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Supplementary webappendix

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Supplement to: Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, the Stroke Genetics Network (SiGN), and the International Stroke Genetics Consortium (ISGC). Identification of additional risk loci for stroke and small vessel disease: a meta-analysis of genome-wide association studies . *Lancet Neurol* 2016; published online April 7. http://dx.doi.org/10.1016/S1474-4422(16)00102-2.

Appendix

FOXF2, a novel risk locus for stroke and small artery disease

The Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, the Stroke Genetics Network (SiGN), and the International Stroke Genetics Consortium (ISGC):

Ganesh Chauhan* (PhD), Corey R. Arnold* (BSc), Audrey Y. Chu* (PhD), Myriam Fornage* (PhD), Azadeh Reyahi (PhD)*, Joshua C. Bis* (PhD), Aki S. Havulinna* (DSc), Muralidharan Sargurupremraj (PhD), Albert Vernon Smith (PhD), Hieab H.H. Adams (MSc), Seung Hoan Choi (MA), Sara L. Pulit (BA), Stella Trompet (PhD), Melissa E. Garcia (MPH), Ani Manichaikul (PhD), Alexander Teumer (PhD), Stefan Gustafsson (PhD), Traci M. Bartz (MS), Céline Bellenguez (PhD), Jean Sebastien Vidal (MD), Xueqiu Jian (PhD), Olafur Kjartansson (MD), Kerri L. Wiggins (MS), Claudia L. Satizabal (PhD), Flora Xue (MS), Samuli Ripatti (PhD), Yongmei Liu (PhD), Joris Deelen (PhD), Marcel den Hoed (PhD), Steve Bevan (PhD), Jemma C. Hopewell (PhD), Rainer Malik (PhD), Susan R. Heckbert (MD), Kenneth Rice (PhD), Nicholas L. Smith (PhD), Christopher Levi (MBBS), Pankaj Sharma (MD), Cathie LM Sudlow (BMBCh), Ali Moussavi Nik (DVM, PhD), John W. Cole (MD), Reinhold Schmidt (MD), James Meschia (MD), Vincent Thijs (MD), Arne Lindgren (MD), Olle Melander (MD), Raji P. Grewal (MD), Ralph L. Sacco (MD), Tatjana Rundek (MD), Peter M Rothwell (MD), Donna K. Arnett (PhD), Christina Jern (MD), Julie A. Johnson (PharmD), Oscar R. Benavente (MD), Sylvia Wassertheil-Smoller (PhD), Jin-Moo Lee (MD, PhD), Quenna Wong (MS), Hugo J. Aparicio (MD), Stefan T Engelter (MD), Manja Kloss (MD), Didier Leys (MD), Alessandro Pezzini (MD), Julie E. Buring (ScD), Paul M Ridker (MD), Claudine Berr (MD), Jean-François Dartigues (MD), Anders Hamsten (MD), Patrik K. Magnusson (PhD), Matthew Traylor (PhD), Nancy L. Pedersen (PhD), Lars Lannfelt (MD), Lars Lind (MD), Cecilia M. Lindgren (PhD), Andrew P. Morris (PhD), Jordi Jimenez-Conde (MD), Joan Montaner (MD), Farid Radmanesh (MD), Agnieszka Slowik (MD), Daniel Woo (MD), Albert Hofman (MD), Peter J. Koudstaal (MD), Marileen LP. Portegies (MD), André G. Uitterlinden (PhD), Anton JM de Craen (PhD), Ian Ford (MD), J. Wouter Jukema (MD), David J Stott (MD), Norrina B. Allen (PhD), Michele M. Sale (PhD), Andrew D Johnson (PhD), David A. Bennett (MD), Philip L. De Jager (MD, PhD), Charles C. White (PhD), Hans Jörgen Grabe (MD), Marcello Ricardo Paulista Markus (MD), Ulf Schminke (MD), Giorgio B Boncoraglio (MD), Robert Clarke (MD), Yoichiro Kamatani (MD), Jean Dallongeville (MD), for the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study, Oscar L Lopez (MD), Jerome I. Rotter (MD), Michael A. Nalls (PhD), Rebecca F. Gottesman (MD), Michael E. Griswold (PhD), David S. Knopman (MD), B. Gwen Windham (MD), Alexa Beiser (PhD), Hugh S Markus (DM), Erkki Vartiainen (MD), Curtis R. French (PhD), Martin Dichgans (MD), for the METASTROKE consortium, Tomi Pastinen (PhD), Mark Lathrop (PhD), Vilmundur Gudnason (MD), Tobias Kurth (MD), Bruce M. Psaty (MD), Tamara B. Harris (MD), Stephen S Rich (PhD), Anita L. deStefano (PhD), Carsten Oliver Schmidt (PhD), Bradford B Worrall (MD), Jonathan Rosand (MD), Veikko Salomaa (MD), Thomas H. Mosley (PhD), Erik Ingelsson (MD, PhD), Cornelia M. van Duijn (PhD), Christophe Tzourio (MD), Kathryn M. Rexrode (MD), Ordan J. Lehmann** (MD, PhD), Lenore J Launer** (PhD), M. Arfan Ikram** (MD), Peter Carlsson** (PhD), Daniel I. Chasman** (PhD), Sarah J Childs** (PhD), William T. Longstreth, Jr.** (MD), Sudha Seshadri** (MD), Stéphanie Debette** (MD)

* Equal contributions; ** Co-directed this work

‡ See appendix for more details on study organization

Affiliations

University Medicine Greifswald, Institute for Community Medicine, SHIP-KEF, Greifswald, Germany (AT, COS); University Medicine Greifswald, Department of Neurology, Greifswald, Germany (US); University Medicine Greifswald, Department of Psychiatry and Psychotherapy, Greifswald, Germany (HJG); University Medicine Greifswald, Department of Internal Medicine B, DZHK (German Centre for Cardiovascular Research), partner site Greifswald, Greifswald, Germany (MRPM); Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA (JEB, PMRi, DIC, AYC, TK); Harvard Medical School, Boston, MA, USA (JEB, PMRi, DIC); Inserm Center U1219 (Bordeaux Population Health Centre), Bordeaux, France (MS, CT, JFD, GC, SD); Institute of Public Health, Charité - Universitätzmedizin, Berlin, Germany (TK); University of Virginia, Charlottesville, VA USA (MMS, AM, SSR); Northwestern University, Chicago, IL, USA (NBA); National institute for Health and Welfare, Helsinki, Finland (ASH, EV, VS); Public Health, University of Helsinki, Finland (SR); Institute for Molecular Medicine Finland (FIMM), University of Helsinki (SR); Wellcome Trust Sanger Institute, UK (SR); Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands (HHHA, MLP, AHo, CMvD, MAI); Department of Neurology, Erasmus MC, Rotterdam, The Netherlands (MLP, PJK); Department of Internal Medicine, Erasmus MC , Rotterdam, The Netherlands (AGU); Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA (JCB, BMP, KLW); Department of Epidemiology, University of Washington, Seattle, WA, USA (BMP, WTL, NLS, SRH); Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA (SRH); Department of Health Services, University of Washington, Seattle, WA, USA (BMP); Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA (BMP); Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, USA (JIR); Division of Genomic Outcomes, Department of Pediatrics, Harbor-UCLA Medical Center, California, USA (JIR); UCLA, California, USA (JIR); Department of Biostatistics, University of Washington, Seattle, WA, USA (TMB, KR, QW); Department of Neurology; University of Washington, Seattle, WA, USA (WTL); Seattle Epidemiologic Research and Information Center of the Department of Veterans Affairs Office of Research and Development, Seattle, WA, USA (NLS); Department of Cardiology, Leiden University Medical Center, Leiden The Netherlands (ST, JWJ); Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands (ST, AJMdC); Department of Molecular Epidemiology, Leiden University Medical Center, Leiden, The Netherlands (JDe); Robertson Center for Biostatistics, University of Glasgow, United Kingdom (IF); Institute of Cardiovascular and Medical Sciences, Faculty of Medicine, University of Glasgow, United Kingdom (DJS); Center for Human Genetics, Division of Public Health Sciences, Wake Forest School of Medicine, Winston Salem, NC, USA (YL); Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Bethesda, MD, USA (TBH, MEGa); Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA (MAN); Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden (SG, MdH, EI); Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA (EI); Department of Medical Sciences, Uppsala University, Uppsala, Sweden (LLi); Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden (LLa); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (NLP, PKM); Genetic and Genomic Epidemiology Unit, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK (CML, APM); Department of Biostatistics, University of Liverpool, Liverpool, UK (APM); Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden (AHa); University of Bordeaux, Bordeaux, France (MS, CT, JFD, GC, SD); Inserm, U1167, F-59000 Lille, France (CeB), Institut Pasteur

de Lille, F-59000 Lille, France (CeB), Univ. Lille, U1167, F-59000 Lille, France (CeB); INSERM U1167, Université Lille, Lille, Lille, France (JDa, DL); Institut Pasteur de Lille, Lille, France (JDa); Department of Neurology, Lille University Hospital, Lille, France (DL); INSERM U1171, Lille, France (DL); INSERM U1061, Montpellier, France (ClB); University Montpellier 1, Montpellier, France (ClB); Department of Neurology, Bordeaux University Hospital, Bordeaux, France (SD, JFD); Boston University School of Medicine, Boston, MA, USA (SD); IRP/NIA/NIH, Bethesda, MD, USA (LJL); Department of Neurology, University of Pittsburgh, PA, USA (OLL); Landspitali National University Hospital, Department of Radiology, Reykjavik, Iceland (OK); Icelandic Heart Association, Kópavogur, Iceland (VG, AVS); University of Iceland, Faculty of Medicine, Reykjavik, Iceland (VG); Institute of Molecular Medicine and Human Genetics Center; University of Texas Health Science Center at Houston, Houston, TX, USA (MF, XJ); Department of Neurology; Johns Hopkins University, Baltimore, MD, USA (RFG); Center of Biostatistics and Bioinformatics; University of Mississippi Medical Center, Jackson, MS, USA (MEGr); Department of Neurology; Mayo Clinic, Rochester, MN, USA (DSK); Department of Medicine, Division of Geriatrics; University of Mississippi Medical Center, Jackson, MS, USA (THM, BGW); CTSU, Nuffield Department of Population Health, University of Oxford, UK (JCH, RC); Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilians University, Munich, Germany (MD, RM); Munich Cluster for Systems Neurology (SyNergy), Munich, Germany (MD); Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK (SB); Departments of Neurology and Public Health Sciences, University of Virginia, Charlottesville, Virginia, USA (BBW); Department of Cerebrovascular Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy (GBB); Department of Neurology and Stroke Center, Basel University Hospital, Switzerland (STE); Neurorehabilitation Unit, University and University Center for Medicine of Aging and Rehabilitation Basel, Felix Platter Hospital, Basel, Switzerland (STE); Department of Neurology, Heidelberg University Hospital, Germany (MK); Department of Clinical and Experimental Sciences, Neurology Clinic, University of Brescia, Italy (AP); McGill University and Genome Quebec Innovation Center (ML, TP); Neurovascular Research Group (NEUVAS), Department of Neurology, IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Universitat Autonoma de Barcelona, Spain (JJC), Neurovascular Research Laboratory and Neurovascular Unit, Institut de Recerca, Hospital Vall d'Hebron, Universitat Autonoma de Barcelona, Spain (JMo), Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA (FR, JR), Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA (FR, JR), J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Boston (FR, JR), MA, Program in Medical and Population Genetics, Broad Institute, Cambridge, MA (FR, JR), Department of Neurology, Jagiellonian University Medical College, Krakow, Poland (AS), Department of Neurology and Rehabilitation Medicine, University of Cincinnati, OH (DW), John Hunter Hospital, Hunter Medical Research Institute and University of Newcastle (CL), Institute of Cardiovascular Research, Royal Holloway college, University of London (ICR2UL) & Ashford and St Peters Hospital, Surrey (PS),Centre for Clinical Brain Sciences & Institute of Genetics and Molecular Medicine, University of Edinburgh (CLMS), University of Maryland School of Medicine and Baltimore VAMC (JWC), Department of Neurology, Clinical Division of Neurogeriatrics, Medical University Graz, Austria (RS),Department of Neurology, Mayo Clinic Jacksonville, Jacksonville, FL, USA (JMe), University of Leuven, Department of Neurosciences, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease, Leuven, Belgium (VT), Vesalius Research Center, Laboratory of Neurobiology, Leuven, Belgium (VT), University Hospitals Leuven, Belgium (VT), Department of Neurology, Austin Health, 145 Studley Rd, Heidelberg, Victoria 3084, Australia (VT), Department of Clinical Sciences Lund, Neurology, Lund University, Lund, Sweden (AL), Department of Neurology and Rehabilitation Medicine, Skåne University Hospital, Lund, Sweden (AL), Lund University Department of Clinical Sciences Malmö (OM), Neuroscience Institute, Saint Francis Medical Center, School of Health and Medical Sciences, Seton Hall University, South Orange, New Jersey, USA (RPG), Department of Neurology, Miller School of Medicine, University of Miami (RLS), Department of Neurology, Miller School of Medicine, University of Miami (TR), Brigham and Women's Hospital (KMR), Nuffield Department of Clinical Neurosciences, University of Oxford (PMRo), Dean's Office, College of Public Health, University of

Kentucky, Kentucky, USA (DKA), Department of Medical and Clinical genetics, Institute of Biomedicine, the Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden (CJ), Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, University of Florida, College of Pharmacy, Gainesville, FL, USA (JAJ), Division of Cardiovascular Medicine, College of Medicine, University of Florida, Gainesville, FL, USA (JAJ), Department of Neurology, University of British Columbia, Vancouver, British Columbia, Canada (ORB), Clinical Neurosciences, University of Cambridge, Cambridge, UK (HSM, MT), Department of Epidemiology and Population Health, Albert Einstein College of Medicine (SWS), Stroke Center, Department of Neurology, Washington University School of Medicine, St Louis, MO, USA (JML),Department of Medical Genetics, University Medical Center Utrecht, Utrecht, Netherlands (SLP), Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, Massachusetts, USA (PLDJ, CCW), Rush Alzheimer's Disease Center, Rush University Medical Center, 600 S Paulina St, Chicago, IL 60612 (DAB), Hôpital Broca, Service de Gérontologie I, and Université Paris Descartes, Sorbonne Paris Cité, Paris, France (JSV), National Heart, Lung, and Blood Institute's Framingham Heart Study Population Sciences Branch, Framingham, Massachusetts, USA (ADJ), Fondation Jean Dausset, Centre d'Etude du Polymorphisme Humain (CEPH), Paris, France (YK), Center for Integrative Medical Sciences, RIKEN, Yokohama, Japan (YK), Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA (AB, ALD, HJA, SS, CLS, SHC, FX), Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA (AB, ALD, SS, SHC, FX), The National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA (AB, ADJ, ALD, AYC, HJA, SS, CLS, SHC, FX), Department of Ophthalmology, University of Alberta, Edmonton, Alberta, Canada (CRF, OJL), Alberta Children's Hospital Research Institute and Department of Biochemistry and Molecular Biology, University of Calgary, Calgary, Alberta, Canada (CRA, SJC), Department of Medical Genetics, University of Alberta, Edmonton, Alberta, Canada (OJL), Department of Chemistry and Molecular Biology, University of Gothenburg, Gothenburg, Sweden (AR, AMN, PC).

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Supplementary Notes

1. Abbreviations

AGES: Age, Gene/Environment Susceptibility-Reykjavik Study
ARIC: Atherosclerosis Risk in Communities
CADISP: Cervical Artery Dissections and Ischemic Stroke Patients
CCS: Causative Classification System
CHARGE: Cohorts for Heart and Aging Research in Genomic Epidemiology
CHD: Coronary Heart Disease
CHS: Cardiovascular Health Study
CI: Confidence Interval
CVD: Cardiovascular Disease
EA: Effect Allele
EAF: Effect Allele Frequency
FHS: Framingham Heart Study
GWAS: Genome Wide Association Study
Health ABC: Health, Aging, and Body Composition (Health ABC) Study
HR: Hazard Ratio
HVH1: Heart and Vascular Health 1
ICD: International Classification of Disease
LD: Linkage Disequilibrium
MA: Minor Allele
MAF: Minor Allele Frequency
MESA: Multi-Ethnic Study of Atherosclerosis
PROSPER: PROspective Study of Pravastatin in the Elderly at Risk
SHIP: Study of Health in Pomerania
SNP: Single Nucleotide Polymorphism
SNV: Single Nucleotide Variant
TOAST: Trial of Org 10172 in Acute Stroke Treatment
ULSAM: Uppsala Longitudinal Study of Adult Men
WGHS: Women's Genome Health Study
3C Study: Three City Study

2. Consortium organization and Sample selection

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.[1]

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. 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.[2]
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.

ARIC

The Atherosclerosis Risk in Communities (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. Over 99% identified as either white or black. Self-identified blacks were excluded from the discovery cohort. 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.[3]
There were 8,939 participants with GWAS data and incident stroke data available for analyses.

CHS

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.[4] 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. Participants were excluded from the 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. Because the other cohorts were predominantly European ancestry, the African American participants were excluded from this analysis to reduce the possibility of confounding by population structure. Beyond laboratory genotyping failures, participants were excluded if they had a call rate<=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. In CHS, only participants who were free of cardiovascular disease at baseline were recruited to provide DNA. Accordingly, these analyses included 3,268 CHS participants.

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;[5] their Offspring and spouses of the Offspring, followed since 1971;[6] and children from the largest Offspring families enrolled in 2000 (Gen 3).[7] 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.

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.[8] 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.[9]
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.

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.[10] 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.

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.[11-13] 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, Mediteranian, 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).[14] 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.

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.[15] 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. A diagnostic interview for mental disorders was performed based on Diagnostic and Statistical Manual for Mental Disorders (IV edition) diagnostic criteria.[16]
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.

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.[17] 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.

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.[18] 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.[18]

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.

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.[19, 20]
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.

TWINGENE

The TwinGene study originates from the Swedish Twin Registry (STR).[21] 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.

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.[22]
Among ULSAM participants with GWAS data (N=1,179), after exclusion of participants with prevalent stroke, N=1,139 participants were available for analyses.

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.[23]

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.

3. Stroke ascertainment and classification

Stroke ascertainment

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.

ARIC

Persons were screened for possible stroke events that occurred through December 31, 2009 using annual phone interviews, follow-up examinations, community hospital surveillance, and death certificates. Any reported hospitalization led to screening and, if suitable, to medical record abstraction. Potential stroke events were selected for abstraction of records if the discharge diagnosis included a cerebrovascular disease code (International Classification of Diseases (ICD), 9th Revision, codes 430 to 438), if a cerebrovascular procedure was mentioned in the discharge summary, or if the CT or MRI report showed evidence of acute cerebrovascular disease.[24] All suspected events were classified by computer algorithm and also by an expert physician reviewer, blinded to the automated results. A second physician reviewer adjudicated disagreements between the computer and the initial reviewer. Briefly, the stroke diagnosis was assigned according to criteria adapted from the National Survey of Stroke.[25] 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. A stroke was classified as "lacunar" when 2 criteria were met: (1) typical location of the infarct (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter); and (2) infarct size of ≤2 cm or unstated size.[26] Definite or probable "cardioembolic" stroke required either (1) autopsy evidence of an infarcted area in the brain and a source of possible cerebral emboli in a vessel or the presence of an embolus in the brain or (2) medical record evidence of a possible noncarotid source of embolus such as moderate or greater valvular heart disease, atrial fibrillation, cardiac or arterial procedure (eg, cardiac catheterization, open heart surgery, cerebral angiography, and carotid endarterectomy), or intracardiac thrombus. Definite or probable ischemic strokes that were not classified as lacunar or cardioembolic, including atherothrombotic and unclassified thrombotic strokes, were labeled "nonlacunar."

