID [18467625](#)) Germline deletion of *Tbx3* in mice results in embryonic lethality with heart, limb, and mammary defects.(PMID [22203979](#),[12668638](#)) *Tbx3* also regulates pluripotency and cell fate in early development.(PMID [20139965](#),[24319661](#)) *TBX3* transcriptional repression controls expression of cell proliferation and senescence factors.(PMID [11748239](#)) These studies highlight the important pleiotropic molecular functions of *TBX3*.

13q14, rs9526212, LRCH1: rs9526212 is located intronic in *LRCH1*. *LRCH1* encodes Leucine Rich Repeats And Calponin Homology Domain Containing 1. *LRCH1* competes with Cdc42 for interaction with DOCK8 and restrains T cell migration.(PMID [28028151](#)) In response to chemokine stimulation, *PKCα* phosphorylates *DOCK8* at its three serine sites, promoting *DOCK8* separation from *LRCH1* and translocation to the leading edge to guide T cell migration.

15q26, rs4932370, FURIN-FES: rs4932370 is located in an intergenic region upstream of *FURIN*. *FURIN* encodes the Furin protein. *FURIN* is the most studied mammalian proprotein convertase. This ubiquitously expressed enzyme is located mainly in the trans-Golgi network (TGN) of the secretory pathway. In addition, *FURIN* cycles between TGN and the cell surface via the endosomal system, and a proportion of it is secreted to the extracellular space.(PMID [12360192](#)) Because *FURIN* is widely expressed, its activity regulates the maturation of numerous precursor proteins. Its substrates include various growth factors and their receptors, enzymes, hormones, cytokines, serum proteins, as well as extracellular matrix proteins. In addition to *FURIN*'s crucial function in the maintenance of cellular homeostasis, it is also involved in the pathogenesis of several diseases. For example, increased *FURIN* levels are associated with aggressive cancers and metastatic activity, and it is highly expressed in chronically inflamed tissues in rheumatoid arthritis (RA) and atherosclerosis.(PMID [21889147](#), [22605541](#))

FES encodes FES Proto-Oncogene, Tyrosine Kinase. It has tyrosine-specific protein kinase activity and this activity is required for maintenance of cellular transformation. Based on its chromosomal location *FES* has been linked to a specific translocation event identified in patients with acute promyelocytic leukemia but it is also involved in normal hematopoiesis as well as growth factor and cytokine receptor signaling.(PMID [12871378](#), [15003822](#)) *FES* transduces inductive signals for terminal macrophage and granulocyte differentiation, and this biological activity is mediated through the activation of lineage-specific transcription factors.(PMID [15003822](#))

17p13, rs11867415, PRPF8: rs11867415 is located intronic in *PRPF8*. *PRPF8* encodes Pre-mRNA Processing Factor 8. The large ~280-kDa U5 snRNP protein is central to the dynamics of spliceosome assembly.(PMID [15840809](#)) It not only establishes direct contacts in the RNA substrate with the 5' splice site, the branch point and the polypyrimidine tract in the 3' splice site, but also engages the U5 and U6 snRNAs.(PMID [26392272](#), [24968230](#)) Mutations in human *PRPF8* that disrupt these interactions, affecting spliceosome assembly and function, are found in autosomal dominant retinitis pigmentosa, a variable-onset hereditary disease that results in a progressively decreasing field of vision due to degeneration of rods and cones. Loss-of-function mutants of human *PRPF8* delay the assembly of spliceosome components on pre-mRNA, and impair the splicing of 9 % of tested genes.(PMID [11468273](#))

19p13, rs2229383, ILF3-SLC44A2: rs2229383 is an exonic, synonymous variant in *ILF3*. *ILF3* encodes Interleukin Enhancer Binding Factor 3, which regulates gene expression and stabilizes mRNAs through interactions with various other molecules. *ILF3* forms a heterodimer with ILF2, which is required for T-cell expression of interleukin 2 and interleukin 12.(PMID [20051514](#), [15817156](#)) The complex is known to negatively regulate microRNA processing (PMID [19398578](#)) and in particular myogenic microRNA processing.(PMID [25918244](#)) The upstream *SLC44A2* gene encodes Solute Carrier Family 44 Member 2 which is expressed in human brain microvascular endothelial cells.(PMID [26746385](#)) Isoform 1 of this protein displays choline transporter activity. *SLC44A2* harbors the neutrophil alloantigen HNA-3a (5b) in its first extracellular loop (R154Q).(PMID [20040764](#))

19p13, rs8103309, SMARCA4-LDLR: rs8103309 is located intergenic between *SMARCA4* and *LDLR*. *SMARCA4* encodes SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin,

Subfamily A, Member 4. The encoded protein is part of the large ATP-dependent chromatin remodeling complex SNF/SWI, which is required for transcriptional activation of genes normally repressed by chromatin. *SMARCA4* is a target gene of the *BACH1* transcription factor according to ChIP-seq analysis in HEK 293 cells.(PMID [21555518](#)) It has been suggested that *SMARCA4* and *SMARCA2* integrate various proinflammatory cues into cell adhesion molecule transactivation in endothelial injury.(PMID [23963727](#)) Additionally, the interaction of *RUNX1* with *SMARCA4* and *INI1* controls hematopoietic-specific gene expression.(PMID [20506188](#))

LDLR encodes the low density lipoprotein receptor. LDL is cleared from plasma by binding to the cell-surface *LDLR* and is internalized by *LDLR*-mediated endocytosis.(PMID [25222343](#)) After internalization, the receptors dissociate from their ligands upon exposure to lower pH in endosomes. (PMID [6299572](#)) *PCSK9* has been shown to play a major role in regulating plasma LDL cholesterol levels through its ability to mediate intracellular degradation of the LDLR.

Lead SNP	Locus	Phenotype	p-value in Europeans-only analysis	p-value in East Asians-only analysis
rs10820405	LINC01492	LAS	4.51E-08	0.263
rs146390073	RGS7	CES	2.20E-08	NA*
rs7610618	TM4SF4-TM4SF1	LAS	1.44E-08	0.3456
rs635634	ABO	AIS	9.18E-09	0.9904
rs34311906	ANK2	AIS	1.07E-08	0.4078
rs9526212	LRCH1	AS	1.78E-08	0.416

Supplementary Table 5 Population specific associations with stroke. Shown are loci reaching genome-wide significant association ($p < 5.0 \times 10^{-8}$) in the Europeans-only meta-analysis while showing no association in the East Asian ancestry meta-analysis ($p > 0.05$ or $MAF < 0.01$). * $MAF < 0.01$

Supplementary Table 6 Variance explained by the 32 lead SNPs. Shown are the lead SNPs of the 32 risk loci for stroke and the phenotypic variance explained as estimated by the method of So et al. Variances are given for the Europeans-only and the East Asian-only meta-analysis. If a SNP was not available in the analysis, variance explained was set to zero.

Enclosed electronic excel file

Supplementary Table 7 Results from the Gene-based tests using VEGAS2. Data were analyzed for each ethnicity and a meta-analysis was calculated using Stouffer's Z. Genome-wide results are displayed in bold ($p < 2.02 \times 10^{-6}$ for Bonferroni correction for the number of genes).

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rsID	Chr	Gene(s)	Location relative to gene	Risk allele/ reference allele	Risk allele frequency, %	Phenotype*	Analysis	OR	95% CI	P-value	log10 (BF)
rs6695915	1p34	PTPRF	Intronic	A/G	86	AS	TRANS	1.07	1.04-1.10	4.25E-07	4.94§
rs638704	1q24	PRRX1	Intergenic	C/T	43	CES	TRANS	1.09	1.06-1.13	1.47E-07	5.41
rs188186531	2q33	ICA1L-WDR12	Intronic	A/T	89	SVS	TRANS	1.21	1.12-1.30	3.69E-07	5.11
rs10017904	4q26	CAMK2D	Intronic	A/G	14	SVS	TRANS	1.17	1.10-1.25	7.22E-07	4.80§
rs4444878	4q35	F11	Intronic	A/C	39	CES	TRANS	1.10	1.06-1.14	5.17E-08	5.80
rs762624	6p21	CDKN1A	Intronic	A/C	63	AIS	TRANS	1.05	1.03-1.07	2.36E-07	5.30
rs35276016	6p22	C6orf62	Intergenic	T/C	8	AS	EUR	1.10	1.06-1.14	1.30E-07	5.56
rs56393506	6q25	LPA	Intergenic	T/C	16	LAS	TRANS	1.17	1.10-1.24	1.33E-07	5.57
rs4727833	7q31	CAV1/2	3'-UTR	G/C	51	CES	TRANS	1.09	1.06-1.13	2.45E-07	5.28
rs16939239	8q21	Chr8q21	Intergenic	A/G	12	CES	TRANS	1.15	1.09-1.22	4.08E-07	5.24
rs11596587	10q22	HK1	Intronic	T/C	10	CES	TRANS	1.22	1.14-1.31	7.58E-08	5.69
rs74154533	10q24	NEURL1	Intronic	G/A	18	CES	TRANS	1.12	1.07-1.17	6.08E-07	5.27
rs60401382	10q26	HTRA1	Intronic	C/T	70	AS	TRANS	1.05	1.03-1.07	6.76E-08	5.88
rs360139	11p15	SWAP70	Downstream	G/A	56	AIS	TRANS	1.05	1.03-1.07	1.57E-07	5.41
rs1564454	13q32	FARP1	Intronic	G/A	42	LAS	TRANS	1.11	1.07-1.16	1.22E-07	5.71
rs9515201	13q34	COL4A2	Intronic	A/C	29	SVS	TRANS	1.11	1.07-1.16	1.05E-07	5.33
rs9521634	13q34	COL4A1	Intronic	C/T	34	AS	TRANS	1.04	1.03-1.06	1.42E-07	5.47
rs339800	13q21	DACH1	Intergenic	T/C	28	AS	TRANS	1.06	1.04-1.08	7.11E-08	5.87
rs12442374	15q21	NEDD4	Intergenic	G/C	14	AS	TRANS	1.06	1.04-1.09	3.70E-07	5.15
rs8028726	15q26	Chr15q26	Intergenic	T/G	44	AIS	TRANS	1.04	1.03-1.06	4.37E-07	5.15
rs2632512	17q22	RNF43	Intronic	T/C	20	AS	TRANS	1.06	1.04-1.08	2.21E-07	5.36

Supplementary Table 8 Subthreshold loci reaching the more liberal threshold for suggestive evidence of association in the transethnic meta-analysis (MANTRA log(BF) > 5). * denotes phenotype reaching the lowest p-value in fixed effects meta-analyses. § $p < 5 \times 10^{-6}$ in the fixed effects analysis. Chr, chromosome; TRANS, MANTRA transethnic meta-analysis; EUR, Europeans-only fixed-effects meta-analysis; OR, odds ratio; CI, confidence interval; BF, Bayes factor; NA, not assessed because of low allele frequency or poor imputation quality in non-European ethnicities.

		Transethnic meta-analysis										Europeans only meta-analysis				
SNP	locus	AS		AIS		LAS		CES		SVS		AS	AIS	LAS	CES	SVS
		MANTRA (BF)	Fixed effects p- value	MANTRA (BF)	Fixed effects p- value	MANTRA (BF)	Fixed effects p- value	MANTRA (BF)	Fixed effects p- value	MANTRA (BF)	Fixed effects p- value	p-value	p-value	p-value	p-value	p-value
rs880315	CASZ1	8.09489	3.62E-10	6.86767	5.51E-09	-0.42721	4.18E-01	0.48014	1.64E-02	4.30326	2.59E-06	6.55E-08	9.99E-07	9.70E-01	1.07E-01	1.03E-04
rs12037987	WNT2B	6.33614	2.73E-08	4.47639	2.16E-06	-0.42041	5.67E-01	1.402	3.45E-03	1.22482	5.13E-03	9.39E-07	1.52E-04	7.52E-01	2.68E-02	5.48E-02
rs12124533	TSPAN2	-0.23427	1.73E-01	-0.12896	9.77E-02	6.60016	1.22E-08	-0.39256	3.28E-01	-0.19473	2.94E-01	1.88E-01	9.75E-02	6.73E-08	3.27E-01	8.17E-01
rs1052053	PMF1 -SEMA4A	11.92471	2.70E-14	9.02067	4.48E-11	1.41473	2.97E-03	2.74953	1.22E-04	4.54696	1.17E-06	2.25E-12	5.26E-09	1.24E-02	6.69E-04	2.67E-04
rs146390073	RGS7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	9.68E-05	9.18E-05	4.22E-03	2.20E-08	4.76E-01
rs12476527	KCNK3	6.47247	6.44E-08	4.96502	1.30E-06	0.14805	6.63E-02	-0.22283	2.40E-01	2.7522	1.71E-04	3.71E-04	2.96E-03	3.35E-01	4.75E-01	1.49E-02
rs7610618	TM4SF4-TM4SF1	-0.5132	4.09E-01	-0.15424	3.02E-01	NA	NA	-0.61247	1.79E-01	0.24181	8.57E-02	1.88E-01	6.62E-02	1.44E-08	8.35E-01	4.63E-02
rs13143308	PITX2	12.72695	1.69E-15	13.41447	1.11E-15	-1.19688	9.89E-01	45.10357	1.86E-47	-0.53951	5.37E-01	1.61E-13	4.88E-14	5.34E-01	5.19E-41	9.96E-01
rs34311906	ANK2	4.82127	9.66E-07	5.67196	1.19E-07	0.55937	2.61E-02	0.61442	3.59E-02	0.59037	1.89E-02	3.64E-07	1.07E-08	5.37E-03	7.13E-03	2.94E-02
rs17612742	EDNRA	0.96463	9.26E-03	1.80238	1.88E-04	9.47422	1.46E-11	-0.55219	9.52E-01	-0.3206	2.01E-01	4.59E-01	3.70E-02	1.05E-06	7.71E-01	3.70E-01
rs6825454	FGA	7.10875	2.62E-09	7.53002	7.43E-10	2.59115	1.61E-04	3.10296	3.11E-05	-0.25554	3.04E-01	1.78E-07	9.23E-08	8.48E-04	7.32E-05	9.83E-01
rs11957829	LOC100505841	6.47058	1.62E-08	6.67074	7.51E-09	-0.16806	2.56E-01	-0.60635	8.23E-01	5.1146	3.92E-07	1.51E-06	7.51E-07	6.99E-01	8.16E-01	1.46E-04
rs6891174	NKX2-5	0.2037	2.00E-02	0.8818	1.33E-02	0.21853	7.98E-02	6.9559	5.82E-09	-0.32097	4.46E-01	8.16E-02	5.81E-02	7.36E-02	3.19E-07	2.34E-01
rs4959130	FOXF2	7.51576	1.42E-09	7.31532	2.83E-09	0.06236	7.40E-02	0.58771	3.56E-02	NA	NA	1.13E-09	1.87E-09	9.18E-02	3.16E-02	3.05E-06
rs16896398	SLC22A7-ZNF318	6.59891	1.30E-08	4.16814	2.42E-06	0.05632	6.95E-02	1.31094	5.10E-03	1.06055	1.18E-02	8.62E-06	7.17E-04	7.94E-01	3.95E-03	5.94E-01
rs2107595	HDAC9-TWIST1	11.72902	4.86E-14	11.58508	9.25E-14	12.99407	3.65E-15	-0.41059	3.12E-01	0.5171	2.46E-02	3.59E-11	2.33E-11	1.44E-13	9.86E-02	6.63E-02
rs42039	CDK6	6.84288	7.32E-09	6.83974	6.55E-09	0.26155	3.97E-02	1.24424	5.46E-03	0.5482	2.91E-02	1.65E-07	2.18E-07	1.10E-01	2.16E-02	2.22E-02
rs7859727	Chr9p21	8.01097	4.22E-10	7.55562	1.05E-09	3.03657	4.46E-05	-0.34512	4.21E-01	1.89019	9.91E-04	7.18E-08	1.76E-07	6.42E-05	6.07E-01	2.32E-02
rs10820405	LINC01492	-0.08706	1.99E-01	-0.07438	1.82E-01	4.74007	1.86E-06	-0.40161	3.21E-01	-1.05236	7.31E-01	1.00E-01	9.28E-02	4.51E-08	1.53E-01	8.69E-01
rs635634	ABO	4.23964	4.40E-06	4.98759	1.79E-06	1.24591	6.93E-03	4.98822	6.21E-07	-0.40477	9.12E-01	6.03E-08	9.18E-09	3.90E-04	3.31E-07	4.30E-01
rs2295786	SH3PXD2A	8.335	1.80E-10	5.35464	2.00E-07	0.82757	5.06E-03	1.08368	6.78E-03	4.14845	4.18E-06	1.43E-07	8.19E-05	2.72E-02	4.97E-03	2.51E-03
rs2005108	MMP12	5.92423	6.43E-08	6.12069	3.33E-08	5.38734	1.69E-07	0.99334	7.91E-03	NA	NA	3.37E-07	1.74E-07	1.61E-06	5.26E-03	7.29E-01
rs72983521	MMP12 *	2.72415	1.17E-04	3.11816	3.96E-05	6.05514	3.38E-08	-0.2067	2.46E-01	NA	NA	6.42E-05	1.72E-05	4.82E-08	1.96E-01	2.73E-01
rs7304841	PDE3A	5.45988	1.60E-07	5.87141	4.93E-08	0.65851	1.96E-02	0.59629	3.43E-02	0.90914	8.42E-03	1.40E-03	5.80E-04	8.78E-01	1.36E-01	3.78E-01

rs3184504	SH2B3	9.60311	8.63E-12	12.04062	2.17E-14	3.80111	4.17E-06	1.86958	1.24E-03	3.98372	6.36E-06	5.89E-12	1.23E-14	3.72E-05	2.46E-03	1.78E-05
rs35436	TBX3	6.29274	2.87E-08	6.05786	3.21E-08	0.2817	6.14E-02	1.75669	1.36E-03	2.49468	2.44E-04	3.26E-04	4.85E-04	1.70E-01	1.82E-02	7.55E-02
rs9526212	LRCH1	7.97154	5.03E-10	7.7099	9.19E-10	2.08625	7.67E-04	0.23922	8.08E-02	-0.01014	5.09E-02	1.78E-08	3.56E-08	7.31E-04	6.83E-02	6.13E-02
rs4932370	FURIN-FES	5.14661	3.12E-07	6.05016	2.88E-08	2.19732	3.36E-04	1.41818	4.07E-03	-0.43993	3.32E-01	1.15E-05	6.32E-07	2.97E-04	2.32E-03	4.46E-01
rs12932445	ZFHX3	5.27628	2.23E-07	4.49034	1.77E-06	0.67441	2.26E-02	15.48565	6.86E-18	-0.25885	2.17E-01	4.99E-06	4.67E-05	1.46E-02	6.88E-13	9.88E-01
rs12445022	ZCCHC14	8.57641	1.05E-10	8.49181	1.28E-10	1.0356	8.61E-03	-1.54037	9.82E-01	6.48023	2.55E-09	1.03E-07	1.81E-07	1.17E-02	9.92E-01	9.26E-08
rs11867415	PRPF8	3.91513	4.50E-06	6.05679	4.81E-08	1.24755	4.77E-03	0.12259	1.00E-01	-0.26081	2.26E-02	1.75E-04	6.58E-07	1.87E-02	5.68E-02	3.01E-01
rs2229383	ILF3-SLC44A2	5.47686	1.38E-07	6.02123	4.72E-08	2.25928	4.70E-04	1.78543	8.50E-04	-0.26099	3.51E-01	8.67E-07	3.71E-07	3.40E-03	9.26E-03	7.98E-01
rs8103309	SMARCA4-LDLR	5.85534	3.40E-08	5.76797	8.35E-08	2.75608	8.53E-05	1.52959	2.64E-03	-0.0932	2.11E-01	3.70E-07	1.07E-06	5.74E-04	1.27E-03	8.33E-01

Supplementary Table 9 Association results for the 32 genome-wide significant loci in AS, AIS and AIS subtypes. Displayed are the MANTRA log(Bayes' factor. BF) and fixed effects p-values from the transethnic meta-analysis and the Europeans-only meta-analysis. Associations reaching genome-wide significance (BF > 6 and p-values <5.0 x 10⁻⁸) are shown in bold. p-values <5.0 x 10⁻² are shown in blue.* the lead SNP of the MMP12 locus in AIS and LAS are in LD (r²=0.54).

Chr	Locus	Position of segment	No. of SNPs in segment	Posterior Probability			
				Model 1	Model 1	Model 3	Model 4
LAS/SVS 12q24	SH2B3	110,336,875-113,261,104	3,589	6.87E-04	6.02E-04	0.969087	0.00143664
LAS/CES 9q34	ABO	135,298,917-137,027,547	5,074	2.15E-04	1.97E-04	0.995321	0.00273861

Supplementary Table 10 Shared genetic influences of individual loci on ischemic stroke subtypes. Shown are overlapping signals for LAS/SVS and LAS/CES with a posterior probability > 0.9 for model 3, pointing to a shared genetic signal at the specified genomic segment. gwas-pw estimates the probability that a given genomic region contains a genetic variant that influences the first trait (model 1), contains a genetic variant that influences the second trait (model 2), contains a genetic variant that influences both traits (model 3), or contains both a genetic variant that influences the first trait and a separate genetic variant that influences the second trait (model 4).

Supplementary Table 11 Results of the conditional analysis (GCTA-COJO) in the European sample. Shown are the 2-SNP or 3-SNP solutions for each lead SNP after conditioning on the lead SNP in Europeans. P-values of SNP2 and SNP3 were considered significant at $p < 5E-8$. SVS is omitted because there were no genome-wide significant signals to investigate.

Enclosed electronic excel file

Study	Trait	Main manuscript Reference	Sample size	Data publicly available
IGEN-BP	SBP, DBP, HTN, PPP, MAP	24	320,251	
ENGAGE	LDL, HDL, TG	25	62,166	x
DIAGRAM	T2D	26	34,840 / 114,981	x
CHARGE_cIMT	cIMT, PLQ	27	31,211	
CHARGE WMH	WMH	28	21,079	
AFGen	AF	29	6,707 / 52,426	
INVENT	VTE	30	7,507 / 52,632	
CARDIoGRAMplusC4D	CAD	31	60,081 / 123,504	x

Supplementary Table 12 Overview of studies with available summary statistics from related vascular traits used for the look-ups and LD score regression analyses. Data were obtained from the respective consortia or downloaded from the following URLs: for blood lipids: http://diagram-consortium.org/2015_ENGAGE_1KG/; for T2D: <http://diagram-consortium.org/downloads.html>; Data on coronary artery disease have been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from www.CARDIOGRAMPLUSC4D.ORG.

Supplementary Table 13 Results from look-ups of the 32 genome-wide significant loci for stroke in published GWAS data from related phenotypes. Column D specifies the index SNPs of the non-stroke phenotype or SNPs in high LD with the index SNP ($r^2 > 0.9$) with the lowest p-value in the respective non-stroke phenotype. Index SNPs or proxy SNPs reaching a p-value $p < 1.30 \times 10^{-4}$ ($0.05/32$ loci/ 12 related vascular traits) in the respective related phenotype are shown. Index SNPs and proxy SNPs reaching genome-wide significance are marked by an asterisk in column G. Column F specifies the r^2 between the index SNP and the lead SNP in stroke.

Enclosed electronic excel file

Phenotype 1	Phenotype 2	Number of SNPs	beta	SE	p-value
Venous Thrombo-embolism	AS	9	0.06	0.01	3.10E-05
	AIS	9	0.07	0.01	1.46E-06
	LAS	9	0.17	0.04	2.37E-06
	CES	9	0.16	0.03	5.54E-08
	SVS	9	-0.04	0.03	2.15E-01
Diastolic Blood Pressure	AS	41	0.05	0.00	3.60E-26
	AIS	41	0.06	0.01	2.44E-27
	LAS	41	0.07	0.01	6.02E-07
	CES	41	0.05	0.01	2.31E-06
	SVS	41	0.05	0.01	1.50E-04
Systolic Blood Pressure	AS	37	0.04	0.00	2.38E-30
	AIS	37	0.04	0.00	1.31E-31
	LAS	37	0.05	0.01	5.11E-09
	CES	37	0.03	0.01	2.37E-06
	SVS	37	0.04	0.01	5.50E-07
Mean Arterial Pressure	AS	30	0.06	0.01	1.54E-22
	AIS	30	0.06	0.01	9.30E-23
	LAS	30	0.10	0.02	1.95E-10
	CES	30	0.04	0.01	4.84E-04
	SVS	30	0.06	0.01	1.59E-05
Pulse Pressure	AS	17	0.06	0.01	7.15E-12
	AIS	17	0.06	0.01	1.21E-10
	LAS	17	0.12	0.02	2.02E-08
	CES	17	0.04	0.02	1.49E-02
	SVS	17	0.05	0.02	7.81E-03
Hypertension	AS	13	0.17	0.03	1.71E-08
	AIS	13	0.15	0.03	2.18E-06
	LAS	13	0.13	0.08	9.68E-02
	CES	13	0.17	0.06	5.79E-03
	SVS	13	0.08	0.07	2.60E-01
HDL levels	AS	71	-0.05	0.02	6.86E-02
	AIS	71	-0.05	0.03	4.56E-02
	LAS	71	-0.15	0.07	2.79E-02
	CES	71	-0.03	0.05	6.34E-01
	SVS	71	-0.19	0.06	2.10E-03
LDL levels	AS	53	0.05	0.02	5.90E-02
	AIS	53	0.04	0.03	1.52E-01
	LAS	53	0.19	0.07	5.69E-03
	CES	53	-0.06	0.05	2.27E-01
	SVS	53	0.04	0.06	5.07E-01
Triglyceride levels	AS	38	0.01	0.03	7.44E-01
	AIS	38	0.01	0.03	7.67E-01
	LAS	38	0.08	0.08	3.29E-01
	CES	38	-0.09	0.07	1.75E-01
	SVS	38	0.18	0.08	1.79E-02
T2 Diabetes	AS	38	0.08	0.02	1.11E-06
	AIS	38	0.09	0.02	2.07E-07
	LAS	38	0.22	0.04	1.54E-07
	CES	38	0.04	0.03	2.21E-01
	SVS	38	0.17	0.04	2.09E-05

Coronary Artery Disease	AS	58	0.16	0.02	9.78E-20
	AIS	58	0.17	0.02	4.04E-19
	LAS	58	0.37	0.05	8.51E-16
	CES	58	0.13	0.04	6.22E-04
	SVS	58	0.08	0.04	7.62E-02

Supplementary Table 14 Results of the weighted genetic risk score (wGRS) analysis in related vascular traits. For each of the related traits, a wGRS was constructed using the indicated number of SNPs and tested for association in the respective stroke phenotype. Given are the effect size beta, the standard error and the p-value. P-values below $p < 5.6 \times 10^{-3}$ correcting for 9 independent phenotypes are shown in bold.

Supplementary Table 15 MR-Egger regression and comparison with Inverse-Variance Weighted (IVW) estimates, for vascular wGRS showing a significant association with stroke risk. IVW estimates are derived from a fixed effects analysis using the GTX software (**Methods**); for the intercept of the MR-Egger analysis (Egger_intercept, **Methods**) we used a significance threshold of $P < 0.05$. effect estimates are given per unit increase in the wGRS; CI: confidence interval; OR: odds ratio

*The MR-Egger intercept estimate was nominally significant ($p = 0.015$) only for the association between the SBP wGRS and AS, and this was no longer the case after removing 6 of 37 SNPs that appeared as outliers on the leave-one-out plot (Methods), leading to causal estimates in broad agreement across regression techniques, with larger standard errors using the MR-Egger method as is typically the case (www.biorxiv.org/content/biorxiv/early/2017/07/05/159442.full.pdf and PMID: 26050253, 28527048). The causal estimates obtained by the weighted median approach (PMID: 27061298) are also in broad agreement with those from the IVW and the MR-Egger ($\beta \pm$ standard error: 0.032 ± 0.005 , OR [95%CI]: 1.03 [1.02-1.04], $p = 9.48 \times 10^{-10}$)

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Phenotype 1	Phenotype 2	European ancestry			East Asian ancestry		
		R(g)	(SE_R(g))	p-value	R(g)	(SE_R(g))	p-value
Venous Thrombo-embolism	AS	0.2815	0.1308	3.13E-02	NA	NA	NA
	AIS	0.2141	0.1253	8.77E-02	NA	NA	NA
	LAS	-0.0934	0.4442	8.34E-01	NA	NA	NA
	CES	0.1875	0.1615	2.46E-01	NA	NA	NA
	SVS	-0.1232	0.2479	6.19E-01	NA	NA	NA
Diastolic Blood Pressure	AS	0.3593	0.1051	6.00E-04	NA	NA	NA
	AIS	0.3114	0.1007	2.00E-03	0.4895	0.1036	2.30E-06
	LAS	0.3308	0.2255	1.42E-01	0.5971	0.2601	2.17E-02
	CES	0.1016	0.1162	3.82E-01	-0.2357	0.327	4.71E-01
	SVS	0.3112	0.1861	9.46E-02	0.3502	0.1352	9.60E-03
Systolic Blood Pressure	AS	0.3799	0.0895	2.18E-05	NA	NA	NA
	AIS	0.3387	0.0855	6.74E-05	0.5254	0.0946	2.80E-08
	LAS	0.6067	0.2345	9.70E-03	0.6864	0.2727	1.21E-02
	CES	0.1827	0.1161	1.16E-01	0.0227	0.2746	9.34E-01
	SVS	0.3533	0.1626	2.98E-02	0.3953	0.1269	1.80E-03
Mean Arterial Pressure	AS	0.3929	0.1001	8.73E-05	NA	NA	NA
	AIS	0.3404	0.0948	3.00E-04	0.5159	0.0979	1.40E-07
	LAS	0.4908	0.2264	3.02E-02	0.6494	0.2642	1.40E-02
	CES	0.1535	0.1145	1.80E-01	-0.1207	0.2871	6.74E-01
	SVS	0.3558	0.1817	5.02E-02	0.3702	0.1287	4.00E-03
Pulse Pressure	AS	0.3202	0.0884	3.00E-04	NA	NA	NA
	AIS	0.294	0.0868	7.00E-04	0.4081	0.1011	5.40E-05
	LAS	0.6341	0.2545	1.27E-02	0.5698	0.2681	3.36E-02
	CES	0.1974	0.1339	1.41E-01	0.2741	0.3385	4.18E-01
	SVS	0.2589	0.1479	8.01E-02	0.3162	0.1356	1.97E-02
Hypertension	AS	0.3138	0.1402	2.52E-02	NA	NA	NA
	AIS	0.2654	0.1325	4.58E-02	0.6235	0.1501	3.26E-05
	LAS	0.6587	0.3503	6.00E-02	0.5691	0.2963	5.48E-01
	CES	0.0984	0.2064	6.33E-01	-0.3895	0.479	4.61E-01
	SVS	0.4589	0.2542	7.11E-02	0.4170	0.1978	3.50E-02
HDL levels	AS	-0.2347	0.0716	1.00E-03	NA	NA	NA
	AIS	-0.2337	0.0675	5.00E-03	-0.0155	0.1262	9.02E-01
	LAS	-0.7982	0.4177	5.61E-02	-0.084	0.1492	5.74E-01
	CES	-0.0596	0.0991	5.47E-01	0.1041	0.2429	6.68E-01
	SVS	-0.2629	0.1269	3.80E-02	0.0373	0.1537	8.09E-01
LDL levels	AS	0.0484	0.0773	5.31E-01	NA	NA	NA
	AIS	0.0817	0.0818	3.18E-01	-0.0925	0.1099	4.00E-01
	LAS	0.2710	0.2619	3.01E-01	-0.0404	0.1986	8.39E-01
	CES	-0.0815	0.1126	4.50E-01	0.0255	0.2442	9.17E-01
	SVS	-0.0905	0.1732	6.01E-01	0.0572	0.138	6.79E-01
Triglyceride levels	AS	0.1502	0.0545	5.90E-03	NA	NA	NA
	AIS	0.1612	0.0538	2.70E-03	0.1899	0.0749	1.12E-02
	LAS	0.6480	0.3687	7.92E-02	0.2503	0.1122	2.57E-02
	CES	0.0265	0.0684	7.00E-01	0.2468	0.1773	1.64E-01
	SVS	0.0665	0.1064	5.33E-01	0.1956	0.11	7.53E-02
T2 Diabetes	AS	0.2865	0.0663	1.50E-05	NA	NA	NA
	AIS	0.2721	0.0668	4.70E-05	0.6925	0.0505	7.64E-43
	LAS	0.6356	0.3443	6.52E-02	0.3638	0.1142	1.40E-03
	CES	-0.0016	0.1050	9.88E-01	0.1627	0.1711	3.42E-01
	SVS	0.3186	0.1526	3.74E-02	0.6855	0.1032	3.15E-11
Coronary Artery Disease	AS	0.5209	0.0522	1.82E-23	NA	NA	NA
	AIS	0.5132	0.0535	8.80E-22	NA	NA	NA
	LAS	1.112*	0.4964	2.51E-02	NA	NA	NA
	CES	0.2925	0.0632	3.66E-06	NA	NA	NA
	SVS	0.4446	0.1123	7.47E-05	NA	NA	NA

Supplementary Table 16 Shared genetic contribution between stroke and related vascular traits as determined by LD scores regression. Significant correlations are shown in bold. R(g), genetic correlation, SE, standard error. P-values below $p < 5.6 \times 10^{-3}$ correcting for 9 independent phenotypes are shown in bold.

Supplementary Table 17 Results of the epigwas analysis. Shown is the enrichment p-value of GWAS results in specific tissues. EpiGWAS was used to calculate enrichment p-values for H3K4me1 (enhancers), H3K4me3 (promoters) and H3K9ac (active promoters)

Enclosed electronic excel file

Supplementary Table 18 Results of DEPICT pathway analysis. For each stroke subtype, SNPs with $BF > 5$ from the trans-ethnic meta-analysis were analysed. Gene sets with a $FDR < 0.05$ were considered significant. Columns E-N show the Z-scores of the genes in the gene set.

Enclosed electronic excel file

Supplementary Table 19 Results from the Ingenuity Pathway Analysis. Shown are enrichment p-values for the corresponding Ingenuity canonical pathway and the proteins involved in the respective pathway. P-values are derived from Fisher's exact test. FDR < 0.05 was considered significant and are displayed in bold. For The IPA Diseases and Bio Functions and for the IPA Tox Functions, p-values are given for the enrichment of specific function annotations.

Enclosed electronic excel file

Supplementary Table 20 Results from the VEGAS2 pathway analysis. Shown are pathways for each stroke subtype, the ethnicity specific p-values and the meta-analysis p-value. Pathways with $FDR < 0.05$ were considered significant and are displayed in bold (CES only)

Enclosed electronic excel file

Supplementary Table 21 Results of the 95% credible set analysis. Results were obtained separately in European, East Asian, and African American ancestry samples. Shown is the number of SNPs in the 95% credible set (numerator) and the total number of SNPs in the analysis (denominator, $r^2 > 0.1$)

Enclosed electronic excel file

Supplementary Table 22 Detailed functional and biological information on SNPs at the 32 stroke risk loci. Shown are the lead SNPs and all proxy SNPs with $r^2 > 0.8$. We show information on nearby genes, the genomic consequence (intergenic, intronic, missense, regulatory), chromatin marks, eQTLs (GRASP_v2, GTEX_v6, BIOS, BLUEPRINT, STARNET, UCLA and HGVD), meQTLs (BLUEPRINT and ARIC) and pQTLs (KORA). We also give information whether this specific SNP is included in the 95% credible set analysis and the p-value of the Riviera-beta-analysis.