CHS

Participants were examined annually from enrollment to 1999 and continued to be under surveillance for stroke following 1999.[27, 28] 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).[29] 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.[30] Nonetheless, the two approaches are quite similar.

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;[31-33] 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

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.[34] 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.[35] 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

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

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.[38, 39]

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);[40] 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.

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.[17] Stroke subtyping definition distinguishes ischemic versus hemorrhagic events according to TOAST criteria.[30]

MESA

New occurrences of stroke were recorded over 7-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.[41] 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.

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 end points. 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

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.[42] 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.[43] One twin was randomly selected per pair if data were available for both twins.

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 (B Wiberg). 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.[22, 44]

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.[30]

Stroke Classification

Strokes were classified as ischemic if there was imaging (CT or MRI within 4 weeks), surgical or autopsy evidence excluding a hemorrhage. In some studies (FHS, Rotterdam), if the preponderance of indirect evidence (e.g. deficit limited to one limb or completely resolved within 72 hours, atrial fibrillation in persons not on anticoagulants) suggested the event was an ischemic rather than a hemorrhagic stroke. A stroke was classified as hemorrhagic if there was imaging, surgical, lumbar puncture or autopsy evidence of hemorrhage. Also, in some studies (FHS, Rotterdam) a minority of strokes were classified as hemorrhagic in the absence of direct evidence to the contrary, when the participant lost consciousness permanently or died within hours after onset of focal signs. The stroke type was defined as unknown if there was insufficient information available to categorize the event as ischemic or hemorrhagic. All ischemic and hemorrhagic strokes and strokes of unknown type were included in the analyses of total stroke. Subarachnoid hemorrhages were excluded from all analyses since the heritability, risk factors and pathophysiologic mechanisms underlying subarachnoid hemorrhages are distinctly different from other stroke subtypes. Persons with a subarachnoid hemorrhage were censored at the time of the event.

When information on ischemic stroke subtypes was available we classified ischemic stroke into cardioembolic and non-cardioembolic ischemic stroke. The latter category comprised large artery ischemic stroke, small-vessel disease ischemic stroke and ischemic strokes of other or unknown subtype. Ischemic stroke subtyping paradigms are detailed above for each study.

In all but 2 studies information on stroke type (ischemic versus hemorrhagic) was available, and a GWAS of incident ischemic stroke was run in 78,642 participants (3,028 with incident ischemic stroke). Information on ischemic stroke subtypes was available in 10 cohorts, totaling 60,430 participants (2,496 with incident ischemic stroke, classified as cardioembolic in 602 and non-cardioembolic in 1,770 participants). Only six cohorts (42,840 participants) had sufficient events for analysis of incident intracerebral hemorrhage (N=277) (**Table 1**).

4. Genotyping quality control filters and imputation

The consortium was formed after the individual studies had finalized their GWAS platforms, and the studies included used different platforms (**Supplementary Table 1**).

As detailed previously,[45] participant-specific quality controls included filters for call rate, heterozygosity, and number of Mendelian errors per individual. SNP-specific quality controls included filters for call rate, minor allele frequency, Hardy-Weinberg equilibrium, and differential missingness by outcome or genotype (mishap test in PLINK, http://pngu.mgh.harvard.edu/purcell/plink/).

The set of genotyped input SNPs used for imputation in each study was selected based on their highest quality GWA data (see **Supplementary Table 2** for quality control filter applied prior to imputation). Programs used for imputation are detailed in **Supplementary Table 3**. For each imputed SNP, imputation quality was estimated using the R-square metric or the ratio of the empirically observed dosage variance to the expected binomial dosage variance.

5. Screening for latent population substructure

Studies were screened for latent population substructure, including cryptic relatedness, using suitable programs (**Supplementary Table 2**).[46-48] When appropriate, components related to the phenotype under study were included as covariates in the linear regression. TWINGENE and FHS included related individuals and used the following methods to adjust for relatedness of the population: TWINGENE excluded one twin from each pair randomly, creating an unrelated subset; FHS used a linear mixed effects model accounting for familial relatedness.[49]

We studied quantile-quantile (Q-Q) plots to ensure that the p-value distributions in each of the cohorts conformed to a null distribution at all but the extreme tail. We also calculated the genomic inflation factor lambda, which measures over-dispersion of test-statistics from association tests indicating population stratification and can be used to apply genomic control.[50]

Genomic inflation factors (λ) by study and by phenotype are shown in **Supplementary Table 6**.

6. Study specific regression and meta-analysis techniques

At a study-specific level, using genome-wide multivariable Cox regression after verifying the proportional hazards assumption, we tested the association of genetic variants with incident stroke (all stroke, IS, cardioembolic and non-cardioembolic IS) under an additive genetic model, adjusting

for sex, age, and when relevant, principal components of population stratification, study site or familial structure (**Supplementary Table 5**). Time between date of DNA draw and occurrence of first stroke was used as an endpoint. In secondary analyses we tested for associations with incident ICH. Participants known to be stroke-free were right censored at death or at the time of their last follow-up examination or health status update. Participants with subarachnoid hemorrhage or alternative stroke type or subtype were censored at time of event. Meta-analysis of study-specific association statistics was performed at two sites (G.C. and A.Y.C.) using inverse variance weighted meta-analysis with METAL.

Prior to meta-analysis genetic variant and allele names were harmonized across all studies, duplicate markers and markers not present in the 1000G pIv3 reference panel were removed. Only genetic variants with absolute value of regression coefficient <5, standard error >0 and <10,000, and effective allele count >10 were retained for analysis. Effective allele count was defined as twice the product of minor allele frequency, imputation accuracy (R^2), and number of cases. We also restricted our analyses to common variants with a minor allele frequency >0.05. Moreover, genetic variants available in less than five studies or in less than 50% of the total number of cases were discarded. Genomic control was applied before and after meta-analysis.

We undertook the meta-analyses with METAL,[51] using inverse-variance weighted meta-analysis as our primary method after applying genomic control within each individual study. Beta estimates were weighted by their inverse variance and a combined estimate was obtained by summing the weighted betas and dividing by the summed weights. Hence results for SNPs imputed with low certainty were down-weighted because the low quality of imputation implicates a large variance. In contrast, studies with large sample sizes and with directly genotyped or well-imputed SNPs had a greater effect on the meta-analyses p-value because of small variances.

Genomic inflation factors at the study-specific and meta-analysis level are shown in **Supplementary Table 6** and **Supplementary Figure 1**.

All SNPs with a p-value < $5x10^{-6}$ and a minor allele frequency > 0.05 were selected for in silico replication.

7. Follow-up studies

Sample description

In silico follow-up association analyses were performed in four independent, non-overlapping, mostly hospital-based genetic association studies of stroke, totaling 19,816 stroke patients (mean age at event 61 years, **Table 1**) and 50,988 controls from the SiGN [Stroke genetics network] study (16,851 cases, 32,473 controls),[52] the METASTROKE consortium (1,729 cases, 7,925 controls),[53] the Heart and Vascular Health 1 (HVH1) study (681 cases, 1,331 controls),[54] and the Cervical Artery Dissections and Ischemic Stroke Patients (CADISP) consortium (555 cases, 9,259 controls).[55]

Great care was taken to exclude any potential overlap in samples between discovery and follow-up samples used in this analysis.

SiGN

In total this sample consists of 16,851 ischemic stroke cases and 32,473 stroke-free controls. The SiGN data used in this analysis consists of the following studies: (i) case-only or case-control studies: Australian Stroke Genetics Collaborative (ASGC), Base de Datos de Ictus del Hospital del Mar (BASICMAR), Bio-Repository of DNA in Stroke (BRAINS), Edinburgh Stroke Study (EDINBURGH), Massachusetts General Hospital - Genes Affecting Stroke Risks and Outcomes Study (MGH-GASROS), Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), Genetics of Early Onset Stroke (GEOS), Austrian Stroke Prevention Study (GRAZ), Ischemic Stroke Genetics Study (ISGS), Sibling with Ischemic Stroke Study (SWISS), Krakow stroke genetics study (KRAKOW), The Leuven Stroke genetics study (LEUVEN), Lund Stroke Register (LUND), The Malmö Diet and Cancer Study (MALMÖ), Middlesex County Ischemic Stroke Study (MCISS), Miami Stroke Registry (MIAMISR), Northern Manhattan Study (NOMAS), MUNICH stroke study (MUNICH), Nurses' Health Study (NHS), Oxford Vascular Study (OXVASC), Reasons for Geographic and Racial Differences in Stroke (REGARDS), The Sahlgrenska Academy Study of Ischemic Stroke (SAHLSIS), Secondary Prevention of Small Subcortical Strokes (SPS3), St George's stroke cohort (ST. GEORGE'S), Vitamin Intervention for Stroke Prevention (VISP), Women's Health Initiative Observational Study (WHI-OS), Washington University St. Louis Stroke Study (WUSTL); (ii) control-only cohorts: ADHD, The Health Aging and Body Composition Study (Health ABC), Health Retirement Study (HRS), INMA, Kooperative Gesundheitsforschung in der Region Augsburg (KORA), OAI, Hispanic Community Health Study/Study of Latinos (HCHS/SOL), Wellcome Trust Case-Control Consortium 2 (WTCCC2). Individual studies participating in the METASTROKE study and stroke ascertainment methods are described in detail elsewhere.

The phenotypes tested were: all ischemic stroke (IS); cardioembolic IS; large artery IS; small artery occlusion IS as defined primarily by the TOAST subtyping system, and in secondary analyses by the CCS Causative and CCS Phenotypic subtyping systems.[52]

Except for 4,963 African-American and 3,371 Hispanic participants (cases and controls), all replication samples were of European ancestry.

For organization of the SiGN consortium please see below.

The GWAS results from the SiGN consortium (distinct from the results presented here, which represent only look-ups of suggestive loci from the population-based incident stroke GWAS) have been submitted for publication.

METASTROKE

In total, this sample consists of 1,729 IS cases and 7,925 stroke-free controls. The METASTROKE data used in this analysis consists of the following studies:[53] Massachusetts General Hospital - Genes Affecting Stroke Risks and Outcomes Study – Affymetrix (MGH-GASROS_affy, 203 patients with ischemic stroke, 3030 controls), MGH-GASROS - Illumina (205 patients with ischemic stroke, 377 controls), Milano Besta Institute Stroke Study (MILANO, 366 patients with ischemic stroke, 407 controls), Ischemic Stroke Genetics Study and Sibling with Ischemic Stroke Study (ISGS/SWISS, 61 patients with ischemic stroke, 1370 controls), Heart Protection Study (HPS, 588 patients with ischemic stroke, 571 controls) and Women's Health Initiative Hormone Therapy (WHI-HT, 306 patients with ischemic stroke and 2170 controls). Individual studies participating in the METASTROKE study and stroke ascertainment methods are described in detail elsewhere.[53] Participants from MGH-GASROS, ISGS/SWISS and WHI included in METASTROKE and SiGN do not overlap.

TOAST subtypes were available for all IS patients except from the HPS study. In total 206 patients with large artery IS, 276 patients with cardioembolic IS, and 159 patients with small artery occlusion IS were available for IS subtype analyses.

All participants were of European ancestry.

HVH1

The setting for this study was Group Health (GH), a large integrated health care system in western Washington State. 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,[54, 56, 57] and are briefly summarized below. 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.[28] 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.

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.[55] 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 forIS 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,[30] using a more detailed subtype description from an early version of the Causative Classification System (CCS).[58]

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.[55]

All participants were of European ancestry.

Genotyping, imputation and analytic models

Follow-up analyses were performed using logistic regression under an additive genetic model, adjustment variables are detailed below for each study. Meta-analysis of study-specific association statistics (SiGN, METASTROKE, HVH1, CADISP) was then performed using inverse variance weighted meta-analysis with METAL.[51]

SiGN

The SiGN discovery analysis was comprised of primarily case-only and control-only groups of samples genotyped on a variety of Illumina genotyping platforms, ranging in size from the Illumina 550K to the Illumina 5M. A number of the samples had been previously genotyped; an additional ~9,700 cases were newly genotyped on the Illumina 5M at the Center for Inherited Disease Research (CIDR).

All cohorts were initially QC'd individually, and samples with high missingness (>10%) and duplicate samples were removed. All A/T and C/G SNPs and duplicate markers were removed. Cases and controls were then pooled first on genotyping platform, so as to maximize the number of SNPs retained in the analysis for downstream imputation. Then, principal component analysis was used to determine a group of European-ancestry samples. Additionally, a hypervolume analysis, based on principal components, was used to define a set of African-ancestry and Hispanic samples. A small number of Asian-ancestry samples were excluded from the analysis.

Once array- and ancestry-specific strata of cases and controls had been defined, these strata were cleaned again. Samples with high missingness (>10%), kinship >0.0625 (using the KING method for African-ancestry and Hispanic samples), PCA outliers, and inbreeding outliers (Europeans and Africans only) were dropped. SNPs were filtered based on missingness, deviations from Hardy-Weinberg equilibrium, differentiation from 1000 Genomes reference samples (Europeans only), and differential missingness between cases and controls. An initial genome-wide association study was run on the genotyped SNPs in each stratum using the all stroke phenotype to check that quality control had been effective and lambda was appropriately behaved (<1.05, in line with previous stroke studies). After quality control, 16,851 cases and 31,259 controls were available for the discovery analyses.

Samples were prephased using SHAPEIT2 (Europeans and Africans were pre phased using 1000 Genomes Phase I as a reference panel) and imputed with IMPUTE2. The Europeans were imputed with a reference panel based on the merging of the 1000 Genomes Phase I samples (1,092 individuals) and all unrelated individual available from the Genome of the Netherlands Project (N=499). African-ancestry and Hispanic samples were imputed with 1000 Genomes Phase I only. After imputation, SNPs out of HWE ($p<10^{-6}$) or with an info score <0.5 were removed from the analysis.

GWAS was run in each of the stratum on the imputed dosages using SNPTEST and correcting for sex and the top ten principal components.

After GWAS, SNPs with frequency <1% were dropped. Summary-level results from each stratum were combined using inverse variance-weighted fixed-effects meta-analysis. We analyzed genome-wide z-scores from the CCS Causative, CCS Phenotypic, and TOAST subtype-based meta-analyses to confirm moderate to strong genetic correlation of the subtyping methods, indicating that TOAST-subtyped cases were suitable for replication analysis. All SNPs with $p < 10^{-6}$ after the discovery meta-analyses were selected for replication.

METASTROKE

Genotyping platforms and quality control filters are described in detail elsewhere.[53] Each site imputed their data to the latest 1000 Genomes imputation panel using either MaCH or IMPUTE2. A detailed analysis plan was distributed and each site analyzed their data accordingly using a logistic regression model without covariates.

Summary statistics were collected from the individual sites and meta-analyzed using a fixed-effects inverse-variance model. Before meta-analysis, individual variants were excluded if their imputation quality was below 0.3 or if their minor allele frequency was below 1%.

HVH1

Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai using the Illumina 370CNV BeadChip system and genotypes were called using the Illumina BeadStudio software. Samples were excluded from analysis for sex mismatch or call rate < 95%. The following variant exclusions were applied to obtain a cleaned set of variants for imputation: call rate < 97%, HWE P < 10-5, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0. The genotypes of the 3741 participant retained after quality control were pre-phased using MaCH. The phased genotypes were imputed into a reference panel of 1092 individual of multiple ethnicities from the Phase1 version 3 haplotypes of Thousand Genomes project using minimac (release stamp 2012-11-16). Imputation of the X chromosome was limited to the non pseudo-autosomal region and was imputed separately by gender.

Logistic regression was used to investigate the association of each SNP with the risk of stroke and MI, adjusting for the matching factors of age, sex, hypertension status and index year. We used linear additive models and estimated risk for each additional copy of the variant allele, using R.

CADISP

All DNA samples were genotyped at the Centre National de Génotypage, Evry, France (CNG, www.cng.fr) on a Human610-Quad BeadChip or Illumina Human 660W-Quad BeadChip® (Illumina, San Diego, USA). Illumina BeadStudio® was used for genotype calling.[55] Sample quality control filters were set to exclude individuals with a call rate <0.95 (<0.96 for BRAINS samples), individuals showing discrepancies between genetically inferred sex and given clinical data (X heterozygosity <0.10 but given sex is female, and X heterozygosity >0.20 but given sex is male), and duplicates. Estimation of IBD status was performed using PLINK (version 1.07),[59] to identify potential cryptic relatedness. When strongly related subjects were identified (full siblings or parent-offspring relationship), one of them only was selected for the analysis. Finally, non-European individuals determined by principal component analysis with HapMap2 samples (CEU, CHB, JPT, and YRI) were removed.

After quality control we used 472,862 autosomal single nucleotide polymorphisms (SNPs) and 10,029 X-chromosomal SNPs for analyses. Imputation to the 1000G phaseI v3 reference panel was performed using SHAPE-IT for pre-phasing and IMPUTE2 for imputation.

Logistic regression was performed using Probabel, adjusting for sex and the first 10 principal components.

NINDS-SiGN consortium organization / committee members

Administrative:

Steven J. Kittner, MD, MPH (chair; Department of Neurology, University of Maryland School of Medicine and Veterans Affairs Maryland Health Care System, Baltimore, MD, USA);

Cameron A. Dell, BS (Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, USA) ;

Dale M. Gamble, MHSc, CCRP (Department of Neurology, Mayo Clinic, Jacksonville, FL, USA);

Mary J. Sparks, RN, BSN (Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, USA)

Steering/PIs of Discovery Studies:

Donna K. Arnett, PhD, MSPH (Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA);

Oscar Benavente, MD, FRCP (Department of Neurology, University of British Columbia, Vancouver, British Columbia, Canada);

John W. Cole, MD, MS (Department of Neurology, University of Maryland School of Medicine and Veterans Affairs Maryland Health Care System, Baltimore, MD, USA);

Martin Dichgans, MD (Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilians University, Munich, Germany ; Munich Cluster for Systems Neurology (SyNergy), Munich, Germany) ;

Raji P. Grewal, MD (Neuroscience Institute, Saint Francis Medical Center, School of Health and Medical Sciences, Seton Hall University, South Orange, New Jersey, USA);

Christina Jern, MD, PhD (Institute of Biomedicine, the Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden);

Jordi Jiménez Conde, MD, PhD (Department of Neurology, Neurovascular Research Group (NEUVAS) IMIM-Hospital del Mar (Institut Hospital del Mar d'Investigacions Mèdiques), Universitat Autonoma de Barcelona/DCEXS-Universitat Pompeu Fabra, Barcelona, Spain);

Julie A. Johnson, PharmD (Department of Pharmacotherapy and Translational Research and Center for Pharmacogenomics, College of Pharmacy, University of Florida, Gainesville, FL, USA ; Division of Cardiovascular Medicine, College of Medicine, University of Florida, Gainesville, FL, USA);

Jin-Moo Lee, MD, PhD (Stroke Center, Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA);

Christopher Levi, MBBS, BMed Sci, FRACP (John Hunter Hospital, Hunter Medical Research Institute and University of Newcastle, NSW, Australia);

Arne Lindgren, MD PhD (Department of Clinical Sciences Lund, Neurology, Lund University, Lund, Sweden; Department of Neurology and Rehabilitation Medicine, Neurology, Skåne, University Hospital, Lund, Sweden);

Hugh S. Markus, DM (Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK);

Olle Melander, MD, PhD (Lund University, Department of Clinical Sciences, Malmö University Hospital, Malmö, Sweden);

James F. Meschia, MD (Department of Neurology, Mayo Clinic, Jacksonville, FL, USA);

Kathryn Rexrode, MD, MPH (Brigham and Women's Hospital, Boston, MA, USA);

Jonathan Rosand, MD, MSc (Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge MA, USA; Department of Neurology and Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA; Department of Neurology, Harvard Medical School, Boston, MA, USA);

Peter M. Rothwell, FMedSci (Stroke Prevention Research Unit, Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK);

Tatjana Rundek, MD, PhD, FANA (Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA);

Ralph L. Sacco, MD, MS, FAHA, FAAN, FANA (Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA) ;

Reinhold Schmidt, MD (Department of Neurology, Clinical Division of Neurogeriatrics, Medical University Graz, Graz, Austria);

Pankaj Sharma, MD, PhD, FRCP (Institute of Cardiovascular Research, Royal Holloway University of London (ICR2UL), Egham, UK; St Peter's and Ashford Hospitals, UK);
Agnieszka Slowik, MD, PhD (Department of Neurology, Jagiellonian University Medical College, Krakow, Poland);
Cathie LM Sudlow, DPhil, FRCP(E) (Centre for Clinical Brain Sciences & Institute of Genomic and Molecular Medicine, University of Edinburgh, UK);
Vincent Thijs, MD, PhD (KU Leuven - University of Leuven, Department of Neurosciences, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), Leuven, Belgium; VIB, Vesalius Research Center, Laboratory of Neurobiology, Leuven, Belgium; University Hospitals Leuven, Department of Neurology, Leuven, Belgium);
Sylvia Wassertheil-Smoller, PhD (Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA);
Daniel Woo, MD, MS (University of Cincinnati College of Medicine, Cincinnati, OH, USA);
Bradford B. Worrall, MD, MSc (Departments of Neurology and Public Health Sciences, University of Virginia, Charlottesville, VA, USA)

PIs of Control Studies:
Rebecca D. Jackson, MD (Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine and the Center for Clinical and Translational Science, The Ohio State University, Columbus, OH);
Martina Müller-Nurasyid, PhD (Institute of Genetic Epidemiology, Helmholtz Zentrum München – Germany; Research Center for Environmental Health, Neuherberg, Germany; Department of Medicine I, Ludwig-Maximilians-University Munich, Munich, Germany; DZHK (German Centre for Cardiovascular Research), partner site Munich; Heart Alliance, Munich, Germany);
Mike A. Nalls, PhD (Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA);
Marta Ribasés, PhD, BSc (Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addictions,
Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain; Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Spain; Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Spain);
David R. Weir, PhD (Survey Research Center, University of Michigan, Ann Arbor, MI, USA)

Data Management:
Patrick F. McArdle, PhD (chair; Department of Medicine and Program for Personalized and Genomic Medicine, University of Maryland School of Medicine, Baltimore, MD);
Tushar Dave, MS (Department of Medicine and Program for Personalized and Genomic Medicine, University of Maryland School of Medicine, Baltimore, MD, USA)

Analysis:
Braxton D. Mitchell, PhD, MPH (chair; Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, MD, USA; Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, MD, USA);
Yu-Ching Cheng, PhD (Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA);

Paul I.W. de Bakker, PhD (Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands; Department of Epidemiology, University Medical Center Utrecht, Utrecht, The Netherlands);
Myriam Fornage, PhD (Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX, USA);
Cathy C. Laurie, PhD (Department of Biostatistics, University of Washington, Seattle, WA, USA);
Ani Manichaikul, PhD (Center for Public Health Genomics, Biostatistics Section, Department for Public Health Sciences, University of Virginia, Charlottesville, VA, USA);
Jeffrey R. O'Connell, DPhil (Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, MD, USA);
Sara L. Pulit, BA (Department of Medical Genetics, Institute for Molecular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands);
Stephen S. Rich, PhD (Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA);
Quenna Wong, MS (Department of Biostatistics, University of Washington, Seattle, WA, USA);
Huichun Xu, MD, PhD (Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA)

Phenotype:
James F. Meschia, MD (co-chair; Department of Neurology, Mayo Clinic, Jacksonville, FL, USA);
Bradford B. Worrall, MD, MSc (co-chair; Departments of Neurology and Public Health Sciences, University of Virginia, Charlottesville, VA, USA);
Hakan Ay, MD (AA Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; Stroke Service, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA);
Robert D. Brown Jr., MD, MPH (Department of Neurology, Mayo Clinic, Rochester, MN, USA)

Imaging:
Jonathan Rosand, MD, MSc (chair; Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge MA, USA; Department of Neurology and Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA; Department of Neurology, Harvard Medical School, Boston, MA, USA);
Natalia S. Rost, MD, MPH (Stroke Division, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114);
Ona Wu, PhD (Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, MA, USA; Department of Radiology, Harvard Medical School, Boston, MA, USA)

Publication:
Kathryn Rexrode, MD, MPH (chair Brigham and Women's Hospital, Boston, MA, USA);
Tatjana Rundek, MD, PhD, FANA (prior chair; Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA);
Agnieszka Slowik, MD, PhD (prior co-chair; Department of Neurology, Jagiellonian University Medical College, Krakow, Poland);
Hakan Ay, MD (AA Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; Stroke Service, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA);

Oscar R. Benavente, MD, FRCP (Department of Neurology, University of British Columbia, Vancouver, British Columbia, Canada);
Steve Bevan, PhD (Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK);
Katrina Gwinn, MD (National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA);
Steven J. Kittner, MD, MPH (chair; Department of Neurology, University of Maryland School of Medicine and Veterans Affairs Maryland Health Care System, Baltimore, MD, USA);
Jin-Moo Lee, MD, PhD (Stroke Center, Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA);
Patrick F. McArdle, PhD (Department of Medicine and Program for Personalized and Genomic Medicine, University of Maryland School of Medicine, Baltimore, MD);
James F. Meschia, MD (Department of Neurology, Mayo Clinic, Jacksonville, FL, USA);
Braxton D. Mitchell, PhD, MPH (Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, MD, USA; Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, MD, USA);
Jonathan Rosand, MD, MSc (Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge MA, USA; Department of Neurology and Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA; Department of Neurology, Harvard Medical School, Boston, MA, USA);
Sylvia Wassertheil-Smoller, PhD (Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA);
Daniel Woo, MD, MS (University of Cincinnati College of Medicine, Cincinnati, OH, USA);
Bradford B. Worrall, MD, MSc (Departments of Neurology and Public Health Sciences, University of Virginia, Charlottesville, VA, USA)

CIDR:
Kimberly F. Doheny, PhD (Center for Inherited Disease Research, Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, MD)

NINDS staff:
Roderick Corriveau, PhD (National Institutes of Health, Bethesda, MD, USA);
Katrina Gwinn, MD (National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA)

8. In silico functional annotation

GRASP2 was used for expression quantitative trait locus (eQTL) analysis (**Supplementary Table 16**).[60] GRASP2 is a large repository of associations between SNPs and phenotype from 1,390 published GWAS results,[60] which was recently updated (version 2.0) with an increase of approximately 2.59 million SNP associations and additional 693 studies.[61] The full GRASP2 catalog was downloaded (http://apps.nhlbi.nih.gov/Grasp/Overview.aspx) and queried for eQTLs. Statistical thresholds for association with gene transcript levels as described in the original papers were used. eQTL associations for suggestive stroke risk variants in non-brain tissue are shown in **Supplementary Table 16.**

GTEx V6 (http://www.gtexportal.org/home/) was also used to mine eQTL. GTex aims at identifying eQTLs in the context of different tissues throughout the body (across 43 tissues from 175 individuals,

including 10 brain sub-regions). Single-tissue eQTL Dataset for significant SNP-gene associations were downloaded (GTex V6)[62] and queried matching the corresponding rsID. SNPs that match the query represents the most significant SNP per gene that functions as an eQTL and satisfies the gene-specific significance threshold that is accounted for multiple testing and estimated using permutation tests. Similarly, GTEx pilot data (GTex V3)[63] on multi-tissue is used to examine eQTL sharing across a range of tissues to evaluate specificity or ubiquity of the identified eQTLs

We used GENEVAR for identification of methylation quantitative trait loci (mQTL, **Supplementary Table 17**).[64] GENEVAR is a Java-based tool designed as a query platform, integrated with multiple datasets on different cell types and cell lines.[64] SNP centric (mQTLs surrounding the query SNPs) and CpG centric (mQTL SNPs centred on the CpG Island) analyses were performed. For the reference dataset, the most recent methylome profile data on adipose tissue collected from 648 healthy female twins was used.[65] Correlation measures from the MuTHER study were used to estimate the strength of relationship between the alleles and the expression intensities, and the Cis analysis was limited to a window of 100kb on either side of the query SNP. A significance threshold of $p < 10^{-4}$ was applied.[60] Using the rsIDs of significant loci, mQTLS surrounding the SNP of interest were identified followed by the identification of the corresponding CpG islands.

In addition, we performed more extensive annotation for the novel stroke risk locus. We implemented a database from 53 gene expression studies of multiple tissue and cell lines.[66] We chose the top variant as well as proxy variants in LD (r^2>0.5 in 1000GpIv3). eQTL associations for index variant and proxies were searched in a collected database of expression SNP (eSNP) results (A.D.J.).
We also used BRAINEAC for identifying variants that operate as eQTL in different brain regions.[67] The BRAINEAC Brain eQTL Almanac is a web-based tool where eQTL data can be queried in the UK Brain Expression Consortium (UKBEC) dataset (http://braineac.org/).[67] It comprises genotype and expression data for twelve brain regions extracted from 134 individuals free of neurodegenerative disorders.

In addition, we performed an eQTL analysis in dorsolateral prefrontal cortex of post-mortem brain tissue: We examined mRNA expression of *FOXF2* and adjacent genes in previously described samples of neuropathologically characterized brain autopsy tissue, drawn from the dorsolateral prefrontal cortex of 508 persons enrolled in the Religious Orders Study and the Rush Memory and Aging Project (ROS/MAP).[68]

We also used RegulomeDB[69] and Haploreg,[70] for functional annotation of variants in the novel locus reaching $p<5x10^{-8}$ in association with stroke (index variants), as well as proxy variants in LD (r^2>0.5 in 1000GpIv3)(**Tables S13-15**). We specifically explored if these variants were enriched for regulatory regions. RegulomeDB is a database that includes high-throughput experimental datasets for regulatory regions from ENCODE and other sources, it also includes computational predictions and manual annotations to identify putative regulatory and functional variants.[69] RegulomeDB combines these data sources into a powerful tool and scores variants (from 1 to 6) to help distinguish functional variants and provides a small set of putative sites with testable hypotheses as to their function. Variants with lower RegulomeDB score have higher probability to act as regulatory variants. HaploReg uses LD information from the 1000 Genomes Project, for visualizing SNPs in LD along with

their predicted chromatin state in nine cell types, conservation across mammals and their effect on regulatory motifs.[70] SNPs are tested for enrichment of cell type-specific enhancers and DNaseI hypersensitive regions.

For mQTL look-up in the International Human Epigenome Consortium we mined large sets of epigenomic data from the International Human Epigenome Consortium (www.ihec.org)

Finally, we performed in silico annotation of the chr6p25 locus for presence of microRNA (miRNA) using the publicly available dataset miRBase.[71] miRBase - http://www.mirbase.org

9. Exploration of known stroke risk loci

In order to relate our results to previous findings, we examined whether known risk loci for ischemic stroke[53, 72-75] and intracerebral hemorrhage[76] (identified mainly in hospital-based case-control association studies) were associated with incident stroke risk in the general population. We constructed a stroke genetic risk score based on published risk loci for ischemic stroke and intracerebral hemorrhage and tested its association with incident all stroke in the general population using the gtx package in R (http://cran.r-project.org/web/packages/gtx/). We used an unweighted genetic risk score, as effect sizes could differ between a case-control, hospital-based study and a population-based, longitudinal setting. In sensitivity analyses a weighted genetic risk score was used, weights being based on effect estimates in the original GWAS.

A stroke genetic risk score combining all 10 known stroke risk variants[53, 72-77] was significantly associated with incident all stroke and ischemic stroke: HR=1.04(1.03-1.06), $p=7.44x10^{-8}$ and HR=1.06(1.04-1.08), $p=2.68x10^{-10}$, by increasing risk allele count. When restricting the genetic risk score to the 8 known risk variants for ischemic stroke, associations with incident all stroke and ischemic stroke were also highly significant: HR=1.04(1.02-1.06), $p=1.30x10^{-5}$ and HR=1.06(1.04-1.08), $p=9.46x10^{-8}$ respectively. Associations were similar when using a weighted genetic risk score (data not shown).

10. Functional experiments

Functional studies in Murine Foxf2 mutants

Construction of the constitutive (*Foxf2*$^{-}$) and conditional (*Foxf2*^{fl}) *Foxf2* null alleles has been described previously.[78] Conditional *Foxf2* knock-out mice (*Foxf2*$^{fl/fl}$ and *Foxf2*$^{-/fl}$ carrying the *CAGG-Cre*^{ERT2} transgene[79]) and controls (*Cre*-negative *Foxf2*$^{fl/fl}$ and *Foxf2*$^{-/fl}$, and *CAGG-Cre*^{ERT2}-positive *Foxf2*$^{fl/+}$ and *Foxf2*$^{+/+}$) were induced at an age of 12 weeks by three intraperitoneal injections, with 48 hours interval, of 5 mg Tamoxifen (Sigma, T5648). Tamoxifen activates Cre^{ERT2}, expressed by *CAGG-Cre*^{ERT2}, which deletes *Foxf2* by recombination between the *loxP* sites that flank exon 1 in *Foxf2*^{fl}.[78] Judged by PCR analysis of biopsies from many organs, including several parts of the brain, the recombination efficiency of *Foxf2*^{fl} was close to 100%,[78] except in the lung. All strains were maintained on a C57Bl/6 background (Charles River, Germany) with some 129/SvJ contribution.

Mice were sacrificed six weeks after induction, perfused with 4% paraformaldehyde in phosphate buffered saline, and the brains were processed for embedding in paraffin or epoxy resin, and sectioned. Sections were stained with hematoxylin and eosin, or Richardson's Methylene Blue/Azur

II, or immunostained with anti-glial fibrillary acidic protein (rabbit polyclonal anti-GFAP; DAKO #Z0334), followed by detection with biotinylated secondary antibody (goat anti-rabbit, BD Pharmingen #550338) and streptavidin–Alexa Flour conjugate (Invitrogen).
Experiments were approved by the Gothenburg Animal Ethics committee.

Functional studies in Zebrafish foxf2 mutants

Zebrafish brain dissection, in situ *hybridization and sectioning*

Expression of *foxf2a* and *foxf2b* (duplicate orthologs of human *FOXF2*), *notch3 and pdgfrβ* was analyzed in the brain of 4 day post fertilization and 1-month old zebrafish larvae as described.[80, 81] Fish were anaesthetized by tricaine overdose, dissected, fixed in 4% paraformaldehyde overnight at 4°C, and placed in 100% methanol for long term storage. RNA probes were synthesized using T7 RNA polymerase from PCR fragments derived from cDNA or plasmid template. *In situ* hybridization was carried out as described.[82] Transgenic endothelial cells tagged with mCherry were detected using rabbit α-mCherry antibody (Stratagene 632496, 1:200) and visualized by a DAB peroxidase substrate kit (Vectastain; Vector Labs). Brains were embedded using the JB-4 polymer (Polysciences Inc., Warrington PA, USA) and cut into 7 micron sections using a Leica RM2265 glass knife microtome. Sections were dried on slides and mounted in Permount (Fisher Scientific, Mississauga) under a coverslip. Images were captured with a Leica DMR microscope at 100x magnification.

TALEN mutagenesis and genotyping

Genetic mutations were induced in the *foxf2b* locus by TALEN mutagenesis.[83, 84] The left TALEN targets 5'TGTCAAAGAGTAAAAA'3' and right TALEN targets 5'CCCGGAGAAACCGCCCTA 3'. The 29bp spacer sequence between the two binding sites 5' GACCAACTCAGGTCTGCGACGCCCGGAGA3' included an BcpCN1 restriction endonuclease site (underlined). foxf2^{ca22} has a single base pair insertion while *foxf2b*^{ca23} has a 14 bp indel (5 bp deletion and 19 bp insertion). Both mutations result in a frameshift and a premature stop in the conserved Fox DNA binding domain. This allele is predicted to lead to a truncated protein, abrogating transcriptional regulatory function. Genotype-phenotype correlations were made by sizing of products on an agarose gel after PCR (CA23 f: GCATAGCGCAGTGTCAAAGA and CA23 r: GGTTGGTGCGCTCTGAATTG).

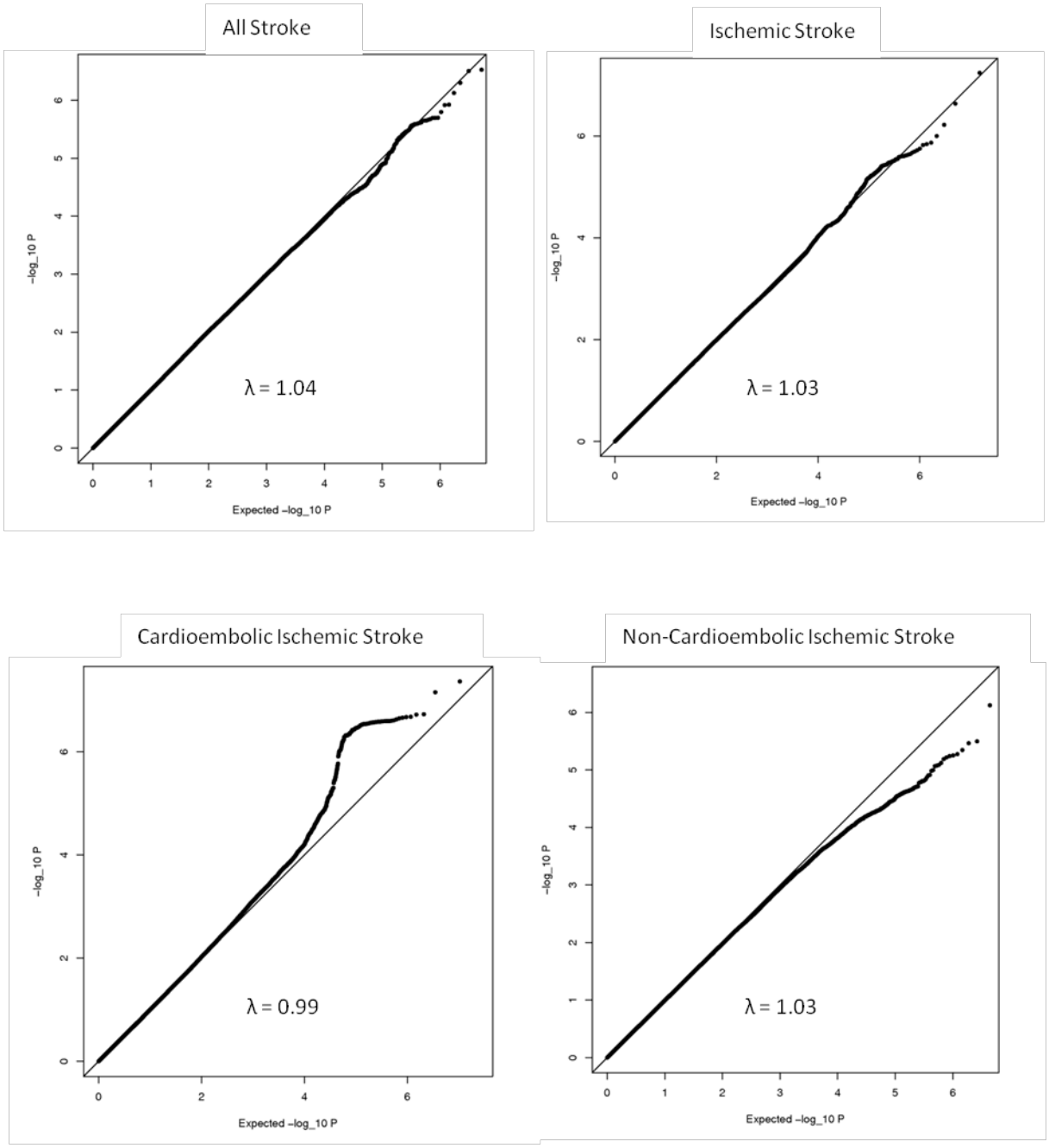
Confocal imaging

Live acta2:GFP zebrafish embryos were imaged at 4-6 days post fertilization using a Zeiss LSM 700 confocal microscope, mounted in 1% low-melt agarose. Data are presented as percentages of total embryos assayed which show 0th, 1st, 2nd, 3rd, 4th or higher order of vessel branch coverage by acta2:GFP fluorescent signal.[85] After imaging, embryos were genotyped by removal from agarose and total genomic DNA extraction by incubation in base buffer (25mM NaOH, 0.2mM EDTA, pH 12) at 95°C for 30 min, and then stabilized in neutralization buffer (40mM Tris-HCl, pH 5)[86] prior to genotyping as outlined above.