Enclosed electronic excel file

Supplementary Table 23 Relation of the lead and proxy SNPs ($r^2>0.8$) from 32 stroke risk loci with the best cis eQTL, meQTL and pQTL from various human bio-resources, grouped per tissue or cell type. Shown is the stroke subtype showing the most significant association; for meQTL CpG probe numbers are indicated in bracket after the gene name.

Enclosed electronic excel file

Supplementary Table 24 Biological candidate gene prioritization of 149 genes located in the 32 stroke associated risk loci. For each gene we first list the biological score derived from 14 biological criteria and the overall score by including other biological information. All colored boxes have a value of 1, values of 0 signify no information or not satisfied criteria. For the genomic context, filled red boxes indicate that the criteria are satisfied. Filled blue boxes indicate significant QTL association (eQTL: gene-expression; meQTL: methylation; pQTL: protein). Filled yellow boxes indicate overlap with H3K4me3, H3K9ac and H3K4me1 peaks in cells types that showed significant enrichment in Epigwas analysis. Filled green boxes indicate significantly enriched pathways. Filled purple boxes indicate overlap with drug target genes (ATC-C: Cardiovascular; ATC-B01: Antithrombotic).

Enclosed electronic excel file

Supplementary Table 25 Results of the drug class enrichment analysis. Shown is the number of genes falling into the respective Anatomical Therapeutic Chemical (ATC) drug class together with the respective statistics for genome-wide loci ($BF > 6$) and suggestive loci ($BF > 5$) both with and without the SH2B3 locus.

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Study	No. of SNPs passing QC
CHARGE	9,478,234
METASTROKE	8,940,233
SIGN	9,256,608
DECODE	7,855,222
EPIC-CVD	7,398,053
Young Lacunar DNA	7,846,740
SIFAP	8,234,135
INTERSTROKE EUR	3,984,831
HVH1	7,598,761
Glasgow	2,110,148
CADISP	9,109,502
Barcelona	8,486,260
FINLAND	7,208,625
SAHLSIS	5,816,883
MDC	5,840,041
HVH2	6,367,660
ICH	7,669,007
Biobank Japan	7,567,123
HISAYAMA	7,444,658
RACE1	7,409,565
RACE2	8,430,980
SDS	5,111,778
COMPASS	15,639,475
INTERSTROKE ASN	3,789,783
INTERSTROKE LAT	5,904,129

Supplementary Table 26 Overview of SNPs passing quality control (QC). For each study, the number of SNPs passing centralized QC are given. Number are based on the any stroke (AS) phenotype.

Supplementary Table 27 Information on the SNPs selected for the wGRS analysis. Given are the related vascular traits from which the respective wGRS were derived, the marker name (rs_id), the risk/other allele and the beta used as weight for the wGRS approach

Enclosed electronic excel file

2. Supplementary Figures

Supplementary Figure 1 QQ-Plots and Manhattan plots for any stroke (AS) for the transeethnic fixed-effects meta-analysis (QQ-plot), the transeethnic MANTRA meta-analysis (Manhattan plot) and the Europeans-only fixed effects meta-analysis (QQ-plot and Manhattan plot). For the QQ-plots, shown in black are the observed versus expected $-\log(p\text{-value})$ distributions from both fixed effect-analyses. The red line shows the expected (null) distribution of the statistic. For the Manhattan plots, shown are the $\log_{10}(\text{BF})$ for the transeethnic MANTRA analysis and the $-\log(p\text{-value})$ for the Europeans-only analysis for each variant studied. Genomic inflation values (λ) were estimated to be 1.174 for the trans-ethnic analysis and 1.134 for the Europeans-only analysis. The LD score regression intercept was estimated to be 1.061 for the Europeans-only analysis.

Supplementary Figure 2 QQ-Plots and Manhattan plots for any ischemic stroke (AIS) for the transeethnic fixed-effects meta-analysis (QQ-plot), the transeethnic MANTRA meta-analysis (Manhattan plot) and the Europeans-only fixed effects meta-analysis (QQ-plot and Manhattan plot). For the QQ-plots, shown in black are the observed versus expected $-\log(p\text{-value})$ distributions from both fixed effect-analyses. The red line shows the expected (null) distribution of the statistic. For the Manhattan plots, shown are the $\log_{10}(\text{BF})$ for the transeethnic MANTRA analysis and the $-\log(p\text{-value})$ for the Europeans-only analysis for each variant studied. Genomic inflation values (λ) were estimated to be 1.166 for the trans-ethnic analysis and 1.122 for the Europeans-only analysis. The LD score regression intercept was estimated to be 1.049 for the Europeans-only analysis.

Supplementary Figure 3 QQ-Plots and Manhattan plots for large artery stroke (LAS) for the transeethnic fixed-effects meta-analysis (QQ-plot), the transeethnic MANTRA meta-analysis (Manhattan plot) and the Europeans-only fixed effects meta-analysis (QQ-plot and Manhattan plot). For the QQ-plots, shown in black are the observed versus expected $-\log(p\text{-value})$ distributions from both fixed effect-analyses. The red line shows the expected (null) distribution of the statistic. For the Manhattan plots, shown are the $\log_{10}(\text{BF})$ for the transeethnic MANTRA analysis and the $-\log(p\text{-value})$ for the Europeans-only analysis for each variant studied. Genomic inflation values (λ) were estimated to be 1.112 for the trans-ethnic analysis and 1.146 for the Europeans-only analysis. The LD score regression intercept was estimated to be 1.095 for the Europeans-only analysis.

Supplementary Figure 4 QQ-Plots and Manhattan plots for cardioembolic stroke (CES) for the transeethnic fixed-effects meta-analysis (QQ-plot), the transeethnic MANTRA meta-analysis (Manhattan plot) and the Europeans-only fixed effects meta-analysis (QQ-plot and Manhattan plot). For the QQ-plots, shown in black are the observed versus expected $-\log(p\text{-value})$ distributions from both fixed effect-analyses. The red line shows the expected (null) distribution of the statistic. For the Manhattan plots, shown are the $\log_{10}(\text{BF})$ for the transeethnic MANTRA analysis and the $-\log(p\text{-value})$ for the Europeans-only analysis for each variant studied. Genomic inflation values (λ) were estimated to be 1.123 for the trans-ethnic analysis and 1.141 for the Europeans-only analysis. The LD score regression intercept was estimated to be 1.070 for the Europeans-only analysis.

Supplementary Figure 5 QQ-Plots and Manhattan plots for small vessel stroke (SVS) for the transeethnic fixed-effects meta-analysis (QQ-plot), the transeethnic MANTRA meta-analysis (Manhattan plot) and the Europeans-only fixed effects meta-analysis (QQ-plot and Manhattan plot). For the QQ-plots, shown in black are the observed versus expected $-\log(p\text{-value})$ distributions from both fixed effect-analyses. The red line shows the expected (null) distribution of the statistic. For the Manhattan plots, shown are the $\log_{10}(\text{BF})$ for the transeethnic MANTRA analysis and the $-\log(p\text{-value})$

for the Europeans-only analysis for each variant studied. Genomic inflation values (λ) were estimated to be 1.090 for the trans-ethnic analysis and 1.127 for the Europeans-only analysis. The LD score regression intercept was estimated to be 1.079 for the Europeans-only analysis.

Supplementary Figure 6 Regional Association Plots for lead variants. (A-A') Results from the transeethnic meta-analysis and (B'-F') Europeans-only meta-analysis. Shown in purple is the lead variant for the respective stroke phenotype as specified in Table 1. Shown is the region for the top signal $\pm 500\text{kb}$. The y-axis represents the $\log_{10}(\text{BF})$ or $-\log(\text{p-value})$ from the transeethnic MANTRA analysis or Europeans-only fixed-effects meta-analysis, respectively. Variants in LD with the lead variant are shown in red ($r^2 > 0.8$), orange ($r^2 > 0.6$), green ($r^2 > 0.4$) and blue ($r^2 > 0.2$). Grey peaks represent estimated recombination rates.

Supplementary Figure 7 Forest plots for lead variants at the 32 loci reaching genome-wide significance. Shown are study names, effect sizes and 95% confidence intervals for each study contributing summary statistics to the respective variant. Effect direction is the direction of the risk allele. Also shown are meta-analysis effect sizes and confidence intervals for each ethnicity separately, where appropriate. The transeethnic meta-analysis value is from the transeethnic fixed-effects meta-analysis; OR: Odds Ratio, CI: confidence interval.

Supplementary Figure 8 Comparison of allele frequencies and effect sizes in Europeans and East Asians. (A) Shown are the effect allele frequencies in Europeans and East Asians. Data were drawn from the any ischemic stroke (AIS) dataset. Each symbol represents one lead SNP. (B-E) Odds Ratios in Europeans and East Asians for AIS (B), LAS (C), CES (D) and SVS (E) with respect to the minor allele.

Supplementary Figure 9 Results of the gene-based tests. Shown are Manhattan plots for the VEGAS2 gene-based tests in AS (A), AIS (B), LAS (C), CES (D) and SVS (E). Each symbol represents one tested gene. The y-axis represents the $-\log(\text{p-values})$ from the gene-based tests. The dashed grey line corresponds to the Bonferroni corrected significance threshold of $p < 2.14 \times 10^{-6}$ (23,350 genes). Due to space restrictions, gene names are only shown in (C-E).

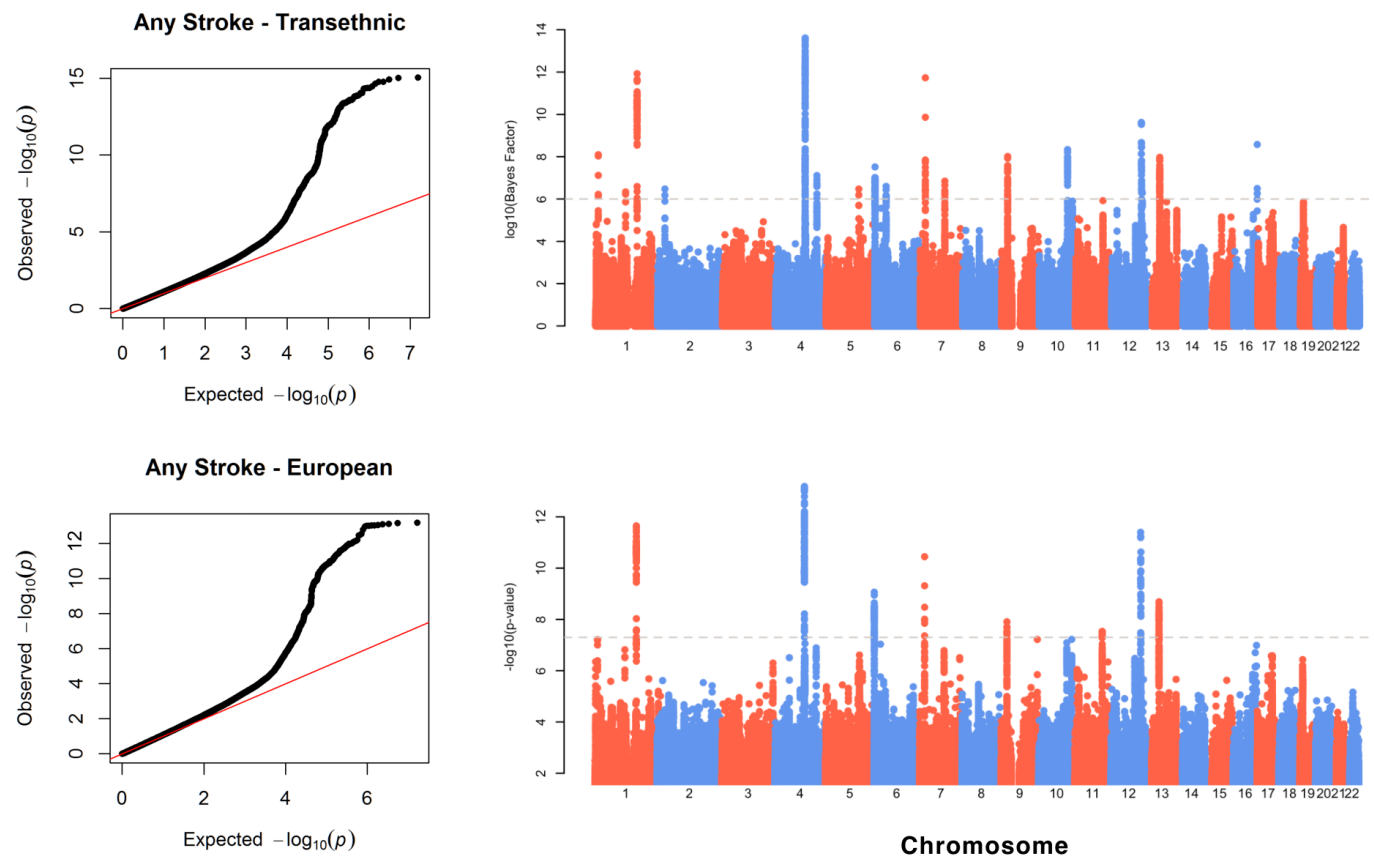
Supplementary Figure 10 Regional association plot of variants at the ICA1L-WDR12 locus. (A-C) The variant rs149163995 acts as an eQTL for multiple genes at this locus and the association is confined to the SVS phenotype (C). No clear signal is visible for LAS (A) or CES (B). Shown in purple is the lead variant rs149163995. Shown is the region for the top signal $\pm 500\text{kb}$. The y-axis represents the $\log_{10}(\text{BF})$ from the transeethnic MANTRA analysis. Variants in LD with the lead variant are shown in red ($r^2 > 0.8$), orange ($r^2 > 0.6$), green ($r^2 > 0.4$) and blue ($r^2 > 0.2$). Grey peaks represent estimated recombination rates.

Supplementary Figure 11 Results of the gwas-pw analysis. Shown are the SNP-wise results for the gwas-pw analysis for (A) the LAS-SVS analysis and (B) the LAS-CES analysis. The x-axis represents the genomic region found to be significant ($\text{PP_model } 3 > 0.9$). For each variant analysed, the posterior probability for model 3 is plotted on the y-axis. Shown are also the analysis results for each single trait in the Europeans-only analysis with p-values transformed to $\log_{10}(\text{Bayes Factors})$ using Wakefield's method for each SNP displayed on the y-axis. (C for the LAS-SVS analysis and D for the LAS-CES analysis). For all plots, the lead variant (purple) is the variant with the highest PP for model 3 in the SNP-wise results. Variants in LD with the lead variant are shown in red ($r^2 > 0.8$), orange ($r^2 > 0.6$), green ($r^2 > 0.4$) and blue ($r^2 > 0.2$). Grey peaks represent estimated recombination rates.

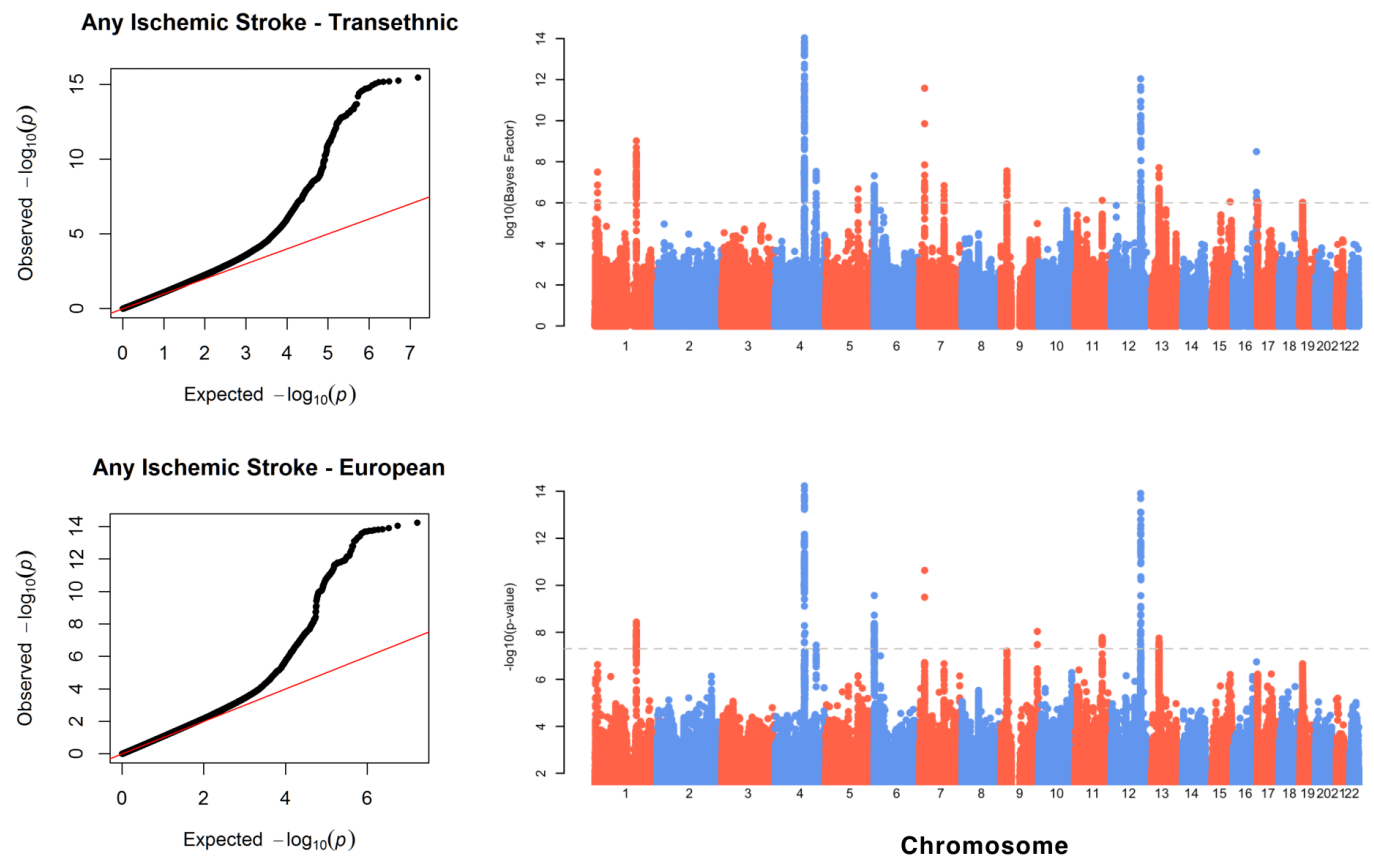
Supplementary Figure 12 Results of the conditional analysis at the PITX2 locus. Shown are the unconditioned analysis in the Europeans-only fixed-effects meta-analysis, the conditional analysis on rs2466455 and the conditional analysis on both rs2466455 and rs1906611. Shown is the region for the top signal $\pm 500\text{kb}$. The y-axis represents the $-\log(\text{p-value})$ from the Europeans-only fixed-effects meta-analysis. Variants in LD with the lead variant are shown in red ($r^2 > 0.8$), orange ($r^2 > 0.6$), green ($r^2 > 0.4$) and blue ($r^2 > 0.2$). Grey peaks represent estimated recombination rates.

Supplementary Figure 13 RiVIERA credible SNP set analysis. Shown are the GWAS association statistics for each locus studies, (A) PMF1-SEMA4A, (B) SH3PXD2A and (C) EDNRA, the final RiVIERA posterior probability (PPA), the weighted Epigenome information using the RoadMap epigenome data of 127 tissue types with information on 7 chromatin marks (H3K4me1, H3K4me3, H3K36me3, H3K27me3, H3K9me3, H3K27ac, H3K9ac) as well as DNA accessibility marks (DNaseI). Also shown are PolII binding sites and transcription factor (TF) binding sites in the region. Epigenetic enrichment over a fixed window size (50bp) per tissue group was generated by taking the cumulative sum of empirical prior weighted global epigenetic enrichment. Tissues were grouped into 19 groups as defined in the NIH RoadMap epigenome project.

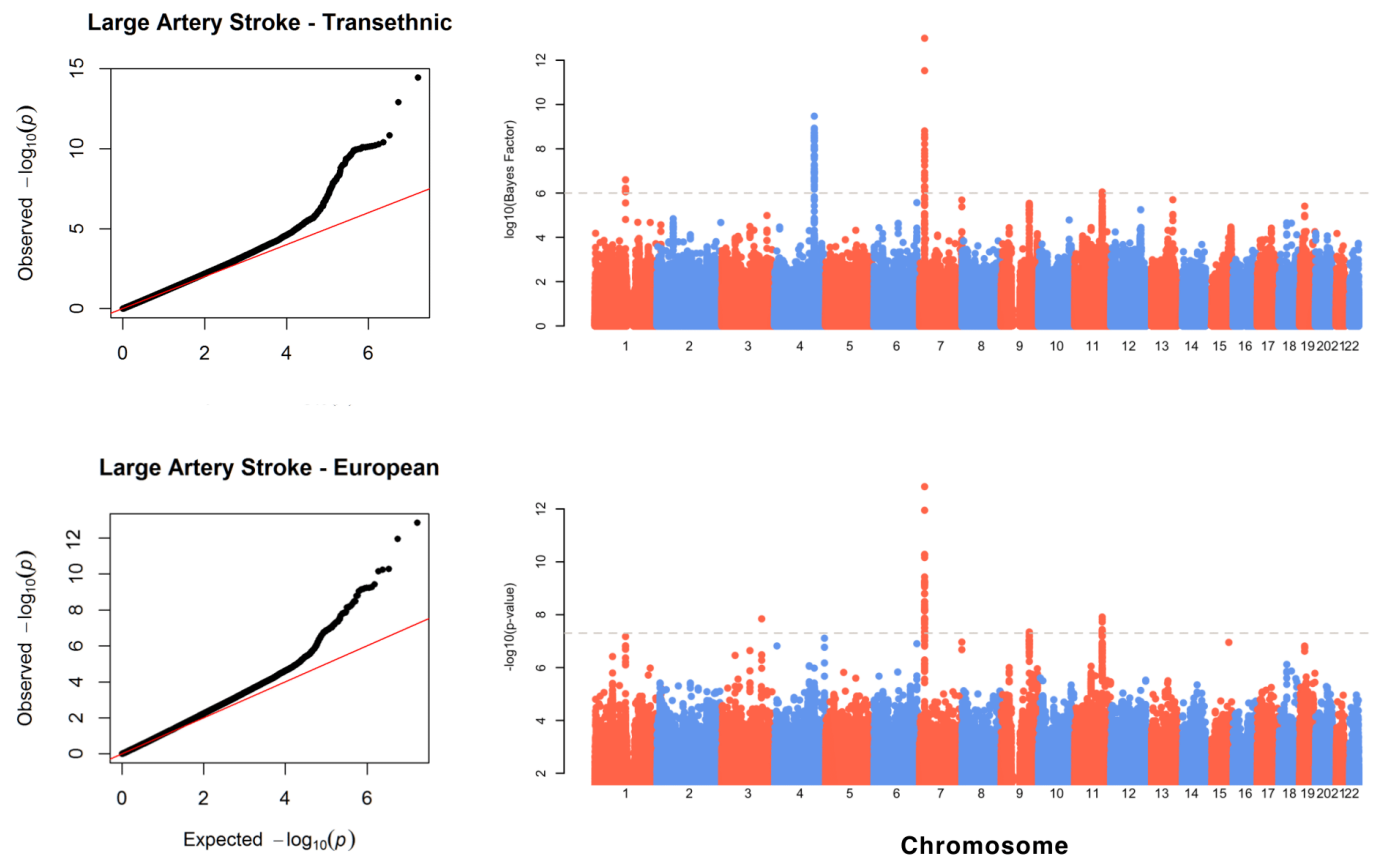
Supplementary Figure 1



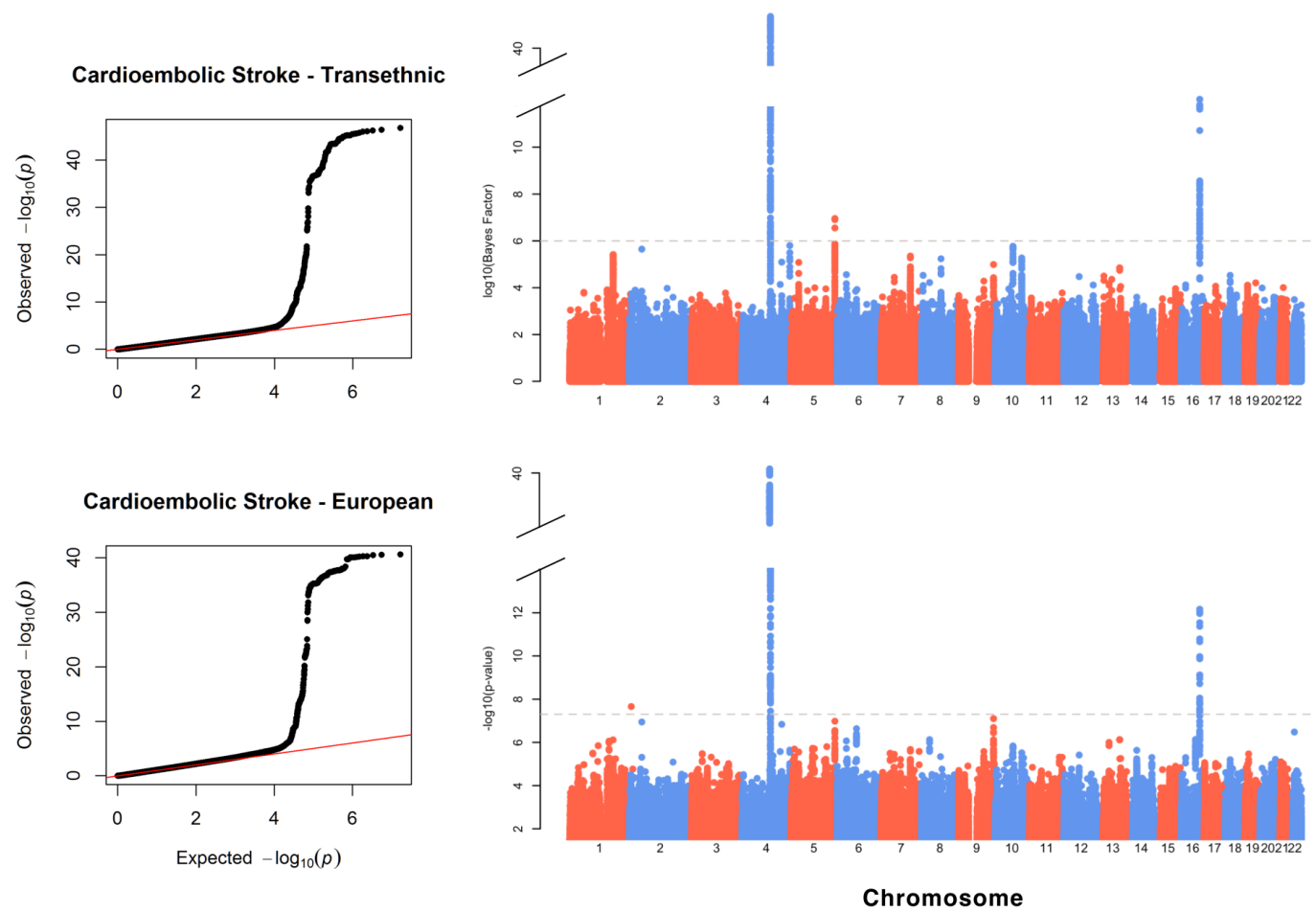
Supplementary Figure 2



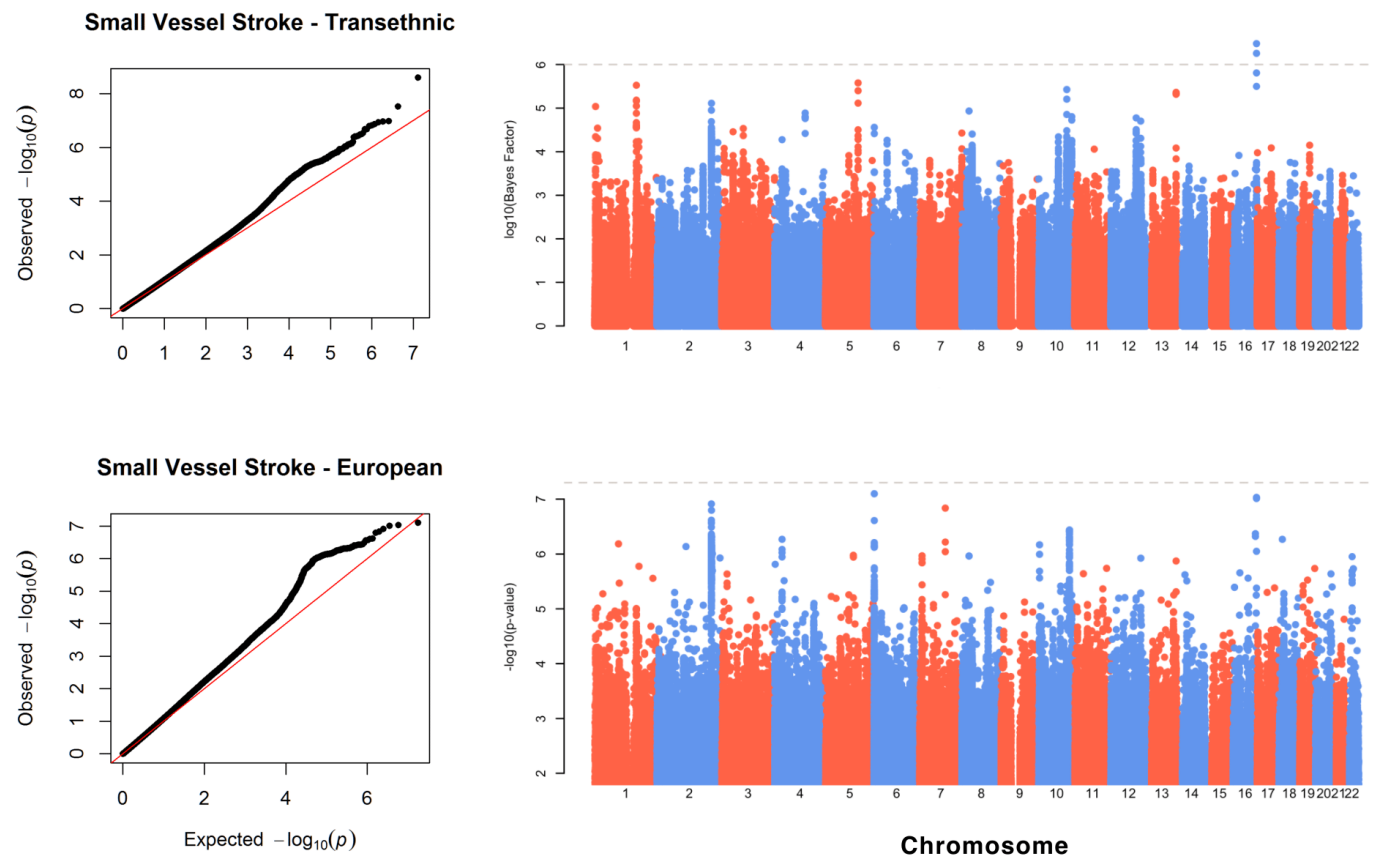
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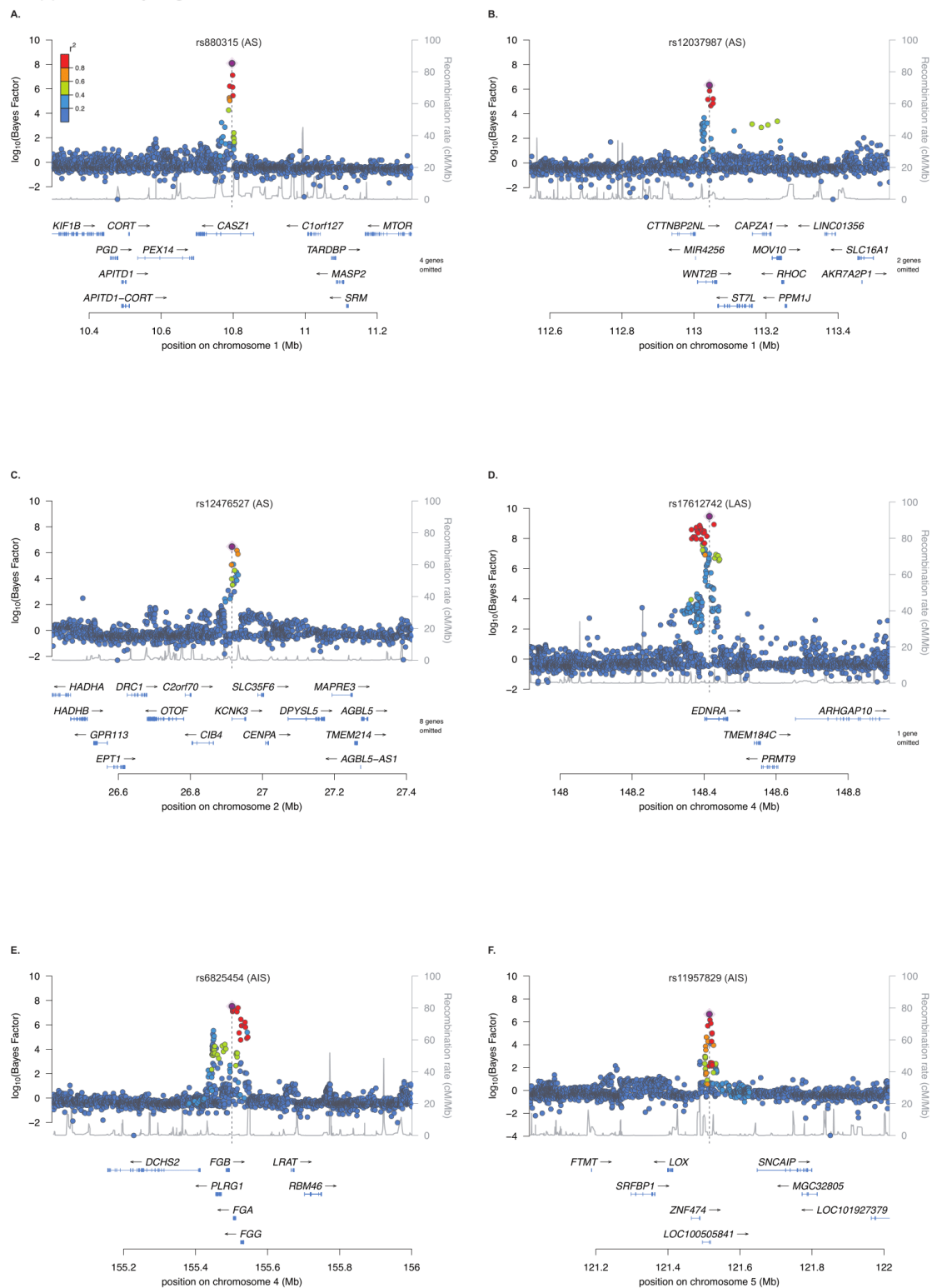
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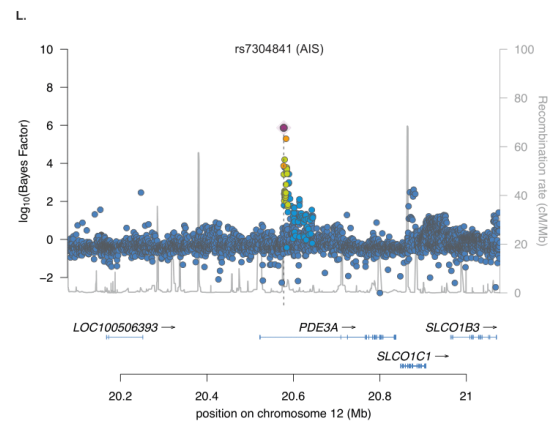
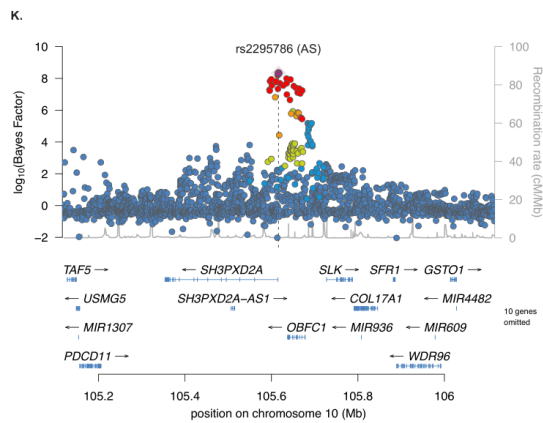
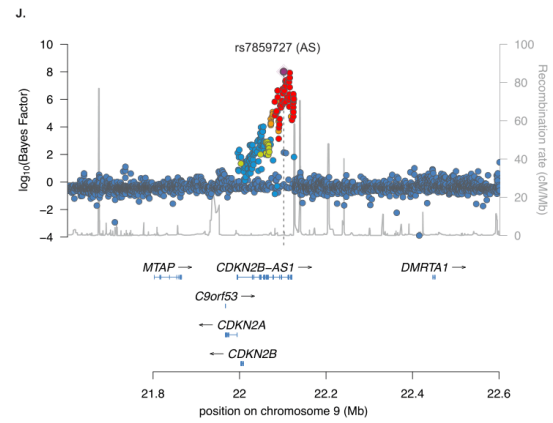
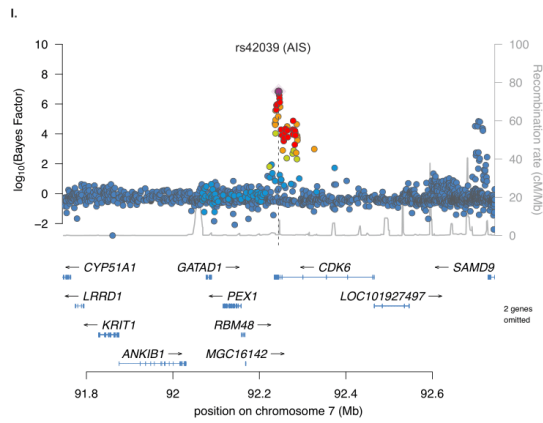
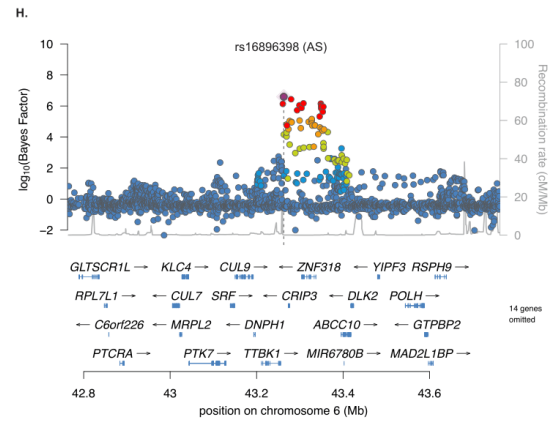
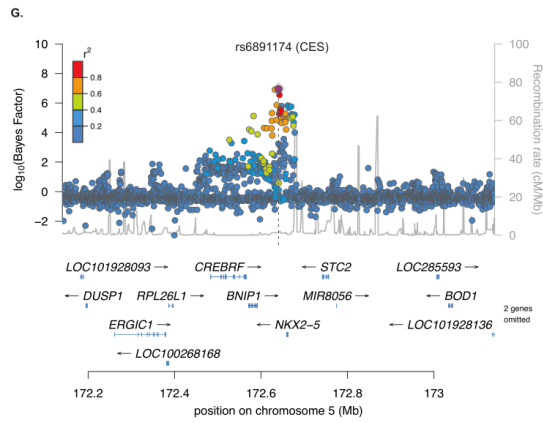