11. Brain MRI and WMH burden analysis in patients with chr6p25 segmental deletions

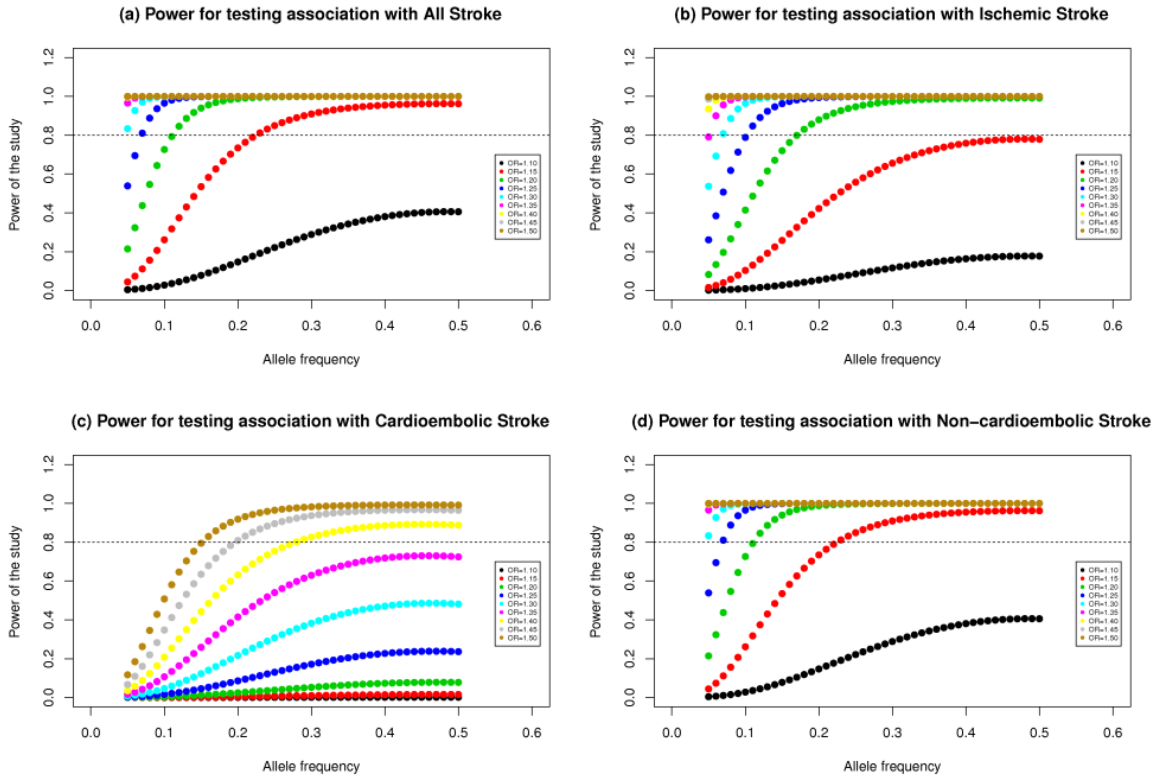
In patients with *FOXC1*-attributable Axenfeld-Rieger syndrome WMHs were identified and quantified using the 2D segmentation algorithm in OsiriX (Pixmeo, Switzerland). WMH volume was compared between two patients with a 300kb segmental deletion encompassing both *FOXC1* and *FOXF2* and two patients with a 30kb segmental deletion encompassing *FOXC1* only. Data presented are mean WMH volume (cm^3) ± standard error.

Supplementary Figure 1: QQ plots for population based GWAS (discovery stage)



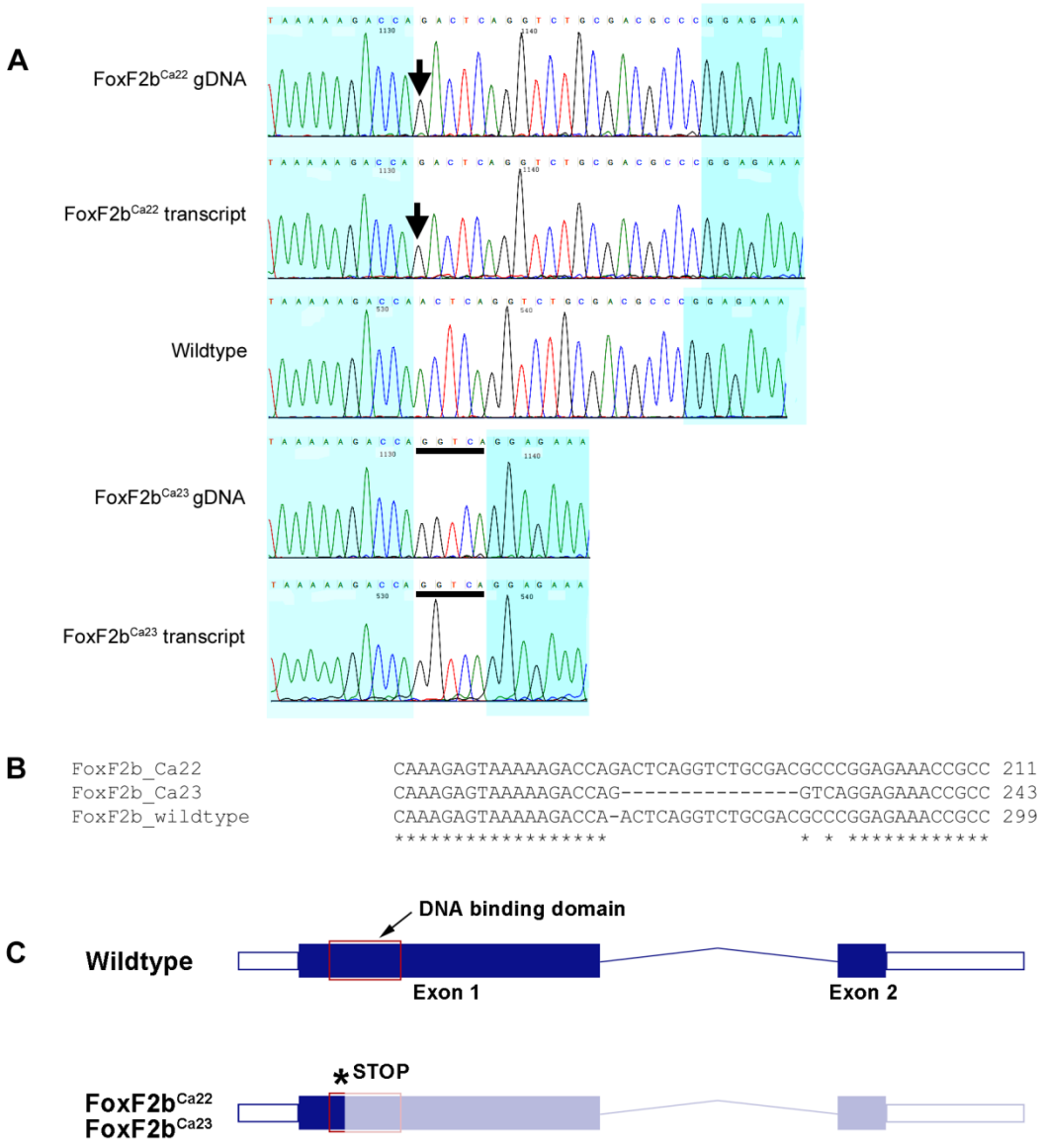
Quantile-Quanitle (QQ) plots of the P-values (observed versus expected) in the population based GWAS (discovery stage) for the four phenotypes are presented along with the genomic inflation factor (λ). λ ~1 suggests no inflation.

Supplementary Figure 2: Power of the study (discovery stage) for various stroke subtypes



Power to detect genetic associations with stroke in the discovery stage was calculated using the Quanto software under the additive mode of inheritance assuming a population risk of 10%. The number of cases (All stroke, N=4,348; Ischemic stroke, N=3,028; Cardioembolic stroke, N=602, Non-cardioembolic stroke, N=1,770) and controls (N=80,613) used for calculation was based on the discovery stage of the analysis (Table 1)

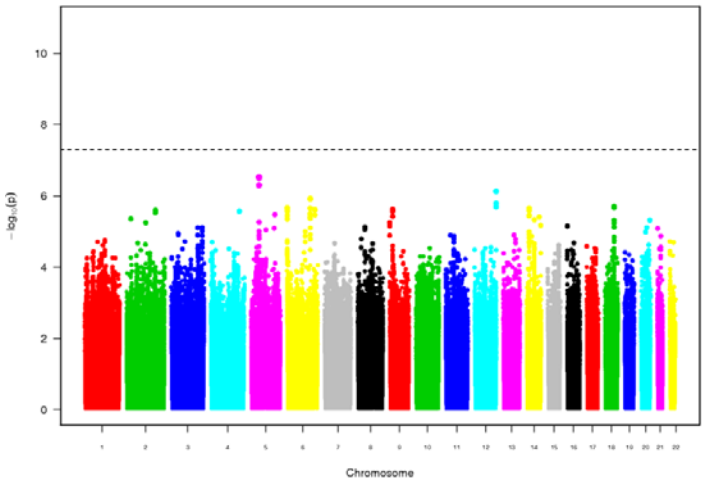
Supplementary Figure 3: Creation of foxf2b$^{-/-}$ zebrafish by introducing a deletion in the first exon of foxf2b



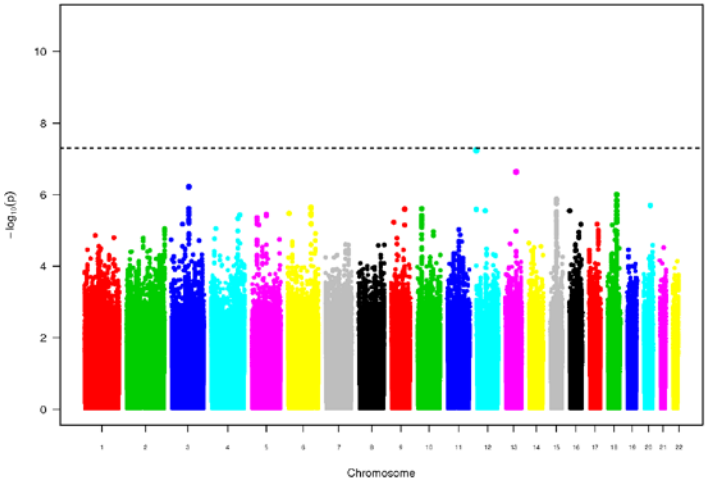
(A) Sequence of wildtype and mutant *foxf2*^{Ca23} and *foxf2*^{Ca22} alleles at the genomic (gDNA) and transcript levels shows a single base pair insertion in *foxf2*^{Ca22} and an indel in the *foxf2*^{Ca23} locus. (B) Alignment of mutant and wild type alleles. (C) Both mutations result in frameshift mutations that result in a premature stop codon in the DNA binding domain.

Supplementary Figure 4: Manhattan plots for population based GWAS (discovery stage)

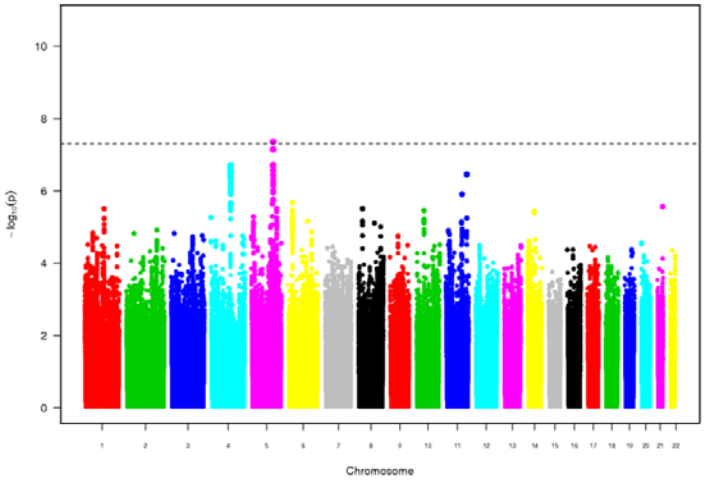
All Stroke



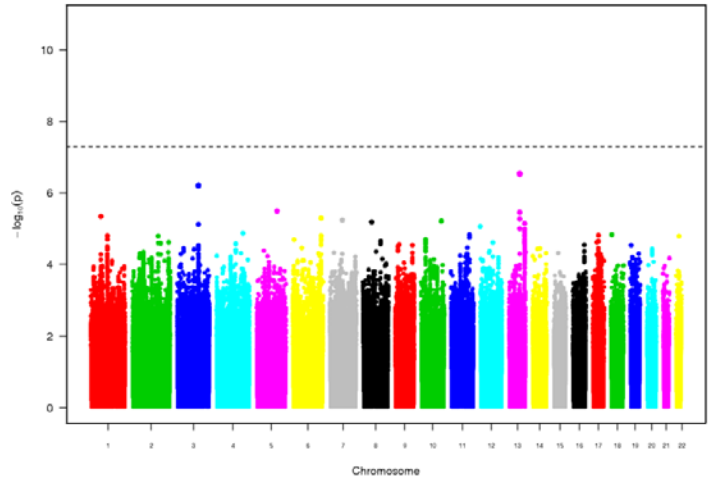
Ischemic Stroke



Cardioembolic Ischemic Stroke

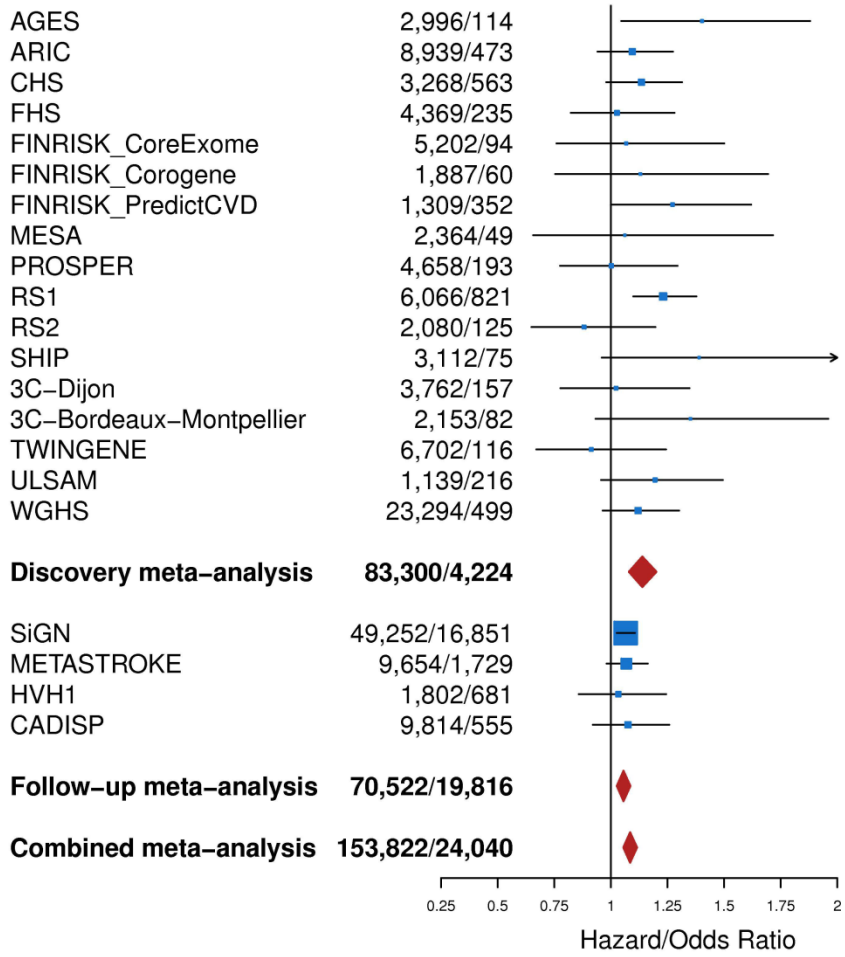


Non-Cardioembolic Ischemic Stroke



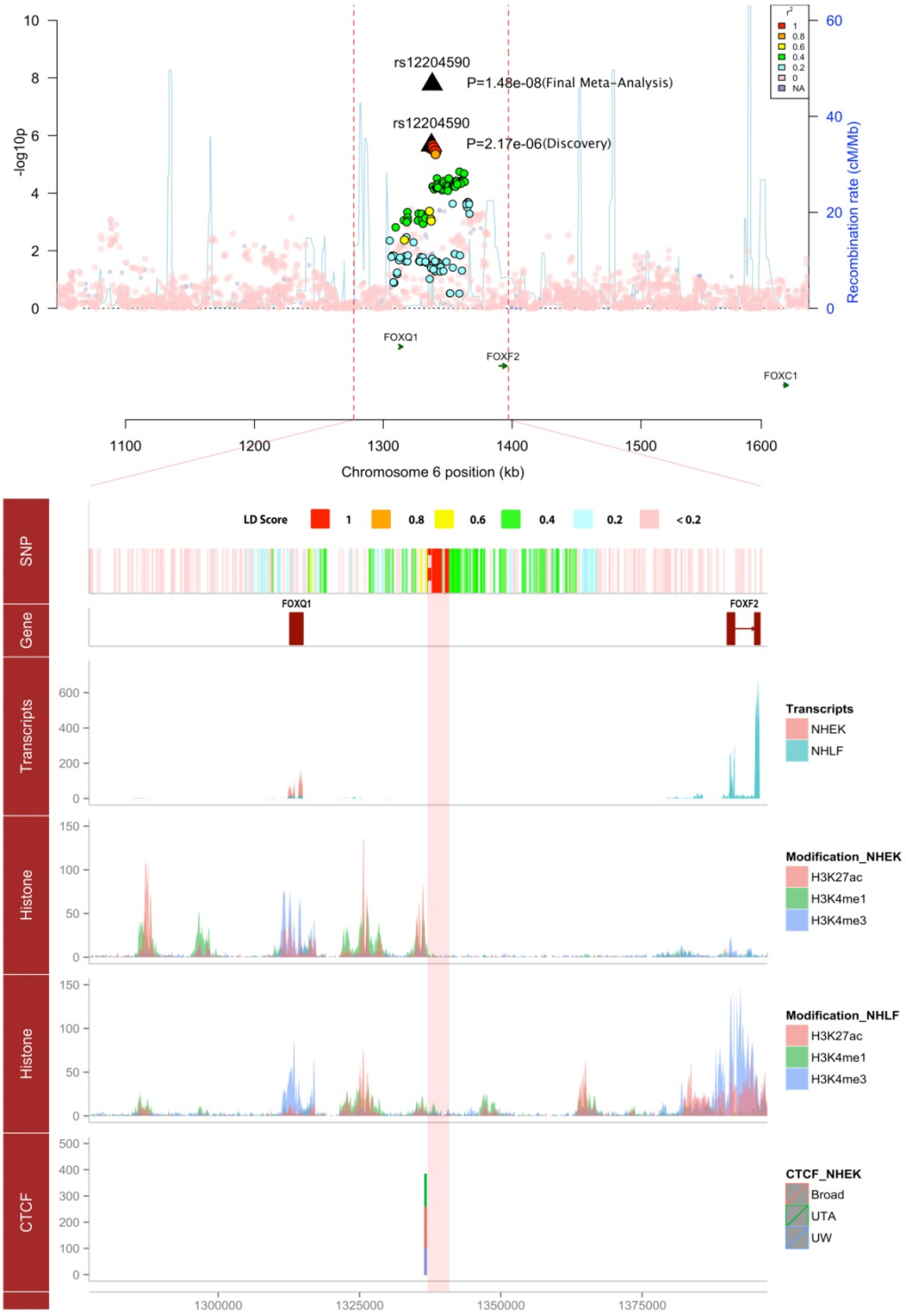
Negative log of the association P-values in the population based GWAS (discovery stage) for the four phenotypes are plotted against the chromosomal location. The different colours represent different chromosomes. The dotted line represents genome wide significance threshold ($P<5\times10^{-8}$).

Supplementary Figure 5: Forest plot of associations between rs12204590 and stroke in all discovery and follow-up samples



Information for rs12204590 was missing in Health ABC (124 cases and 1,537 controls); Associations are with "all stroke" in the discovery cohorts and in HVH1, and with "ischemic stroke" in SiGN, METASTROKE, and CADISP (these studies did not include patients with intracerebral hemorrhage)

Supplementary Figure 6: Regional association plot centered around rs12204590 with tracks for transcripts, histones and CTCF peaks



In the top panel all SNPs in the discovery stage (circles) are plotted with the –log of their p-values against their genomic positions. Association results for rs12204590 from the final meta-analysis are also plotted. The color of the circles represents the linkage disequilibrium between SNPs. The blue peaks represent estimated recombination rates in the region. Genes are shown as green arrows with direction of arrows suggesting direction of transcription. Tracks in the bottom were added using data from the UCSC genome browser and

focus on the genomic region encompassing the top SNP and SNPs in LD with it. Details of the tracks are mentioned below.

SNP: this track shows the SNPs encompassing the selected region (color coded for their LD values), White dotted lines in the track shows position of the top SNP (s12204590)

Gene: shows protein coding genes in the region.

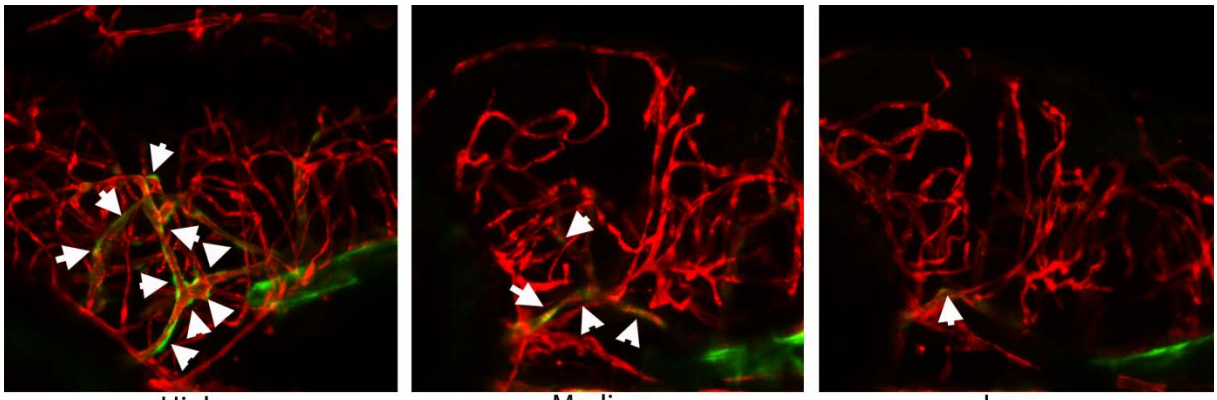
Transcripts: shows transcript levels based on mRNA sequencing data for two cell types, Normal Human Epidermal Keratinocytes (NHEK) and Normal Human Lung Fibroblasts (NHLF).

Histone: shows the distribution of three types of histone H3 modifications: acetylation of lysine 27 of H3 (H3K27ac), mono-methylation of lysine 4 of H3 (H3K4me1) and tri-methylation of lysine 4 of H3 (H3K4me3). Histone tracks in NHEK (4^{th} track) and NHLF (5^{th} track) cells are shown separately. These histone modifications were quantified using ChIP-seq assays and represent regulatory regions associated with actively transcribed genes.

CTCF: shows the distribution of CCCTC-binding factor (CTCF) in NHEK cells based on ChIP-seq experiments.[87]

Faint-red bar; shows that the top SNP and SNPs in high LD are located in the predicted *FOXF2* regulatory region, centromeric (right) of the regulatory boundary marked by the insulator element (CTCF peak), in a region that is covered with active histone modification marks only in a cell type (NHLF) that expresses *FOXF2*.

Supplementary Figure 7: Two color images of cerebral vessel smooth muscle branch order coverage



Transgenes marking endothelial cells (kdrl:mCherry)^{ci5} and smooth muscle cells (acta2:GFP)^{ca7} were scored for smooth muscle cells (green) on different branches of the cerebral vasculature (red). 'High' is scored as smooth muscle covering 4 or more branch orders, 'Medium' as covering 2-3 branch orders and 'Low' as 0-1 branch orders.

Supplementary Table 1: Genotyping parameters

Study	Genotyping platforms - SNP panel	Gentoyping center	Genotype calling algorithme
AGES	Illumina HumanCNV370 Duo BeadChip®	NIA, NIH, USA	Illumina Bead Studio
ARIC	Affymetrix GeneChip SNP Array 6.0®	Broad Institute, USA	Birdseed
CHS	Illumina HumanCNV370 Duo BeadChip®	Genotyping Laboratory at Cedars-Sinai, USA	Illumina Bead Studio
FHS	Affymetrix GeneChip Human Mapping 500K Array® +50K Human Gene Focused Panel®	Affymetrix (Santa Clara), USA	Affymetrix BRLMM
FINRISK CoreExome	Illumina HumanCoreExome	Sanger Institute, Hinxton, UK	Illumina Bead Studio
FINRISK Corogene	Illumina 610K	Sanger Institute, Hinxton, UK	Illumina Bead Studio
FINRISK PredictCVD	Illumina Omni Express	Sanger Institute, Hinxton, UK	Illumina Bead Studio
Health-ABC	Illumina Human 1M-duo	Center for Inherited Disease Research	Illumina Bead Studio
MESA	Affymetrix GeneChip SNP Array 6.0®	Broad Institute, USA	Birdseed v2
PROSPER	Illumina 660K BeadChip	Erasmus MC, Rotterdam, Nethelands	Illumina Bead Studio
Rotterdam Study I	Illumina HumanHap550-Duo BeadChip®	Erasmus MC, Rotterdam, Nethelands	Illumina Bead Studio
Rotterdam Study II	Illumina HumanHap550-Duo BeadChip®	Erasmus MC, Rotterdam, Nethelands	Illumina Bead Studio
SHIP	Affymetrix GeneChip SNP Array 6.0®	Affymetrix (Santa Clara), USA	Birdseed2
TWINGENE	Illumina HumanOmniExpress	Uppsala SNP&SEQ Technology Platform	GenCall, genomeStudio
ULSAM	Illumina HumanOmni2.5 + Metabochip	Uppsala SNP&SEQ Technology Platform	GenCall, GenomeStudio
WGHS	HumanHap300 Duo ‘‘+’’ chips or HumanHuman300	Amgen	Illumina Bead Studio
3C-Dijon	Illumina Human 610-Quad BeadChip	Centre National de Génotypage, France	Illumina BeadStudio
3C-Bordeaux-Montpellier	Illumina Human 610-Quad BeadChip	Centre National de Génotypage, France	Illumina BeadStudio

Supplementary Table 2: Quality control filters before imputation and methods for assessing population structure

Study	Sample call rate	SNP call rate	MAF	HWE p-value	Assessment of Population Stratification
AGES	< 97%	< 98%	< 0.01	< 10-6	EIGENSTRAT
ARIC	< 95%	< 95%	< 0.01	< 10-5	EIGENSTRAT
CHS	≤ 95%	< 97%	< 0.01	< 10-5	PCA
FHS	< 97%	< 97%	< 0.01	< 10-6	EIGENSTRAT
FINRISK CoreExome	< 98%	< 95%	MAC<2	< 10-6	MDS
FINRISK Corogene	< 95%	< 95%	< 0.01	< 10-6	MDS
FINRISK PredictCVD	< 95%	< 95%	< 0.01	< 10-6	MDS
Health-ABC	<99%	<97%	< 0.01	< 10 -7	EIGENSTRAT
MESA	95%	95%	n.a.	n.a.	EIGENSTRAT
PROSPER	< 97.5%	< 98%	< 0.01	< 10-6	IBD matrix
Rotterdam Study I	< 97.5%	< 98%	< 0.01	< 10-6	IBD matrix
Rotterdam Study II	< 97.5%	< 98%	< 0.01	< 10-6	IBD matrix
SHIP	< 92%	< 80%	n.a.	10-4.	PCA and MDS
TWINGENE	< 97%	< 97%	< 0.01	< 10-7	PCA
ULSAM	< 95%	<99% (MAF<5%) or <95% (MAF≥5%)	< 0.01	< 10-6	MDS
WGHS	< 98%	< 90%	< 0.01	< 10-6	EIGENSTRAT
3C-Dijon	< 95%	< 98%	< 0.01	< 10-6	EIGENSTRAT
3C-Bordeaux-Montpellier	< 95%	< 98%	< 0.01	< 10-6	EIGENSTRAT

Exclusion criteria for samples and SNPs are presented along with the method for assessing population stratification

Supplementary Table 3: Imputation algorithms

Study	Imputation software	Imputation reference panel
AGES	MACH v 1.0.16	Backbone 1000G v3 all ethnicities
ARIC	IMPUTE 2	1000G Phase1v3 all ethnicities
CHS	MACH	1000G Phase1v3 all ethnicities
FHS	MACH	1000G Phase1v3 all ethnicities
FINRISK CoreExome	SHAPEIT2 (pre-phasing) and IMPUTE2	1,000 Genomes haplotypes -- Phase I integrated
FINRISK Corogene	SHAPEIT2 (pre-phasing) and IMPUTE2	1,000 Genomes haplotypes -- Phase I integrated
FINRISK PredictCVD	SHAPEIT2 (pre-phasing) and IMPUTE2	1,000 Genomes haplotypes -- Phase I integrated
Health-ABC	MACH (version 1.0.16)	HapMap CEPH reference panel (release 22, build 36)
MESA	IMPUTE 2.2.2	1000G Phase1v3 all ethnicities
PROSPER	IMPUTE 2	1000G Phase1v3 all ethnicities
Rotterdam Study I	MACH/Minimac (2012.11.16)	1000G Phase1v3 all ethnicities
Rotterdam Study II	MACH/Minimac (2012.11.16)	1000G Phase1v3 all ethnicities
SHIP	IMPUTE (version 2.2.2)	1000G Phase1v3 all ethnicities
TWINGENE	Minimac, released 2012-10-03	1000G phase1 (v3) all ethnicities
ULSAM	IMPUTE v.2.2.2	1000G phase1 (v3) all ethnicities
WGHS	MACH (version 1.0), minimac (release 5/29/2012)	1000G Phase1v3 all ethnicities
3C-Dijon	MACH (version 1.0), minimac (release 11/16/2012)	1000G Phase1v3 all ethnicities
3C-Bordeaux-Montpellier	SHAPEIT2 (pre-phasing) and IMPUTE2	1000G, March 2012, MACGT1, all ethnicities

Supplementary Table 4: Filtering applied at the study level before uploading

Study	Singletons removed (y/n)	Filtering on			
		MAF	R-square	Standard Error	Other
AGES	No	NA	NA	NA	NA
ARIC	Yes	<0.01	0.3	SE=0	NA
CHS	No	NA	NA	NA	SNPs with dosage variance < 0.01 were excluded
FHS	No	<0.05	NA	NA	|beta|<5
FINRISK CoreExome	Yes	NA	NA	NA	Unidentifiable models
FINRISK Corogene	Yes	NA	NA	NA	Unidentifiable models
FINRISK PredictCVD	Yes	NA	NA	NA	Unidentifiable models
Health-ABC	No	NA	NA	NA	NA
MESA	Yes	<0.01	0.5	NA	P-values reported as NA or 0
PROSPER	No	NA	NA	SNPs with SE = 0, SE = nan or SE = -nan were removed	NA
Rotterdam Study I	No	NA	NA	SNPs with SE = 0, SE = nan or SE = -nan were removed	NA
Rotterdam Study II	No	NA	NA	SNPs with SE = 0, SE = nan or SE = -nan were removed	NA
SHIP	yes (according to EUR Panel)	NA	NA	NA	monomorphic SNPs removed
TWINGENE	No	NA	0.3	SE=0	NA
ULSAM	No	NA	0.4	SE=0	NA
WGHS	No	NA	NA	NA	NA
3C-Dijon	No	NA	NA	NA	NA
3C-Bordeaux-Montpellier	No	NA	NA	NA	NA

Supplementary Table 5: Software used for performing Cox regression and the covariates per study

Study	Software used (Probabel [version], other…)	Covariates other than age and sex (PCs, study site…)	Comments
AGES	ProbABEL v0.1-9e	None	
ARIC	ProbABEL v.0.3.0-pacox-beta-1	Center, PC1-4	
CHS	R version 2.15	Clinic, PC1-PC2	
FHS	R version 2.15.3	PC3	GEE was used to account for familial relationship
FINRISK CoreExome	R version 2.15	PC1-10, Eastern vs. western FINLAND	
FINRISK Corogene	R version 2.15	PC1-10	
FINRISK PredictCVD	R version 2.15	Sampling weights, PC1-10, FINRISK cohort, Eastern vs. western FINLAND	Case-cohort sample analyzed with proper methods
Health-ABC	R	PC1, Study site	
MESA	R	PC1, PC2	
PROSPER	SNPtest	PC1-PC4	
Rotterdam Study I	ProbABEL v.0.3.0-pacox-beta-1	None	P-values were calculated based on a Chi2-distribution with R. Some p-values are 0, because R did not output p-values lower than 10^-300. When very rare SNPs are removed these p-values will be probably removed too.
Rotterdam Study II	ProbABEL v.0.3.0-pacox-beta-1	None	P-values were calculated based on a Chi2-distribution with R. Some p-values are 0, because R did not output p-values lower than 10^-300. When very rare SNPs are removed these p-values will be probably removed too.
SHIP	R version 2.14.0	None	
TWINGENE	R 2.15.2, ProbABEL 0.4.1	PC1-4	
ULSAM	R 2.15.2, ProbABEL 0.4.1	PC1-2	
WGHS	ProbABEL v.0.0-6	PC1-10	
3C-Dijon	ProbABEL v. 0.1-3-pacoxph-fix-1	PC1-PC4	
3C-Bordeaux-Montpellier	Probabel (v0.4.1)	PC1	

Supplementary Table 6: Genomic inflation factor (λ) by study and by phenotype

Study	All stroke	Ischemic stroke	Cardioembolic Ischemic stroke	Non-cardioembolic Ischemic stroke
AGES	1.02	1.00	--	--
ARIC	1.02	1.02	1.01	1.01
CHS	1.02	1.01	1.01	1.01
FHS	1.01	1.01	1.05	1.02
FINRISK-CoreExome	1.02	1.05	--	--
FINRISK-Corogene	1.01	1.03	--	--
FINRISK-PredictCVD	1.05	1.06	--	--
HABC	1.01	--	--	--
MESA	0.99	1	--	0.99
PROSPER	1.01	--	--	--
Rotterdam Study I	1.01	1.00	1.01	1.00
Rotterdam Study II	1.02	1.01	1.02	1.01
SHIP	1.03	1.01	--	--
TWINGENE	1.00	0.99	--	--
ULSAM	1.02	1.02	1.01	1.01
WGHS	1.01	1.01	1.00	1.02
3C-Dijon	1.01	1.01	1.01	1.01
3C-Bordeaux-Montpellier	1.00	0.98	1.01	0.98

Genomic inflation factor (λ) ~1 suggests no inflation.