Supplementary Figure 5

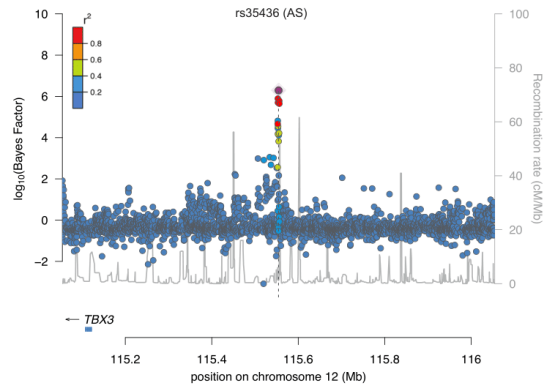


Supplementary Figure 6

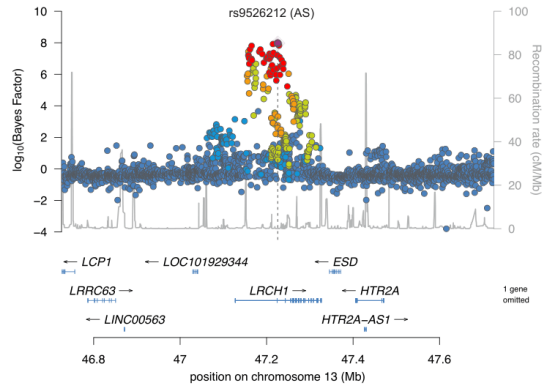




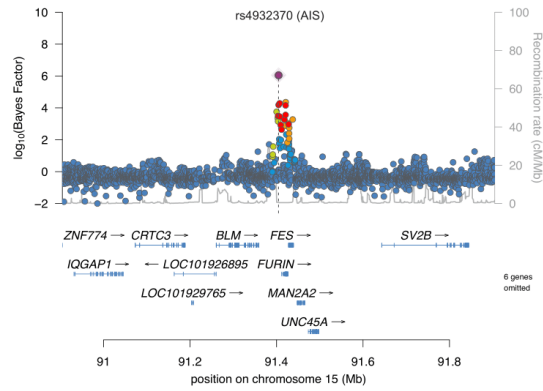
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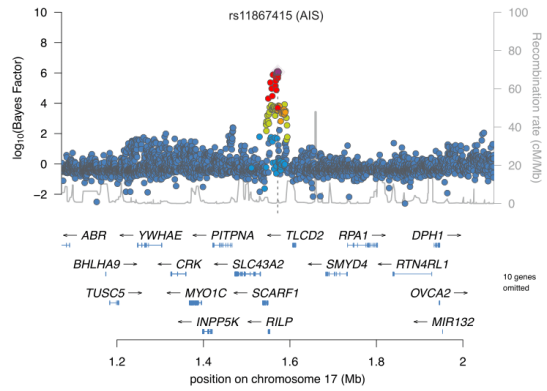
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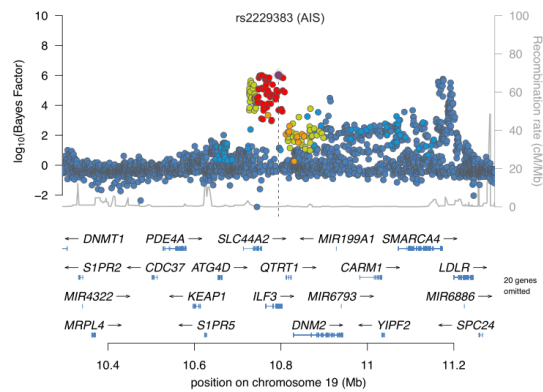
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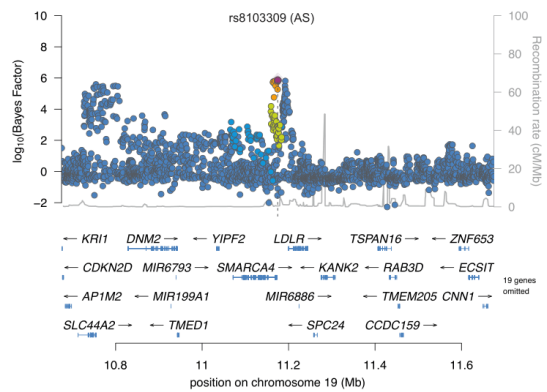
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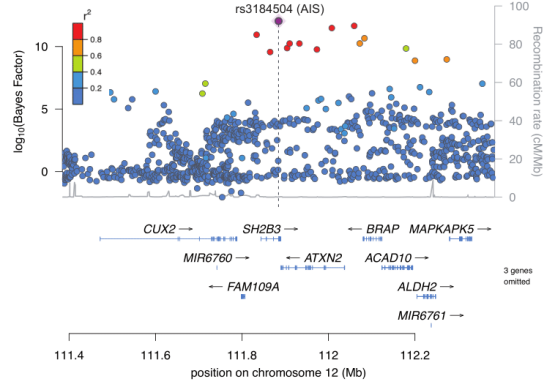
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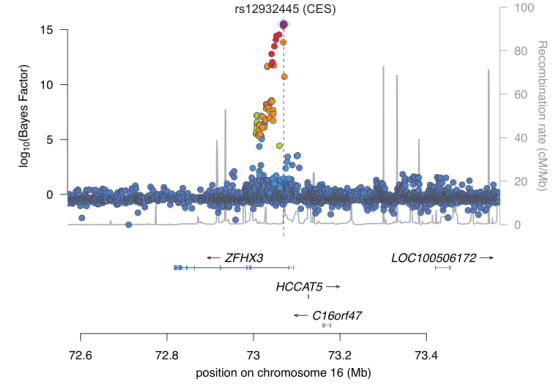
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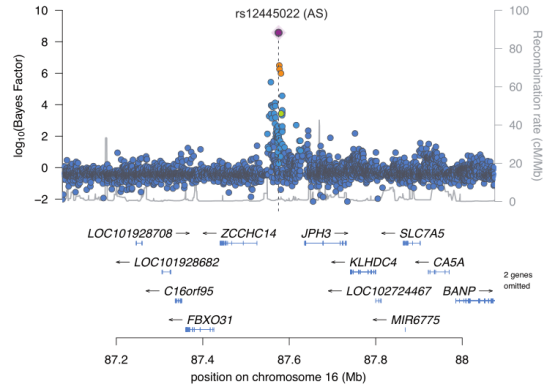
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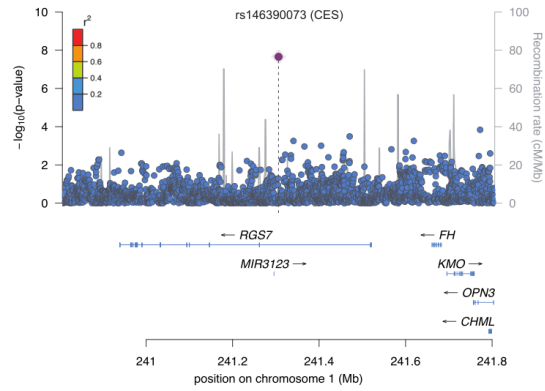
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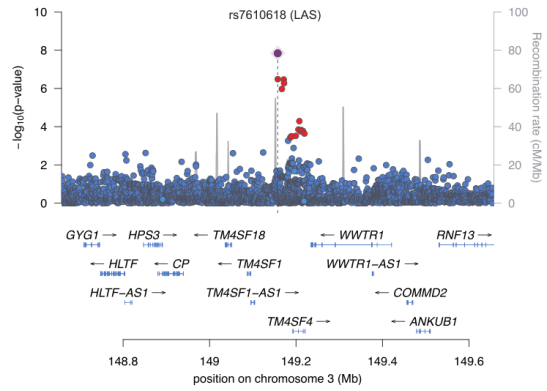
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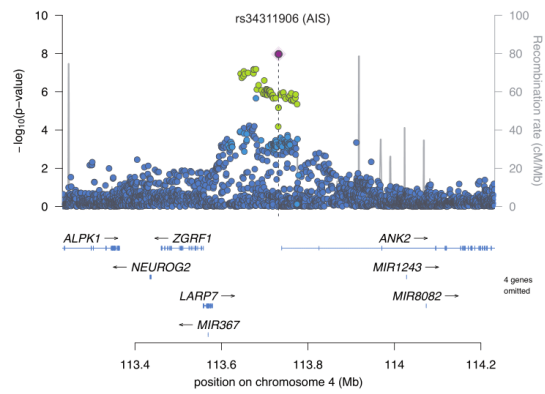
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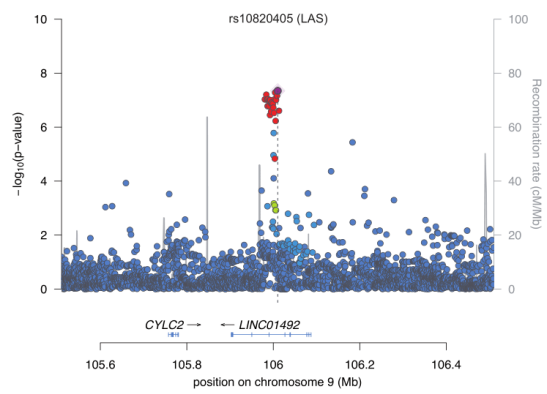
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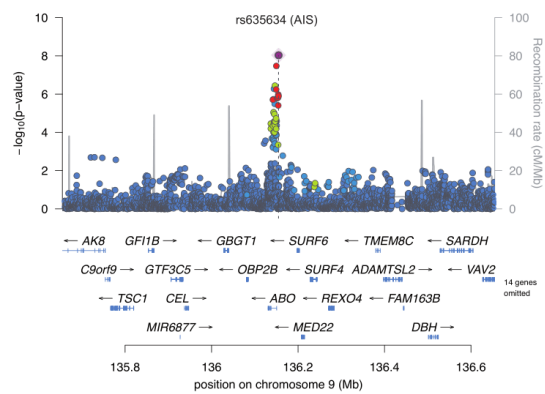
D'.



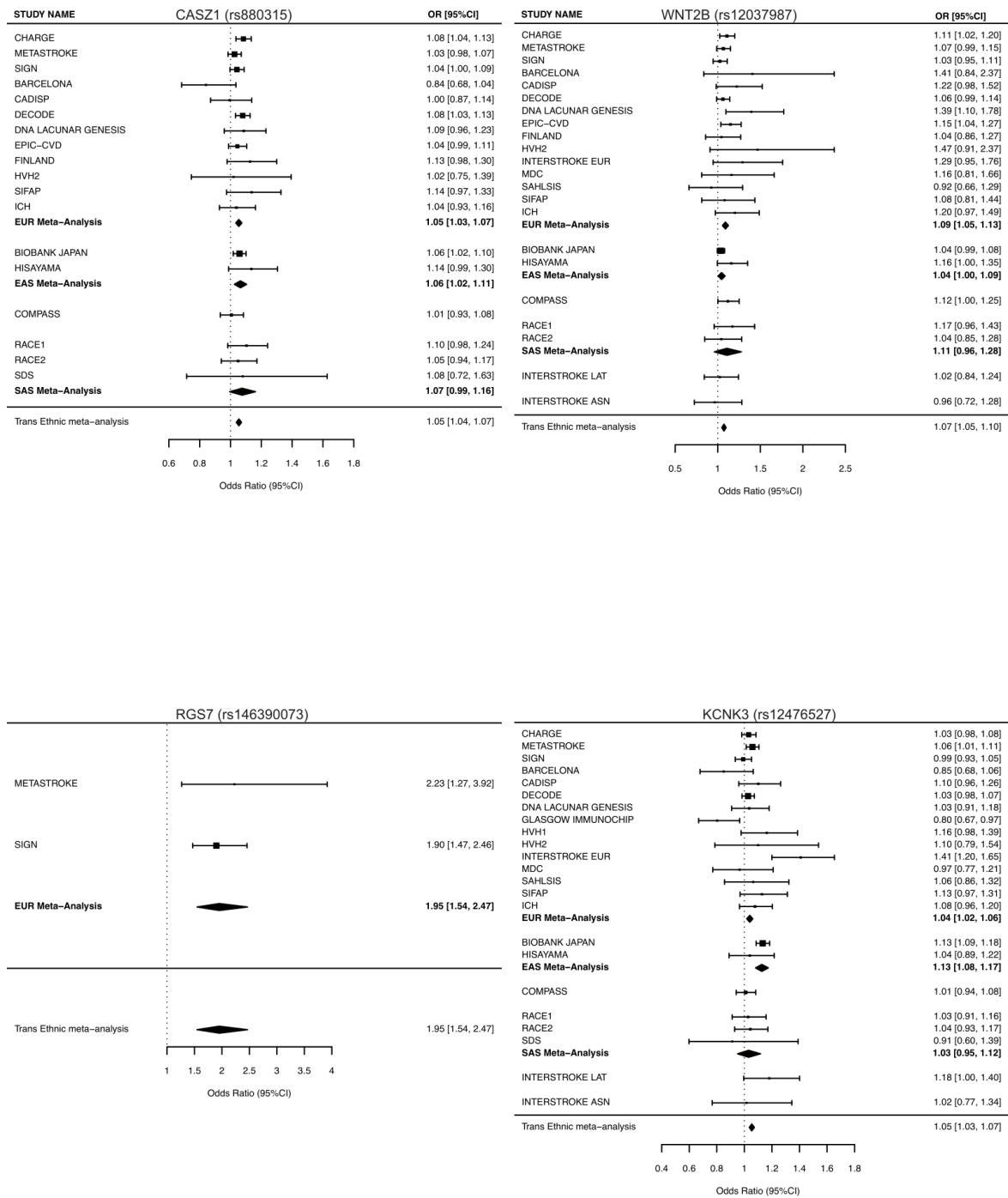
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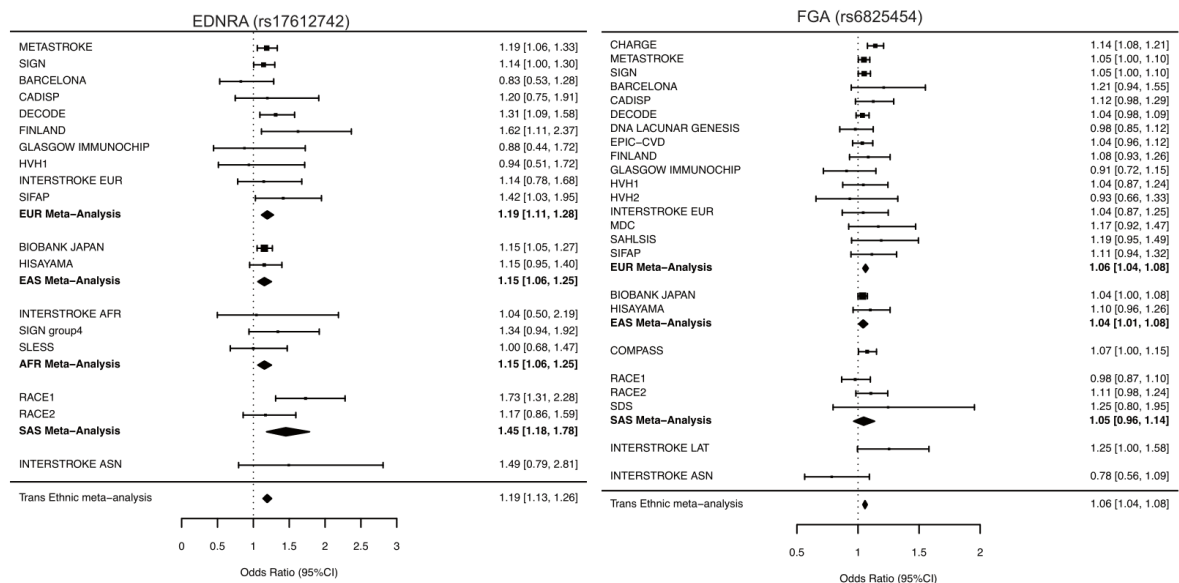
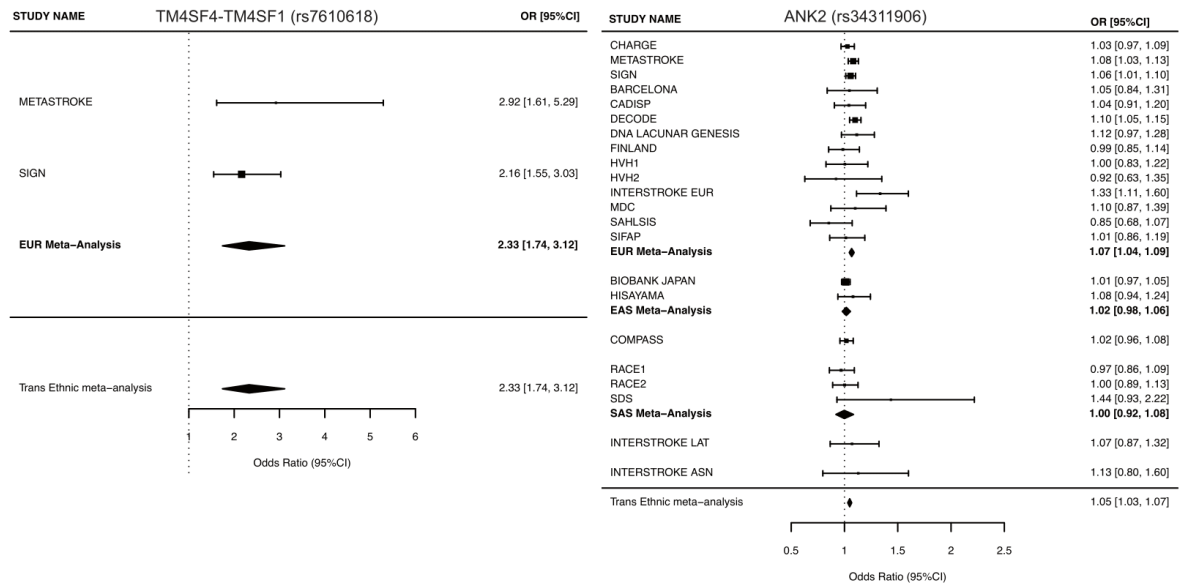


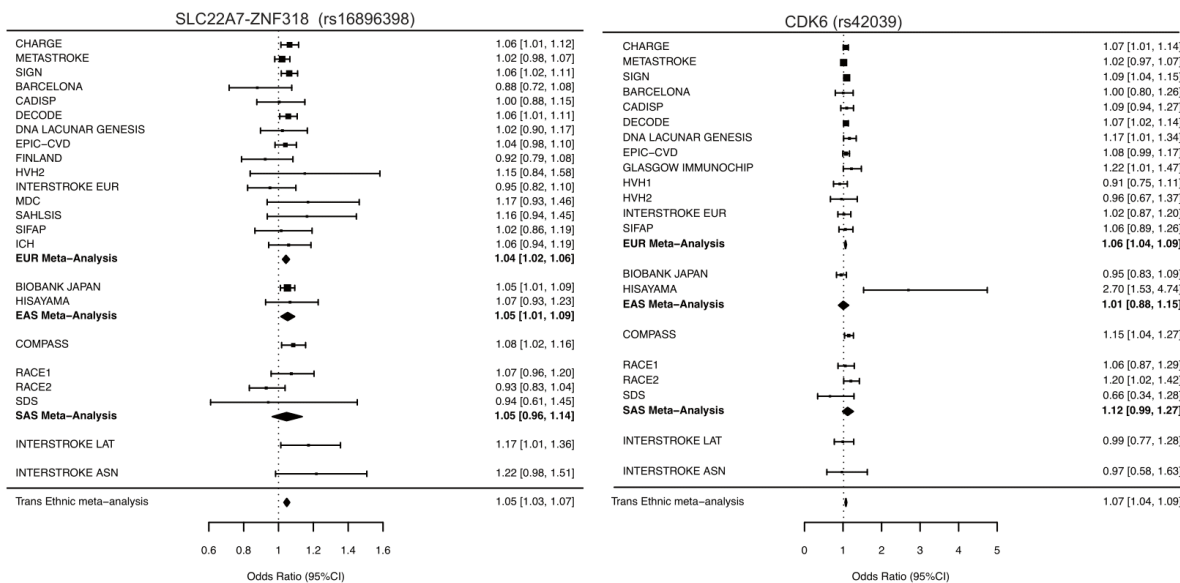
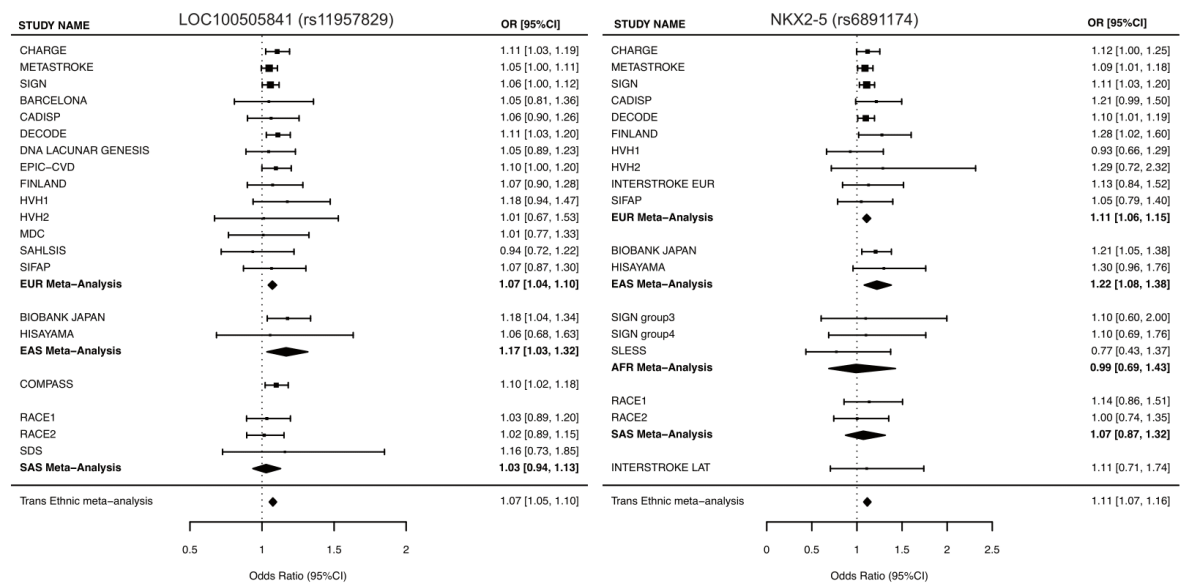
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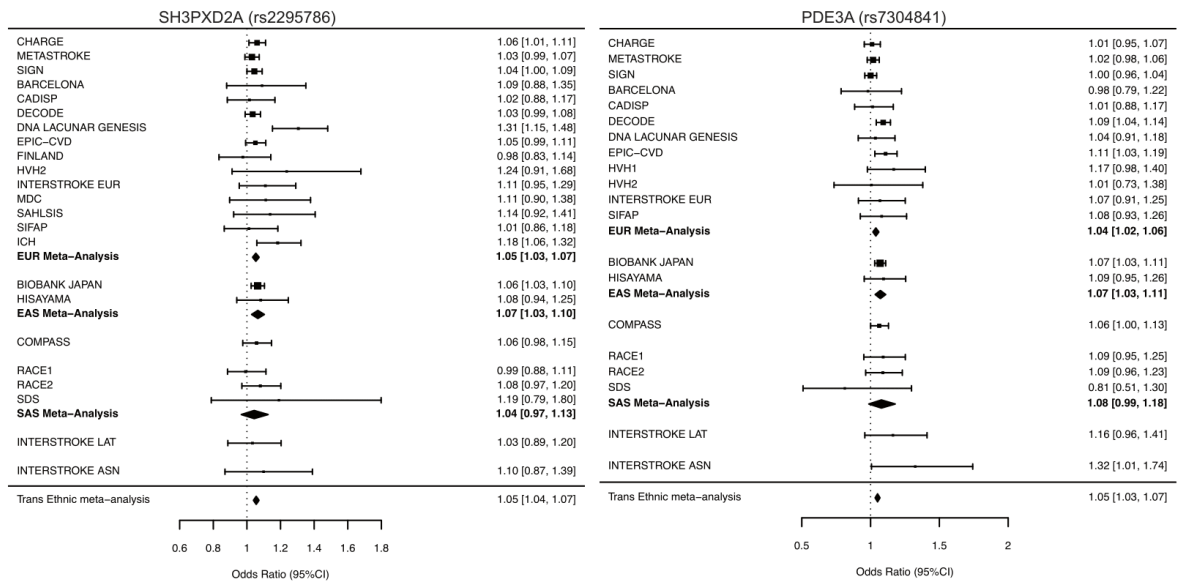
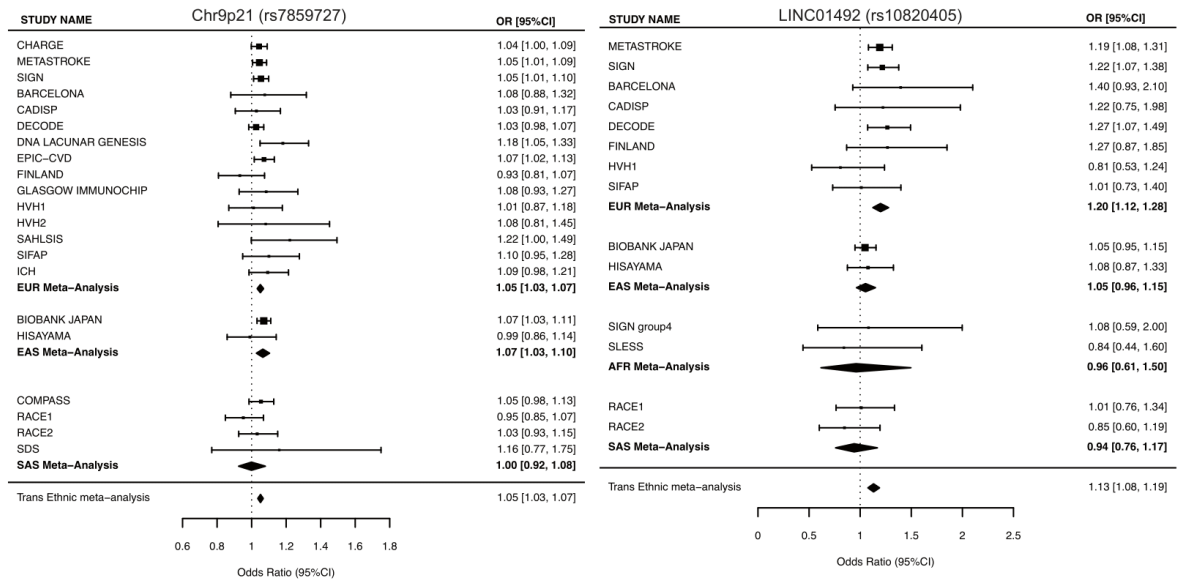


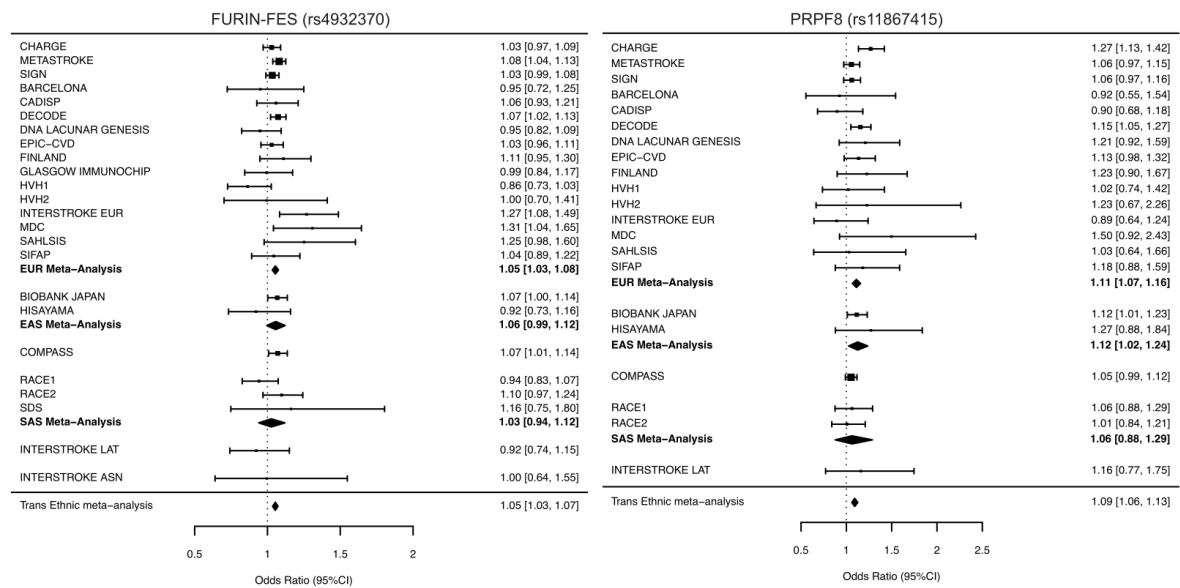
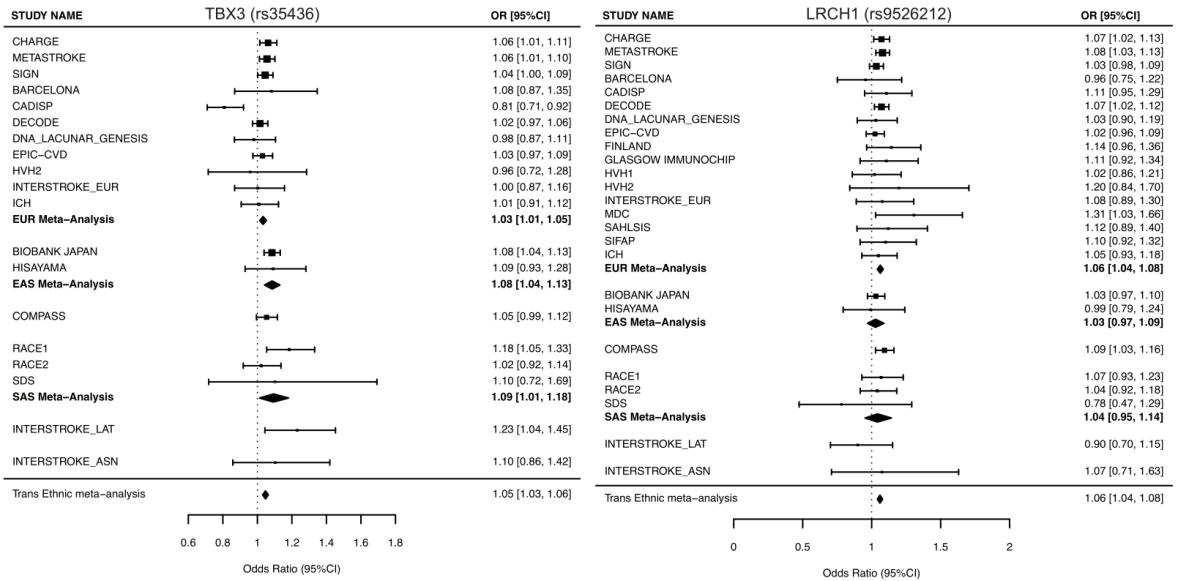
Supplementary Figure 7

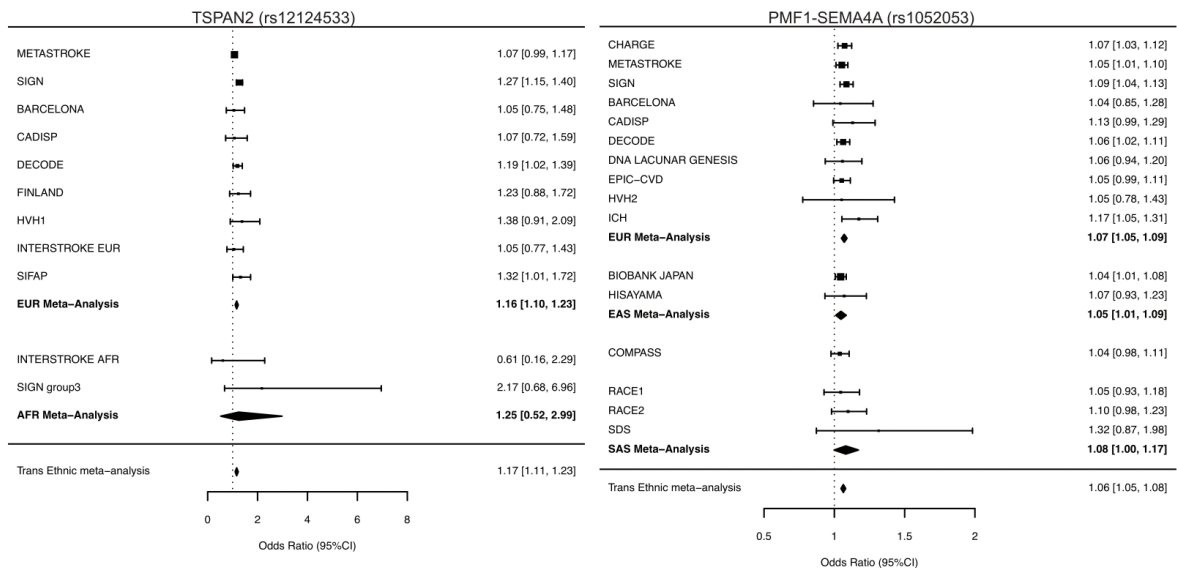
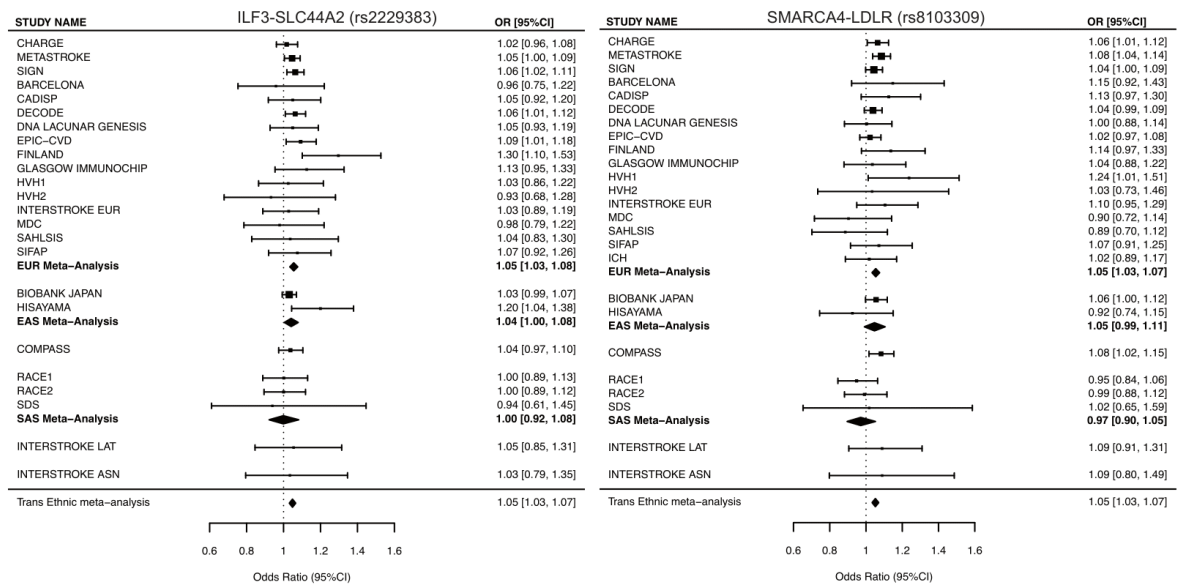


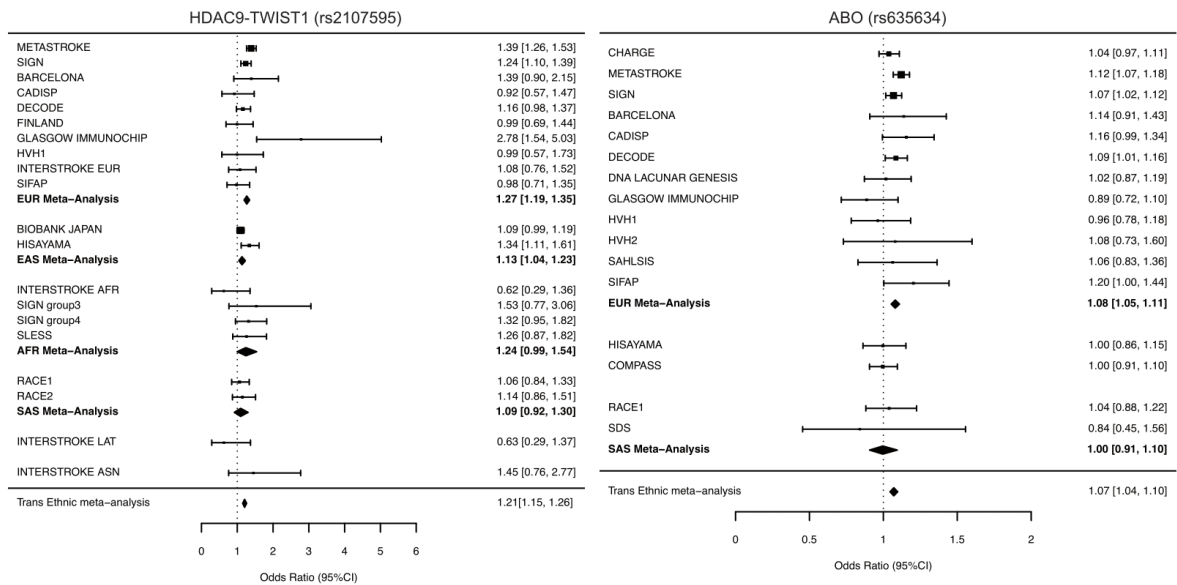
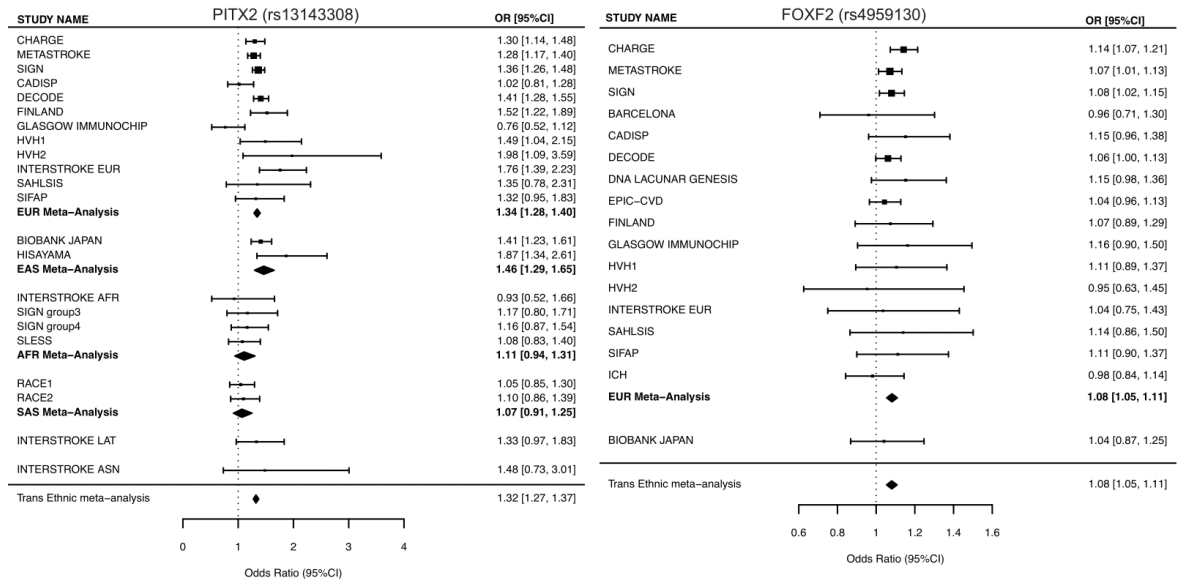


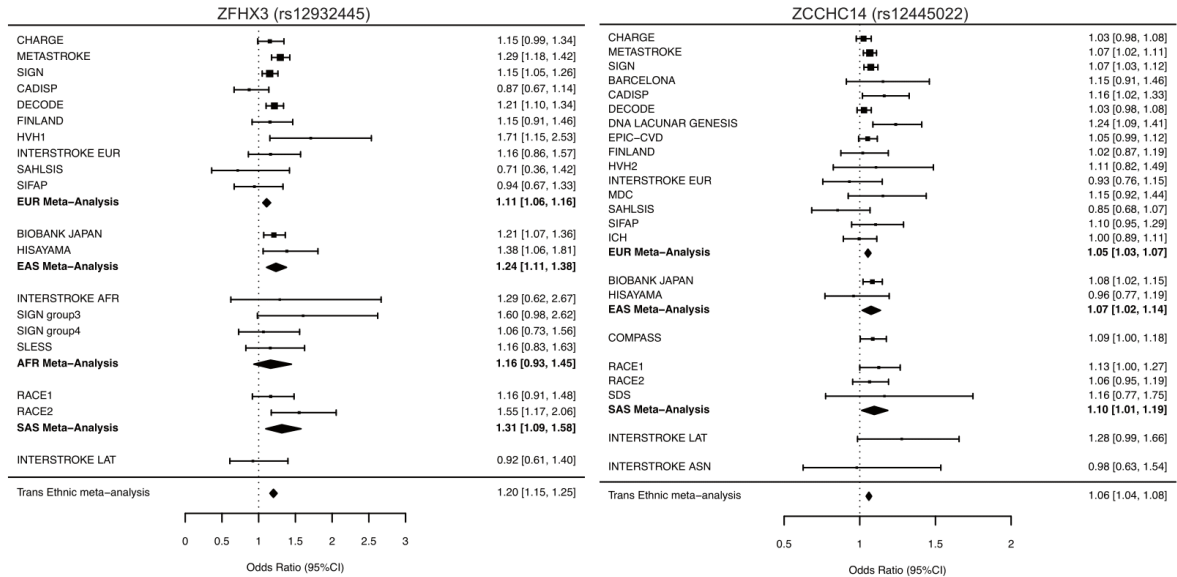
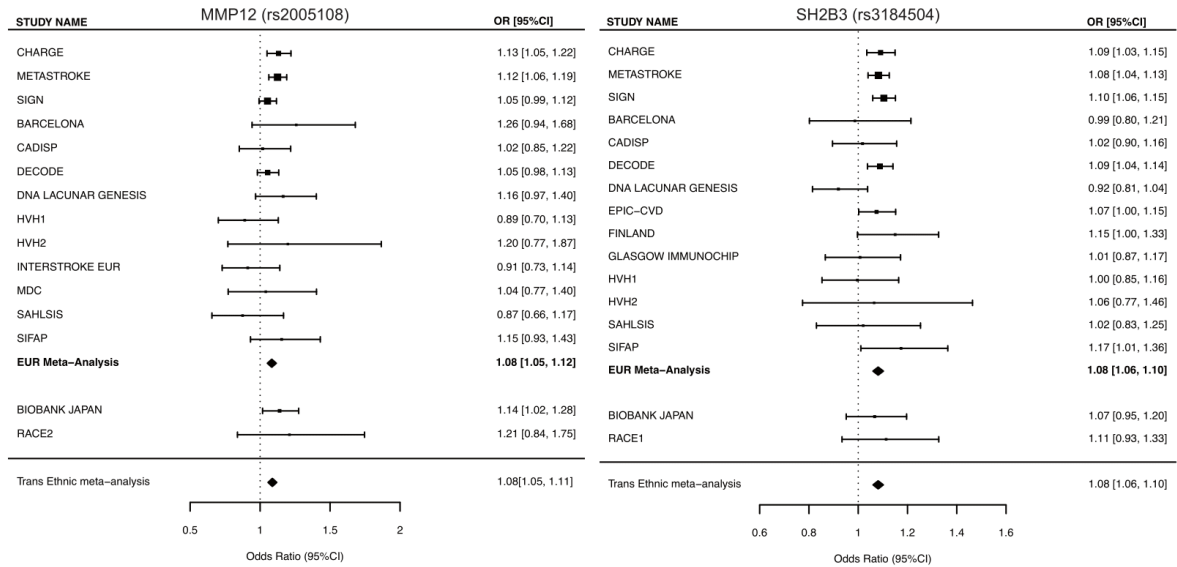




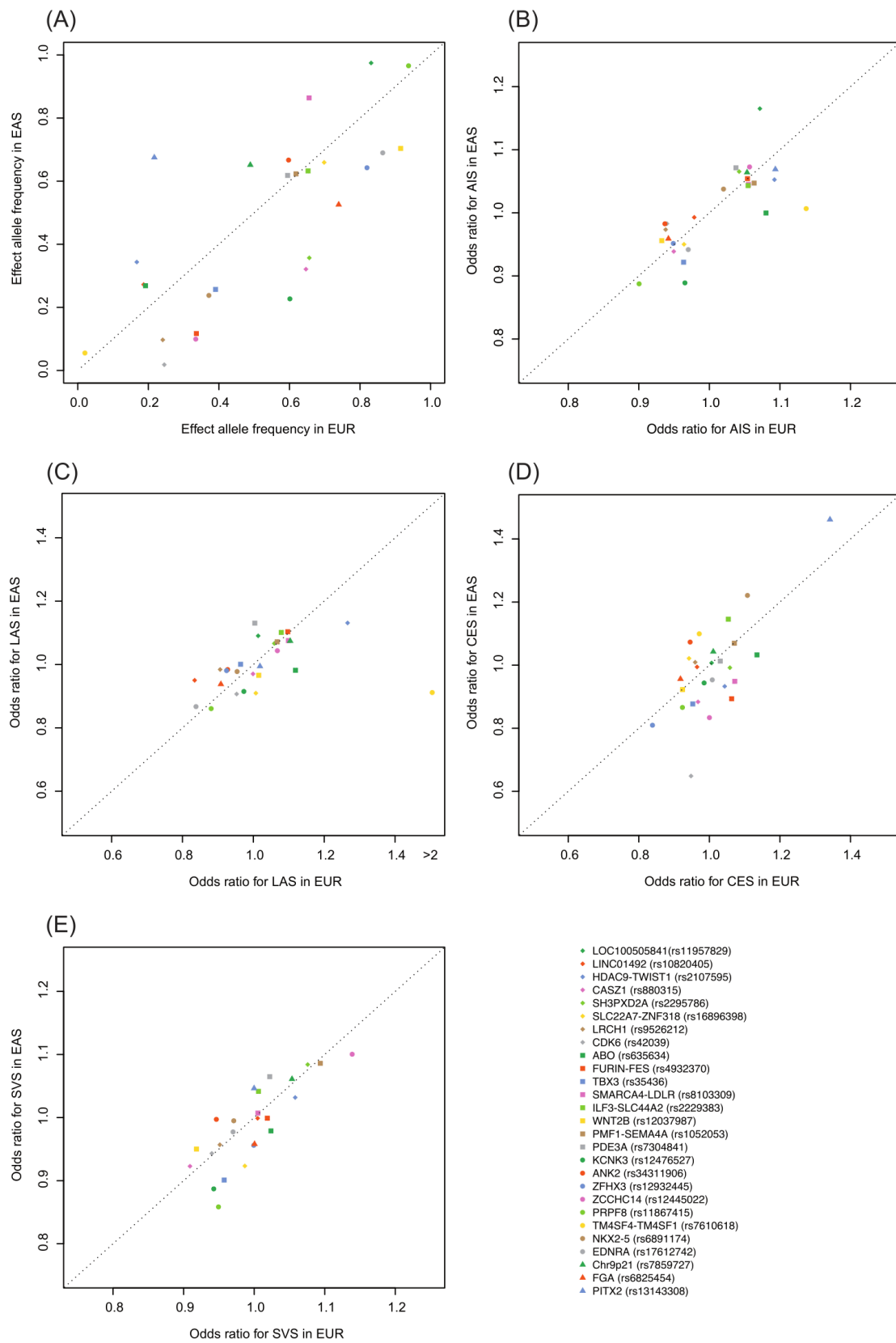




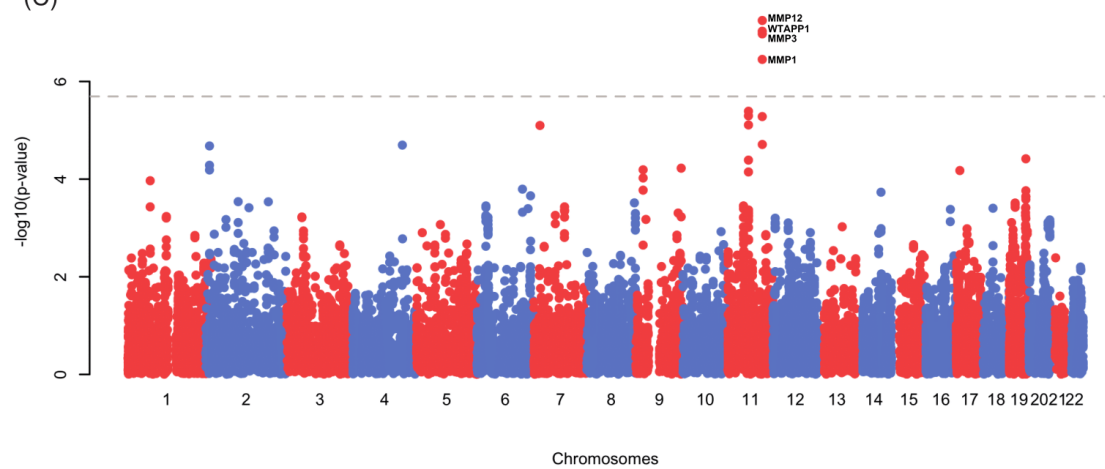
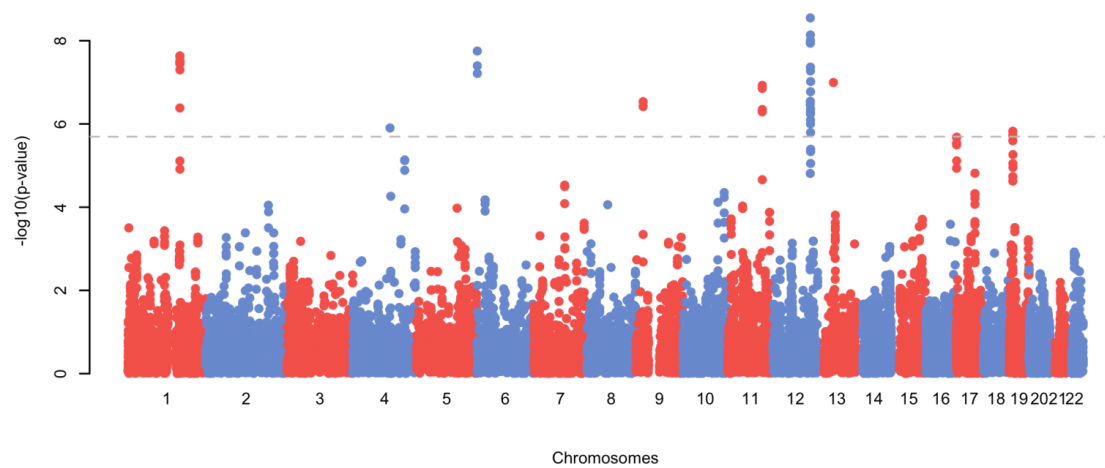
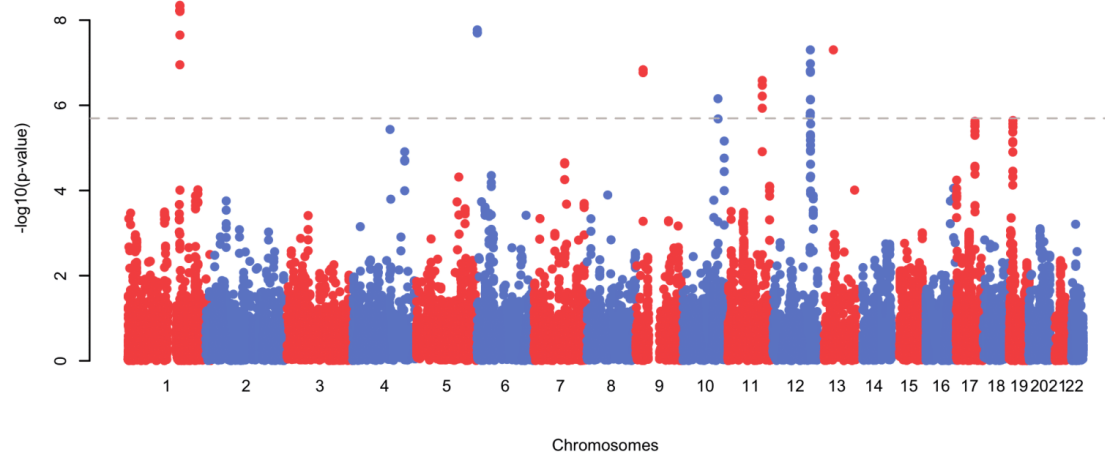




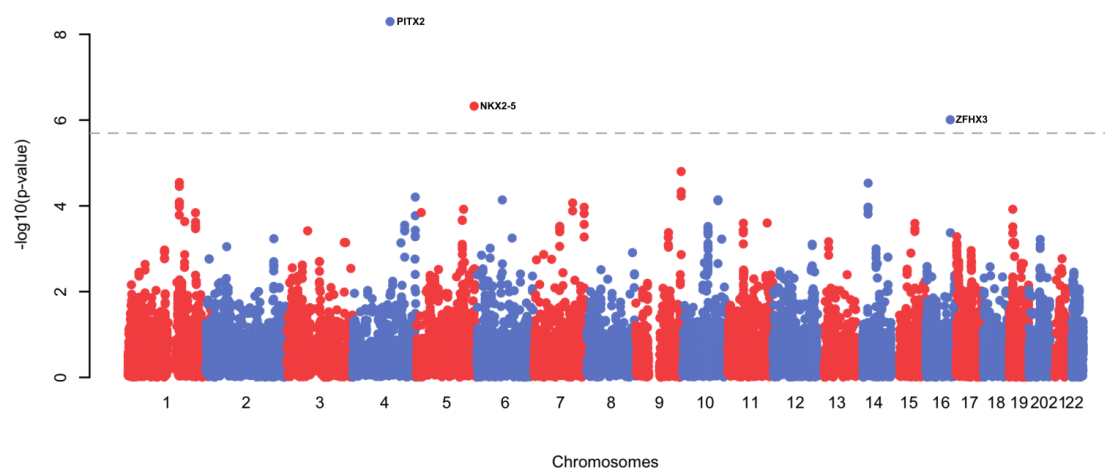
Supplementary Figure 8



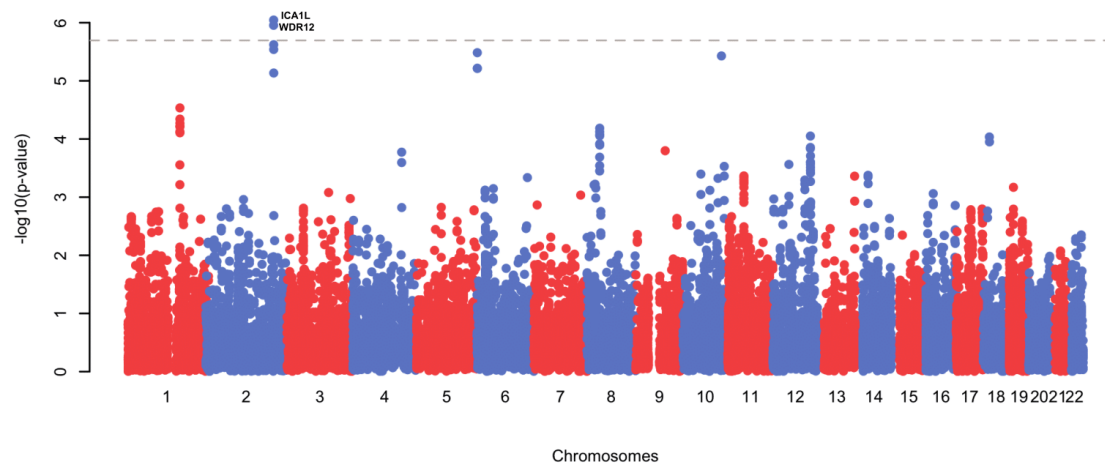
(A)



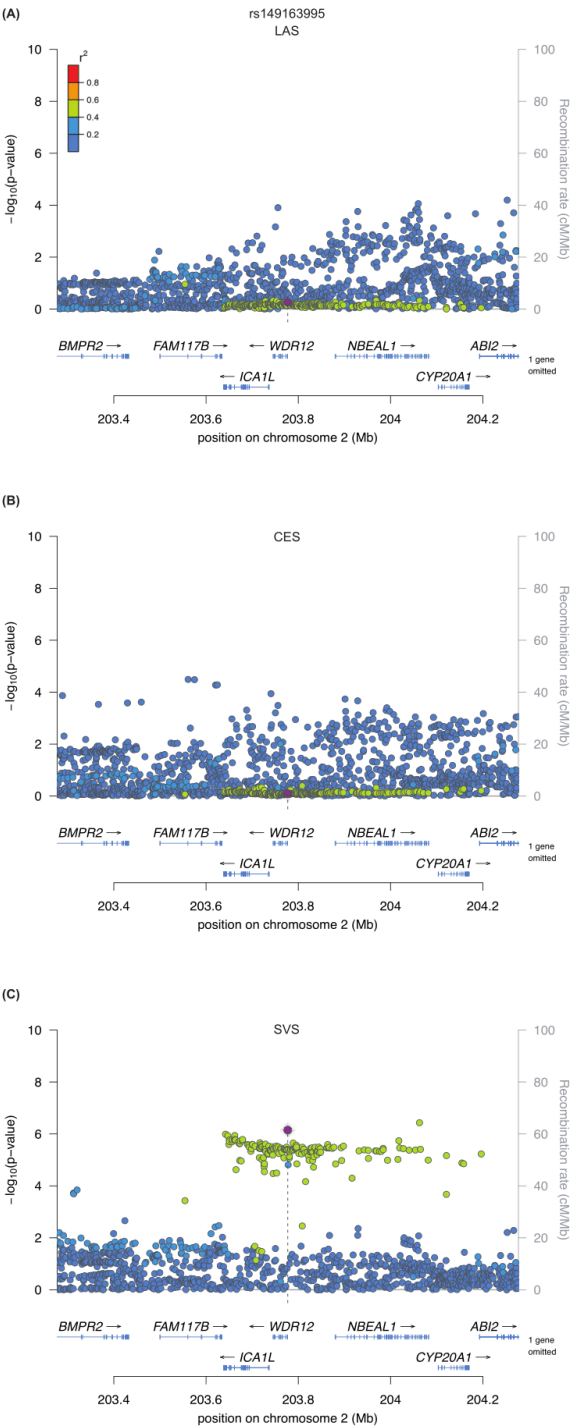
(D)



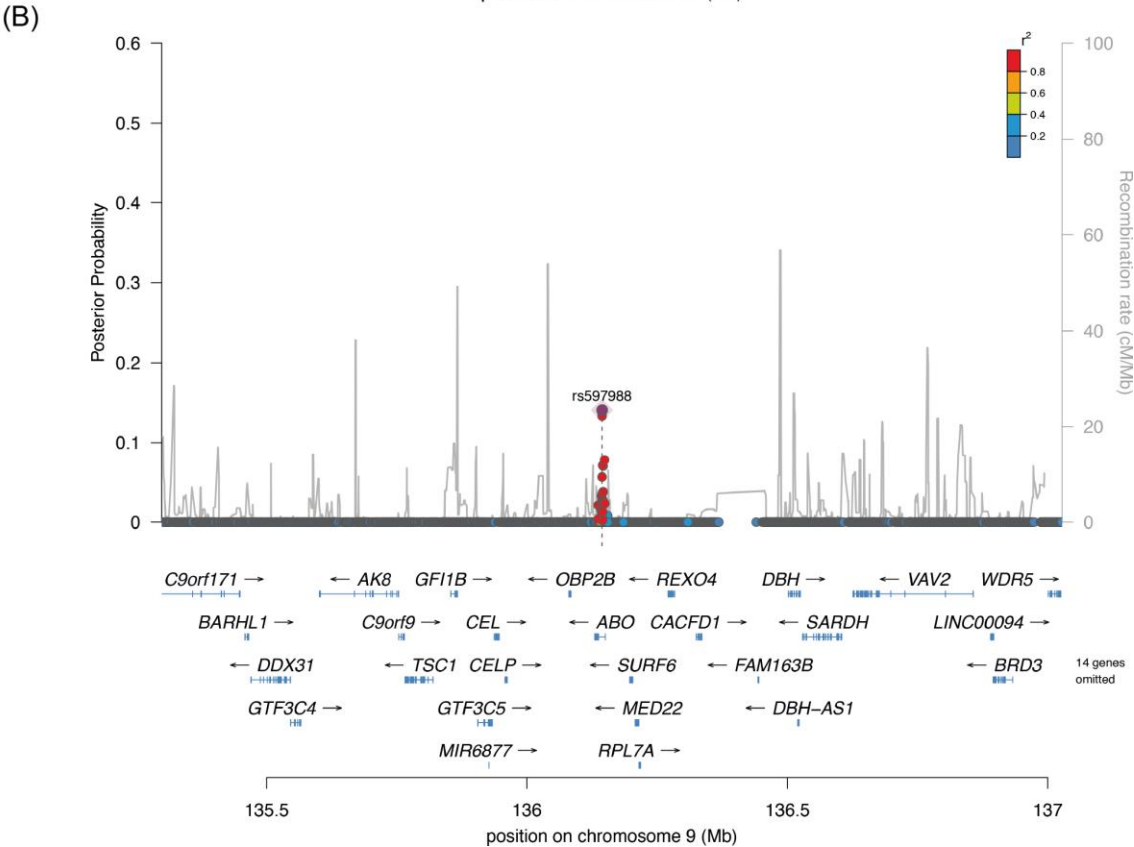
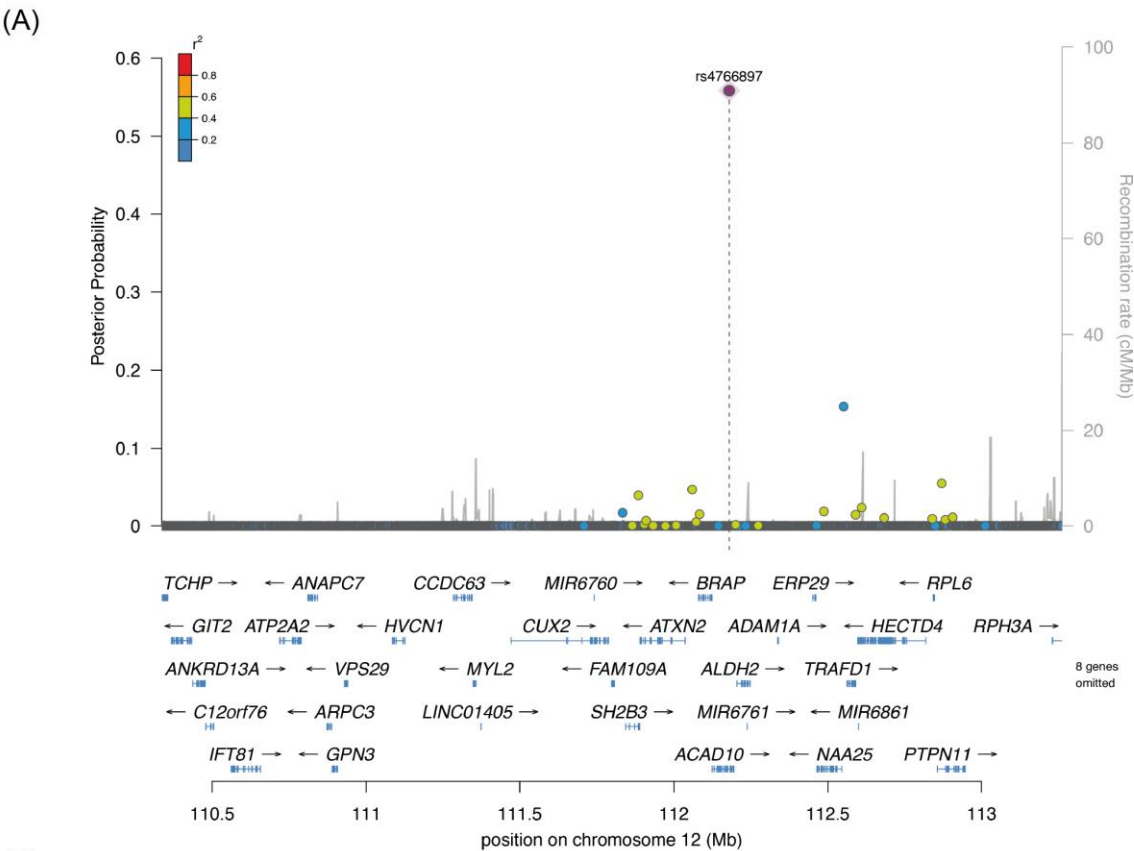
(E)