Supplementary Table 7: List of variants chosen for follow-up, association results in the discovery stage, follow-up studies and meta-analyses

		CHARGE (Discovery)		SiGN		METASTROKE		HVH1		CADISP		Follow-up Meta-analysis		Combined all Meta-analysis	
SNP	Genes	HR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P
All Stroke*															
rs10189949	UBE2E3	1.21 [1.11-1.30]	2.93E-06	1.02 [0.97-1.08]	4.15E-01	1.11 [0.97-1.26]	1.33E-01	1.11 [0.85-1.46]	4.42E-01	0.71 [0.54-0.95]	1.45E-02	1.02 [0.98-1.07]	2.50E-01	1.07 [1.03-1.11]	1.08E-03
rs6433905	UBE2E3	1.21 [1.12-1.31]	2.54E-06	1.02 [0.97-1.08]	4.07E-01	1.11 [0.98-1.27]	1.12E-01	1.09 [0.83-1.44]	5.37E-01	0.72 [0.54-0.95]	1.78E-02	1.03 [0.98-1.07]	2.23E-01	1.07 [1.03-1.12]	8.72E-04
rs12204590	FOXF2	1.14 [1.08-1.20]	2.17E-06	1.07 [1.03-1.11]	1.02E-03	1.07 [0.98-1.16]	1.31E-01	1.03 [0.86-1.24]	7.32E-01	1.08 [0.92-1.26]	3.64E-01	1.06 [1.03-1.09]	2.15E-04	1.08 [1.05-1.12]	1.48E-08
rs12197982	FOXF2	1.14 [1.08-1.20]	2.58E-06	1.06 [1.02-1.10]	1.32E-03	1.07 [0.98-1.16]	1.32E-01	1.04 [0.86-1.25]	7.14E-01	1.08 [0.92-1.26]	3.67E-01	1.05 [1.03-1.09]	2.55E-04	1.08 [1.05-1.11]	2.22E-08
rs12211303	FOXF2	1.14 [1.08-1.20]	2.25E-06	1.06 [1.02-1.10]	1.34E-03	1.07 [0.98-1.16]	1.31E-01	1.04 [0.86-1.25]	7.10E-01	1.07 [0.92-1.26]	3.69E-01	1.06 [1.03-1.09]	1.94E-04	1.08 [1.05-1.11]	2.13E-08
rs12212982	FOXF2	1.13 [1.08-1.20]	2.74E-06	1.06 [1.02-1.10]	1.34E-03	1.07 [0.98-1.16]	1.30E-01	1.04 [0.86-1.25]	7.06E-01	1.07 [0.92-1.26]	3.72E-01	1.06 [1.03-1.09]	1.90E-04	1.08 [1.05-1.11]	2.28E-08
rs12198803	FOXF2	1.13 [1.07-1.19]	3.59E-06	1.06 [1.02-1.10]	2.16E-03	1.07 [0.98-1.16]	1.35E-01	1.04 [0.86-1.25]	7.09E-01	1.07 [0.92-1.25]	3.84E-01	1.05 [1.02-1.08]	3.06E-04	1.08 [1.05-1.11]	5.78E-08
rs12200309	FOXF2	1.13 [1.07-1.19]	4.51E-06	1.06 [1.02-1.10]	2.38E-03	0.98 [0.90-1.07]	7.24E-01	1.03 [0.86-1.25]	7.27E-01	1.09 [0.93-1.27]	3.11E-01	1.04 [1.02-1.07]	2.73E-03	1.07 [1.04-1.10]	1.62E-06
rs712241	OPRM1	1.11 [1.06-1.17]	3.45E-06	1.00 [0.97-1.03]	8.88E-01	1.02 [0.95-1.09]	6.27E-01	0.88 [0.75-1.02]	8.75E-02	1.05 [0.93-1.20]	4.32E-01	1.00 [0.98-1.03]	8.53E-01	1.03 [1.01-1.05]	1.51E-02
rs790919	OPRM1	1.12 [1.07-1.17]	2.44E-06	1.00 [0.97-1.03]	8.81E-01	1.01 [0.95-1.09]	6.97E-01	0.88 [0.76-1.02]	1.00E-01	1.06 [0.93-1.21]	3.69E-01	1.00 [0.98-1.03]	8.03E-01	1.03 [1.01-1.05]	1.32E-02
rs10961053	MPDZ	1.12 [1.07-1.18]	2.41E-06	1.00 [0.97-1.03]	9.12E-01	1.10 [1.02-1.18]	1.67E-02	0.94 [0.79-1.12]	5.24E-01	0.99 [0.87-1.14]	9.37E-01	1.02 [0.99-1.04]	2.12E-01	1.04 [1.01-1.06]	3.16E-03
rs10491751	MPDZ	1.12 [1.07-1.17]	3.77E-06	0.99 [0.96-1.03]	7.15E-01	1.08 [1.00-1.16]	5.58E-02	0.94 [0.79-1.12]	4.62E-01	0.98 [0.85-1.13]	7.86E-01	1.01 [0.99-1.04]	4.15E-01	1.03 [1.01-1.06]	1.21E-02
rs11788315	MPDZ	1.13 [1.07-1.19]	2.69E-06	0.99 [0.96-1.02]	5.25E-01	1.08 [0.99-1.16]	7.35E-02	1.01 [0.84-1.21]	9.21E-01	0.99 [0.85-1.15]	8.94E-01	1.01 [0.98-1.04]	5.02E-01	1.03 [1.01-1.06]	1.36E-02
rs11788316	MPDZ	1.13 [1.07-1.19]	2.49E-06	0.99 [0.96-1.03]	7.34E-01	1.07 [0.99-1.16]	7.38E-02	1.01 [0.84-1.21]	9.28E-01	0.99 [0.85-1.15]	8.91E-01	1.01 [0.99-1.04]	3.80E-01	1.03 [1.01-1.06]	7.53E-03
rs11627959	CFL2	0.89 [0.85-0.93]	2.23E-06	0.99 [0.96-1.02]	6.97E-01	1.00 [0.93-1.08]	9.35E-01	1.00 [0.85-1.17]	9.57E-01	1.03 [0.90-1.18]	6.23E-01	1.01 [0.98-1.03]	5.28E-01	0.97 [0.95-0.99]	1.11E-02
14:35163898:T_TA	CFL2	0.88 [0.84-0.93]	2.57E-06	n.a.	n.a.	n.a.	n.a.	1.02 [0.86-1.20]	8.56E-01	n.a.	n.a.	1.02 [0.86-1.20]	8.56E-01	0.90 [0.85-0.94]	8.71E-06
rs8003414	CFL2	0.89 [0.85-0.94]	3.49E-06	0.99 [0.96-1.02]	6.32E-01	1.00 [0.93-1.08]	8.96E-01	0.99 [0.84-1.16]	8.90E-01	1.04 [0.91-1.19]	5.83E-01	1.01 [0.98-1.03]	5.74E-01	0.97 [0.95-0.99]	1.14E-02
rs12883300	CFL2	0.89 [0.85-0.94]	3.71E-06	0.99 [0.96-1.02]	6.70E-01	1.00 [0.93-1.08]	8.99E-01	0.96 [0.82-1.12]	5.81E-01	1.02 [0.90-1.17]	7.20E-01	1.01 [0.98-1.03]	6.24E-01	0.97 [0.95-0.99]	9.42E-03
rs4899120	SYNE2	1.19 [1.11-1.29]	4.71E-06	1.02 [0.97-1.07]	5.02E-01	1.00 [0.88-1.14]	9.78E-01	1.05 [0.80-1.37]	7.28E-01	1.16 [0.92-1.46]	2.13E-01	1.02 [0.99-1.07]	2.27E-01	1.06 [1.02-1.10]	2.00E-03
Ischemic Stroke†															
rs62262077	ALCAM	1.17 [1.10-1.24]	6.04E-07	0.99 [0.96-1.02]	5.19E-01	1.03 [0.95-1.12]	4.62E-01	1.03 [0.84-1.26]	7.82E-01	1.02 [0.88-1.18]	8.25E-01	1.03 [1.01-1.06]	1.49E-02	1.03 [1.01-1.06]	1.49E-02
rs7649869	ALCAM	1.15 [1.09-1.22]	2.48E-06	0.98 [0.95-1.01]	1.52E-01	1.04 [0.96-1.12]	3.74E-01	1.02 [0.84-1.22]	8.70E-01	1.01 [0.88-1.16]	9.13E-01	1.02 [1.00-1.04]	9.72E-02	1.02 [1.00-1.04]	9.72E-02
rs12152354	ALCAM	1.15 [1.08-1.21]	3.73E-06	0.98 [0.95-1.02]	2.99E-01	1.03 [0.95-1.11]	4.57E-01	1.03 [0.86-1.24]	7.61E-01	1.00 [0.87-1.16]	9.53E-01	1.02 [1.00-1.05]	5.71E-02	1.02 [1.00-1.05]	5.71E-02
rs7633149	ALCAM	1.15 [1.08-1.21]	3.72E-06	0.98 [0.95-1.02]	3.00E-01	1.03 [0.95-1.11]	4.57E-01	1.03 [0.86-1.24]	7.61E-01	1.00 [0.87-1.16]	9.53E-01	1.02 [1.00-1.05]	5.71E-02	1.02 [1.00-1.05]	5.71E-02

rs4894921	ALCAM	1.15 [1.08-1.21]	3.06E-06	0.99 [0.95-1.02]	3.83E-01	1.04 [0.97-1.13]	2.75E-01	1.02 [0.85-1.23]	8.14E-01	1.00 [0.87-1.15]	9.77E-01	1.03 [1.00-1.05]	3.44E-02	1.03 [1.00-1.05]	3.44E-02
rs10037362	CDH6	1.27 [1.15-1.41]	4.41E-06	0.98 [0.93-1.03]	3.96E-01	0.99 [0.87-1.12]	8.37E-01	0.93 [0.69-1.26]	6.49E-01	0.86 [0.66-1.13]	2.69E-01	1.01 [0.97-1.05]	5.54E-01	1.01 [0.97-1.05]	5.54E-01
rs35470188	CDH6	1.27 [1.14-1.40]	5.19E-06	0.98 [0.93-1.03]	4.09E-01	0.99 [0.87-1.12]	8.38E-01	0.93 [0.69-1.25]	6.08E-01	0.86 [0.66-1.13]	2.82E-01	1.01 [0.97-1.05]	5.40E-01	1.01 [0.97-1.05]	5.40E-01
rs2209804	C10orf114	0.82 [0.75-0.89]	3.98E-06	1.00 [0.96-1.04]	9.92E-01	0.99 [0.90-1.09]	8.83E-01	0.97 [0.78-1.21]	7.92E-01	1.02 [0.85-1.22]	8.58E-01	0.97 [0.94-1.00]	6.96E-02	0.97 [0.94-1.00]	6.96E-02
rs58809874	C10orf114	0.82 [0.75-0.89]	5.41E-06	1.01 [0.97-1.05]	6.45E-01	0.99 [0.90-1.09]	8.48E-01	0.97 [0.78-1.21]	7.81E-01	1.02 [0.85-1.22]	8.38E-01	0.98 [0.95-1.01]	1.72E-01	0.98 [0.95-1.01]	1.72E-01
rs7068408	C10orf114	0.82 [0.75-0.89]	4.20E-06	1.00 [0.96-1.04]	8.82E-01	1.00 [0.90-1.10]	9.32E-01	0.97 [0.78-1.21]	7.95E-01	1.03 [0.86-1.23]	7.79E-01	0.98 [0.95-1.01]	1.07E-01	0.98 [0.95-1.01]	1.07E-01
rs7086407	C10orf114	0.82 [0.75-0.89]	4.41E-06	1.00 [0.96-1.04]	9.85E-01	0.99 [0.90-1.10]	8.83E-01	0.97 [0.78-1.21]	8.04E-01	1.03 [0.86-1.24]	7.55E-01	0.97 [0.95-1.00]	8.46E-02	0.97 [0.95-1.00]	8.46E-02
rs11012681	C10orf114	0.82 [0.75-0.89]	4.90E-06	1.00 [0.96-1.04]	9.23E-01	1.00 [0.90-1.10]	9.65E-01	0.97 [0.77-1.21]	7.87E-01	1.03 [0.86-1.24]	7.54E-01	0.97 [0.95-1.00]	9.04E-02	0.97 [0.95-1.00]	9.04E-02
rs4448595	C10orf114	0.83 [0.77-0.90]	2.50E-06	1.01 [0.97-1.05]	7.17E-01	1.02 [0.93-1.12]	6.90E-01	0.89 [0.72-1.10]	2.81E-01	0.96 [0.81-1.14]	6.47E-01	0.98 [0.95-1.00]	8.77E-02	0.98 [0.95-1.00]	8.77E-02
rs12245880	C10orf114	0.84 [0.77-0.90]	7.27E-06	1.00 [0.97-1.04]	8.10E-01	1.00 [0.91-1.10]	9.51E-01	0.90 [0.73-1.11]	3.17E-01	0.96 [0.80-1.14]	6.18E-01	0.97 [0.95-1.00]	6.71E-02	0.97 [0.95-1.00]	6.71E-02
rs1243181	C10orf114	1.14 [1.08-1.20]	3.84E-06	0.99 [0.96-1.02]	6.24E-01	1.01 [0.94-1.08]	7.47E-01	1.07 [0.92-1.26]	3.82E-01	1.00 [0.88-1.13]	9.45E-01	1.01 [0.99-1.03]	2.64E-01	1.01 [0.99-1.03]	2.64E-01
rs11833579	NINJ2	1.19 [1.12-1.27]	5.74E-08	0.98 [0.95-1.01]	2.15E-01	0.96 [0.88-1.04]	2.85E-01	1.04 [0.85-1.29]	6.92E-01	0.96 [0.82-1.12]	5.74E-01	1.01 [0.98-1.03]	4.66E-01	1.01 [0.98-1.03]	4.66E-01
rs12425791	NINJ2	1.18 [1.10-1.27]	2.59E-06	0.99 [0.95-1.03]	5.95E-01	0.96 [0.88-1.04]	2.95E-01	1.02 [0.80-1.32]	8.51E-01	1.01 [0.86-1.18]	9.11E-01	1.01 [0.99-1.04]	3.16E-01	1.01 [0.99-1.04]	3.16E-01
rs77744591	SPRY2	1.23 [1.11-1.36]	4.14E-05	1.03 [0.97-1.09]	3.19E-01	1.05 [0.93-1.20]	4.15E-01	1.03 [0.77-1.39]	8.22E-01	0.95 [0.75-1.21]	6.93E-01	1.05 [1.01-1.09]	1.42E-02	1.05 [1.01-1.09]	1.42E-02
Cardioembolic stroke[‡]															
rs4284256	FCRL3	1.41 [1.22-1.64]	3.13E-06	0.96 [0.90-1.04]	3.13E-01	0.93 [0.78-1.12]	4.55E-01	1.03 [0.69-1.55]	8.78E-01	0.98 [0.75-1.28]	8.98E-01	0.96 [0.90-1.01]	1.29E-01	1.02 [0.97-1.09]	4.14E-01
rs17042059	PITX2	1.51 [1.28-1.78]	9.63E-07	1.37 [1.28-1.48]	5.97E-17	1.06 [0.88-1.28]	5.20E-01	1.67 [1.10-2.53]	1.61E-02	1.05 [0.80-1.39]	7.18E-01	1.33 [1.26-1.41]	3.61E-21	1.34 [1.26-1.43]	7.64E-21
rs78652110	PITX2	1.51 [1.28-1.78]	9.21E-07	1.37 [1.27-1.48]	3.93E-16	1.14 [0.94-1.36]	1.76E-01	1.68 [1.10-2.54]	1.53E-02	1.05 [0.80-1.39]	7.10E-01	1.34 [1.26-1.43]	1.99E-21	1.35 [1.27-1.44]	4.57E-21
rs10014075	PITX2	1.51 [1.28-1.78]	9.14E-07	1.38 [1.28-1.49]	2.05E-17	1.14 [0.95-1.36]	1.75E-01	1.68 [1.10-2.55]	1.54E-02	1.05 [0.80-1.39]	7.10E-01	1.35 [1.27-1.43]	1.06E-22	1.36 [1.28-1.44]	2.37E-22
rs10026140	PITX2	1.50 [1.27-1.76]	1.23E-06	1.39 [1.29-1.49]	8.32E-19	1.13 [0.94-1.36]	1.76E-01	1.67 [1.10-2.52]	1.53E-02	1.05 [0.79-1.39]	7.44E-01	1.35 [1.28-1.43]	5.04E-24	1.36 [1.28-1.45]	1.42E-23
rs61189242	PITX2	1.51 [1.28-1.78]	9.59E-07	1.35 [1.26-1.46]	1.43E-15	1.14 [0.94-1.36]	1.75E-01	1.68 [1.10-2.55]	1.59E-02	1.05 [0.79-1.39]	7.31E-01	1.33 [1.25-1.41]	5.22E-21	1.34 [1.26-1.42]	1.69E-20
rs79469997	PITX2	1.51 [1.28-1.78]	9.40E-07	1.35 [1.26-1.46]	1.41E-15	1.14 [0.94-1.36]	1.75E-01	1.68 [1.10-2.55]	1.58E-02	1.05 [0.79-1.39]	7.33E-01	1.33 [1.25-1.41]	4.43E-21	1.34 [1.26-1.42]	1.38E-20
rs12650941	PITX2	1.51 [1.28-1.78]	8.16E-07	1.35 [1.26-1.46]	1.39E-15	1.14 [0.94-1.36]	1.76E-01	1.68 [1.10-2.56]	1.58E-02	1.05 [0.79-1.39]	7.35E-01	1.33 [1.25-1.41]	4.32E-21	1.34 [1.26-1.42]	1.25E-20
rs28650220	PITX2	1.51 [1.28-1.78]	8.64E-07	1.34 [1.25-1.45]	4.93E-15	1.13 [0.94-1.36]	1.86E-01	1.68 [1.10-2.56]	1.58E-02	1.05 [0.79-1.39]	7.43E-01	1.32 [1.25-1.40]	1.91E-20	1.33 [1.25-1.41]	5.50E-20
rs4529121	PITX2	1.51 [1.28-1.78]	7.44E-07	1.38 [1.28-1.49]	1.92E-17	1.14 [0.94-1.36]	1.76E-01	1.69 [1.11-2.56]	1.42E-02	1.05 [0.80-1.39]	7.23E-01	1.35 [1.27-1.43]	1.05E-22	1.36 [1.28-1.44]	2.01E-22
rs10024267	PITX2	1.53 [1.30-1.80]	3.04E-07	1.37 [1.28-1.48]	5.15E-17	1.13 [0.94-1.36]	1.81E-01	1.69 [1.12-2.57]	1.29E-02	1.08 [0.82-1.42]	5.91E-01	1.34 [1.26-1.42]	2.28E-22	1.35 [1.27-1.44]	2.00E-22
rs74964720	PITX2	1.53 [1.30-1.80]	2.69E-07	1.38 [1.29-1.49]	1.12E-17	1.13 [0.95-1.36]	1.74E-01	1.70 [1.12-2.57]	1.25E-02	1.08 [0.82-1.42]	5.86E-01	1.35 [1.27-1.43]	4.33E-23	1.36 [1.28-1.45]	3.55E-23
rs78936896	PITX2	1.53 [1.30-1.80]	2.68E-07	1.38 [1.28-1.49]	1.57E-16	1.13 [0.95-1.36]	1.75E-01	1.70 [1.12-2.57]	1.25E-02	1.08 [0.82-1.42]	5.83E-01	1.34 [1.27-1.43]	4.93E-22	1.36 [1.28-1.44]	4.38E-22
4:111647912:G_GTG	PITX2	1.51 [1.27-1.80]	3.44E-06	n.a.	n.a.	n.a.	n.a.	1.70 [1.12-2.59]	1.34E-02	n.a.	n.a.	1.70 [1.12-2.59]	1.34E-02	1.54 [1.31-1.80]	1.64E-07