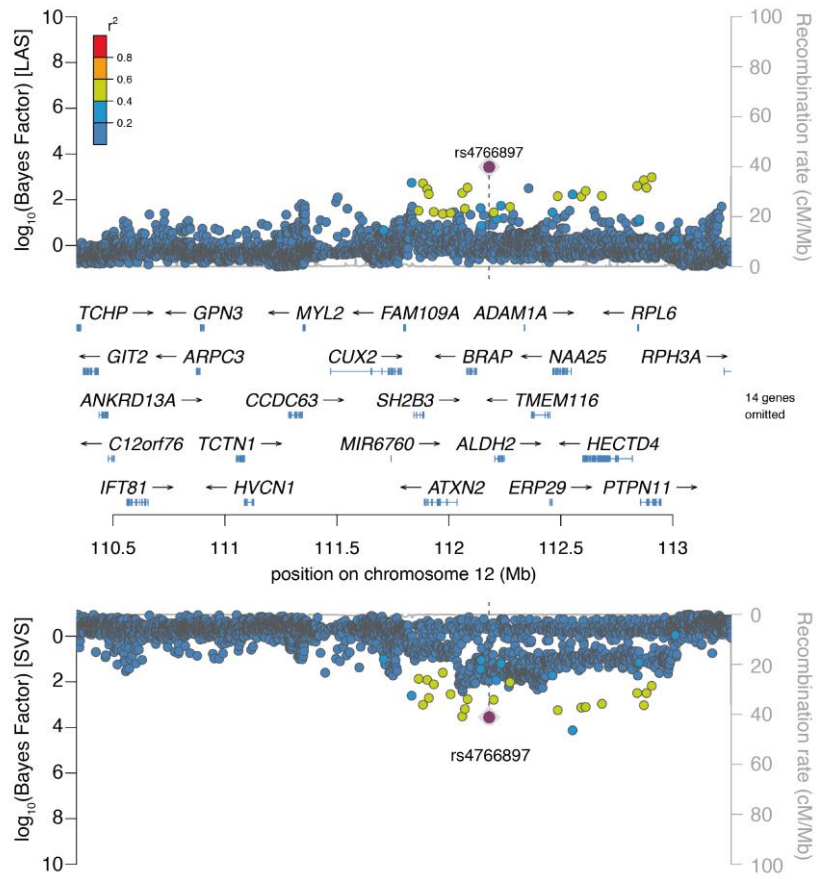
Supplementary Figure 10



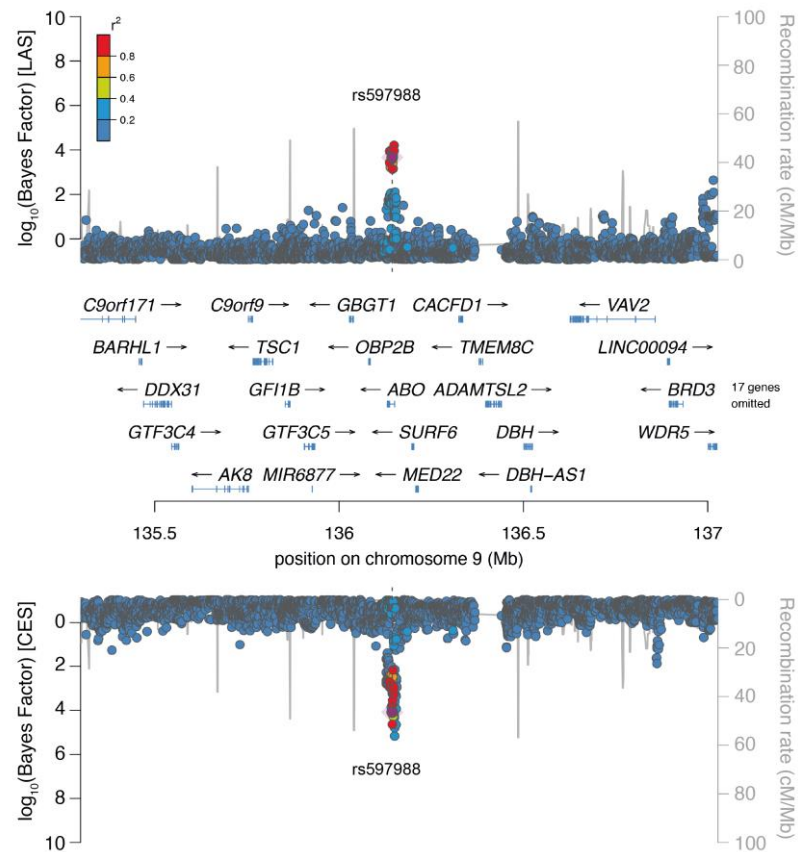
Supplementary Figure 11



(C)

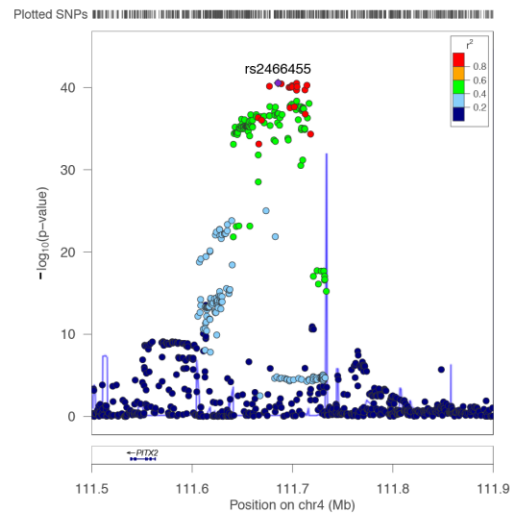


(D)

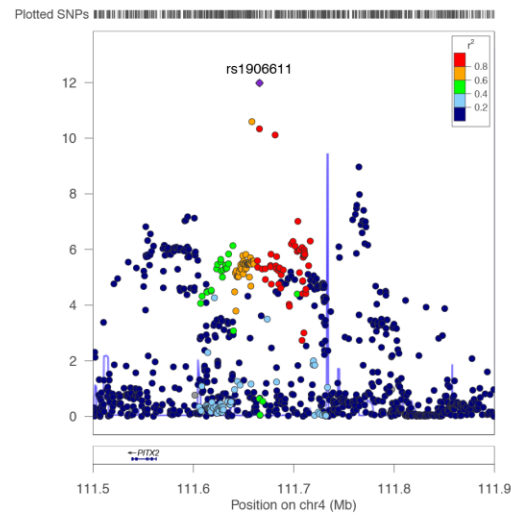


Supplementary Figure 12

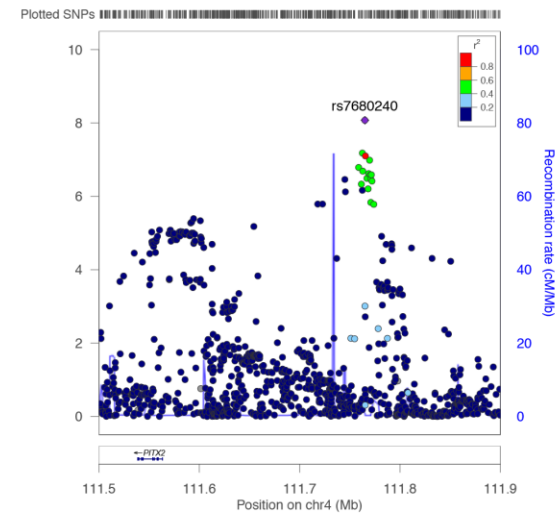
Unconditioned analysis



Conditional on rs2466455

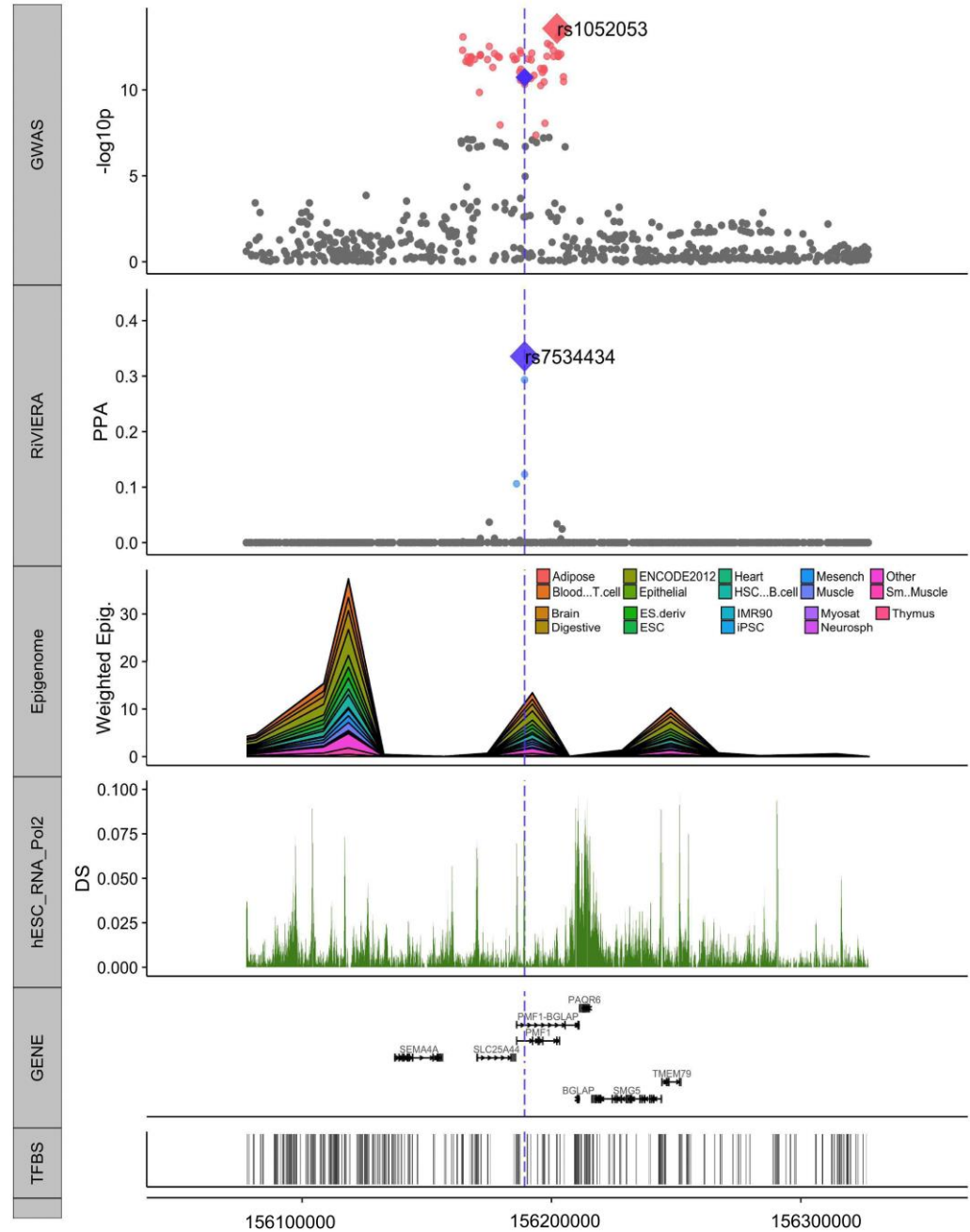


Conditional on rs2466455 & rs1906611

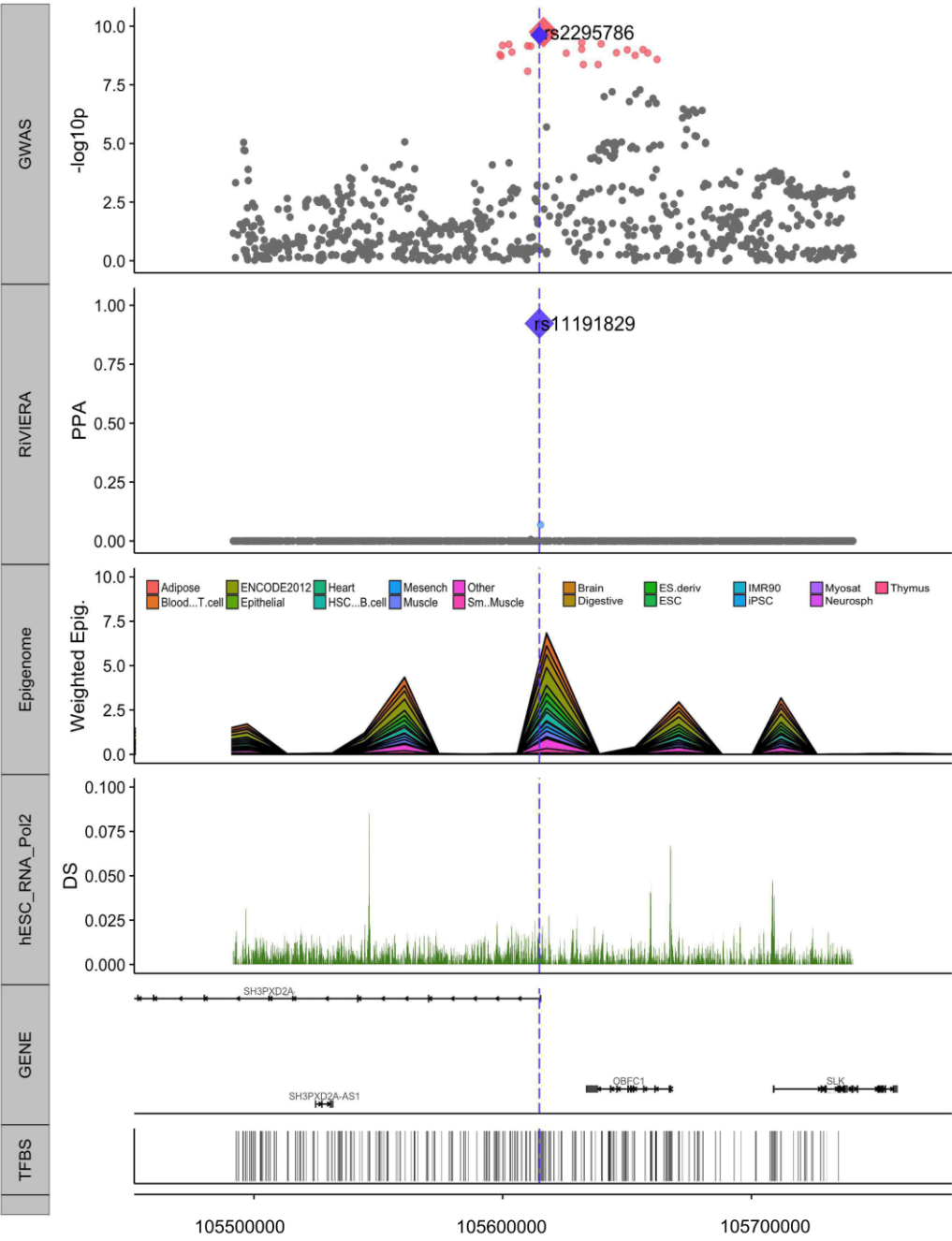


Supplementary Figure 13

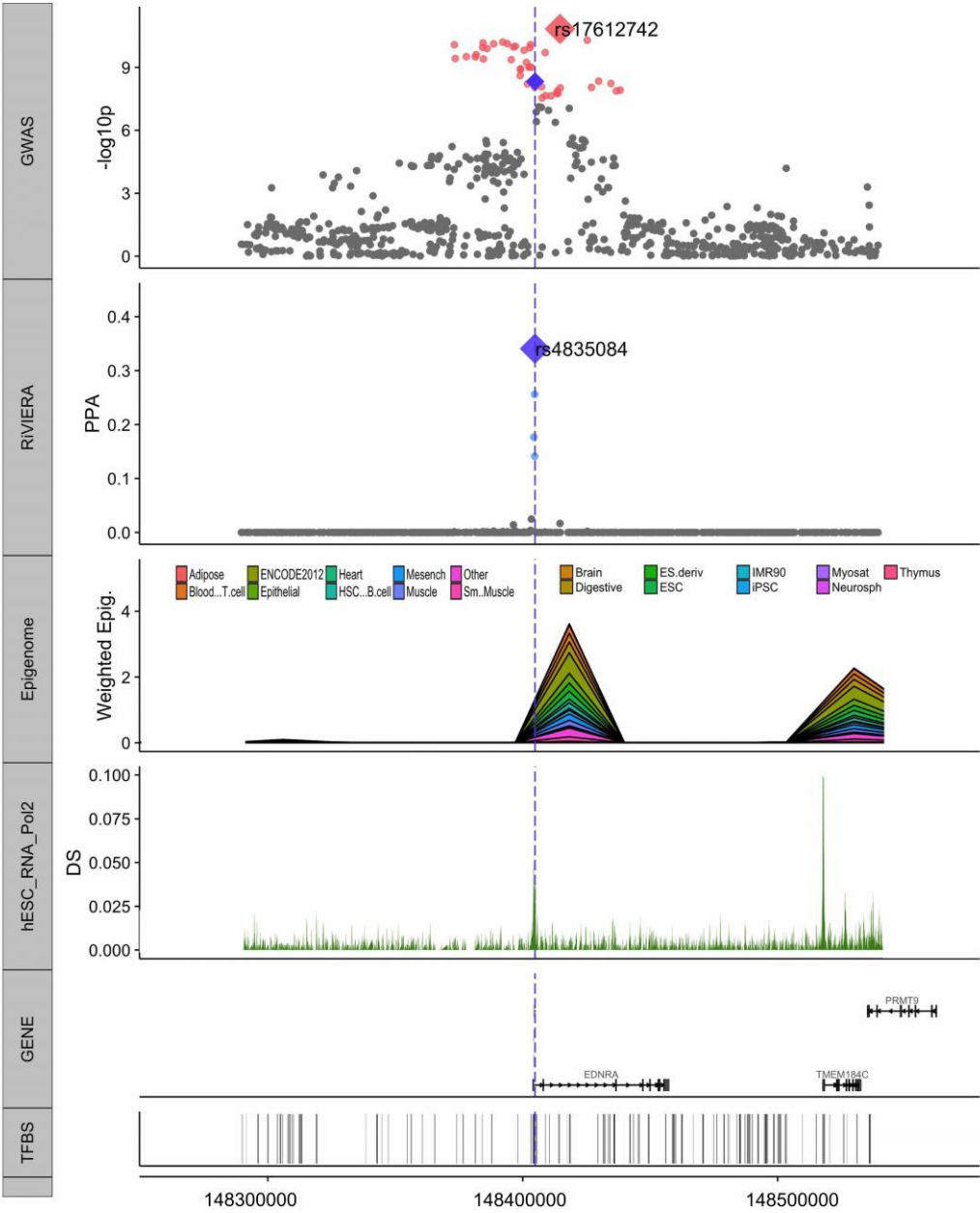
(A) PMF1-SEMA4A



(B) SH3PXD2A



(C) EDNRA



3. Supplementary Note

3.1 Description of study populations in the MEGASTROKE consortium

Stroke was defined according to the World Health Organization (WHO), i.e. rapidly developing signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin. Strokes were defined as ischemic stroke (IS) or intracerebral hemorrhage (ICH) based on clinical and imaging criteria. IS was further subdivided into the following categories mostly using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria): i) large vessel ischemic stroke (LV-IS); ii) cardioembolic ischemic stroke (CE-IS); iii) small vessel ischemic stroke (SV-IS). Subarachnoid hemorrhages were excluded from all analyses. Study-populations and study-specific stroke ascertainment and subtyping are described below.

METASTROKE consortium

Australian Stroke Genetics Collaborative (ASGC)

ASGC stroke cases comprised European-ancestry stroke patients admitted to four clinical centres across Australia (The Neurosciences Department at Gosford Hospital, Gosford, New South Wales (NSW); the Neurology Department at John Hunter Hospital, Newcastle, NSW; The Queen Elizabeth Hospital, Adelaide; and the Royal Perth Hospital, Perth) between 2003 and 2008. Stroke was defined by WHO criteria as a sudden focal neurologic deficit of vascular origin, lasting more than 24 hours and confirmed by imaging such as computerised tomography (CT) and/or magnetic resonance imaging (MRI) brain scan. Other investigative tests such as electrocardiogram, carotid doppler and transoesophageal echocardiogram were conducted to define IS mechanism as clinically appropriate. Cases were excluded from participation if aged <18 years, diagnosed with haemorrhagic stroke or transient ischemic attack rather than IS, or were unable to undergo baseline brain imaging. Based on these criteria, a total of 1230 IS cases were included in the current study. IS subtypes were assigned using TOAST criteria, based on 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 Caucasian ancestry and residing in the Hunter Region, NSW, Australia. Detailed recruitment methods for the HCS have been previously described.¹ Briefly, participants were randomly selected from the NSW State electoral roll and contacted by mail between 2004 and 2007. Consenting participants completed five detailed self-report questionnaires and attended the HCS data collection centre, at which time a series of clinical measures were obtained. A total of 1280 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 relevant institutional ethics committees.

Bio-Repository of DNA in Stroke (BRAINS)

The Bio-Repository of DNA in Stroke (BRAINS) is an international study recruiting highly phenotyped patients with stroke. For the purposes of the current work all patients were Caucasians.

Diagnosis of stroke was confirmed using positive imaging (MRI or CT) and ischemic stroke subtypes were assigned using TOAST criteria, based on clinical, imaging and risk factor data. Controls were European-Ancestry, stroke-free participants from the shared WTCCC controls, a prospectively

collected cohort of individuals born in 1958 (1958 Birth Cohort). The cohort has been described in detail elsewhere.²

Genetics of Early Onset Stroke (GEOS) Study

GEOS is a population-based case-control study designed to identify genes associated with early-onset stroke in patients with first-ever ischemic stroke aged 15-49 years from the greater Baltimore-Washington area between 1992 and 2008. Only patients of European descent are included in this meta-analysis.

Cases were identified through discharge surveillance from 59 participating hospitals and direct physician referral from a defined geographic region. Abstracted medical records were reviewed and adjudicated for ischemic stroke subtype by two neurologists, with discrepancies resolved by a third neurologist. Controls with no history of ischemic stroke were identified through random digit dialing and were frequency-matched to cases based on sex, age, geographic location and, during the later study periods, ethnicity.

Heart Protection Study (HPS)

The Heart Protection Study (HPS) was a large randomized trial involving individuals at increased risk of vascular events.³ Between 1994-1997 20,536 men and women aged 40-80 years were recruited from 69 collaborating hospitals in the United Kingdom (with ethics committee approval). Participants were eligible for inclusion provided they had non-fasting blood total cholesterol concentrations of at least 135 mg/dL (3.5 mmol/L) and either a previous diagnosis of coronary disease, ischemic stroke, other occlusive disease of non-coronary arteries, diabetes mellitus, or (if were men 65 years or older) treated hypertension. None of them was on statin therapy. At the initial screening visit, all participants provided written consent and began a “run-in” phase involving 4 weeks of placebo followed by 4 to 6 weeks of 40 mg simvastatin daily, after which compliant and eligible individuals were randomly allocated 40 mg simvastatin daily or matching placebo for approximately 5 years. Individuals entering HPS with a clinical diagnosis of ischemic stroke were used as cases in the METASTROKE study. Individuals entering HPS with pre-existing diabetes but no history of cerebrovascular disease, coronary heart disease or peripheral vascular disease were used as controls.

Ischemic Stroke Genetics Study (ISGS)/ Siblings With Ischemic Stroke Study (SWISS)

SWISS is a prospective multicenter affected sibling pair study of first-ever or recurrent ischemic stroke. Subjects were recruited from 54 enrolling hospitals across the US and Canada. Samples were collected between 1999-2011. Ischemic stroke probands were enrolled at 66 US medical centers and 4 Canadian medical centers. All recruits were extensively clinically phenotyped and have imaging-confirmed ischemic stroke using either CT or MRI brain scans. 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 who also have a history of at least one living sibling with a history of stroke. Probands were excluded if 1) they had a mechanical aortic or mitral valve at the time of the index ischemic stroke, central nervous system vasculitis, or bacterial endocarditis or 2) 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 direct contact when permitted by Institutional Review Boards. Concordant siblings had their diagnosis of ischemic stroke confirmed by review of medical records by a central 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. Discordant siblings of the proband were confirmed to be stroke-free using the Questionnaire for Verifying Stroke-free Status. DNA samples were genotyped using the

Illumina 660 array and data analyses were supported by the high-performance computational capabilities of the Biowulf Linux cluster at the NIH (<http://biowulf.nih.gov>).

The Ischemic Stroke Genetic Study (ISGS) is a multicenter study where inpatient cases were recruited from five United States academic medical centers.⁴ Cases are adult men and women over the age of 18 years diagnosed with first-ever ischemic stroke confirmed by a study neurologist on the basis of history, physical examination and CT or MR imaging of the brain who were enrolled within 30 days of onset of stroke symptoms. Cases exclusion criteria include: a mechanical aortic or mitral valve at the time of the index ischemic stroke, central nervous system vasculitis, bacterial endocarditis, 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 with the diagnostic evaluation including head CT (95%) or MRI (83%), electrocardiography (92%), cervical arterial imaging (86%), and echocardiography (74%). Medical records from all cases were centrally reviewed by a vascular neurology committee and assigned ischemic stroke subtype diagnoses according to criteria from the Trial of ORG10172 (TOAST), the Oxfordshire Community Stroke Project, and the Baltimore-Washington Young Stroke Study.

MGH Genes Affecting Stroke Risk and Outcome Study (MGH-GASROS)

Cases were all consecutive patients aged 18 years presenting with ischemic stroke and admitted to the Massachusetts General Hospital (MGH) Stroke Unit through the Emergency Department, or evaluated in the MGH Neurology outpatient clinics, as well as on the inpatient Medical and Vascular Surgical services from January 2003 to July 2008. Only patients of European ancestry (confirmed by principal component analysis using genome-wide SNP data) were included in the present analysis. Ischemic stroke was defined as either (1) a radiographically proven (head CT or MRI) infarct associated with the appropriate clinical stroke syndrome, or (2) a fixed neurological deficit persisting more than 24 hours, consistent with a vascular pattern of involvement and without radiographic evidence of demyelinating disease, or other non-vascular structural disease. Patients with specific vascular disorders (vasculitis, subacute bacterial endocarditis, fibromuscular dysplasia, vasospasm) were excluded from the study. All subjects were evaluated by a neurologist upon presentation and provided informed consent. Clinical and laboratory data were collected during the admission for qualifying ischemic stroke event. Diagnostic work-up included: head CT (100%), brain MRI (90%), cervical and intracranial vessel imaging using CTA or MRA (75%), carotid and/or transcranial ultrasound (24%), echocardiography (86%), and Holter monitoring (16%). Controls were recruited among the stroke-free adults presenting to the MGH outpatient clinics and matched with the stroke cases on the basis of age, sex and ancestry information obtained from principal component analysis of GWAS data.

Milano

This study includes consecutive Italian patients referred to Besta Institute from 2000 to 2009 with stroke and included in the Besta Cerebrovascular Diseases Registry (CEDIR). Ischemic stroke cases, first ever or recurrent, confirmed on brain imaging, were selected for this study. All cases were of self-reported Caucasian ancestry and had clinically relevant diagnostic workup performed. All cases were phenotyped by an experienced stroke neurologist according to TOAST criteria, based on relevant clinical imaging and available information on cardiovascular risk factors. Controls are Italian individuals enrolled within the PROCARDIS Study, with no personal or sibling history of coronary heart disease before age 66 years.

Wellcome Trust Case-Control Consortium 2 (WTCCC2)

The WTCCC2 samples were genotyped as part of the WTCCC 2 ischemic stroke study.⁵ Stroke cases included samples recruited by investigators at St. George's University London (SGUL), University of

Oxford, University of Edinburgh 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. The University of Edinburgh collection comprised 727 ischaemic stroke cases, consecutively collected as part of the Edinburgh Stroke Study. Cases were of self-reported Caucasian ancestry, with ischaemic stroke subtypes determined according to TOAST criteria based on relevant clinical and imaging data. 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, and ascertained as part of the national child development study.⁶ 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.⁷ 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.

VISP

Population. VISP 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. 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)

Stroke Ascertainment. 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.

Genotyping. Samples were genotyped at the Center for Inherited Disease Research using the Illumina HumanOmni1-Quad_v1-0_B BeadChip (Illumina, San Diego, CA, USA). Genotype data from the VISP study, through GARNET, is available via dbGAP, Study Accession: phs000343.v1.p1; http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000343.v3.p1)

WHI

The Women's Health Initiative Hormone Trial HT (WHI-HT) consisted of two separate clinical trials in postmenopausal women ages 50 to 79 years at baseline—a trial of combined estrogen and progestin (Estrogen plus Progestin or E+P) in women who had an intact uterus at baseline (n=16,608)⁸ and a trial of estrogen (Estrogen Alone or E-Alone) in women who had a prior hysterectomy at baseline (n=10,739).⁹ Postmenopausal women who gave written informed consent were enrolled in the WHI at 40 clinical centers in the United States. Exclusions for safety reasons included prior diagnosis of breast cancer or other cancers within the past 10 years (except nonmelanoma skin cancer). Women with systolic blood pressure (SBP) of 200 mm Hg or higher or diastolic blood pressure (DBP) of 105 mm Hg or higher were advised to see their physician within a specified period depending on blood pressure level and were temporarily excluded from the clinical trials until their blood pressure was determined to be under control. Stroke diagnosis requiring and/or occurring during hospitalization was based on rapid onset of a neurological deficit attributable to an obstruction or rupture of an arterial vessel system. Hospitalized incident stroke events were identified by semiannual questionnaires and adjudicated following medical record review, which occurred both locally and centrally. Ischemic strokes were further classified by the central neurologist adjudicators according to the Oxfordshire and Trial of Org 10172 Acute Stroke Trial (TOAST) criteria to examine stroke subtypes. The TOAST classification focuses on the presumed underlying stroke mechanism and requires detailed investigations (such as brain computed tomography, magnetic resonance imaging, angiography, carotid ultrasound, and echocardiography).

NINDS-SIGN consortium

BASEde datos de ICtus del hospital del MAR (BASICMAR)

BASICMAR is an ongoing prospective study of all acute strokes assessed since 2005 at the IMIM-Hospital Universitari del Mar (Barcelona, Spain). It includes both first-ever and recurrent strokes. There were no exclusion criteria regarding age or race-ethnicity of the individuals. All patients had an electrocardiogram (ECG), a blood analysis, and neuroimaging at the acute stage. Additional diagnostic procedures were performed when clinically indicated. A follow-up of three months after stroke was completed for all survivors.

Ischemic stroke etiologic subtypes were classified according to TOAST criteria.¹⁰ For this study, only individuals of European origin with ischemic stroke were selected from BASICMAR, with eligible events defined as a clinical syndrome of any duration associated with a radiographically proven acute infarct, without radiographic evidence of a demyelinating or neoplastic disease or other structural disease including primary intracerebral hemorrhage.

GCKSS

The GCKSS is a population-based epidemiologic study of stroke in blacks and whites that is designed to measure temporal trends and racial differences in incidence of stroke. The catchment area includes two southwestern Ohio, U.S.A., counties (Hamilton, which includes the city of Cincinnati, and Clermont to the east) and three Northern Kentucky, U.S.A., counties (Boone, Kenton, and Campbell) to the south of Cincinnati across the Ohio River. As part of the GCKSS, for calendar years 1999 and 2005, prospective cohorts of first-ever and recurrent ischemic stroke cases were assembled using "hot pursuit" methodology at all local hospitals in the region (18 in 1999, and 17 in 2005), except for one hospital that is solely devoted to treating pediatric cases. Participants remained eligible if they were in a treatment trial, but participation in a treatment trial was not required for enrollment. Subjects with all degrees of severity of stroke were eligible, and no particular racial group was intentionally oversampled (about 80% were white participants and 20% black). Study research nurses prospectively screened inpatient admission and emergency department logs to identify acute

ischemic stroke patients. When a case was identified and the treating physician had given permission to approach the patient, a study nurse asked the subject or a proxy (the most closely related competent individual, preferably a person living with the subject prior to the stroke) to consent to participate in the cohort. After consent was granted, a study nurse performed an extensive interview, and a blood sample was obtained for genetic analysis. In addition, a study nurse abstracted information about the individual, the subject's medical history, the stroke event, and imaging studies from the hospital chart. A study physician reviewed every abstract, along with the imaging studies, to verify that an acute stroke had occurred, and to classify the event according to TOAST¹⁰ and CCS criteria.¹¹

GRAZ

Between 1994 and 2003, subjects with first-ever and recurrent ischemic strokes admitted to the stroke unit of the Department of Neurology, Medical University of Graz (Graz, Austria) were included. All race-ethnic groups were eligible and there was no intentional oversampling. All age groups were allowed, though only subjects above the age of 18 were admitted to our department. Ischemic stroke was defined as an episode of focal neurological deficits with acute onset and lasting > 24 hours. There were no selection criteria based on stroke severity. Those individuals in treatment trials were excluded. 685 subjects were eligible to participate in this study (278 women, 407 men). All cases were Caucasian. Mean age was 68.9 ± 13.8 years with an age range from 19 – 101 years. In addition to a standardized protocol including a laboratory examination and carotid ultrasound or magnetic resonance angiography and ECG, 304 subjects underwent neuroimaging by CT and 381 by MRI. More extensive cardiac examination, including transesophageal echocardiography or transthoracic echocardiography and Holter, was performed in subjects with suspected cardiac embolism. Stroke subtypes were assessed according to modified TOAST criteria¹ and were conducted by trained stroke neurologists.

KRAKOW

All consecutive subjects with ischemic stroke (fulfilling WHO criteria¹²(3)) who were admitted to the Stroke Unit at the Jagiellonian University (Krakow, Poland) and who provided informed consent were included in the study. The Stroke Unit serves as a stroke emergency center for one district of Krakow, Poland (200,000 inhabitants) and as a referral center for South East Poland (up to 15% of all admissions). For this on-going, prospective single-center, hospital-based study participants with first ever or recurrent strokes were recruited from January 22, 2002 to September 9, 2010. The local research ethics committee approved the study. Participants in treatment trials were excluded. All subjects were of European origin. Stroke severity was not a criterion for inclusion or exclusion. All cases had performed clinically relevant diagnostic workup, including brain imaging with CT (100%) and/or MRI (up to 20%) as well as ancillary diagnostic investigations including duplex ultrasonography of the carotid and vertebral arteries (approximately 90%), and transthoracic echocardiography (approximately 70%). Magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and ambulatory ECG monitoring, transesophageal echocardiography and blood tests for hypercoagulability were performed. Stroke cases were classified into etiologic subtypes according to TOAST.¹⁰ All cases were phenotyped independently by two experienced stroke neurologists with review of original imaging. Cases were subsequently classified additionally using the CCS system¹¹.

Leuven Stroke Genetics Study (LSGS)

Cases of European descent with cerebral ischemia, defined as a clinical stroke with imaging confirmation or a TIA with a new ischemic lesion on diffusion-weighted imaging, who were admitted to the Stroke Unit of the University Hospitals (Leuven, Belgium) were enrolled in the LSGS between 2005 and 2009. All participants from the LSGS study underwent brain imaging (MRI in 91% of

patients, CT in the remainder) and a standardized protocol including lab examination, carotid ultrasound or CTA and cardiac examination (echocardiography and ambulatory ECG monitoring) in all patients. Based on clinical presentation and results from the diagnostic work-up, cases were classified into ischemic stroke etiologic subtypes according to modified TOAST criteria¹⁰ by a single reviewer. The reviewer had access to all information and imaging. Large-vessel disease was defined as either occlusive or significant stenosis (corresponding to > 50% luminal diameter reduction according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria¹³ of a clinically relevant pre-cerebral or cerebral artery, presumably due to atherosclerosis. Carotid ultrasound was used as a screening tool, and in principle, additional imaging with CTA or MRA was performed when a high-grade stenosis was identified. In case CTA was used as the primary imaging modality, stenosis was confirmed by carotid ultrasound. In case of posterior circulation infarcts on imaging, CTA or MRA was used as the primary imaging modality to determine the degree of stenosis. Probable causes of cardiac embolism were excluded. The presence of a patent foramen ovale was not considered a cardiac source in this context. Intracranial atherosclerosis was considered present only if repeat imaging after at least one week revealed a similar degree of stenosis or persistent occlusion. If not, the findings were interpreted as an embolism from a proximal source. Small-vessel disease was defined as a symptomatic infarct of < 20 mm on DWI in areas supplied by single, small penetrating branches from middle cerebral artery, posterior cerebral artery or basilar artery in the absence of both a cardioembolic source and significant stenosis/occlusion due to atherosclerosis of an appropriate major brain artery. Cardioembolic stroke was defined as ischemic stroke in the presence of atrial fibrillation, sick sinus syndrome, myocardial infarction in the past four weeks, cardiac thrombus, infective endocarditis, atrial myxoma, prosthetic mitral or aortic valve, valvular vegetations, left ventricular akinetic segment, dilated cardiomyopathy, or patent foramen ovale or atrial septal aneurysm. Significant stenosis/occlusion due to atherosclerosis of an appropriate pre-cerebral or cerebral artery should be excluded. Other determined cause of stroke included those with arterial dissection, vasculitis, hematologic disorders, monogenic syndromes and complications of cardiovascular procedures. Dissection was diagnosed by typical findings on contrast-enhanced MRA and T1-fat suppressed MRI. Cryptogenic stroke was defined when no cause was identified despite an extensive evaluation. Strokes associated with significant aortic arch atheroma with plaques of ≥ 4 mm were also considered cryptogenic strokes. In addition to this primary classification, cases were reclassified using CCS.¹¹

Lund Stroke Register (LSR)

The LSR is an ongoing study including consecutive subjects with first-ever stroke since March 1, 2001 from the local uptake area of Skåne University Hospital, Lund (Sweden). Stroke was defined using the WHO criteria.¹² Subjects aged 18 years or older with stroke caused by cerebral infarct, intracerebral hemorrhage or subarachnoid hemorrhage are included. Cases are included regardless of stroke severity, race-ethnic group belonging, or participation in any treatment trial. Those with iatrogenic or traumatic stroke are excluded.

In the discovery phase of the SiGN study, subjects from LSR with first-ever ischemic stroke between March 1, 2001 and February 28, 2010 were included if they or their next of kin provided informed consent. Age over 90 years was set to 90 years to maintain anonymity. Every participant underwent CT, MRI, or autopsy of the brain; and ECG. Echocardiography, ultrasound, CTA or MRA of cerebral arteries was performed when judged clinically relevant. The subtype of ischemic stroke was determined using CCS.¹¹

For the secondary phase of SiGN, LSR individuals not included in the SiGN discovery phase participated after genotyping in the South Swedish genome-wide association study as follows: first ever ischemic stroke cases recruited in 2006 and 2010 to 2012, and age- and sex-matched LSR control

subjects without stroke recruited in 2001 to 2002 and 2006 to 2007 from the same geographical area with use of the official Swedish population register.

Middlesex County Ischemic Stroke Study (MCISS)

The MCISS was initiated as a prospective hospital based stroke registry at the New Jersey Neuroscience Institute (Edison, NJ, U.S.A.). All cases over age 18 years were included, and no specific ethnic/racial group was targeted or excluded. From 2000 to 2009, 1,139 subjects with ischemic strokes were enrolled in this registry. There was no selection criterion based upon stroke severity, and both first-ever and recurrent strokes were included. Cases that were participants in treatment trials were not excluded. The major race/ethnic groups are Whites (67.2%), African Americans (14.3%), Asian Indians (8.2%), Hispanic (5.5%) and others (4.8%, Chinese and other Asians). All subjects with clinical suspicion of a stroke were admitted through the emergency room to a dedicated stroke unit supervised by a vascular neurologist. After a history and neurological examination, a standardized series of investigations were performed: complete blood count and differential, comprehensive metabolic panel, electrolytes, blood urea nitrogen, creatinine, lipid panel (total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride levels, homocysteine levels, a cerebral MRI/MRA (if the MRI could not be performed, a head CT scan was done), carotid duplex ultrasound, ECG and an echocardiogram. The diagnosis of cerebral infarct was confirmed by the imaging studies. The epidemiological and clinical data on these participants was collected prospectively. Two independent investigators (one of which was a board-certified neurologist with expertise in vascular neurology) reviewed the data, and all strokes were classified into etiological subtypes using TOAST criteria¹⁰. In addition, the Oxfordshire stroke classification¹⁴ was applied, and the vascular distribution of stroke was tabulated. All procedures, including the generation of the databases and recruitment of the stroke subjects, were conducted following Institutional Review Board policies and procedures at the New Jersey Neuroscience Institute/JFK Hospital.

Miami Stroke Registry and Biorepository (MIAMISR)

The MIAMISR at the University of Miami/Jackson Memorial Hospital (Miami, FL, U.S.A.) is an ongoing prospective hospital registry of consecutive patients subjects with prevalent stroke (ischemic and hemorrhagic) and TIA with available neuroimaging (CT or MRI) who provide informed consent. There are no specific exclusion criteria with the respect to age, stroke severity, disability or participation in treatment trials. It was established in November of 2008 in order to investigate stroke type, ischemic stroke subtypes, stroke genetics and stroke outcomes in diverse ethnic population of Miami. The stroke population is predominately Hispanic (63%), with Cuba (32%), Nicaragua (4.8%), Colombia (4.8%), and Puerto Rico (4.1%) contributing the most subjects. Jackson Memorial Hospital is a 1,550-bed county hospital affiliated with the University of Miami with approximately 900 stroke and TIA admissions per year. Demographic and clinical data along with blood samples for genetic and other research have been collected prospectively during the hospitalizations. Follow-up information was obtained at 90 days by telephone interview or in person. Trained research staff obtained written informed consent from the stroke patients or the health care proxy when available for participation in MIAMISR.¹⁵

Nurses' Healthy Study (NHS)

The NHS cohort consists of 121,700 female registered nurses aged 30 – 55 years who were residing in 11 U.S. states and who were enrolled in 1976 through responding to a mailed questionnaire on their medical history and lifestyle practices. They have been followed with biennial mailed questionnaires collecting information on disease risk factors and health status. From 1989 – 1990, blood samples were collected from 32,826 participants. Among these participants, we prospectively identified incident strokes and confirmed ischemic stroke cases by medical record review. Clinical symptoms

consistent with stroke and exclusion of alternate etiologies were required for classification of stroke. Virtually all cases had imaging, but confirmation on CT or MRI was not required. No participants were excluded based on race/ethnicity. Neither stroke severity nor enrollment in a treatment trial was part of the eligibility criteria.

Northern Manhattan Study (NOMAS)

NOMAS is an ongoing population-based study designed to determine stroke incidence, risk factors and outcome in an urban multiethnic population.¹⁶ NOMAS started in 1993 as a case-control study of index ischemic stroke cases admitted to the Columbia University Presbyterian Medical Center (New York, NY, U.S.A.) and affiliated hospitals and matching community controls (Northern Manhattan Stroke Study, NOMASS) and continued as a prospective stroke incidence study by following up controls in 1997 (NOMAS). Demographic and clinical data were collected prospectively during the hospitalizations and annually by phone or in person. Genetic samples were derived from two sources: (a) the population-based case-control study conducted from 1993-98 (NOMASS) and (b) the ongoing prospective cohort study (NOMAS). First-ever ischemic stroke cases were identified for the case-control study by screening of patient admissions, discharge codes, and referrals for neuroimaging at 15 acute care hospitals in the defined study area and multiple approaches to monitor for non-hospitalized cases. Incident ischemic stroke cases were identified from the prospective cohort study through follow-up visits and scheduled telephone contacts. Ischemic stroke cases from both sources were followed at 6 months by telephone and then annually afterwards in order to assess functional status and other outcomes. The administrative coordinating center of NOMAS moved from New York to Miami in 2007. The Institutional Review Boards of both institutions, Columbia University and the University of Miami (Miami, FL, U.S.A.), approved the study.

Reasons for Geographic and Racial Differences in Stroke (REGARDS)

The REGARDS study is a U.S. national, population-based, longitudinal cohort of 30,239 African American and white adults aged ≥ 45 years, recruited January 2003 to October 2007 with ongoing follow-up. Suspected stroke is queried every six months and triggered by participant self-report of stroke, stroke symptom(s), hospitalization, or proxy report of death. Stroke severity and participation in a treatment trial did not limit inclusion in this study. Medical records for these reported events are retrieved and reviewed by at least two members of a committee of stroke experts with disagreements resolved by a third adjudicator. A symptom-based approach, independent of neuroimaging outcome, is used to confirm events using the WHO definition of stroke.¹² An infarct did not need to be seen on brain imaging to be included in this study. Ischemic stroke subtype classification is conducted using the TOAST system.^{10, 17}

Secondary Prevention of Small Subcortical Strokes (SPS3)

The SPS3 trial (NCT00059306) is a randomized, multicenter, Phase 3 trial of antiplatelet therapy and antihypertensive therapy. Participants are randomized to aspirin alone or the combination of aspirin and clopidogrel. Participants are also randomized to two groups of blood pressure control: either to a target systolic blood pressure of 130 – 149 mm Hg or < 130 mm Hg. Principal eligibility criteria include man or woman at least 30 years of age with clinical evidence of small subcortical stroke and brain MRI evidence of small subcortical infarct. Subjects were required to not have evidence of ipsilateral symptomatic cervical carotid stenosis or high-risk cardioembolic sources for embolism. Further details of eligibility criteria have been published.¹⁸ Primary outcomes include ischemic and hemorrhagic stroke. DNA samples were collected from 38% (1,139/3,020) of participants in the trial. These samples were obtained from 46% (37/81) participating centers across the U.S., Canada, Spain, Mexico, Chile, Ecuador and Peru. No additional eligibility criteria were necessary beyond informed

consent for participating in the DNA sub-study. A total of 0.9% (10/1,139) of DNA donors gave sample at time of randomization, with the remainder donating at a later time point in follow-up.

Washington University St. Louis (WUSTL) Study

The WUSTL patient collection included ischemic stroke cases admitted to Barnes-Jewish Hospital/Washington University Medical Center (St. Louis, MO, U.S.A.) for genetic studies starting from August 1, 2008. Participants were identified for the genetic studies by screening admissions at our tertiary care hospital (both in the Emergency Department and on the Inpatient Stroke Service) without regard to age, race or ethnicity, including both first-ever and recurrent strokes. Subjects were retained in the study if their discharge diagnosis was ischemic stroke (without requirement for the stroke to be visualized on CT or MRI). Demographic and clinical data were collected prospectively during the hospitalization and at 90 days, by phone or in person. Genetic samples were derived from subjects enrolled in 3 different studies: (a) Acute tPA pharmacogenomics study (Ischemic stroke cases who received tPA and were admitted to BJH/Washington University; serial NIHSS scores,¹⁹ and data on hemorrhagic transformation was collected) (b) Recovery Genomics after Ischemic Stroke Study (ReGenesIS, Ischemic stroke cases with NIHSS > 3 points without underlying chronic neurological disease, and expected survival up to 3 months after stroke), and (c) the Cognitive Recovery and Rehabilitation Group (CRRG) Registry (all ischemic stroke cases admitted to BJH/Washington University who consent to entering their clinical data into a stroke registry, and the collection of blood for genetic analysis). Cases that were part of a treatment trial were excluded from the tissue plasminogen activator pharmacogenomics and ReGenesIS study, but not the CRRG registry.

Controls for discovery analysis

Attention-deficit Hyperactivity Disorder (ADHD)

The Vall d'Hebron Research Institute (VHIR) cohort included 435 blood donors of Caucasian origin recruited from 2004 to 2008 at the Hospital Universitari Vall d'Hebron (Barcelona, Spain) to identify loci conferring susceptibility to Attention-Deficit Hyperactivity Disorder. Seventy-six percent of participants were male (N = 330) and the average age at assessment was 43.8 years (s.d. = 14.3). Genome-wide genotyping was performed with the Illumina HumanOmni1-Quad BeadChip platform. The study was approved by the ethics committee of the institution and informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Health ABC (HABC)

The Health Aging and Body Composition (Health ABC) Study is a National Institute on Aging (NIA)-sponsored cohort study of the factors that contribute to incident disability and the decline in function of healthier older persons, with a particular emphasis on changes in body composition in old age. Between April 15, 1997 and June 5, 1998, the Health ABC study recruited 3,075 70 – 79 year old community-dwelling adults (41% African American), who initially had no indications of disability related to mobility and activities of daily living. The key components of Health ABC include a baseline exam, annual follow-up clinical exams, and phone contacts every six months to identify major health events and document functional status between clinic visits.

The core yearly examination for Health ABC includes measurement of body composition by dual energy x-ray absorptiometry (DXA), walking ability, strength, an interview that includes self-report of limitations and weight, and a medication survey. At baseline, visceral adiposity was measured by computerized tomography (CT). Provision has been made for banking of blood specimens and

extracted DNA (HealthABC repository). The overall goal of this project is to identify genetic determinants of visceral adiposity.

Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) was initiated in 2006 to investigate the prevalence and risk factors affecting several health conditions, including heart, lung and blood disorders, kidney and liver function, diabetes, cognitive function, dental conditions and hearing disorders.^{24,25} Participants aged 18 – 74 self-identified as Hispanic or Latino, with substantial representation of Mexican, Puerto Rican, Dominican, Cuban, Central and South American groups. They were recruited from four field centers in the United States: San Diego, CA; the Bronx, NY; Chicago, IL; and Miami, FL. 12,803 study participants consented to genetic studies and will be included in the HCHS/SOL dbGaP posting.

Genotyping of the HCHS/SOL participants was performed at Illumina Microarray Services using the SOL HCHS Custom 15041502 array (annotation version “B3”, genome build 37), which includes 2,575,443 variants (of which 2,427,090 are in common with the Illumina HumanOmni2.5 and 148,353 are custom content).

Health and Retirement Study (HRS)

The University of Michigan Health and Retirement Study (HRS) is a longitudinal panel study that surveys a representative sample of more than 20,000 Americans over the age of 50 every two years. Supported by the National Institute on Aging (NIA U01AG009740) and the Social Security Administration, the HRS explores the changes in labor force participation and the health transitions that individuals undergo toward the end of their work lives and in the years that follow.

Since its launch in 1992, the study has collected information about income, work, assets, pension plans, health insurance, disability, physical health and functioning, cognitive functioning, and health care expenditures.

HRS is intended to be a nationally representative sample with 2:1 oversampling of minority groups including African-American and Hispanic/Latino populations.²⁶ In Phases I – II, 12,507 study participants were included in the dbGaP posting.

Genotyping of the HRS Phase I – II participants was performed at CIDR using the Illumina HumanOmni2.5-4v1 array (annotation version “D”, genome build 37) and released a total of 2,443,179 variants.

Infancia y Medio Ambiente (INMA)

The INfancia y Medio Ambiente (Environment and Childhood) project is a research project comprising a Spanish population-based birth cohort created to study the role of the environmental pollutants during pregnancy and first stages of life and their effects on childhood growth and development. The cohort was established between 2003 and 2008 from mothers enrolled in four regions within Spain and included their infants.

MONICA/KORA Augsburg Study

For the German MUNICH discovery samples and the Stroke in Young Fabry Patients (SIFAP) samples, independent control groups were selected from Caucasians of German origin participating into the population KORAgene study. This survey represents a sex- and age stratified random sample of all German residents of the Augsburg area and consists of individuals 25 – 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.

KORA samples were genotyped on the Illumina Human 550k platform. QC was identical for all WTCCC cohorts.

KRAKOW

The control group included unrelated subjects taken from the population of southern Poland. Control subjects had no apparent neurological disease based on the findings in a structured questionnaire and a neurological examination. Local research ethics committees approved the study and informed consent was obtained from all participants.

Leuven Stroke Genetics Study (LSGS)

Control individuals were recruited in the same population amongst healthy individuals, spouses of patients suffering from neurological diseases (amyotrophic lateral sclerosis, ischemic stroke or multiple sclerosis), and from the Leuven University Gerontology Database as previously described.²⁷

Osteoarthritis Initiative (OAI)

The OAI is a publicly and privately funded prospective longitudinal cohort with a primary objective of identifying risk factors for incidence and progression of tibiofemoral knee OA. The OAI utilized a focused population-based recruitment to enroll 4,674 men and women between the ages of 45 – 79 years who either had radiographic symptomatic knee OA or who were without radiographic symptomatic OA in both knees but were considered high risk for OA because they had two or more known risk factors for knee OA. Subjects were recruited into the baseline phase of the OAI at multiple sites throughout the US between 2004 and 2006. All subjects were invited back for follow-up examinations to assess incidence or progression of OA annually, for up to 5 years.

Phenotype data from the baseline and follow-up examinations are available for public access from the Osteoarthritis Initiative (OAI) database.

The Genetic Components of Knee Osteoarthritis (GeCKO) Study was initiated in 2009 as a genetic ancillary study to perform a genome-wide association study to identify genetic variants associated with radiographic osteoarthritis. This study included 4,482 individuals participating in the parent OAI study genotyped on the Illumina HumanOmni2.5M

CHARGE consortium

We combined data from white participants in eighteen large, prospective community-based cohort studies, participating in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium.²⁰

All participating studies approved guidelines for collaboration, and a neurology working-group arrived at a consensus on phenotype harmonization, covariate selection and analytic plans for within-study analyses and meta-analysis of results. Each study has an Institutional Review Board that approved the consent procedures, examination and surveillance components, data security processes, genotyping protocols and current study design.

The structure of each participating cohort study is summarized below.

Age, Gene/Environment Susceptibility (AGES) -Reykjavik Study

The AGES-Reykjavik Study is a single center prospective cohort study based on the Reykjavik Study. The Reykjavik Study was initiated in 1967 by the Icelandic Heart Association to study cardiovascular disease and risk factors.²¹ The cohort included men and women born between 1907 and 1935 who lived in Reykjavik at the 1967 baseline examination. Re-examination of surviving members of the cohort was initiated in 2002 as part of the AGES-Reykjavik Study. The AGES-Reykjavik Study is designed to investigate aging using a multifaceted comprehensive approach that includes detailed measures of brain function and structure. All cohort members were European Caucasians. Briefly, as part of a comprehensive examination, all participants answered a questionnaire, underwent a clinical examination and had blood drawn. Among AGES participants with GWAS data (N=3,219), after exclusion of participants with prevalent stroke (N=224), and those without follow-up for incident stroke events (N=114), N=2,996 participants were available for analyses.

Stroke ascertainment in AGES: Incident stroke cases were ascertained from multiple sources including hospital, general practice, nursing home records and death certificates. All possible cases were adjudicated with standard TOAST criteria by two Neurologists and a Neuroradiologist with expertise in evaluating stroke cases for epidemiologic studies.

Cardiovascular Health Study (CHS) – European Ancestry

The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥ 65 years conducted across four field centers.²⁹ The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons was enrolled for a total sample of 5,888. Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. Because the other cohorts in the CHARGE analysis were predominantly European ancestry, the African American participants were excluded from this analysis to reduce the possibility of confounding by population structure. European ancestry participants were excluded from this GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack, or lack of available DNA. Beyond laboratory genotyping failures, participants were excluded if they had a call rate $\leq 95\%$ or if their genotype was discordant with known sex or prior genotyping. After quality control, genotyping was successful for 3,268 European ancestry participants. CHS was approved by institutional review committees at each field center and individuals in the present analysis had available DNA and gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

Stroke ascertainment in CHS: Participants were examined annually from enrollment to 1999 and continued to be under surveillance for stroke following 1999.^{22, 23} Since baseline, participants have

also been contacted twice a year to identify potential cardiovascular events, including stroke. In addition, all hospitalizations were screened for potential stroke events. For suspected fatal and non-fatal events occurring with or without hospitalization, information was collected from the participant or next of kin, from medical records, and, if needed, from the participant's physician. When available, scans or reports of CT, MRI or both were reviewed centrally. Final at a consensus conference using all available information vascular neurologists adjudicated the occurrence of fatal and non-fatal stroke, stroke types, and subtypes. Stroke definitions were derived from the criteria used for the Systolic Hypertension in the Elderly Program (SHEP).²⁴ Stroke types were ischemic, hemorrhagic and other based on brain imaging. Hemorrhagic stroke subtypes were intra-parenchymal, subarachnoid, and other. Ischemic stroke subtypes were 1) small vessel, 2) large vessel, 3) cardioembolic, and 4) other that included mostly uncertain subtypes. The approach used in CHS was developed before the TOAST criteria were published in 1993.¹⁰ Nonetheless, the two approaches are quite similar.

FHS

The Framingham Heart Study (FHS) is a three-generation, single-site, community-based, ongoing cohort study that was initiated in 1948 to investigate prospectively the risk factors for CVD including stroke. It now comprises 3 generations of participants (N=10,333): the Original cohort followed since 1948;²⁵ their Offspring and spouses of the Offspring, followed since 1971;²⁶ and children from the largest Offspring families enrolled in 2000 (Gen 3).²⁷ Gen 3 participants were not included in this analysis since they are young (mean age 40±9 years) and few have suffered strokes. The Original cohort enrolled 5209 men and women who comprised two-thirds of the adult population then residing in Framingham, MA. Survivors continue to receive biennial examinations. The Offspring cohort comprises 5124 persons (including 3514 biological offspring) who have been examined approximately once every 4 years. The population of Framingham was virtually entirely white (Europeans of English, Scots, Irish and Italian descent) in 1948 when the Original cohort was recruited. At the initial examination participants were asked for country of birth and whether or not they had any Italian ancestry. At a later examination (the 8th) the Offspring cohort participants were asked to identify their race from the following choices: Caucasian or white, African-American or black, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska native or 'prefer not to answer'. They were either asked to identify their ethnicity as either 'Hispanic or Latino' or not. Almost all the FHS Original and Offspring participants are white/Caucasian and none were excluded from the discovery cohort. FHS participants had DNA extracted and provided consent for genotyping in the 1990s. All available eligible participants underwent genome-wide genotyping. In 272 persons (31 with stroke), small amounts of DNA were extracted from stored whole blood and required whole genome amplification prior to genotyping. Cell lines were available for most of the remaining participants. Among FHS participants with GWAS data (N=4,535), after exclusion of participants with prevalent stroke (N=138), and those without follow-up for incident stroke events (N=12), N=4,385 participants were available for analyses.

Stroke ascertainment in FHS: At each clinic exam, participants receive questionnaires, physical examinations and laboratory testing; between examinations they remain under surveillance (regardless of whether or not they live in the vicinity) via physician referrals, record linkage and annual telephone health history updates. Incident strokes have been identified since 1948 through this ongoing system of FHS clinic and local hospital surveillance and methods used have been detailed previously;²⁸⁻³⁰ they include review of medical records and collaboration with local general practitioners, emergency rooms and imaging facilities. If a participant saw a physician or was admitted to the hospital, visited an emergency room or obtained any brain imaging between biennial examinations for symptoms suggestive of TIA or stroke, a stroke neurologist from the Heart Study attempted to visit the person within 48 hours and recorded a complete history and neurological examination; this was repeated at 1,

3 and 6 months. All medical records from practitioners, hospitals, imaging centers, rehabilitation centers and nursing homes were procured for review. A panel of 3 investigators (at least 2 neurologists) adjudicated the diagnosis of stroke and determined stroke subtype in each case based on the Framingham evaluations and external records. The recruitment of Original and Offspring cohort participants at FHS had occurred long before the DNA collection with the result that the majority of stroke events in the FHS (although ascertained prospectively) were prevalent at the time of DNA collection and were excluded from these analyses. While this reduced the sample size from FHS, the meta-analyses presented here focused on incident events.

FINRISK

FINRISK surveys are cross-sectional, population-based studies conducted every 5 years since 1972 to monitor the risk of chronic diseases. For each survey, a representative random sample was selected from 25- to 74-year-old inhabitants of different regions in Finland. The survey included a questionnaire and a clinical examination, at which a blood sample was drawn, with linkage to national registers of cardiovascular and other health outcomes. The study protocol has been described elsewhere.³¹ The current study included eligible individuals from FINRISK surveys conducted in 1992, 1997, 2002, and 2007. The GWAS genotyping has been done earlier in several phases for different substudies: PredictCVD, Corogene and CoreExome.

PredictCVD is a case-cohort sample from FINRISK 1992, 1997, 2002 and 2007 studies, consisting of all CVD (either CHD or stroke) cases, plus so-called sub-cohort, representative of the general study cohort. Such sample must be analyzed taking into account the sampling weights (inverse inclusion probabilities). Information on case-cohort sampling and analyses were described elsewhere.³² Among PredictCVD participants with GWAS data (N=1,877), after exclusion of participants with prevalent stroke (N=22), or incident or prevalent CHD (but who were not in the sub-cohort, N=552), N=1,303 participants were available for analyses. Among Corogene controls with GWAS data (N=1,893), after exclusion of participants with prevalent stroke (N=6), N=1,887 participants were available for analyses. The CoreExome participants were participants from FINRISK 1997 and 2002 cohorts for whom a GWAS was not done earlier (as part of PredictCVD or Corogene studies). Among CoreExome participants with GWAS data (N=5,288), after exclusion of participants with prevalent stroke (N=86), N=5,202 participants were available for analyses.

Stroke ascertainment in FINRISK: During follow-up, participants were monitored for stroke through linkage of the study database with the National Hospital Discharge Register and the National Causes-of-Death Register. The clinical outcomes were linked to study subjects using their unique national social security ID, which is assigned to every permanent resident of Finland. The registers are countrywide covering all cardiovascular events that have led either to hospitalization or death in Finland. Their stroke diagnoses have been validated.³³ With both registers the diagnostic classification was done using the Finnish adaptation of ICD-codes: I63; not I63.6, I64 (ICD-10) / 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 (ICD-9) / 433, 434, 436 (ICD-8) for Ischemic stroke excluding any hemorrhagic strokes, and I60-I61, I63-I64 (not I63.6) (ICD-10) / 430, 431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 (ICD-9) / 430, 431 (except 431.01, 431.91), 433, 434, 436 (ICD-8) for all-stroke including SAH. ICD-8 codes 430, 431 (excluding codes 431.01, 431.91 of the Finnish adaptation of ICD-8*), 432, 433, 434 or with ICD-9 codes 430, 431, 433 (excluding codes 4330X, 4331X, 4339X of the Finnish adaptation of ICD-9*), 434 (excluding code 4349X of the Finnish adaptation of ICD-9*), 436, 437, 438 or with ICD-10 codes I60, I61, I63 (excluding I63.6), I64 or I69.³⁴ The stroke was classified as a first-ever event if there was no evidence of a previous stroke event in the patient's history. An event found in either register was sufficient for diagnosis.

Health, Aging, and Body Composition (Health ABC) Study

The Health ABC study is a prospective cohort study designed to examine the associations between body composition, weight-related health conditions, and functional limitations in older adults aged 70-79 years at inception.³⁵ In 1997-1998, 3,075 participants were recruited from a random sample of white and all African-American Medicare eligible residents in the Pittsburgh, PA and Memphis, TN metropolitan areas. Genome-wide genotyping was performed in 1732 white participants and 1663 met all QC criteria. All participants provided informed consent and protocols were approved by the institutional review boards at both study sites.

Among Health ABC participants with GWAS data (N=1663), after exclusion of participants without follow-up for incident stroke events (N=2), N=1,661 participants were available for analyses.

Stroke ascertainment in Health, Aging, and Body Composition (Health ABC) Study: Participants were screened for stroke events every 6 months alternating between semi-annual phone interviews and annual clinical visits. Any self-reported hospitalization for stroke led to medical record abstraction and verification by a Health ABC Disease Adjudicator at each site. Date and causes of death were obtained from the death certificate. Causes of death were adjudicated based on the review of medical records, proxy information and autopsy report (when performed).^{36, 37} Stroke subtyping was done from medical records review. If the medical record indicated the event was hemorrhagic or ischemic in nature, this was recorded in the Health ABC data.

Rotterdam Study

The Rotterdam Study is a population-based cohort study among inhabitants of a district of Rotterdam (Ommoord), The Netherlands, and aims to examine the determinants of disease and health in the elderly with a focus on neurogeriatric, cardiovascular, bone, and eye disease.³⁸⁻⁴⁰ All inhabitants aged ≥ 55 years (N=10,275) were invited and the participation rate was 78%, yielding a total of 7983 subjects. All participants gave written informed consent to retrieve information from treating physicians. Baseline measurements were obtained from 1990 to 1993 and consisted of an interview at home and two visits to the research center for physical examination. At this baseline examination ancestry was determined by self-report. Participants were asked to identify with one of the following categories that best described their ancestry: Dutch, Caucasian, Asian, Indian, Indonesian, Mediterranean, Negroid. Less than 1% of participants chose an ancestry other than Dutch or Caucasian. Survivors have been re-examined three times: in 1993-1995, 1997-1999, and 2002-2004. All persons attending the baseline examination in 1990-93 consented to genotyping and had DNA extracted. Genome-wide genotyping was attempted in persons with high-quality extracted DNA.

In 1990-1993, 7 983 persons 55 years of age or over participated and were re-examined every 3 to 4 years. In 1999, 3 011 individuals who had become 55 years of age or moved into the study district since the start of the study were added to the cohort (Rotterdam Study-II).⁴¹ All participants had DNA extracted at their first visit. Genotyping was attempted in participants with high-quality extracted DNA.

Among Rotterdam Study-I participants with GWAS data (N=6,291), after exclusion of participants with prevalent stroke (N=179), and those without follow-up for incident stroke events (N=46), N=6,066 participants were available for analyses.

Among Rotterdam Study-II participants with GWAS data (N=2,157), after exclusion of participants with prevalent stroke (N=76), and those without follow-up for incident stroke events (N=1), N=2,080 participants were available for analyses.

Stroke ascertainment in Rotterdam: All participants have been continuously monitored for major events (including stroke) through automated linkage of the study database with files from general practitioners and the municipality. In addition physician files from nursing homes and general practitioner records of participants who moved out of the Ommoord district were reviewed twice a

year. For suspected stroke and TIA events, both fatal and non-fatal, additional information (including neuroimaging) was obtained from general practitioner' and hospital records and research physicians discussed available information with an experienced stroke neurologist to verify all diagnoses and to subclassify the strokes. Strokes were subclassified into ischemic or hemorrhagic based on neuroimaging (CT or MRI within 3 weeks) mentioned in medical records. If a hemorrhage was shown the stroke was subclassified as hemorrhagic, if there were no signs of hemorrhage, the stroke was subclassified as ischemic. Furthermore, strokes were subclassified according to TOAST criteria based on the diagnostic workup mentioned in medical records.^{42, 43}

Study of Health in Pomerania (SHIP)

The "Study of Health in Pomerania" is a population-based epidemiological study in the region of Western Pomerania, Germany.⁴⁴ In brief, from the total population of West Pomerania comprising 213 057 inhabitants in 1996, a two-stage stratified cluster sample of adults aged 20–79 years was drawn. The net sample (without migrated or deceased persons) comprised 6 265 eligible subjects, out of which 4 308 completed their baseline examinations. From July 2007 to October 2010 the 'Life-Events and Gene-Environment Interaction in Depression' (LEGENDE) study was carried out in the SHIP cohort. After exclusion of SHIP- 1 participants without GWAS data and a positive lifetime prevalence of stroke before the SHIP-1 examination (N=188), N=3,112 participants were available for analyses.

Stroke ascertainment in SHIP: SHIP participants were followed-up after a median (range) of 5.0 (4.3–8.5) years on average. New stroke events were identified based on the following sources: Self-report by participants during the follow-up visit at the clinic center, with specific questions asking for a physician diagnosis (self-reported physician's diagnosis of stroke);⁴⁵ ICD codes based on the statutory health insurance, a survey among family doctors, inpatient visits at the Greifswald University Hospital, and Death Certificates. We included cases with fatal and non-fatal strokes. For in- and outpatient data we defined any stroke as cases with a coded ICD I61, I63, I64, I69.1, I69.3, I69.4 diagnosis. For ischemic stroke we included all cases with I63.x codes based on in- and outpatient data. Data from participants with self-reported events lacking an external validation were right censored at the estimated date of event. All participants with any stroke event from any source before the baseline examination were excluded from analyses.

Women's Genome Health Study (WGHS)

The WGHS (Women's Genome Health Study) is a large cohort for genome-wide genetic analysis of a wide range of clinical phenotypes among >25 000 women, 45 years or older at baseline and with ongoing follow-up observation, now for approximately 18 years.⁴⁶ The population is derived from participants in the Women's Health Study (WHS) who provided a blood sample at baseline. By design, participants included in the WGHS were free from dementia and stroke at baseline. Similarly, follow-up for incident stroke events was complete in the WGHS. Therefore, the total number of WGHS participants with whole genome genetic data for analysis was N=23,294.

Stroke ascertainment in WGHS: Since enrollment WGHS participants were followed-up annually for the occurrence of relevant clinical endpoints including stroke. The end-point ascertainment was continued in a blinded fashion through the scheduled end of the trial (March 31, 2004), when the cohort was converted to observational mode. Follow-up and validation of reported end points continues through the ongoing observational period. When a stroke endpoint was reported to occur, full medical reports were obtained and reviewed by an endpoints committee of physicians unaware of randomized treatment assignment. A confirmed stroke was defined as a new neurologic deficit of sudden onset that persisted for >24 h. Clinical information as well as computed tomographic scans or

MRI were used to distinguish hemorrhagic from ischemic events.⁴⁶ Stroke subtyping definition distinguishes ischemic versus hemorrhagic events according to TOAST criteria.¹⁰

Multi-Ethnic Study of Atherosclerosis (MESA)

The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease.⁴⁷ MESA researchers study a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Thirty-eight percent of the recruited participants are white, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent. Only white participants were used for the present analysis.

Participants were recruited from six field centers across the United States: Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University and University of California - Los Angeles. The first examination took place over two years, from July 2000 - July 2002. It was followed by four examination periods that were 17-20 months in length. Participants have been contacted every 9 to 12 months throughout the study to assess clinical morbidity and mortality.⁴⁷

Prevalent stroke was an exclusion criterion for MESA at baseline. Among MESA white participants with GWAS data (N=2,685), we excluded those with unexpected ancestry as inferred by principal components (N=124), those with unexpected relatedness (N=35), and those without follow-up for incident stroke events (N=162), N=2,364 participants were available for analyses.

Stroke ascertainment in MESA: New occurrences of stroke were recorded over 9-years of follow-up. In brief, a telephone interviewer contacted each participant every 9–12 months. Information about all new cardiovascular conditions, hospital admissions, cardiovascular outpatient diagnoses, treatments, and deaths were obtained. To verify self-reported diagnoses, information was collected from death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnoses, using ICD-9 and ICD-10 codes. In the case of out-of-hospital deaths, next-of-kin interviews or questionnaires were administered to physicians, relatives or friends. Two physicians from the MESA study events committee independently reviewed all medical records for end point classification and assignment of incidence dates. The reviewers were blinded to the study data. If the reviewing physicians disagreed on the event classification, they adjudicated differences. Neurologists reviewed and classified stroke as present if there was a focal neurologic deficit lasting 24 hours or until death, or if <24h, there was a clinically relevant lesion on brain imaging and no nonvascular cause. Patients with focal neurological deficits secondary to brain trauma, tumor, infections, or other non-vascular cause were excluded.⁴⁸ Ischemic strokes were distinguished from hemorrhagic stroke using findings on imaging, surgery, autopsy, or some combination of these. Ischemic stroke subtypes were assigned based on an extension of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) scheme to try to reduce the number classified as undetermined.

PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)

PROSPER was a prospective multicenter randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in elderly. Between December 1997 and May 1999, we screened and enrolled subjects in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden). Men and women aged 70-82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total number of 5804 subjects were randomly assigned to pravastatin or placebo. A large number of prospective tests were performed including Biobank tests and cognitive function measurements. A detailed description of the study has been published elsewhere.^{49, 50}

Among PROSPER participants with GWAS data (N=5,244), after exclusion of participants with prevalent stroke (N=586), and those without follow-up for incident stroke events (N=0), N=4,658 participants were available for analyses.

Stroke ascertainment in PROSPER: Stroke was defined as any event that meets the criteria listed below:

(a) Ischemic stroke (1 of the following conditions must be met): (1) Rapid onset of focal neurologic deficit lasting ≥ 24 hours or leading to death plus evidence from neuroimaging (computed tomography or magnetic resonance imaging) showing cerebral/cerebellar infarction or no abnormality, or postmortem examination showing cerebral and/or cerebellar infarction. (2) Rapid onset of global neurologic deficit (e.g., coma) lasting ≥ 24 hours or leading to death plus evidence from neuroimaging showing infarction, or postmortem examination showing infarction. (3) Focal neurologic deficit (mode of onset uncertain) lasting ≥ 24 hours or leading to death plus evidence from neuroimaging showing infarction, or postmortem examination showing infarction.

(b) Primary intracerebral and/or cerebellar hemorrhage (1 of the following conditions must be met): (1) Rapid onset of focal neurologic deficit lasting ≥ 24 hours or leading to death, plus neuroimaging or postmortem examination showing primary intracerebral and/or cerebellar hemorrhage. (2) Rapid onset of global neurologic deficit (e.g., coma) lasting ≥ 24 hours or leading to death, plus evidence from neuroimaging or postmortem examination showing primary intracerebral and cerebellar hemorrhage. (3) Focal neurologic deficit (mode of onset uncertain) lasting ≥ 24 hours or leading to death, plus evidence from neuroimaging or postmortem examination showing primary intracerebral and/or cerebellar hemorrhage.

(c) Not known (1 of the following conditions must be met): (1) Rapid onset of focal neurologic deficit lasting ≥ 24 hours or leading to death, without neuroimaging or postmortem data available. (2) Rapid onset of global neurologic deficit (e.g., coma) lasting ≥ 24 hours or leading to death, without neuroimaging or postmortem data available. (3) Focal neurologic deficit (mode of onset uncertain) lasting ≥ 24 hours or leading to death, without neuroimaging or postmortem data available.

The PROSPER Endpoints Committee was responsible for the classification of all possible study endpoints. The Committee received all annual study electrocardiograms showing serial changes, information regarding domiciliary visits or hospitalizations associated with possible myocardial infarction, and information on all deaths (including postmortem reports, death certificates, hospital records, general practitioners' records, and/or interviews of family members or witnesses).

TWINGENE

The TwinGene study originates from the Swedish Twin Registry (STR).⁵¹ The STR conducted mailed questionnaires in 1961, 1963, 1967 and 1970 for all like-sexed twins born between 1886 and 1925, and in 1973 for all like-sexed pairs born in 1926–1958. A more recent STR wave contacted adult twins via the Screening Across the Lifespan Twin (SALT) study (1998–2002), which targeted all twins born in 1958 or earlier. For TwinGene, which took place between 2004 and 2008, 12 614 twins who had previously taken part in the SALT study donated a blood sample during in-person testing.

Among TWINGENE participants with GWAS data (N=9,617), after random exclusion of one twin from each pair and exclusion of participants with prevalent stroke, N=6,702 participants were available for analyses.

Stroke ascertainment in TWINGENE: Data on stroke were extracted from the Swedish National Patient Register and the Cause of Death Register using the twins' personal identification numbers; the information was based on the International Classification of Disease (ICD). Only main diagnoses were considered for cardiovascular outcomes. For stroke, the following ICD codes were used: ICD-8 codes 430–436, ICD-9 codes 430–436 and ICD-10 codes I60–I64 and G45.⁵² Further classification into stroke subtypes was done using ICD-8 codes 432–434, ICD-9 codes 433–434, and ICD-10 code I63 for

ischemic stroke, and ICD-8 codes 430-431, ICD-9 codes 430-432, and ICD-10 codes I60-I62 for hemorrhagic stroke.⁵³ One twin was randomly selected per pair if data were available for both twins.

Uppsala Longitudinal Study of Adult Men (ULSAM)

ULSAM is a unique, ongoing, longitudinal, epidemiologic study based on all available men, born between 1920 and 1924, in Uppsala County, Sweden. The men were investigated at the ages of 50, 60, 70, 77, 82 and 88 years. The ULSAM cohort focuses on identification of metabolic risk factors for cardiovascular disease, to which all 50-year-old men living in Uppsala, Sweden, in 1970-974 were invited. The ULSAM originally comprised 2322 participants (82% of the invited). A re-investigation was performed around 20 years later between 1991 and 1995.⁵⁴

Among ULSAM participants with GWAS data (N=1,179), after exclusion of participants with prevalent stroke, N=1,139 participants were available for analyses.

Stroke ascertainment in ULSAM: Information on the occurrence of stroke was extracted from the Swedish Hospital Discharge Record and Cause of Death Registries and validated by examination of all the medical records by one physician. They cover hospitalization and mortality from strokes using ICD-8 codes 430-431 and 433-434, ICD-9 codes 430-432, 434 or ICD-10 codes I60-I64. Further classification into stroke subtypes was done using ICD-8 codes 433-434, ICD-9 code 434, and ICD-10 code I63 for ischemic stroke, and ICD-8 codes 430-431, ICD-9 codes 430-432 and ICD-10 codes I60-I62 for hemorrhagic stroke.^{54, 55}

3C-Study

The Three-City study is a prospective study aiming to assess the association between vascular diseases and risk of dementia. The detailed protocol of the study has been previously described.⁵⁶ The Three-City cohort is composed of non-institutionalized individuals aged 65 years and over, randomly selected from electoral rolls of three cities of France (Bordeaux, Dijon, and Montpellier), and agreeing to participate in the study. Between March 1999 and March 2001, 9,294 persons were enrolled (4,931 in Dijon, 2,104 in Bordeaux and 2,259 in Montpellier).

Up to five face-to-face examinations were performed during follow-up. Trained nurses and psychologists performed interviews and physical and cognitive measurements at the participant's home and at the study centre. As imputation was performed separately in the 3C-Dijon sample on the one hand and the Bordeaux and Montpellier samples on the other hand, analyses were run separately in these datasets (3C-Dijon and 3C-Bordeaux-Montpellier).

In the 3C-Dijon study, among participants with GWAS data (N=4,077), after exclusion of participants with prevalent stroke (N=204), and those without follow-up for incident stroke events (N=111), N=3,762 participants were available for analyses.

In the 3C-Bordeaux-Montpellier study, after exclusion of participants without GWAS data and with prevalent stroke and those without follow-up for incident stroke events N=2,153 participants were available for analyses.

Stroke ascertainment in 3C-Study: At each follow-up visit, participants or informants for deceased participants were systematically questioned about the occurrence of any severe medical event or hospitalization since the last contact. For those reporting a possible stroke event, all available clinical information was collected from hospital records, and interviews with the participant's physician, nursing home staff (for participants admitted in a nursing home during follow-up) or family. Expert panels including at least one physician specialized in vascular medicine reviewed all available clinical information and classified each event according to the International Classification of Diseases – 10th Edition. Stroke was confirmed if the participant had a new focal neurological deficit of sudden onset attributable to a cerebrovascular event that persisted for more than 24 hours. Stroke was classified by

the panel as ischemic stroke, intracerebral hemorrhage or of unspecified type and ischemic stroke (IS) was classified by the panel according to the TOAST classification into cardioembolic IS, large-artery IS, small vessel disease IS, IS of other etiologies, and IS of undetermined etiology.¹⁰

EPIC

EPIC is a multi-centre prospective cohort study of 519,978 participants (366,521 women and 153,457 men, mostly aged 35–70 years) recruited between 1992 and 2000 in 23 centres located in 10 European countries.⁵⁷ Participants were invited mainly from population-based registers (Denmark, Germany, certain Italian centres, the Netherlands, Norway, Sweden, UK). Other sampling frameworks included: blood donors (Spain and Turin and Ragusa in Italy); screening clinic attendees (Florence in Italy and Utrecht in the Netherlands); people in health insurance programmes (France); and health conscious individuals (Oxford, UK). About 97% of the participants were of white European ancestry. Prevalent CVD was ascertained through self-reported history of MI or angina, or registry-ascertained CVD event prior to baseline. EPIC-CVD employs a nested case-cohort design,⁵⁸ analogous to the EPIC-InterAct study for type-2 diabetes which established a common set of referents through selection of a random sample of the entire cohort (“subcohort”).⁵⁹

Stroke ascertainment in EPIC: Centres were asked to ascertain suspected stroke cases from registries, hospital records or self-report (i.e. follow-up questionnaires). Stroke events were defined by ICD10 codes as follows: Ischemic I63, Haemorrhagic I61, SAH I60, Unclassified I64, Other CRBV I62, I65-I69, F01. Incident stroke cases have been defined as fatal and non-fatal. All centres have recorded cause-specific mortality through mortality registries and/or active follow-up, and have ascertained and validated incident fatal and non-fatal stroke through a combination of methods.

Ascertained non-fatal stroke events were validated by clinical symptoms and imaging evidence (CT/MRI) or confirmed through hospital/GP records (with assessment of notes) or confirmed through hospital records (without assessment of notes). Individuals were excluded if they had clinical symptoms but no validation was possible e.g. there was no imaging evidence, nor GP/primary care records (without assessment of notes) or registry information. Fatal stroke events were validated either by autopsy or hospital records and death certificate or by death certificate if they died in hospital. Individuals where validation was not possible were excluded. Participants with a history of stroke or MI at baseline were excluded. No further stroke subtyping was performed.

AIDHS/SDS

Asian Indian Diabetic Heart Study/Sikh Diabetes Study (AIDHS/SDS) is a case-control study designed to investigate the association between genetic and environmental factors and their risk on type 2 diabetes (T2D) and cardiovascular disease in a population of Punjabi ancestry from India.^{60, 61} All AIDHS/SDS participants were recruited from the northern part of India between 2003 to 2006. Information regarding stroke was obtained from patient records. Stroke was defined on the basis of an event requiring hospitalization. Diagnosis of ischemic stroke was established based on either evidence of an infarction in neuroimaging (CT/MRI scan) or symptom duration >24 hours. A total of 52 (3.3%) participants had a stroke. A total of 1,566 subjects included in this investigation were available with genome-wide genotyping data (Illumina’s 660W-Quad BeadChip). Imputation was performed using IMPUTE2 with the reference panel of 1092 worldwide subjects from 1000 Genomes Project Phase I integrated variant set (March 2012 release) in NCBI Build 37 (hg19) coordinates as described previously.⁶² Both men and women aged 20-90 years participated. Inclusion was based on those with Sikh surnames of North Indian origin, and speaking the Punjabi language. Excluded were individuals of South, East and Central Indian origin. All blood samples were obtained at the baseline visits. All participants signed a written informed consent for the investigations. The study was reviewed and approved by the University of Oklahoma Health Sciences Center’s Institutional Review Board, as well as the Human Subject Protection Committees at the participating hospitals and institutes in India.

VHIR-FMT-Barcelona

The Barcelona cohort is a subset of Caucasian Ischemic stroke subjects that were enrolled as a part of the Genetic contribution to functional Outcome and Disability after Stroke (GODs) project. Cases were selected through demonstration of acute ischemic stroke in a neuroimaging study during the first 7 days after stroke. We included cases with a first-ever and with a recurrent stroke. We did not include lacunar strokes due to the study was focused only on disability after stroke of non-lacunar cases. We did not use age or stroke severity as exclusion criteria. Participants were not part of a treatment trial. Etiologic subgroups were classified following TOAST criteria. Controls were healthy subjects older than 40 years old without history of ischemic stroke. The control cohort was collected in primary care centers from Barcelona city and some hospital in the Spanish Network as a part of the Investigating Silent Stroke in hYpertensives: A magnetic resonance imaging Study (ISSYS) and Genotyping RECurrence Risk Of Stroke (GRECOS) study. All the samples (cases and controls) were genotyped using the Infinium Human Core Exome Chip (Illumina). Written informed consent was obtained from all subjects with approval from the ethics committee of all participating institutions.

Biobank Japan

BioBank Japan Project was started in 2003 and collected DNA and clinical information from a total of 200,000 patients suffering from at least one of 47 common diseases. Eligibility of cases was determined by physicians from a collaborative network of 66 hospitals. Overall, 16,256 ischemic stroke cases were registered at the biobank, named as BBJ. Of all ischemic stroke cases, 1,256 were classified as large artery strokes, 710 as cardioembolic and 4,613 as small vessel stroke. Clinical information was collected by standardized questionnaire through medical records survey. As for the controls, we used genotyping information of 27,294 individuals aged over 40 years from three population based controls: Japan Multi-Institutional Collaborative Cohort Study (J-MICC), Japan Public Health Center-based Prospective Study (JPHC), and the Tohoku Medical Megabank Project (TMM).

Stroke ascertainment in Biobank Japan: Stroke patients > 40 years old were selected from BioBank Japan. Ischemic stroke was diagnosed by physicians at collaborating hospitals and its subtypes were determined by medical record survey according to the TOAST criteria.

CADISP

The Cervical Artery Dissections and Ischemic Stroke Patients (CADISP) study was designed to identify genetic risk variants for cervical artery dissections (CeAD), a major cause of ischemic stroke in young adults.⁶³ As part of a secondary analysis, patients with an ischemic stroke without cervical artery dissection (non-CeAD ischemic stroke) were also recruited, in the same centers as CeAD patients. These were patients with a diagnosis of ischemic stroke, in whom CeAD had been formally ruled out according to CADISP inclusion criteria (see attachment). Non-CeAD ischemic stroke patients were frequency-matched on age (by 5-year intervals) and gender on CeAD patients. A total of 658 non-CeAD ischemic stroke patients were included in Belgium, Finland, France, Germany, Italy, and Switzerland. We excluded 19 patients due to unavailability of geographically matched healthy controls, or due to non-European origin; of the remaining 639 non-CeAD IS patients, 613 individuals had good quality DNA available and were genotyped at the CNG. Of these, a total of 555 non-CeAD IS patients aged < 60 years, who were successfully genotyped and met genotyping quality control criteria, were used for the present analysis.

The abstracted hospital records of cases were reviewed and adjudicated for IS subtype by a neurologist in each participating center. Each item required for the subtype classification was also recorded in a standardized fashion. Based on this, IS subtypes were then centrally re-adjudicated by a panel of

neurologists, in agreement with the TOAST system,¹⁰ using a more detailed subtype description from an early version of the Causative Classification System (CCS).⁶⁴

The majority of controls (N=9,046, of which 74 Finns and 8,972 non-Finnish Europeans) were selected from an anonymized control genotype database at the Centre National de Génotypage [CNG], in order to match cases for ethnic background, based on principal component analysis. European reference samples from the genotype repository at the CNG were also analyzed simultaneously to provide improved geographical resolution. Additional Finnish controls were recruited within the CADISP study, both from the general population and among spouses and unrelated friends of CADISP patients, within the Helsinki area. A total of 234 individuals were eligible for genotyping at the CNG. Of these, 213 individuals who were genotyped successfully and met quality control criteria were available for the present analysis.⁶³ All participants were of European ancestry.

COMPASS

COMPASS contains African American participants from several cohort studies. Diagnosis of stroke was adjudicated by a physician. The study has been described previously,⁶⁵ details on the individual cohorts are as follows.

Atherosclerosis Risk in Communities (ARIC) Study

The ARIC study is a prospective population-based study of atherosclerosis and clinical atherosclerotic diseases in 15,792 men and women, including 11,478 non-Hispanic white participants, drawn from 4 U.S. communities (Suburban Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina, and Jackson, Mississippi). In the first three communities, the sample reflects the demographic composition of the community. In Jackson, only black residents were enrolled. Ancestry was self-reported during an interview. Participants were handed a card and asked to tell the interviewer which best described his or her race. Choices offered were: White, Black, American Indian/Alaskan Native, Asian/Pacific Islander, Other: specify. Over 99% identified as either white or black. Only self-identified blacks were included in for COMPASS. Participants were between age 45 and 64 years at their baseline examination in 1987-1989 when blood was drawn for DNA extraction and participants consented to genetic testing. Only individuals free of stroke or TIA at baseline were included in the analysis. Single-nucleotide polymorphisms (SNPs) were genotyped on the Affymetrix 6.0 chip and were imputed to ≈ 2.5 million SNPs based on a panel of cosmopolitan reference haplotypes from HapMap CEU and YRI (HapMap II CEU and YRI (build 35, release 21)). MACH v1.0.16 was used to perform genotype imputations and allele dosage information was summarized in the imputation results.

Stroke ascertainment in ARIC: Hospitalized strokes that occurred by December 31, 2012 were included in the present study. During annual telephone contacts, trained interviewers asked each ARIC participant to list all hospitalizations during the past year. Hospital records for any hospitalizations identified were then obtained. In addition, all local hospitals annually provided lists of stroke discharges (International Classification of Diseases, Ninth Revision, Clinical Modification codes 430 to 438), which were scrutinized for ARIC participant discharges. Details on quality assurance for ascertainment and classification of stroke are described elsewhere. Briefly, the stroke diagnosis was assigned according to criteria adapted from the National Survey of Stroke. Strokes secondary to trauma, neoplasm, hematologic abnormality, infection, or vasculitis were excluded, and a focal deficit lasting <24 hours was not considered to be a stroke. Out-of-hospital stroke was not ascertained and validated; thus, these potential stroke events were not included. Strokes were classified into hemorrhagic stroke (subarachnoid and intracerebral hemorrhage) and ischemic stroke (thrombotic and embolic brain infarction). A stroke was classified as ischemic when a brain CT or MRI revealed acute infarction and showed no evidence of hemorrhage. All definite ischemic strokes were further classified as lacunar, nonlacunar thrombotic, or cardioembolic on the basis of the recorded neuroimaging results. For this analysis, the hemorrhagic strokes identified by ARIC were censored at the time of their occurrence.

Cardiovascular Health Study (CHS) – African-Americans

The Cardiovascular Health Study (CHS) is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥ 65 years conducted across four field centers [PMID: 1669507]. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons were enrolled for a total sample of 5,888. Because the COMPASS consortium focused on non-European samples, only self-described African-Americans contributed to the COMPASS analyses.

Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai among CHS African-American participants who consented to genetic testing and had DNA available using Illumina HumanOmni1-Quad_v1 BeadChip system.

Beyond laboratory genotyping failures, participants were excluded if they had a call rate $\leq 95\%$ or if their genotype was discordant with known sex or prior genotyping (to identify possible sample swaps). After quality control, genotyping was successful for 823 African-American participants.

CHS was approved by institutional review committees at each field center and individuals in the present analysis had available DNA and gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

The Healthy Aging in Neighborhoods of Diversity across the Life Span Study (HANDLS) – African Americans

In the absence of non-stroke control samples from the VISP, ISGS, and SWISS studies, controls from the Healthy Aging in Neighborhoods of Diversity across the Life Span study (HANDLS) study were used for the VISP and SWISS-ISGS case-control analyses (with no overlap across studies). Controls were sex and race/ethnicity-matched and randomly selected from all HANDLS participants not reporting history of stroke at baseline or reporting adjudicated stroke during follow-up.

HANDLS is an interdisciplinary, community-based, prospective longitudinal epidemiologic study examining the influences of race and socioeconomic status (SES) on the development of age-related health disparities among socioeconomically diverse African Americans and whites in Baltimore, MD, USA. This study assesses physical parameters over a 20-year period while evaluating genetic, biologic, demographic, and psychosocial influences. HANDLS recruited 3,722 participants (2200 African Americans (59%) and 1522 whites (41%)) from Baltimore, MD.

Stroke Ascertainment. Stroke status at baseline was determined through self-report while incident strokes, other vascular events, and deaths were determined using medical records and clinic visits during follow-up.

Genotyping was focused on a subset of participants self-reporting as African American and was performed at the Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health. Genotype data (for up to 907,763 SNPs) were generated for 1,024 participants using either Illumina 1M and 1M duo arrays ($n=709$), or a combination of 550K, 370K, 510S and 240S to equate the million SNP level of coverage. Inclusion criteria for genetic data in HANDLS includes concordance between self-reported sex and sex estimated from X chromosome heterogeneity, $> 95\%$ call rate per participant (across all equivalent arrays), concordance between self-reported African ancestry and ancestry confirmed by analyses of genotyped SNPs, and no cryptic relatedness to any other samples at a level of proportional sharing of genotypes $> 15\%$ (effectively excluding 1st cousins

and closer relatives from the set of probands used in analyses). In addition, SNPs included in the analysis were filtered for HWE p-value $> 1e-7$, missing by haplotype p-values $> 1e-7$, minor allele frequency > 0.01 , and call rate $> 95\%$. Data analyses utilized the high-performance computational capabilities of the Biowulf Linux cluster at the NIH, Bethesda, Md. (<http://biowulf.nih.gov>).

INTERSTROKE-African Americans

INTERSTROKE is an international, multi-centered, case-control study of stroke investigating the global burden of risk factors across 32 countries and 18 different ethnic groups around the world. A detailed report of the study design has been published (Neuroepidemiology. 2010; 35:36-44). Briefly, cases were patients with acute first stroke (within 5 days of symptoms onset and 72 hours of hospital admission) in whom neuroimaging (CT or MRI) was performed. The TOAST classification system was used to define ischemic stroke subtypes. Cases were excluded if 1) they were unable to communicate due to severe stroke without a valid surrogate respondent (e.g. first-degree relative or spouse), 2) they were hospitalized for acute coronary syndrome/myocardial infarction, or 3) stroke was attributed to non-vascular causes (e.g. tumor). Controls were selected from the community and had no history of stroke.

A subset of INTERSTROKE participants consenting to genetic analysis with sufficient DNA quantities were genotyped on the Illumina Infinium Cardiometabo BeadChip. All samples were genotyped at a central site (the Genetic Molecular Epidemiology Laboratory in Hamilton, Ontario, Canada). Samples were excluded if they had 1) a high proportion of missing variants (missingness > 0.05), 2) inconsistencies between reported and genetically determined sex or ethnicity or 3) exhibited cryptic relatedness. Genotyped variants were excluded if they were rare (MAF < 0.01), exhibited high missingness across samples (missingness > 0.01), or deviated from hardy-weinberg equilibrium ($P < 5 \times 10^{-6}$). Pre-phasing and imputation were performed with SHAPEIT2 and IMPUTE, respectively, using the 1000Genomes Phase 1 Version 3 (November 23, 2010 subversion) reference panel. Imputed variants were removed if they were rare (MAF < 0.01) or of poor quality (INFO SCORE < 0.30).

Ischemic Stroke Genetic Study (ISGS)-African Americans

ISGS is a multicenter inception cohort study. Cases were recruited from inpatient stroke services at five United States academic medical centers. Cases are adult men and women over the age of 18 years diagnosed with first-ever ischemic stroke confirmed by a study neurologist on the basis of 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 at the time of the index ischemic stroke, central nervous system vasculitis, or bacterial endocarditis. 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. Diagnostic evaluation included: head CT (95%) or MRI (83%), electrocardiography (92%), cervical arterial imaging (86%), and echocardiography (74%). Medical records from all cases were centrally reviewed by a vascular neurology committee and assigned ischemic stroke subtype diagnoses according to TOAST criteria, Oxfordshire Community Stroke the Baltimore-Washington Young Stroke Stud. DNA was donated to the NINDS DNA Repository (Coriell Institute, Camden, NJ) for eligible samples with appropriate written informed consent. DNA samples were genotyped using the Illumina 610 array and data analyses were supported by the high-performance computational capabilities of the Biowulf Linux cluster at the NIH (<http://biowulf.nih.gov>).

Jackson Heart Study (JHS)

The JHS is a single-site, prospective, population-based study designed to explore the environmental, behavioral, and genetic factors that influence the development of CVD among African Americans. A total of 5,301 women and men between the ages of 21 and 94 were recruited between 2000 and 2004 from a tri-county area of Mississippi: Hinds, Madison, and Rankin Counties. Participants were

recruited from four sources, including (1) randomly sampled households from a commercial listing; (2) ARIC participants; (3) a structured volunteer sample that was designed to mirror the eligible population; and (4) a nested family cohort. Overviews of the JHS including the sampling and recruitment, sociocultural, and laboratory methods have been described and published previously.⁶⁶⁻⁶⁹

The institutional review boards of the following participating institutions approved the study: the University of Mississippi Medical Center, Jackson State University, and Tougaloo College. All of the participants provided written informed consent. Unrelated participants were between 35 and 84 years old, and members of the family cohort were ≥ 21 years old when consent for genetic testing was obtained and blood was drawn for DNA extraction.

The baseline examination consisted of a home interview, self-administered questionnaires, and a clinic visit. Medications taken in the prior 2 weeks were brought to clinic and transcribed verbatim with subsequent coding by a pharmacist. After an overnight fast, anthropometric and seated blood pressure measurements were obtained and venipuncture/urine collection was performed in accordance with the National Committee for Clinical Laboratory Standards. Blood pressure was measured by trained technicians using a Hawksley random zero manometer and determined by the arithmetic average of two readings taken 1 minute apart after a five-minute rest.⁷⁰

Stroke Assessment in the JHS: In addition to the standard JHS examinations, participants were contacted by telephone annually beginning in 2005 to obtain interim information about cardiovascular events. (ICD-9 code 428 for hospitalizations). During the annual follow up phone call, participants or designated representative provide self-reported information of hospitalization or death. Identification and abstraction of CVD illness and death data are performed by a certified medical record abstractor. Incident stroke is defined as stroke that occurred while the participants was enrolled the study, i.e. stroke event occurred after the baseline visit. Strokes are classified as either definite or probable stroke. The definition of stroke was based on the World Health Organization (WHO) criteria for definition of stroke or clinical criteria in which case the WHO criteria might not have been satisfied, but there is clinical evidence sufficient for a diagnosis of stroke to be made. More details on identification and classification of stroke events in the JHS have already been published.^{71, 72} Although not directly relevant in this study, ischemic stroke subtyping in the JHS was done the TOAST classification criteria.

The Sea Islands Genetics Network (SIGNET) & REasons for Geographic And Racial Differences in Stroke (REGARDS) – African Americans

The Sea Islands Genetics Network (SIGNET) study consists of the REasons for Geographic And Racial Differences in Stroke (REGARDS), the Sea Islands Genetic African American Registry (Project SuGAR), a COBRE for Oral Health study (COBRE), and the Systemic Lupus Erythematosus in Gullah Health study (SLEIGH). All subjects are African Americans (AA), and all provided written informed consent.

All SIGNET samples (n= 4,298) were genotyped using the Affymetrix Genome-Wide Human SNP Array 6.0. Imputation was performed using MACH (version 1.0.16) to impute all autosomal SNPs using the CEU+YRI reference panel (as supplied by Goncalo Abecasis) from build 36 (2,318,207 SNPs in total).

REGARDS is an observational cohort of 30,239 AA and white men and women enrolled in their homes after a telephone interview in 2003-7 (Howard VJ et al., 2005). Participants were a national sample oversampled from the southeastern stroke belt (56%) and were 58% female and 42% black by design. Participants were followed every 6 months by telephone to ascertain health outcomes, with validation of stroke, coronary heart disease, death and other ancillary study endpoints. For SIGNET, we selected all AA REGARDS type 2 diabetes (T2D) cases recruited from SC, GA, NC, and AL, and an equivalent number of race, sex, and age-strata matched diabetes-free controls. We also included all participants not already included that were current residents of the 15-county “Low Country” region of SC and GA (SC counties Beaufort, Berkeley, Charleston, Colleton, Dorchester, Georgetown, Hampton, Horry, Jasper; GA counties Bryan, Camden, Chatham, Glynn, Liberty, McIntosh). The subset of REGARDS participants genotyped under SIGNET are referred to as SIGNET-REGARDS.

GWAS genotyping was completed among 2398 SIGNET-REGARDS AA participants, including 1149 with diabetes and 1249 without diabetes.

Siblings with Ischemic Stroke Study (SWISS) – African Americans

SWISS is a prospective multicenter affected sibling pair study of first-ever or recurrent ischemic stroke. Subjects were recruited from 54 enrolling hospitals across the US and Canada. Samples were collected between 1999-2011. Ischemic stroke probands were enrolled at 66 US medical centers and 4 Canadian medical centers. All recruits were extensively clinically phenotyped and have imaging-confirmed ischemic stroke using either CT or MRI brain scans. 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 who also have a history of at least one living sibling with a history of stroke. Probands were excluded if 1) they had a mechanical aortic or mitral valve at the time of the index ischemic stroke, central nervous system vasculitis, or bacterial endocarditis or 2) 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 direct contact when permitted by Institutional Review Boards. Concordant siblings had their diagnosis of ischemic stroke confirmed by review of medical records by a central 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. Discordant siblings of the proband were confirmed to be stroke-free using the Questionnaire for Verifying Stroke-free Status. DNA samples were genotyped using the Illumina 660 array and data analyses were supported by the high-performance computational capabilities of the Biowulf Linux cluster at the NIH (<http://biowulf.nih.gov>).

Women's Health Initiative (WHI) – African Americans

The goal of the WHI was to investigate the etiology and prevention of chronic disease in postmenopausal women. Approximately 161,000 postmenopausal women 50–79 years of age from 40 clinical centers in the US were recruited between 1993 and 1998. WHI consists of an observational study (OS), and clinical trials (CT) of postmenopausal hormone therapy (estrogen alone or estrogen plus progestin), a calcium and vitamin D supplement trial, and a dietary modification trial. A subset of 8,515 African American women who provided consent for DNA analysis were randomly selected for genome-wide genotyping as part of the SNP Health Association Resource (SHARe).

Genetic data were obtained from genome-wide scans using the Genome-wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA, www.affymetrix.com) of 909,622 single nucleotide polymorphisms (SNPs). Genotyping quality control included examination of concordance rates for blinded and unblinded duplicates. Approximately 1% of SNPs failed genotyping and SNPs with call rates < 95% or concordance rates < 98%, or minor allele frequency < 1% were excluded. In addition to the genotyping, SNPs were imputed using 1000 Genomes Project phase 1 integrated variant set (Aug 2012). Principal components were calculated for each individual and evaluated for their contribution to ancestral variation. Because most of the ancestral variation was explained by the first 4 PCs, only these were included as covariates in the analyses.

Stroke ascertainment in WHI: All incident strokes, other vascular events, and deaths were identified through self-report at annual (OS) and semi-annual (CT) participant contacts, and through third-party reports by family members and proxies. Medical records were obtained for potential strokes, and adjudication was performed by trained physician adjudicators who assigned a diagnosis. Stroke diagnosis requiring and/or occurring during hospitalization was based on rapid onset of a neurological deficit attributable to an obstruction or rupture of an arterial vessel system. The deficit was not known to be secondary to brain trauma, tumor, infection or other cause and must have lasted more than 24 hours unless death supervened or a lesion compatible with acute stroke was evident on computed tomography or magnetic resonance imaging were classified as ischemic, hemorrhagic or

unknown/missing. Ischemic stroke subtypes were further classified using Trial of Org 10172 in Acute Stroke Treatment (TOAST) analyses, strokes subtypes judged as ‘probable’ or ‘possible’ were combined. African American women passing the above genotyping quality control criteria, with follow-up data, and without a history of stroke at baseline were included in the WHI analyses. All participants provided written, informed consent.

deCODE study

Icelandic ischemic stroke cases (5,520), were identified from a registry of individuals diagnosed with ischemic stroke or TIA at Landspítali University Hospital in Reykjavik, the only tertiary referral centre in Iceland, during the years 1993 to 2013. The ischemic stroke or TIA diagnoses were based on standard WHO criteria and imaging evidence (either CT or MRI), and were clinically confirmed by neurologists. Eligible patients who survived the stroke were invited to participate the genetic study, either by attending a recruitment centre for deCODE’s genetic studies, or they were visited at their home by a study nurse. Patients were classified into causative subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST).

The study is based on whole-genome sequencing of 8,453 Icelanders and Illumina SNP chip genotyping of 151,677 Icelanders. Genotypes for the chip-typed individuals are phased using the method of long-range phasing (Kong et al. Detection of sharing by descent, long-range phasing and haplotype imputation Nat Genet 40, 1068-75, 2008). and genotype probabilities for un-typed variants are imputed into the chip-typed individuals, and their close relatives, using phased genotypes for the 8,453 WGS individuals as reference. Association testing for case–control analysis was performed using logistic regression, adjusting for age and county and assuming a multiplicative model of risk. About 25 million variants, all with imputation info over 0.8, were tested for association. To account for inflation in the test statistics due to cryptic relatedness and stratification within the case and control sample sets, we applied the method of LD score regression (Bulik-Sullivan B. K. et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat. Genet. 47, 291–295, 2015).

Control comprised 254,176 individuals recruited through different genetic projects at at deCODE. Individuals with confirmed stroke (identified by cross-matching with hospital lists) were excluded as controls.

The study was approved by the Data Protection Commission of Iceland and the National Bioethics Committee of Iceland. All participants gave informed consent.

Glasgow Stroke Sample

Cases with ischemic stroke attending the cerebrovascular service of the Western Infirmary, Glasgow, were recruited between 1990 and 2004 as part of an ongoing study of genetic and circulating biomarkers in stroke. All patients underwent brain imaging and extracranial carotid ultrasound in accordance with a standard clinical protocol. The study was approved by the West Ethics Committee. Controls were drawn from shared WTCCC controls obtained from the 1958 Birth Cohort. This is a prospectively collected cohort of individuals born in 1958, and ascertained as part of the national child development study.⁶ Data from this cohort are available as a common control set for a number of genetic and epidemiological studies.

Helsinki 2000 Ischemic Stroke Genetics Study

Helsinki 2000 Ischemic Stroke Genetics Study was designed for investigating genetic factors underlying ischemic stroke in a Finnish population and in the long-term to be incorporated to multicenter multinational similar datasets. The study aims at recruiting 2000 eligible patients and the

study is still recruiting patients. This study received approval from local ethics committee (October 27, 2010; §266 and Amended June 27, 2016; §142). All ischemic stroke cases in this study were recruited from the Helsinki University Central Hospital, which is the only neurological emergency unit for a population of 1.5 million inhabitants⁷³. Only patients with positive neuroimaging findings for a new-onset brain infarction were recruited following written informed consent. Stroke subtyping was performed using the TOAST definition, utilizing electrocardiogram-Holter, carotid Doppler, carotid angiography, and transesophageal echocardiogram. Cardiologist was consulted when considered necessary. Detailed phenotype data were collected and recorded along with venous blood samples stored at -80° C freezer. The controls were obtained from the FINRISK 1992, 1997, and 2002 study⁷⁴ participants residing in the same geographic area (Greater Helsinki region). They were frequency-matched to cases by age and sex, and were free of major adverse cardiovascular events. All included patients and control subjects are of Finnish, Caucasian, origin and were followed-up based on nationwide register data. The FINRISK surveys have been approved by the Coordinating Ethical Committee of the Helsinki and Uusimaa Hospital District and the participants have signed an informed consent. Cases and controls were genotyped on the Illumina HumanExomeCore array.