rs4543199	PITX2	1.53 [1.30-1.80]	2.85E-07	1.37 [1.28-1.48]	4.81E-17	1.13 [0.94-1.36]	1.88E-01	1.70 [1.12-2.57]	1.28E-02	1.08 [0.82-1.42]	5.88E-01	1.34 [1.26-1.42]	2.34E-22	1.35 [1.27-1.44]	1.88E-22
rs12647316	PITX2	1.51 [1.29-1.78]	5.90E-07	1.37 [1.28-1.48]	4.39E-17	1.13 [0.94-1.36]	1.92E-01	1.72 [1.14-2.60]	1.04E-02	1.11 [0.85-1.46]	4.43E-01	1.35 [1.27-1.43]	7.82E-23	1.36 [1.27-1.44]	1.71E-22
rs12647393	PITX2	1.52 [1.30-1.79]	3.55E-07	1.38 [1.29-1.49]	1.92E-18	1.13 [0.94-1.36]	1.86E-01	1.69 [1.12-2.55]	1.21E-02	1.08 [0.82-1.41]	6.06E-01	1.35 [1.27-1.43]	7.32E-24	1.36 [1.28-1.45]	8.61E-24
rs10019689	PITX2	1.51 [1.28-1.78]	6.35E-07	1.39 [1.29-1.50]	3.97E-19	1.07 [0.89-1.28]	4.61E-01	1.69 [1.12-2.54]	1.25E-02	1.09 [0.83-1.43]	5.30E-01	1.35 [1.27-1.43]	9.20E-24	1.36 [1.28-1.44]	1.65E-23
rs4626276	PITX2	1.53 [1.30-1.80]	2.92E-07	1.39 [1.29-1.49]	9.66E-18	1.15 [0.96-1.38]	1.21E-01	1.70 [1.12-2.58]	1.25E-02	1.08 [0.82-1.42]	5.79E-01	1.35 [1.27-1.43]	1.87E-23	1.37 [1.28-1.45]	1.70E-23
rs4469143	PITX2	1.53 [1.30-1.80]	2.58E-07	1.39 [1.29-1.49]	8.88E-18	1.13 [0.94-1.36]	1.86E-01	1.71 [1.13-2.59]	1.18E-02	1.08 [0.82-1.42]	5.77E-01	1.35 [1.27-1.43]	4.68E-23	1.36 [1.28-1.45]	2.89E-23
rs79654735	PITX2	1.53 [1.30-1.80]	2.63E-07	1.39 [1.29-1.49]	8.87E-18	1.13 [0.94-1.36]	1.88E-01	1.70 [1.13-2.58]	1.18E-02	1.08 [0.82-1.42]	5.76E-01	1.35 [1.27-1.43]	3.76E-23	1.36 [1.28-1.45]	2.96E-23
rs28392642	PITX2	1.53 [1.30-1.80]	2.81E-07	1.38 [1.28-1.48]	3.88E-17	1.13 [0.94-1.35]	1.99E-01	1.70 [1.12-2.58]	1.21E-02	1.08 [0.82-1.42]	5.82E-01	1.34 [1.26-1.42]	2.15E-22	1.36 [1.28-1.44]	1.64E-22
rs77672008	PITX2	1.53 [1.30-1.80]	2.62E-07	1.39 [1.29-1.49]	8.88E-18	1.13 [0.94-1.36]	1.88E-01	1.71 [1.13-2.58]	1.18E-02	1.08 [0.82-1.42]	5.75E-01	1.35 [1.27-1.43]	3.83E-23	1.36 [1.28-1.45]	2.93E-23
rs76013973	PITX2	1.53 [1.30-1.80]	2.55E-07	1.39 [1.29-1.49]	8.89E-18	1.13 [0.94-1.36]	1.88E-01	1.70 [1.13-2.58]	1.18E-02	1.08 [0.82-1.42]	5.75E-01	1.35 [1.27-1.43]	3.90E-23	1.36 [1.28-1.45]	2.87E-23
rs17042076	PITX2	1.52 [1.30-1.79]	3.42E-07	1.39 [1.29-1.49]	5.34E-19	1.13 [0.94-1.36]	1.91E-01	1.69 [1.12-2.55]	1.20E-02	1.09 [0.82-1.43]	5.62E-01	1.35 [1.28-1.43]	2.31E-24	1.37 [1.29-1.45]	2.10E-24
rs4434326	PITX2	1.53 [1.30-1.80]	2.78E-07	1.37 [1.28-1.48]	4.09E-17	1.13 [0.94-1.35]	1.97E-01	1.70 [1.12-2.58]	1.21E-02	1.08 [0.82-1.42]	5.80E-01	1.34 [1.26-1.42]	2.19E-22	1.36 [1.28-1.44]	1.66E-22
rs17042081	PITX2	1.53 [1.30-1.80]	2.57E-07	1.39 [1.29-1.49]	8.95E-18	1.13 [0.94-1.36]	1.87E-01	1.71 [1.13-2.58]	1.18E-02	1.08 [0.82-1.42]	5.73E-01	1.35 [1.27-1.43]	3.82E-23	1.36 [1.28-1.45]	2.82E-23
rs4833436	PITX2	1.53 [1.30-1.80]	2.57E-07	1.40 [1.30-1.51]	9.15E-19	1.13 [0.94-1.36]	1.87E-01	1.71 [1.13-2.58]	1.17E-02	1.08 [0.82-1.42]	5.72E-01	1.36 [1.28-1.44]	5.32E-24	1.37 [1.29-1.46]	3.32E-24
rs11098088	PITX2	1.53 [1.30-1.80]	2.55E-07	1.39 [1.29-1.49]	9.01E-18	1.13 [0.94-1.36]	1.86E-01	1.71 [1.13-2.58]	1.17E-02	1.08 [0.82-1.42]	5.72E-01	1.35 [1.27-1.43]	3.87E-23	1.36 [1.28-1.45]	2.80E-23
rs11098089	PITX2	1.53 [1.30-1.80]	2.56E-07	1.38 [1.28-1.49]	2.62E-17	1.13 [0.94-1.36]	1.86E-01	1.70 [1.13-2.58]	1.18E-02	1.08 [0.82-1.42]	5.71E-01	1.35 [1.27-1.43]	1.16E-22	1.36 [1.28-1.44]	8.91E-23
rs17042088	PITX2	1.53 [1.30-1.80]	2.51E-07	1.39 [1.29-1.49]	9.06E-18	1.13 [0.94-1.36]	1.86E-01	1.71 [1.13-2.58]	1.17E-02	1.08 [0.82-1.42]	5.71E-01	1.35 [1.27-1.43]	3.85E-23	1.36 [1.28-1.45]	2.77E-23
rs79631257	PITX2	1.53 [1.30-1.80]	2.66E-07	1.39 [1.29-1.49]	8.20E-18	1.13 [0.94-1.36]	1.86E-01	1.71 [1.13-2.58]	1.16E-02	1.08 [0.82-1.42]	5.70E-01	1.35 [1.27-1.43]	3.46E-23	1.36 [1.28-1.45]	2.57E-23
rs74496596	PITX2	1.53 [1.30-1.80]	2.69E-07	1.39 [1.29-1.49]	9.09E-18	1.13 [0.94-1.36]	1.86E-01	1.71 [1.13-2.58]	1.16E-02	1.08 [0.82-1.42]	5.70E-01	1.35 [1.27-1.43]	4.08E-23	1.36 [1.28-1.45]	2.88E-23
rs75187510	PITX2	1.53 [1.30-1.80]	2.75E-07	1.39 [1.29-1.49]	8.53E-18	1.13 [0.94-1.36]	1.84E-01	1.71 [1.13-2.59]	1.16E-02	1.08 [0.82-1.43]	5.70E-01	1.35 [1.27-1.43]	3.75E-23	1.36 [1.28-1.45]	2.71E-23
rs77860854	PITX2	1.53 [1.30-1.80]	2.89E-07	1.38 [1.28-1.49]	1.52E-16	1.13 [0.94-1.36]	1.84E-01	1.71 [1.13-2.59]	1.16E-02	1.08 [0.82-1.43]	5.69E-01	1.34 [1.27-1.43]	6.58E-22	1.36 [1.28-1.44]	5.25E-22
rs12648785	PITX2	1.51 [1.28-1.78]	1.04E-06	1.39 [1.29-1.49]	9.06E-18	1.12 [0.93-1.35]	2.14E-01	1.71 [1.13-2.60]	1.19E-02	1.09 [0.82-1.43]	5.61E-01	1.35 [1.27-1.43]	4.03E-23	1.36 [1.28-1.45]	9.62E-23
rs12639820	PITX2	1.53 [1.30-1.80]	3.08E-07	1.39 [1.29-1.49]	9.04E-18	1.13 [0.94-1.36]	1.84E-01	1.71 [1.13-2.59]	1.16E-02	1.08 [0.82-1.43]	5.69E-01	1.35 [1.27-1.43]	3.89E-23	1.36 [1.28-1.45]	3.15E-23
rs74900776	PITX2	1.53 [1.30-1.80]	3.49E-07	1.39 [1.29-1.50]	3.39E-18	1.13 [0.94-1.36]	1.84E-01	1.70 [1.12-2.57]	1.20E-02	1.08 [0.82-1.43]	5.69E-01	1.35 [1.28-1.44]	1.73E-23	1.37 [1.29-1.45]	1.50E-23
rs76756825	PITX2	1.53 [1.30-1.80]	3.35E-07	1.39 [1.29-1.49]	8.82E-18	1.13 [0.94-1.36]	1.83E-01	1.71 [1.13-2.59]	1.15E-02	1.08 [0.82-1.43]	5.68E-01	1.35 [1.27-1.43]	3.82E-23	1.36 [1.28-1.45]	3.11E-23
rs11944778	PITX2	1.52 [1.29-1.78]	4.84E-07	1.39 [1.29-1.49]	5.10E-19	1.13 [0.94-1.36]	1.86E-01	1.69 [1.12-2.55]	1.16E-02	1.08 [0.82-1.42]	5.94E-01	1.35 [1.28-1.43]	3.13E-24	1.36 [1.29-1.45]	3.29E-24
rs7436333	PITX2	1.51 [1.28-1.78]	8.69E-07	1.39 [1.29-1.49]	8.28E-18	1.12 [0.93-1.34]	2.28E-01	1.69 [1.11-2.57]	1.37E-02	1.06 [0.80-1.39]	6.84E-01	1.35 [1.27-1.43]	1.16E-22	1.36 [1.28-1.44]	1.45E-22
rs4447925	PITX2	1.53 [1.30-1.79]	3.80E-07	1.39 [1.29-1.49]	8.03E-18	1.13 [0.94-1.36]	1.83E-01	1.71 [1.13-2.59]	1.15E-02	1.08 [0.82-1.43]	5.66E-01	1.35 [1.27-1.43]	3.52E-23	1.36 [1.28-1.45]	3.07E-23
rs75021220	PITX2	1.51 [1.29-1.78]	5.18E-07	1.44 [1.34-1.56]	1.33E-20	1.13 [0.94-1.36]	1.84E-01	1.69 [1.13-2.55]	1.15E-02	1.08 [0.82-1.42]	5.91E-01	1.38 [1.30-1.47]	1.80E-25	1.40 [1.31-1.49]	1.48E-25

rs28521134	PITX2	1.52 [1.29-1.78]	5.07E-07	1.39 [1.29-1.49]	5.63E-19	1.13 [0.94-1.36]	1.80E-01	1.69 [1.13-2.55]	1.15E-02	1.08 [0.82-1.42]	5.91E-01	1.35 [1.28-1.43]	3.30E-24	1.36 [1.29-1.45]	3.35E-24
rs76229004	PITX2	1.53 [1.30-1.80]	3.78E-07	1.39 [1.29-1.49]	6.83E-18	1.13 [0.94-1.36]	1.81E-01	1.71 [1.13-2.58]	1.16E-02	1.08 [0.82-1.43]	5.63E-01	1.35 [1.27-1.43]	3.26E-23	1.36 [1.28-1.45]	2.80E-23
rs17042093	PITX2	1.53 [1.30-1.79]	3.78E-07	1.38 [1.28-1.49]	1.52E-17	1.13 [0.94-1.36]	1.82E-01	1.71 [1.13-2.59]	1.14E-02	1.09 [0.83-1.43]	5.61E-01	1.35 [1.27-1.43]	6.90E-23	1.36 [1.28-1.45]	5.92E-23
rs11930528	PITX2	1.51 [1.29-1.78]	5.22E-07	1.37 [1.27-1.48]	7.64E-17	1.14 [0.95-1.37]	1.65E-01	1.69 [1.12-2.55]	1.16E-02	1.08 [0.82-1.42]	5.93E-01	1.34 [1.26-1.42]	3.22E-22	1.35 [1.27-1.44]	3.33E-22
rs56758856	PITX2	1.53 [1.30-1.80]	3.73E-07	1.39 [1.29-1.50]	5.32E-18	1.13 [0.94-1.36]	1.80E-01	1.71 [1.13-2.59]	1.14E-02	1.09 [0.83-1.43]	5.61E-01	1.35 [1.27-1.43]	3.00E-23	1.37 [1.28-1.45]	2.38E-23
rs78073007	PITX2	1.54 [1.31-1.82]	2.14E-07	1.39 [1.29-1.50]	1.82E-17	1.18 [0.98-1.41]	8.55E-02	1.66 [1.10-2.51]	1.57E-02	1.01 [0.76-1.35]	9.24E-01	1.36 [1.28-1.44]	4.06E-23	1.37 [1.29-1.46]	3.73E-23
rs17042098	PITX2	1.54 [1.31-1.81]	2.20E-07	1.40 [1.29-1.50]	2.75E-18	1.17 [0.98-1.41]	9.04E-02	1.66 [1.10-2.51]	1.57E-02	1.01 [0.76-1.35]	9.21E-01	1.36 [1.28-1.44]	1.18E-23	1.37 [1.29-1.46]	7.07E-24
rs1906611	PITX2	1.55 [1.29-1.86]	2.32E-06	1.41 [1.28-1.54]	2.95E-13	1.15 [0.95-1.40]	1.60E-01	1.63 [1.05-2.53]	2.97E-02	1.03 [0.77-1.40]	8.27E-01	1.36 [1.27-1.46]	4.82E-18	1.37 [1.28-1.47]	1.07E-17
rs1906610	PITX2	1.54 [1.28-1.85]	3.16E-06	1.42 [1.29-1.56]	1.93E-13	1.17 [0.96-1.42]	1.20E-01	1.63 [1.05-2.54]	2.99E-02	1.03 [0.76-1.39]	8.63E-01	1.36 [1.27-1.46]	3.71E-18	1.38 [1.28-1.48]	7.42E-18
rs17042102	PITX2	1.54 [1.31-1.81]	2.37E-07	1.40 [1.30-1.50]	2.90E-18	1.17 [0.98-1.41]	8.63E-02	1.66 [1.10-2.51]	1.54E-02	1.01 [0.76-1.35]	9.20E-01	1.36 [1.28-1.44]	1.03E-23	1.37 [1.29-1.46]	7.50E-24
rs17042112	PITX2	1.54 [1.31-1.81]	2.26E-07	1.40 [1.29-1.50]	2.99E-18	1.17 [0.98-1.41]	8.65E-02	1.66 [1.10-2.51]	1.54E-02	1.02 [0.76-1.35]	9.15E-01	1.36 [1.28-1.44]	9.64E-24	1.37 [1.29-1.46]	6.50E-24
rs17042115	PITX2	1.53 [1.30-1.80]	4.96E-07	1.39 [1.29-1.50]	1.16E-17	1.17 [0.97-1.41]	1.06E-01	1.66 [1.09-2.51]	1.71E-02	1.01 [0.75-1.34]	9.72E-01	1.36 [1.28-1.44]	3.88E-23	1.37 [1.28-1.45]	6.62E-23
rs77309872	PITX2	1.53 [1.30-1.81]	2.84E-07	1.39 [1.29-1.50]	5.16E-18	1.17 [0.98-1.41]	8.60E-02	1.69 [1.13-2.55]	1.15E-02	1.02 [0.76-1.35]	9.14E-01	1.36 [1.28-1.44]	1.92E-23	1.37 [1.29-1.45]	1.24E-23
rs17042121	PITX2	1.53 [1.30-1.81]	2.90E-07	1.39 [1.29-1.50]	2.50E-18	1.18 [0.98-1.41]	8.59E-02	1.69 [1.13-2.55]	1.15E-02	1.02 [0.76-1.35]	9.13E-01	1.36 [1.28-1.44]	9.37E-24	1.37 [1.29-1.46]	5.56E-24
rs60409120	PITX2	1.52 [1.29-1.79]	4.06E-07	1.40 [1.30-1.51]	7.17E-19	1.18 [0.98-1.41]	8.39E-02	1.68 [1.12-2.52]	1.18E-02	1.01 [0.76-1.34]	9.42E-01	1.36 [1.28-1.45]	2.43E-24	1.38 [1.29-1.46]	2.34E-24
rs10516563	PITX2	1.53 [1.30-1.81]	2.93E-07	1.38 [1.28-1.49]	2.43E-17	1.10 [0.91-1.32]	3.29E-01	1.70 [1.13-2.55]	1.14E-02	1.02 [0.77-1.35]	9.02E-01	1.34 [1.26-1.42]	7.70E-22	1.35 [1.27-1.44]	5.81E-22
rs150844214	PITX2	1.53 [1.30-1.80]	3.26E-07	1.40 [1.30-1.51]	6.53E-19	1.18 [0.98-1.41]	8.53E-02	1.68 [1.12-2.51]	1.18E-02	1.01 [0.76-1.35]	9.24E-01	1.36 [1.28-1.45]	3.05E-24	1.38 [1.29-1.46]	1.61E-24
rs79687642	PITX2	1.55 [1.31-1.83]	2.62E-07	1.40 [1.30-1.51]	1.82E-18	1.18 [0.98-1.42]	8.93E-02	1.70 [1.12-2.59]	1.22E-02	1.01 [0.75-1.34]	9.68E-01	1.36 [1.28-1.45]	8.04E-24	1.38 [1.29-1.47]	4.53E-24
rs144691425	PITX2	1.55 [1.31-1.84]	2.98E-07	1.41 [1.31-1.52]	4.38E-19	1.17 [0.97-1.42]	9.96E-02	1.73 [1.14-2.63]	1.02E-02	1.01 [0.76-1.36]	9.33E-01	1.37 [1.29-1.46]	2.11E-24	1.38 [1.30-1.47]	1.37E-24
rs4833443	PITX2	1.54 [1.31-1.82]	3.16E-07	1.41 [1.30-1.52]	5.73E-19	1.17 [0.97-1.41]	9.69E-02	1.69 [1.11-2.56]	1.36E-02	1.01 [0.76-1.35]	9.32E-01	1.37 [1.29-1.45]	4.15E-24	1.38 [1.30-1.47]	2.27E-24
rs4605724	PITX2	1.53 [1.30-1.81]	2.93E-07	1.39 [1.29-1.50]	4.26E-18	1.09 [0.91-1.32]	3.38E-01	1.69 [1.12-2.55]	1.24E-02	1.02 [0.77-1.35]	8.96E-01	1.35 [1.27-1.43]	2.01E-22	1.36 [1.28-1.45]	1.36E-22
rs77699185	PITX2	1.53 [1.30-1.81]	2.93E-07	1.41 [1.30-1.51]	5.34E-19	1.17 [0.98-1.41]	8.98E-02	1.69 [1.12-2.55]	1.24E-02	1.02 [0.77-1.36]	8.95E-01	1.37 [1.29-1.45]	2.42E-24	1.38 [1.30-1.47]	1.35E-24
rs78115319	PITX2	1.54 [1.30-1.81]	2.75E-07	1.39 [1.29-1.50]	4.76E-18	1.17 [0.98-1.41]	8.95E-02	1.67 [1.11-2.52]	1.48E-02	1.02 [0.77-1.36]	8.84E-01	1.36 [1.28-1.44]	2.29E-23	1.37 [1.29-1.46]	1.27E-23
rs2350269	PITX2	1.53 [1.30-1.81]	3.01E-07	1.40 [1.30-1.51]	6.45E-19	1.17 [0.98-1.41]	9.03E-02	1.69 [1.12-2.55]	1.22E-02	1.02 [0.77-1.35]	9.00E-01	1.37 [1.29-1.45]	6.24E-24	1.38 [1.30-1.47]	1.62E-24
4:111687147:G_GAA	PITX2	1.52 [1.28-1.80]	2.16E-06	n.a.	n.a.	n.a.	n.a.	1.69 [1.12-2.55]	1.22E-02	n.a.	n.a.	1.69 [1.12-2.55]	1.22E-02	1.54 [1.31-1.81]	9.30E-08
rs6533527	PITX2	1.52 [1.30-1.79]	3.75E-07	1.41 [1.31-1.52]	1.90E-19	1.10 [0.91-1.32]	3.29E-01	1.68 [1.12-2.51]	1.17E-02	1.01 [0.76-1.35]	9.24E-01	1.36 [1.28-1.44]	1.26E-23	1.37 [1.29-1.46]	7.17E-24
4:111688953:A_ATA	PITX2	1.50 [1.27-1.78]	2.79E-06	n.a.	n.a.	n.a.	n.a.	1.68 [1.12-2.52]	1.22E-02	n.a.	n.a.	1.68 [1.12-2.52]	1.22E-02	1.53 [1.31-1.79]	1.22E-07
4:111689334:TG_T	PITX2	1.51 [1.27-1.79]	2.60E-06	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1.51 [1.27-1.79]	2.60E-06
rs17042144	PITX2	1.53 [1.30-1.80]	3.23E-07	1.40 [1.30-1.51]	2.28E-18	1.17 [0.97-1.41]	9.30E-02	1.69 [1.12-2.54]	1.26E-02	1.02 [0.77-1.36]	8.92E-01	1.36 [1.28-1.45]	1.17E-23	1.37 [1.29-1.46]	6.34E-24