Hisayama-FSR study

A detailed study description was described previously⁷⁵. The individuals with ischemic stroke were recruited from seven hospitals in Fukuoka Prefecture, Japan (Kyushu University Hospital, Hakujyujii Hospital, Fukuoka Red Cross Hospital, Kyushu Medical Center, Imazu Red Cross Hospital, Fukuoka Higashi Medical Center, and Seiai Rehabilitation Hospital) in 2004 (The Fukuoka Stroke Registry [FSR]). In the genome-wide association study, 1113 cases with ischemic stroke (370 large artery stroke, 137 cardioembolic stroke, 483 small vessel occlusion, 123 undetermined subtype) were included. Control subjects were enrolled from the participants in the Hisayama Study, an ongoing population-based epidemiological study of cardiovascular disease in the town of Hisayama, Fukuoka Prefecture, Japan. A total of 3,328 individuals aged 40 years or older participated in the screening survey and underwent a comprehensive assessment in 2002-2003. After excluding subjects with a history of stroke or coronary heart disease, 901 control subjects were included in the genome-wide association study.

Stroke ascertainment in the Hisayama-FSR study: Ischemic stroke was defined as a sudden non-convulsive, focal neurologic deficit lasting longer than 24 hours due to brain ischemia. The diagnoses of ischemic stroke and its subtypes for all cases were made by stroke neurologists of the hospitals, referring to detailed clinical features and ancillary laboratory examinations: namely, cerebral angiography, brain imaging (including computed tomography and magnetic resonance imaging), echocardiography, and carotid duplex imaging. Subtypes of ischemic stroke were determined on the basis of the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke and the TOAST classification.

Heart and Vascular Health Study (HVH 1 & 2)

The setting for this study was Group Health (GH), a large integrated health care system in western Washington State (Kaiser Permanente Washington, as of February 2017). Data were utilized from an ongoing case-control study of incident myocardial infarction (MI) and stroke cases with a shared common control group. Methods for the study have been described previously and are briefly summarized below.⁷⁶⁻⁷⁸ The study was approved by the human subjects committee at GH, and written informed consent was provided by all study participants. All study participants were GH members and aged 30-79 years. MI and stroke cases were identified from hospital discharge diagnosis codes and were validated by medical record review. Controls were a

random sample of GH members frequency matched to MI cases on age (within decade), sex, treated hypertension, and calendar year of identification. The index date for controls was a computer-generated random date within the calendar year for which they had been selected. For stroke cases, the index date was the date of admission for the first acute stroke. Participants were excluded if they were recent enrollees at GH, had a history of prior stroke, or if the incident event was a complication of a procedure or surgery.

Trained medical record abstractors collected eligibility and risk factor information from a review of the GH medical record using only data available prior to the index date and through a telephone interview. Medication use was ascertained using computerized GH pharmacy records. A venous blood sample was collected from all consenting subjects, and DNA was extracted from white blood cells using standard procedures.

Diagnostic criteria for ischemic stroke were adopted from the Cardiovascular Health Study.²³ These criteria included (1) rapid onset of neurologic deficit or subarachnoid hemorrhage, (2) deficit persisting for longer than 24 hours unless computed tomography or magnetic resonance imaging show evidence of permanent damage, and (3) no underlying brain trauma, tumor, or infection to cause symptoms.

Ischemic stroke cases satisfied one or more of the following criteria: (a) Focal deficit, without evidence of blood on CT or MRI, (b) Focal deficit, with mottled appearance in the appropriate location on CT, or (c) surgery or autopsy evidence of infarction.

Among ischemic strokes, the subtypes were defined as follows:

Small artery IS required either: (a) CT/MRI demonstrates a deep area of infarction (decreased density) less than 2 cm. across, or (b) A normal CT, but the clinical syndrome is typical of a lacunar infarction, that is: a pure motor stroke, a pure sensory stroke, hemiparesis plus ataxia, or dysarthria plus a clumsy hand. Cardioembolic IS required either (a) a recognized source of emboli such as atrial fibrillation, endocarditis, mitral stenosis, thrombus in heart, recent MI or cardiac surgery, or (b) a mottled appearance consistent with infarction on the CT. Large artery IS was defined by the absence of apparent source of emboli or evidence of lacunar infarction and evidence of large vessel atherosclerosis by carotid ultrasound or angiography.

All participants were of European ancestry.

INTERSTROKE (integrated European, Asian, and Latin americans)

INTERSTROKE is an international, multi-centered, case-control study of stroke investigating the global burden of risk factors across various regions and ethnic groups around the world. A detailed report of the study design has been published.⁷⁹ Briefly, cases were stroke patients with acute first stroke (within 5 days of symptoms onset and 72 hours of hospital admission) in whom neuroimaging (CT or MRI) was performed. Stroke was defined with the WHO clinical criteria for stroke. The TOAST classification system was used to define ischemic stroke subtypes. Cases were excluded if 1) they were unable to communicate due to severe stroke without a valid surrogate respondent (e.g. first-degree relative or spouse), 2) they were hospitalized for acute coronary syndrome/myocardial infarction, or 3) stroke was attributed to non-vascular causes (e.g. tumor). Controls were selected from the community and had no history of stroke. The study was approved by the ethics committees in all participating centres. All participants, or their proxy, provided written informed consent before taking part in the study.

MDC

MDC is a prospective, population-based cohort study that included 28 449 randomly selected men (born between 1923 and 1945) and women (born between 1923 and 1950) at baseline examinations between 1991 and 1996.⁸⁰

Controls were drawn from the same cohort matched for gender, age, and time of baseline investigation. All participants provided written informed consent, and the study was approved by the ethical committee at Lund University, Lund, Sweden.

Stroke ascertainment in MDC: Subjects with ischemic stroke after the baseline examination were identified in the Stroke Register of Malmö until December 31, 2005. A specialized nurse from the stroke register systematically searched for and registered patients with stroke who lived in the city of Malmö. The research nurse, with a senior physician, validated the diagnosis by reviewing medical records. Criteria for stroke was rapidly developing clinical signs of local or global loss of cerebral function lasting for >24 hours or leading to death before then, with no apparent cause other than cerebral ischemia or hemorrhage. Stroke was classified as subarachnoid hemorrhage (International Classification of Diseases, Ninth Revision [ICD-9] code 430), intracerebral hemorrhage (ICD 431), cerebral infarction (ICD 434), and undetermined stroke. Subjects with stroke before the baseline examination were excluded.

RACE

The Risk Assessment of Cerebrovascular Events (RACE) Study, Pakistan is a retrospective case-control study designed to identify and evaluate genetic, lifestyle and biomarker determinants of stroke and its subtype in Pakistan. Samples were recruited from six hospital centres in Pakistan. Cases were eligible for inclusion in the study if they: (1) are aged at least 18 years; (2) presented with a sudden onset of neurological deficit affecting a vascular territory with sustained deficit at 24 hours verified by medical attention within 72 hours after onset (onset is defined by when the patient was last seen normal and not when found with deficit); (3) the diagnosis was supported by CT/MRI; and (4) presented with a Modified Rankin Score of < 2 prior to the stroke. TOAST and Oxfordshire classification systems were used to sub-phenotype all stroke cases. Control participants were individuals enrolled in the Pakistan Risk of Myocardial Infarction Study (PROMIS), a case/control study of acute MI based in Pakistan.⁸¹ Controls in PROMIS were recruited following procedures and inclusion criteria as adopted for RACE cases. In order to minimize any potential selection biases, PROMIS controls selected for this stroke study were frequency matched to RACE cases based on age and gender and were recruited in the following order of priority: (1) non-blood related or blood related visitors of patients of the out-patient department; (2) non-blood related visitors of stroke patients; (3) patients of the out-patient department presenting with minor complaints.

SAHLSIS

SAHLSIS is a case-control study of ischemic stroke based in Gothenburg, Sweden. Adult subjects who presented with first-ever or recurrent acute ischemic stroke before 70 years of age were recruited consecutively at stroke units in western Sweden from 1998 to 2012. All participants were of European origin. Patients were not excluded based on stroke severity or whether they were enrolled in a treatment trial. All participants underwent ECG and neuroimaging at the acute stage (all by CT and 58% also by MRI). Additional diagnostic work-up was performed when clinically indicated. Inclusion criteria was ischemic stroke which was defined as an episode of focal neurological deficits with acute onset and lasting > 24 hours or until death, with no apparent non-vascular cause, and no signs of primary hemorrhage on brain imaging. Subjects were excluded if they had a diagnosis of cancer at advanced stage, infectious hepatitis or human immunodeficiency virus. Ischemic stroke was assigned according to modified TOAST criteria.

SIFAP

The SIFAP study is a multicenter study carried out to determine the frequency of Fabry disease in an unselected group of young adult patients with acute cerebrovascular events defined as having had an acute ischemic stroke or transient ischemic attack less than three months before enrollment into the

study. The study is briefly summarized here. First-ever (80.5%) and recurrent ischemic strokes were included. MRI was a mandatory procedure but, in the case of negative or missing MRI, a qualified stroke neurologist could confirm the clinical diagnosis. For this project, ischemic stroke cases recruited from 15 sites throughout Germany and determined not to have Fabry Disease were included in the analysis. All were of European ancestry and had age of first stroke of 18 – 55 years. The diagnosis of Fabry disease was based in males as well as in females in the first level on the sequencing data of the entire exon structure including promoter of the α -galactosidase gene. In cases where a mutation was detected, biochemical analysis was done. Stroke cases from SIFAP were genotyped at CIDR (Baltimore, MD) using the Illumina Human Omni 2.5MQuad array. Only those cases without Fabry disease were selected for genotyping. Controls free of cardiovascular diseases were selected from the KORA Study previously genotyped at CIDR in the same platform. The Cooperative Health Research in the Region of Augsburg (KORA) study is a population-based study of cardiovascular and metabolic traits carried out in the region of Augsburg, Southern Germany. A subset of control subjects (N = 28) was re-genotyped together with cases to provide cross-set duplicates. This joint clustering was used to minimize possible artifactual differences in allelic frequency between cases and controls due to genotyping at different times, and the cross-set duplicates were used to detect such artifacts that may have occurred.

SLESS

The South London Ethnicity and Stroke Study (SLESS) is a prospective study begun in 1999 that has recruited consecutive black patients with stroke from a contiguous catchment area covered by 3 hospitals in South London (Guy's and St Thomas' Hospitals, King's College Hospital, and St George's Hospital).⁸² Ethnicity was defined according to the UK Census 2001 definition and classified as Black African or Black Caribbean. Recruitment of black controls was done by random selection from General Practice lists in the catchment areas of St George's, Guys and St Thomas, and King's College Hospital between 1999 and 2012. Potential controls were selected from age and gender strata matched to stroke cases. Furthermore controls were identified within St George's University of London and St George's Hospital staff and contacted via email. Additionally, posters inviting healthy Black African and Black Caribbean individuals were displayed in local leisure centres, General Practice surgeries, churches and communities centres within the same catchment area as the that of the cases. The study was reviewed and approved by the Wandsworth Local Research Ethics Committee, and informed consent was obtained from all participants. One consultant neurologist performed stroke subtyping using data collected on a standard proforma with additional review of all original brain imaging in all patients, as well as review of original notes when necessary. The pathophysiological Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtyping classification was used for subtyping of ischemic stroke.

Stroke ascertainment in SLESS: One consultant neurologist performed stroke subtyping using data collected on a standard proforma with additional review of all original brain imaging in all patients, as well as review of original notes when necessary. The pathophysiological Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtyping classification was used for subtyping of ischemic stroke.

UK - young lacunar stroke DNA resource

A total of 1,029 Caucasian patients with lacunar stroke, aged ≤ 70 years, were recruited from 72 specialist's stroke centres throughout the UK between 2002 and 2012, as part of the Young Lacunar Stroke DNA Resource. DNA samples were available in 930 patients. An additional 82 Caucasian patients of all ages with lacunar stroke were recruited from St. George's Hospital, London as part of the GENESIS study.⁸³ Lacunar stroke was defined as a clinical lacunar syndrome, with an anatomically compatible lesion on MRI (subcortical infarct ≤ 15 mm in diameter). All patients

underwent full stroke investigation including brain MRI, imaging of the carotid arteries and ECG. Echocardiography was performed when appropriate. All MRIs and clinical histories were reviewed centrally by one physician. Exclusion criteria were: stenosis >50% in the extra- or intracranial cerebral vessels, or previous carotid endarterectomy; cardioembolic source of stroke, defined according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria as high or moderate probability; cortical infarct on MRI; subcortical infarct > 15mm in diameter, as these can be caused by embolic mechanisms (striatocapsular infarcts); any other specific cause of stroke (e.g. lupus anticoagulant, cerebral vasculitis, dissection, monogenic cause of stroke). All cases were screened for *NOTCH3* CADASIL and Fabry disease mutations and positive cases excluded.

Unrelated Caucasian controls, free of clinical cerebrovascular disease, were obtained by random sampling, stratified for age and sex, from general practice lists from the same geographical location as the patients. All patients and controls underwent a standardized clinical assessment and completed a standardized study questionnaire. MRI was not performed in controls.

The study was approved by the Multi-Centre Research Ethics Committee (04/MRE00/36) and informed consent was obtained from all participants.

ICH

Case and control subjects included in the discovery phase were subjects of European ancestry aged >55 years in the Genetics of Cerebral Hemorrhage with Anticoagulation¹³ (GOCHA) study (multicenter study in the US) and aged >18 years in the Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) studies I and II in Cincinnati, OH; Hospital del Mar Intracerebral Hemorrhage study and Vall d'Hebron Hospital ICH study in Barcelona, Spain; Jagiellonian University Hemorrhagic Stroke Study in Krakow, Poland; and the Lund Stroke Register 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.

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, 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.

The Stockholm-Tartu Atherosclerosis Reverse Network Engineering Task (STARNET) study – the worlds largest genetics of gene expression study.

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Coronary artery disease (CAD) patients eligible for coronary artery by-pass grafting CABG and non-CAD patients (controls) eligible for other open-thorax surgery at the Tartu University Hospitals were asked to participate. All patients were informed about the study by the attending doctor and in writing and gave written consent (Ethical Approvals Dnr 154/7 and 188/M-1, 2007). Patients with other severe, active systemic disease (e.g., active systemic inflammatory disease and cancer) were excluded. Pre-operative blood samples were collected for biochemical screens and isolation of primary blood monocytes. The primary end point was the extent of coronary atherosclerosis (CAD score), assessed by pre-operative angiography; controls had no significant CAD requiring angioplasty or CABG. Each participant completed a questionnaire to assess disease history, current drug regimens, and lifestyle factors (e.g., daily activity, alcohol consumption, and smoking habits). In total, up to 114 continuous and noncontinuous variables were assessed in each participant. All participants are of Caucasian ethnicity (10% Swedish, 10% Russian, and 80% Estonian). Of the 600 cases, 31% are females; 32% have diabetes, 75% hypertension, and 67% hyperlipidaemia, and 33% had a heart attack before the age of 60 years. According to the New York Heart Association (NYHA) criteria, 45% are class I (CAD, but no symptoms and no limitation in ordinary physical activity, stable angina), 42% are class II (mild shortness of breath and/or angina with slight limitation during ordinary activity), 9% are class III (marked limitation in activity due to symptoms, even during less-than-ordinary activity, such as walking 20–100 m, and comfortable only at rest) and 1% are class IV (severe limitations, symptoms while at rest, mostly bedbound patients). The 5-year follow-up of mortality and morbidity (CAD and other diseases) after the primary open thorax surgery is ongoing.

A total of 7 RNA samples/patient from this cohort (atherosclerotic and non-atherosclerotic arterial wall (Uppsala/CGN), liver, skeletal muscle, subcutaneous and abdominal visceral fat) were sequenced using the HighSeq2000 platform. DNA for all 600 patients was genotyped with OmniExpressExome arrays (Illumina, ~900k SNPs). Now completed, this dataset covering DNA variants of exomes and non-exome variants down to 5% major allele frequency together with RNA sequence at 25 million read-depths for > 3500 RNA samples (from 7 tissues) obtained from the same 600 patients.

For studies appearing multiple times in the description of sample collection, great care was taken to remove sample overlap.

3.2 Study-specific acknowledgements

METASTROKE

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GEOS: Genetics of Early Onset Stroke (GEOS) Study, Baltimore, USA was supported by the NIH Genes, Environment and Health Initiative (GEI) Grant U01 HG004436, as part of the GENEVA consortium under GEI, with additional support provided by the Mid-Atlantic Nutrition and Obesity Research Center (P30 DK072488), and the Office of Research and Development, Medical Research Service, and the Baltimore Geriatrics Research, Education, and Clinical Center of the Department of Veterans Affairs. Genotyping services were provided by the Johns Hopkins University Center for Inherited Disease Research (CIDR), which is fully funded through a federal contract from the NIH to the Johns Hopkins University (contract number HHSN268200782096C). Assistance with data cleaning was provided by the GENEVA Coordinating Center (U01 HG 004446; PI Bruce S Weir). Study recruitment and assembly of datasets were supported by a Cooperative Agreement with the Division of Adult and Community Health, Centers for Disease Control and Prevention and by grants from NINDS and the NIH Office of Research on Women's Health (R01 NS45012, U01 NS069208-01).

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ISGS and SWISS: The Ischemic Stroke Genetics Study (ISGS) was supported by the NINDS (R01 NS42733; PI Dr Meschia). The Sibling with Ischemic Stroke Study (SWISS) was supported by the NINDS (R01 NS39987; PI Dr Meschia). Both SWISS and ISGS received additional support, in part, from the Intramural Research Program of the National Institute on Aging (Z01 AG000954-06; PI Andrew Singleton). SWISS and ISGS used samples and clinical data from the NIH-NINDS Human Genetics Resource Center DNA and Cell Line Repository (<http://ccr.coriell.org/ninds>), human subject protocol Nos. 2003-081 and 2004-147. SWISS and ISGS used stroke-free participants from the Baltimore Longitudinal Study of Aging (BLSA) as controls with the permission of Dr Luigi Ferrucci. The inclusion of BLSA samples was supported, in part, by the Intramural Research Program of the National Institute on Aging (Z01 AG000015-50), human subject protocol No. 2003-078. This study used the high-performance computational capabilities of the Biowulf Linux cluster at the NIH (<http://biowulf.nih.gov>). For SWISS and ISGS cases of African ancestry, a subset of the Healthy

Aging in Neighborhoods of Diversity across the Life Span study (HANDLS) were used as stroke-free controls. HANDLS is funded by the National Institute of Aging (1Z01AG000513; PI Michele K. Evans).

MGH-GASROS: MGH Genes Affecting Stroke Risk and Outcome Study (MGH-GASROS) was supported by NINDS (U01 NS069208), the American Heart Association/Bugher Foundation Centers for Stroke Prevention Research 0775010N, the NIH and NHLBI's STAMPEED genomics research program (R01 HL087676), and a grant from the National Center for Research Resources. The Broad Institute Center for Genotyping and Analysis is supported by grant U54 RR020278 from the National Center for Research resources.

MILANO: MILANO: Milano - Besta Stroke Register Collection and genotyping of the Milan cases within CEDIR were supported by the Italian Ministry of Health (Grant Numbers: RC 2007/LR6, RC 2008/LR6; RC 2009/LR8; RC 2010/LR8; GR-2011-02347041). FP6 LSHM-CT-2007-037273 for the PROCARDIS control samples.

WTCCC2-UK: Wellcome Trust Case-Control Consortium 2 (WTCCC2) was principally funded by the Wellcome Trust, as part of the Wellcome Trust Case Control Consortium 2 project (085475/B/08/Z and 085475/Z/08/Z and WT084724MA). The Stroke Association provided additional support for collection of some of the St George's, London cases. The Oxford cases were collected as part of the Oxford Vascular Study which is funded by the MRC, Stroke Association, Dunhill Medical Trust, National Institute of Health Research (NIHR) and the NIHR Biomedical Research Centre, Oxford. The Edinburgh Stroke Study was supported by the Wellcome Trust (clinician scientist award to C Sudlow), and the Binks Trust. Sample processing occurred in the Genetics Core Laboratory of the Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh. Much of the neuroimaging occurred in the Scottish Funding Council Brain Imaging Research Centre (www.sbirc.ed.ac.uk), Division of Clinical Neurosciences, University of Edinburgh, a core area of the Wellcome Trust Clinical Research Facility and part of the SINAPSE (Scottish Imaging Network—A Platform for Scientific Excellence) collaboration (www.sinapse.ac.uk), funded by the Scottish Funding Council and the Chief Scientist Office. Collection of the Munich cases and data analysis was supported by the Vascular Dementia Research Foundation. M Farrall and A Helgadottir acknowledge support from the BHF Centre of Research Excellence in Oxford and the Wellcome Trust core award (090532/Z/09/Z).

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Study recruitment and collection of datasets for the VISP clinical trial were supported by an investigator-initiated research grant (R01 NS34447; PI James Toole) from the United States Public Health Service, NINDS, Bethesda, Maryland. Control data for comparison with European ancestry VISP stroke cases were obtained through the database of genotypes and phenotypes (dbGAP) High Density SNP Association Analysis of Melanoma: Case-Control and Outcomes Investigation (phs000187.v1.p1; R01CA100264, 3P50CA093459, 5P50CA097007, 5R01ES011740, 5R01CA133996, HHSN268200782096C; PIs Christopher Amos, Qingyi Wei, Jeffrey E. Lee). For VISP stroke cases of African ancestry, a subset of the Healthy Aging in Neighborhoods of Diversity across the Life Span study (HANDLS) were used as stroke free controls. HANDLS is funded by the National Institute of Aging (1Z01AG000513; PI Michele K. Evans).

WHI: Funding support for WHI-GARNET was provided through the NHGRI GARNET (Grant Number U01 HG005152). Assistance with phenotype harmonisation and genotype cleaning, as well as with general study coordination, was provided by the GARNET Coordinating Center (U01 HG005157). Funding support for genotyping, which was performed at the Broad Institute of MIT and Harvard, was provided by the NIH Genes, Environment, and Health Initiative (GEI; U01 HG004424).

SiGN

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Discovery Case-only & Case and Control Cohorts:

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EDINBURGH: The Edinburgh Stroke Study was supported by the Wellcome Trust and the Binks Trust. Sample processing occurred in the Genetics Core Laboratory of the Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh, UK. Much of the neuroimaging occurred in the Scottish Funding Council Brain Imaging Research Centre (www.sbirc.ed.ac.uk), University of Edinburgh, a core area of the Wellcome Trust Clinical Research Facility and part of the Scottish Imaging Network—A Platform for Scientific Excellence (SINAPSE) collaboration (www.sinapse.ac.uk), funded by the Scottish Funding Council and the Chief Scientist Office. Genotyping was performed at the Wellcome Trust Sanger Institute in the United Kingdom and funded by the Wellcome Trust as part of the Wellcome Trust Case Control Consortium 2 project (085475/B/08/Z and 085475/Z/08/Z and WT084724MA).

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MGH-GASROS: The Massachusetts General Hospital Stroke Genetics Group was supported by the NIH Genes Affecting Stroke Risks and Outcomes Study (GASROS) grant K23 NS042720, the American Heart Association/Bugher Foundation Centers for Stroke Prevention Research 0775010N, and NINDS K23NS042695, K23 NS064052, the Deane Institute for Integrative Research in Atrial Fibrillation and Stroke, and by the Keane Stroke Genetics Fund. Genotyping services were provided by the Broad Institute Center for Genotyping and Analysis, supported by grant U54 RR020278 from the National Center for Research Resources.

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REGARDS: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study was supported by a cooperative agreement U01 NS041588 from the NINDS, NIH, and Department of Health and Human Service. A full list of participating REGARDS investigators and institutions can be found at <http://www.regardsstudy.org>.

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VISP: The GWAS component of the VISP study was supported by the United States National Human Genome Research Institute (NHGRI), Grant U01 HG005160 (PI Michèle Sale & Bradford Worrall), as part of the Genomics and Randomized Trials Network (GARNET). Genotyping services were provided by the Johns Hopkins University Center for Inherited Disease Research (CIDR), which is fully funded through a federal contract from the NIH to the Johns Hopkins University. Assistance with data cleaning was provided by the GARNET Coordinating Center (U01 HG005157; PI Bruce S Weir). Study recruitment and collection of datasets for the VISP clinical trial were supported by an investigator-initiated research grant (R01 NS34447; PI James Toole) from the United States Public Health Service, NINDS, Bethesda, Maryland. Control data for comparison with European ancestry VISP stroke cases were obtained through the database of genotypes and phenotypes (dbGAP) High Density SNP Association Analysis of Melanoma: Case-Control and Outcomes Investigation (phs000187.v1.p1; R01CA100264, 3P50CA093459, 5P50CA097007, 5R01ES011740, 5R01CA133996, HHSN268200782096C; PIs Christopher Amos, Qingyi Wei, Jeffrey E. Lee). For VISP stroke cases of African ancestry, a subset of the Healthy Aging in Neighborhoods of Diversity across the Life Span study (HANDLS) were used as stroke free controls. HANDLS is funded by the National Institute of Aging (1Z01AG000513; PI Michele K. Evans).

WHI-OS: The Women's Health Initiatives (WHI) program was funded by the National Heart, Lung, and Blood Institute, NIH, US Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118 to 32119, 32122, 42107-26, 42129-32, and 44221. The Hormones and Biomarkers Predicting Stroke (HaBPS) was supported by a grant from the National Institutes of Neurological Disorders and Stroke (R01NS042618).

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Control-only Cohorts:

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WTCCC2: Wellcome Trust Case-Control Consortium 2 (WTCCC2) was principally funded by the Wellcome Trust, as part of the Wellcome Trust Case Control Consortium 2 project (085475/B/08/Z and 085475/Z/08/Z and WT084724MA). The Stroke Association provided additional support for collection of some of the St George's, London cases. The Oxford cases were collected as part of the Oxford Vascular Study which is funded by the MRC, Stroke Association, Dunhill Medical Trust, National Institute of Health Research (NIHR) and the NIHR Biomedical Research Centre, Oxford.

The Edinburgh Stroke Study was supported by the Wellcome Trust (clinician scientist award to C Sudlow), and the Binks Trust. Sample processing occurred in the Genetics Core Laboratory of the Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh. Much of the neuroimaging occurred in the Scottish Funding Council Brain Imaging Research Centre (www.sbirc.ed.ac.uk), Division of Clinical Neurosciences, University of Edinburgh, a core area of the Wellcome Trust Clinical Research Facility and part of the SINAPSE (Scottish Imaging Network—A Platform for Scientific Excellence) collaboration (www.sinapse.ac.uk), funded by the Scottish Funding Council and the Chief Scientist Office. Collection of the Munich cases and data analysis was supported by the Vascular Dementia Research Foundation. M Farrall and A Helgadottir acknowledge support from the BHF Centre of Research Excellence in Oxford and the Wellcome Trust core award (090532/Z/09/Z).

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Secondary Cohorts:

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WHI-HT: WHI Funding support for WHI-GARNET was provided through the NHGRI GARNET (Grant Number U01 HG005152). Assistance with phenotype harmonisation and genotype cleaning, as well as with general study coordination, was provided by the GARNET Coordinating Center (U01 HG005157). Funding support for genotyping, which was performed at the Broad Institute of MIT and Harvard, was provided by the NIH Genes, Environment, and Health Initiative (GEI; U01 HG004424).

CHARGE

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3.3 BIOBANK JAPAN TRAIT ANALYSIS

The BioBank Japan Project (<http://biobankjp.org>)¹ started at the Institute of Medical Science, the University of Tokyo in 2003 and has so far collected up to 300,000 cases consisting of 47 diseases. Subjects were recruited from 12 medical institutes in Japan including Osaka Medical Center for Cancer and Cardiovascular Diseases, the Cancer Institute Hospital of Japanese Foundation for Cancer Research, Juntendo University, Tokyo Metropolitan Geriatric Hospital, Nippon Medical School, Nihon University School of Medicine, Iwate Medical University, Tokushukai Hospitals, Shiga University of Medical Science, Fukujiji Hospital, National Hospital Organization Osaka National Hospital, and Iizuka Hospital.

We selected type 2 diabetes (T2) cases from individuals registered in BioBank Japan as having a diagnosis of T2D in their medical records ($n = 36,832$). As Genotype data from population-based control individuals ($n = 28,870$ individuals) were accessed through the Tohoku Medical Megabank organization, Japan Public Health Center-based Prospective study, and the Japan Multi-institutional Collaborative Cohort Study.

For lipid traits, we selected subjects enrolled in the BioBank Japan Project with data available for HDL ($n = 70,657$), LDL ($n = 72,866$) and TG ($n = 105,597$). Clinical information and medical measurements of subjects were retrieved from either self-report questionnaires (for age, height, weight, and smoking and drinking habits) or medical records (for other data including HDL, LDL, and TG). Subjects aged < 18 or > 85 , or whose measured values were outside three times of interquartile range (IQR) of upper/lower quartile were excluded. For subjects taking a statin, we applied the following correction for LDL values: i) Measured LDL was adjusted as $LDL / 0.7$; ii) Derived LDL from the Friedewald equation was re-derived as $(TC / 0.8) - HDL - (TG / 5)$. For TG values, we applied a common log transformation to achieve normality. The resulting values of each trait were adjusted for age, sex, top 10 principal components, 47 disease affection status in a linear regression model, and the residuals were normalized by Z-score.

We genotyped all of the samples described above by Illumina HumanOmniExpressExome or in combination of HumanOmniExpress and HumanExome BeadChips, and imputed their genotype dosages using mach and minimac softwares with 1000 Genomes Project Phase 1 (version 3) as reference haplotypes. For type 2 diabetes, we performed logistic regression analysis with age, sex and 20 principal components as covariates using mach2dat. For lipid traits, we conducted linear regression analyses using mach2qtl. All of the analyses assumed additive genetic effects of the SNP dosages. Summary statistics of high-quality common SNPs existed in the HapMap 3 East Asian reference panel were used for LD score regression analysis following the standard procedure. We used the East Asian LD Score retrieved from the authors' website (<https://data.broadinstitute.org/alkesgroup/LDSCORE/>).

3.4 Expression quantitative trait loci (eQTL) analysis other than GTEx-V6, HGVD, BIOS, Blueprint, STARNET, and HAEC

We queried the stroke index SNPs in over 100 separate eQTL datasets in a wide range of tissues. We considered SNPs to have evidence for influencing expression if they were the lead SNP, or in high LD ($r^2 > 0.8$)^{1,2} with the lead eQTL SNPs reported for a particular gene and showed an association of at least $P < 5 \times 10^{-6}$ with expression of a transcript in the original study. A general overview of a subset of >50 eQTL studies has been published (PMID 24973796), with specific citations for >100 datasets included in the current query following here.

Blood cell related eQTL studies included fresh lymphocytes (PMID 17873875), fresh leukocytes (PMID 19966804), leukocyte samples in individuals with Celiac disease (PMID 19128478), whole blood samples (PMIDs 18344981, 21829388, 22692066, 23818875, 23359819, 23880221, 24013639, 23157493, 23715323, 24092820, 24314549, 24956270, 24592274, 24728292, 24740359, 25609184, 22563384, 25474530, 25816334, 25578447), lymphoblastoid cell lines (LCL) derived from asthmatic children (PMIDs 17873877, 23345460), HapMap LCL from 3 populations (PMID 17873874), a separate study on HapMap CEU LCL (PMID 18193047), additional LCL population samples (PMIDs 19644074, 22286170, 22941192, 23755361, 23995691, 25010687, 25951796), neutrophils (PMIDs 26151758, 26259071), CD19+ B cells (PMID 22446964), primary PHA-stimulated T cells (PMIDs 19644074, 23755361), CD4+ T cells (20833654), peripheral blood monocytes (PMIDs 19222302, 20502693, 22446964, 23300628, 25951796, 26019233), long non-coding RNAs in monocytes (PMID 25025429) and CD14+ monocytes before and after stimulation with LPS or interferon-gamma (PMID 24604202), CD11+ dendritic cells before and after *Mycobacterium tuberculosis* infection (PMID 22233810) and a separate study of dendritic cells before or after stimulation with LPS, influenza or interferon-beta (PMID 24604203). Micro-RNA QTLs (PMIDs 21691150, 26020509), DNase-I QTLs (PMID 22307276), histone acetylation QTLs (PMID 25799442), and ribosomal occupancy QTLs (PMID 25657249) were also queried for LCL. Splicing QTLs (PMID 25685889) and micro-RNA QTLs (PMID 25791433) were queried in whole blood.

Non-blood cell tissue eQTLs searched included omental and subcutaneous adipose (PMIDs 18344981, 21602305, 22941192, 23715323, 25578447), visceral fat (PMID 25578447) stomach (PMID 21602305), endometrial carcinomas (PMID 21226949), ER+ and ER- breast cancer tumor cells (PMID 23374354), liver (PMIDs 18462017, 21602305, 21637794, 22006096, 24665059, 25578447), osteoblasts (PMID 19654370), intestine (PMID 23474282) and normal and cancerous colon (PMIDs 25079323, 25766683), skeletal muscle (PMIDs 24306210, 25578447), breast tissue (normal and cancer) (PMIDs 24388359, 22522925), lung (PMIDs 23209423, 23715323, 24307700, 23936167, 26102239), skin (PMIDs 21129726, 22941192, 23715323, 25951796), primary fibroblasts (PMIDs 19644074, 23755361, 24555846), sputum (PMID 21949713), pancreatic islet cells (PMID 25201977), prostate (PMID 25983244), rectal mucosa (PMID 25569741), arterial wall (PMID 25578447) and heart tissue from left ventricles (PMIDs 23715323, 24846176) and left and right atria (PMID 24177373). Micro-RNA QTLs were also queried for gluteal and abdominal adipose (PMID 22102887) and liver (PMID 23758991). Methylation QTLs were queried in pancreatic islet cells (PMID 25375650). Further mRNA and micro-RNA QTLs were queried from ER+ invasive breast cancer samples, colon-, kidney renal clear-, lung- and prostate-adenocarcinoma samples (PMID 24907074).

Brain eQTL studies included brain cortex (PMIDs 19222302, 19361613, 22685416, 25609184, 25290266), cerebellar cortex (PMID 25174004), cerebellum (PMIDs 20485568, 22685416, 22212596, 22832957, 23622250), frontal cortex (PMIDs 20485568, 22832957, 25174004), gliomas (PMID 24607568), hippocampus (PMIDs 22832957, 25174004), inferior olivary nucleus (from medulla) (PMID 25174004), intralobular white matter (PMID 25174004), occipital cortex (PMID 25174004), parietal lobe (PMID 22212596), pons (PMID 20485568), pre-frontal cortex (PMIDs 22031444, 20351726, 22832957, 23622250), putamen (at the level of anterior commissure) (PMID 25174004), substantia nigra (PMID 25174004), temporal cortex (PMIDs 20485568, 22685416, 22832957, 25174004), thalamus (PMID 22832957) and visual cortex (PMID 23622250).

Additional eQTL data was integrated from online sources including ScanDB and the Pritchard Lab (eqtl.uchicago.edu). Cerebellum, parietal lobe and liver eQTL data was downloaded from ScanDB and cis-eQTLs were limited to those with $P < 1.0E-6$ and trans-eQTLs with $P < 5.0E-8$.

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3.6 CONSORTIUM MEMBERSHIP

AFGen Consortium

Please note that the AFGen Consortium participants evolve over time. This is a list of contributors from the manuscript Christophersen et al. *Nature Genetics* 2017. Further information on the AFGen Consortium can be found at www.afgen.org and results are located at www.broadcvdi.org.

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Participating centres (number of enrolled patients per centre; local investigators):

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