4:111689780:TGA_T	PITX2	1.51 [1.27-1.78]	2.48E-06	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1.51 [1.27-1.78]	2.48E-06
rs1906618	PITX2	1.51 [1.28-1.78]	8.01E-07	1.38 [1.29-1.49]	6.36E-18	1.18 [0.98-1.42]	8.37E-02	1.68 [1.12-2.53]	1.23E-02	1.00 [0.75-1.33]	9.95E-01	1.35 [1.27-1.43]	8.50E-23	1.36 [1.28-1.45]	3.36E-23
rs1906617	PITX2	1.52 [1.30-1.79]	3.31E-07	1.39 [1.29-1.50]	1.61E-18	1.14 [0.95-1.37]	1.50E-01	1.64 [1.10-2.44]	1.62E-02	1.03 [0.78-1.36]	8.47E-01	1.35 [1.27-1.43]	4.71E-23	1.37 [1.29-1.45]	1.01E-23
rs78229461	PITX2	1.53 [1.30-1.79]	2.88E-07	1.39 [1.29-1.50]	3.00E-18	1.17 [0.97-1.40]	1.00E-01	1.62 [1.09-2.43]	1.76E-02	1.04 [0.78-1.37]	8.05E-01	1.36 [1.28-1.44]	2.31E-23	1.37 [1.29-1.46]	7.90E-24
rs12646447	PITX2	1.53 [1.31-1.80]	1.92E-07	1.39 [1.29-1.50]	3.15E-18	1.17 [0.98-1.41]	8.35E-02	1.62 [1.09-2.42]	1.77E-02	1.04 [0.78-1.37]	8.04E-01	1.36 [1.28-1.44]	1.89E-23	1.37 [1.29-1.46]	4.72E-24
rs59788391	PITX2	1.53 [1.30-1.80]	2.46E-07	1.41 [1.30-1.52]	1.65E-18	1.17 [0.97-1.41]	9.42E-02	1.63 [1.09-2.44]	1.68E-02	1.04 [0.78-1.38]	7.90E-01	1.36 [1.28-1.45]	1.21E-23	1.38 [1.30-1.47]	3.58E-24
rs12646754	PITX2	1.52 [1.29-1.79]	3.45E-07	1.39 [1.29-1.50]	5.77E-18	1.17 [0.97-1.40]	9.89E-02	1.62 [1.09-2.42]	1.76E-02	1.04 [0.78-1.37]	7.97E-01	1.35 [1.27-1.44]	4.73E-23	1.37 [1.29-1.45]	1.49E-23
rs2129981	PITX2	1.52 [1.29-1.79]	3.68E-07	1.40 [1.30-1.51]	1.75E-18	1.17 [0.97-1.40]	1.01E-01	1.62 [1.09-2.42]	1.73E-02	1.04 [0.78-1.37]	7.94E-01	1.36 [1.28-1.44]	2.21E-23	1.37 [1.29-1.46]	6.50E-24
rs12639654	PITX2	1.53 [1.30-1.79]	2.98E-07	1.40 [1.30-1.51]	2.85E-18	1.17 [0.97-1.40]	9.54E-02	1.63 [1.09-2.43]	1.70E-02	1.04 [0.79-1.38]	7.85E-01	1.36 [1.28-1.44]	2.53E-23	1.38 [1.29-1.46]	7.03E-24
rs6817105	PITX2	1.51 [1.29-1.78]	4.60E-07	1.38 [1.29-1.49]	2.79E-18	1.09 [0.91-1.31]	3.38E-01	1.62 [1.09-2.42]	1.77E-02	1.03 [0.78-1.37]	8.20E-01	1.34 [1.26-1.42]	3.85E-22	1.35 [1.27-1.44]	1.04E-22
rs72900144	PITX2	1.51 [1.29-1.78]	4.15E-07	1.38 [1.28-1.48]	1.28E-17	1.17 [0.98-1.40]	9.08E-02	1.62 [1.09-2.42]	1.74E-02	1.04 [0.78-1.37]	8.05E-01	1.34 [1.27-1.43]	1.13E-22	1.36 [1.28-1.44]	3.29E-23
rs17042171	PITX2	1.51 [1.29-1.78]	4.62E-07	1.38 [1.28-1.49]	4.58E-18	1.17 [0.97-1.40]	9.80E-02	1.61 [1.08-2.40]	1.84E-02	1.03 [0.78-1.37]	8.17E-01	1.34 [1.27-1.43]	5.94E-23	1.36 [1.28-1.44]	1.53E-23
rs7434417	PITX2	1.51 [1.29-1.78]	4.20E-07	1.38 [1.28-1.48]	1.36E-17	1.17 [0.98-1.40]	9.09E-02	1.62 [1.09-2.40]	1.78E-02	1.05 [0.79-1.38]	7.59E-01	1.34 [1.27-1.43]	1.05E-22	1.36 [1.28-1.44]	3.09E-23
rs1906591	PITX2	1.52 [1.29-1.78]	3.99E-07	1.39 [1.29-1.50]	7.12E-18	1.17 [0.97-1.40]	1.01E-01	1.61 [1.09-2.40]	1.79E-02	1.04 [0.78-1.37]	7.91E-01	1.35 [1.27-1.43]	7.06E-23	1.36 [1.28-1.45]	2.17E-23
rs1906592	PITX2	1.51 [1.29-1.78]	4.38E-07	1.37 [1.27-1.48]	4.08E-17	1.17 [0.98-1.40]	9.04E-02	1.61 [1.09-2.40]	1.79E-02	1.04 [0.78-1.37]	8.02E-01	1.34 [1.26-1.42]	2.36E-22	1.35 [1.27-1.44]	1.07E-22
rs72900148	PITX2	1.51 [1.29-1.77]	4.68E-07	1.38 [1.28-1.48]	6.01E-18	1.17 [0.97-1.40]	9.77E-02	1.61 [1.08-2.40]	1.85E-02	1.03 [0.78-1.37]	8.15E-01	1.34 [1.27-1.42]	7.95E-23	1.36 [1.28-1.44]	1.92E-23
rs72900149	PITX2	1.51 [1.29-1.77]	4.70E-07	1.38 [1.28-1.48]	6.07E-18	1.17 [0.97-1.40]	9.84E-02	1.61 [1.08-2.40]	1.84E-02	1.03 [0.78-1.37]	8.15E-01	1.34 [1.27-1.42]	7.94E-23	1.36 [1.28-1.44]	1.96E-23
rs2200732	PITX2	1.51 [1.29-1.77]	4.87E-07	1.38 [1.28-1.48]	6.16E-18	1.17 [0.97-1.40]	9.50E-02	1.61 [1.08-2.39]	1.85E-02	1.03 [0.78-1.37]	8.16E-01	1.34 [1.27-1.43]	5.88E-23	1.36 [1.28-1.44]	1.97E-23
rs2200733	PITX2	1.51 [1.29-1.77]	4.83E-07	1.37 [1.27-1.48]	1.02E-16	1.17 [0.98-1.41]	8.63E-02	1.61 [1.08-2.40]	1.82E-02	1.04 [0.78-1.37]	8.02E-01	1.34 [1.26-1.42]	8.67E-22	1.35 [1.27-1.44]	2.82E-22
rs61303432	PITX2	1.51 [1.29-1.77]	4.61E-07	1.37 [1.27-1.47]	3.92E-17	1.17 [0.98-1.40]	8.69E-02	1.62 [1.09-2.40]	1.72E-02	1.04 [0.78-1.37]	8.03E-01	1.34 [1.26-1.42]	3.07E-22	1.35 [1.27-1.44]	1.00E-22
rs72900155	PITX2	1.51 [1.29-1.77]	4.84E-07	1.38 [1.28-1.48]	6.39E-18	1.17 [0.97-1.40]	9.49E-02	1.61 [1.08-2.40]	1.85E-02	1.03 [0.78-1.37]	8.16E-01	1.34 [1.27-1.43]	7.39E-23	1.36 [1.28-1.44]	2.00E-23
rs72900157	PITX2	1.52 [1.29-1.78]	3.46E-07	1.37 [1.27-1.47]	3.98E-17	1.17 [0.97-1.40]	9.59E-02	1.62 [1.09-2.40]	1.77E-02	1.04 [0.79-1.38]	7.66E-01	1.34 [1.26-1.42]	3.63E-22	1.35 [1.27-1.44]	8.89E-23
rs75725917	PITX2	1.51 [1.29-1.77]	4.82E-07	1.38 [1.28-1.48]	6.49E-18	1.17 [0.97-1.40]	9.49E-02	1.61 [1.08-2.40]	1.85E-02	1.03 [0.78-1.37]	8.16E-01	1.34 [1.27-1.42]	8.00E-23	1.36 [1.28-1.44]	2.05E-23
rs17042175	PITX2	1.51 [1.29-1.77]	4.82E-07	1.38 [1.28-1.48]	6.51E-18	1.17 [0.97-1.40]	9.49E-02	1.61 [1.08-2.40]	1.85E-02	1.03 [0.78-1.37]	8.16E-01	1.34 [1.27-1.42]	7.55E-23	1.36 [1.28-1.44]	2.05E-23
rs4611994	PITX2	1.51 [1.29-1.77]	4.81E-07	1.38 [1.28-1.48]	6.54E-18	1.17 [0.97-1.40]	9.49E-02	1.61 [1.08-2.40]	1.85E-02	1.03 [0.78-1.37]	8.16E-01	1.34 [1.27-1.42]	7.55E-23	1.36 [1.28-1.44]	2.04E-23
rs4540107	PITX2	1.51 [1.29-1.77]	4.57E-07	1.38 [1.28-1.48]	5.71E-18	1.17 [0.97-1.40]	9.52E-02	1.61 [1.08-2.40]	1.82E-02	1.03 [0.78-1.37]	8.28E-01	1.34 [1.27-1.42]	7.72E-23	1.36 [1.28-1.44]	1.75E-23
rs1906593	PITX2	1.51 [1.29-1.77]	4.83E-07	1.38 [1.28-1.48]	5.56E-18	1.17 [0.98-1.41]	8.74E-02	1.61 [1.08-2.40]	1.85E-02	1.03 [0.78-1.37]	8.12E-01	1.35 [1.27-1.43]	5.98E-23	1.36 [1.28-1.44]	1.72E-23
rs1906595	PITX2	1.51 [1.29-1.77]	4.22E-07	1.39 [1.29-1.50]	7.18E-19	1.17 [0.97-1.40]	9.56E-02	1.61 [1.08-2.39]	1.92E-02	1.03 [0.78-1.37]	8.21E-01	1.35 [1.27-1.43]	1.39E-23	1.37 [1.29-1.45]	2.82E-24
rs1906596	PITX2	1.50 [1.28-1.76]	6.55E-07	1.39 [1.29-1.49]	8.88E-19	1.17 [0.97-1.40]	9.70E-02	1.59 [1.07-2.36]	2.18E-02	1.04 [0.79-1.38]	7.79E-01	1.35 [1.27-1.43]	2.59E-23	1.36 [1.28-1.45]	4.52E-24

rs2220427	PITX2	1.52 [1.29-1.78]	3.76E-07	1.39 [1.29-1.49]	1.29E-17	1.10 [0.92-1.32]	3.11E-01	1.61 [1.08-2.39]	1.86E-02	1.04 [0.78-1.37]	7.96E-01	1.34 [1.26-1.42]	1.23E-21	1.35 [1.27-1.44]	3.53E-22
rs12644625	PITX2	1.51 [1.29-1.78]	4.29E-07	1.39 [1.29-1.50]	5.76E-18	1.17 [0.98-1.41]	8.24E-02	1.61 [1.08-2.40]	1.83E-02	1.04 [0.79-1.38]	7.73E-01	1.35 [1.27-1.44]	3.28E-23	1.37 [1.29-1.45]	1.30E-23
rs72184	ZNF608	1.30 [1.17-1.46]	2.29E-06	1.02 [0.96-1.08]	5.33E-01	0.99 [0.87-1.13]	8.99E-01	0.92 [0.67-1.28]	6.35E-01	1.03 [0.85-1.26]	7.43E-01	1.02 [0.97-1.06]	4.90E-01	1.06 [1.01-1.10]	1.75E-02
rs72792276	SLC12A2	1.65 [1.37-1.98]	7.07E-08	0.96 [0.88-1.04]	3.34E-01	1.05 [0.84-1.32]	6.59E-01	0.98 [0.58-1.66]	9.50E-01	0.74 [0.51-1.07]	9.29E-02	0.95 [0.88-1.02]	1.29E-01	1.04 [0.97-1.12]	2.52E-01
rs180910137	SLC12A2	1.62 [1.35-1.94]	2.71E-07	0.95 [0.87-1.03]	2.17E-01	1.06 [0.85-1.33]	6.09E-01	0.98 [0.58-1.67]	9.44E-01	0.74 [0.51-1.07]	9.58E-02	0.94 [0.87-1.01]	7.88E-02	1.03 [0.96-1.11]	3.92E-01
rs72792279	SLC12A2	1.56 [1.31-1.86]	6.56E-07	0.96 [0.88-1.05]	4.04E-01	1.05 [0.84-1.31]	6.86E-01	0.98 [0.58-1.66]	9.45E-01	0.74 [0.51-1.07]	9.24E-02	0.95 [0.89-1.02]	1.49E-01	1.04 [0.97-1.12]	2.52E-01
rs10519971	SLC12A2	1.53 [1.29-1.83]	1.87E-06	0.95 [0.87-1.04]	2.76E-01	1.06 [0.85-1.32]	6.25E-01	0.98 [0.58-1.66]	9.50E-01	0.74 [0.51-1.07]	9.76E-02	0.94 [0.88-1.01]	1.01E-01	1.03 [0.96-1.11]	3.71E-01
rs56657382	SLC12A2	1.56 [1.31-1.85]	6.39E-07	0.96 [0.88-1.05]	4.06E-01	1.04 [0.83-1.30]	7.39E-01	0.96 [0.57-1.63]	8.88E-01	0.74 [0.51-1.07]	9.21E-02	0.95 [0.88-1.02]	1.41E-01	1.04 [0.97-1.12]	2.63E-01
rs17164395	SLC12A2	1.53 [1.29-1.83]	1.78E-06	0.95 [0.87-1.04]	3.02E-01	1.05 [0.84-1.31]	6.90E-01	0.96 [0.56-1.62]	8.70E-01	0.74 [0.51-1.07]	9.74E-02	0.94 [0.88-1.01]	1.01E-01	1.03 [0.96-1.11]	3.64E-01
rs78529289	SLC12A2	1.54 [1.29-1.83]	1.71E-06	0.95 [0.87-1.04]	2.94E-01	1.04 [0.83-1.31]	7.11E-01	0.95 [0.56-1.61]	8.48E-01	0.74 [0.51-1.07]	9.56E-02	0.94 [0.88-1.01]	9.67E-02	1.03 [0.96-1.11]	3.77E-01
rs17839658	SLC12A2	1.55 [1.31-1.85]	5.84E-07	0.97 [0.89-1.05]	4.44E-01	1.04 [0.83-1.30]	7.14E-01	0.93 [0.54-1.58]	7.80E-01	0.79 [0.55-1.12]	1.68E-01	0.95 [0.89-1.02]	1.88E-01	1.05 [0.97-1.12]	2.20E-01
rs13357283	SLC12A2	1.56 [1.31-1.85]	4.81E-07	0.98 [0.90-1.07]	6.65E-01	1.03 [0.82-1.28]	8.04E-01	0.93 [0.55-1.57]	7.78E-01	0.73 [0.51-1.05]	7.98E-02	0.96 [0.90-1.03]	2.34E-01	1.05 [0.98-1.13]	1.59E-01
rs72794361	SLC12A2	1.54 [1.30-1.83]	9.61E-07	0.97 [0.89-1.06]	5.10E-01	1.05 [0.84-1.31]	6.80E-01	0.92 [0.54-1.56]	7.49E-01	0.74 [0.51-1.06]	9.01E-02	0.95 [0.89-1.02]	1.76E-01	1.05 [0.97-1.12]	2.11E-01
rs10478797	SLC12A2	1.55 [1.30-1.84]	6.98E-07	0.96 [0.89-1.05]	3.89E-01	1.03 [0.83-1.29]	7.68E-01	0.94 [0.55-1.58]	8.04E-01	0.72 [0.50-1.04]	6.77E-02	0.95 [0.89-1.02]	1.29E-01	1.04 [0.97-1.11]	3.04E-01
rs72794370	SLC12A2	1.54 [1.30-1.83]	9.78E-07	0.97 [0.89-1.06]	5.13E-01	1.05 [0.84-1.31]	6.69E-01	0.91 [0.53-1.55]	7.18E-01	0.74 [0.51-1.06]	8.96E-02	0.95 [0.89-1.02]	1.81E-01	1.05 [0.97-1.12]	2.10E-01
rs111893267	SLC12A2	1.54 [1.30-1.83]	9.99E-07	0.97 [0.89-1.06]	4.66E-01	1.05 [0.84-1.31]	6.66E-01	0.90 [0.53-1.54]	7.04E-01	0.74 [0.51-1.06]	8.96E-02	0.95 [0.89-1.02]	1.61E-01	1.04 [0.97-1.12]	2.35E-01
rs3805603	SLC12A2	1.55 [1.30-1.84]	6.07E-07	0.98 [0.90-1.07]	7.23E-01	1.03 [0.83-1.29]	7.64E-01	0.90 [0.53-1.52]	6.87E-01	0.73 [0.51-1.06]	8.47E-02	0.96 [0.90-1.03]	2.67E-01	1.05 [0.98-1.13]	1.39E-01
rs147793925	SLC12A2	1.54 [1.29-1.82]	1.13E-06	0.97 [0.89-1.06]	5.20E-01	1.05 [0.84-1.31]	6.53E-01	0.88 [0.52-1.51]	6.52E-01	0.74 [0.51-1.06]	8.94E-02	0.96 [0.89-1.02]	1.97E-01	1.05 [0.97-1.12]	2.13E-01
rs113736209	SLC12A2	1.56 [1.31-1.85]	3.57E-07	0.99 [0.90-1.07]	7.35E-01	1.04 [0.83-1.30]	7.29E-01	0.88 [0.52-1.50]	6.36E-01	0.73 [0.51-1.06]	8.45E-02	0.96 [0.90-1.03]	2.92E-01	1.06 [0.99-1.13]	1.23E-01
rs57249773	SLC12A2	1.53 [1.29-1.82]	1.13E-06	0.97 [0.89-1.06]	5.22E-01	1.05 [0.84-1.31]	6.52E-01	0.88 [0.52-1.50]	6.42E-01	0.74 [0.51-1.06]	8.94E-02	0.96 [0.89-1.02]	1.97E-01	1.05 [0.97-1.12]	2.11E-01
rs72794379	SLC12A2	1.52 [1.28-1.81]	1.91E-06	0.97 [0.89-1.06]	5.23E-01	1.06 [0.85-1.32]	6.21E-01	0.89 [0.52-1.51]	6.58E-01	0.73 [0.50-1.05]	7.38E-02	0.96 [0.89-1.02]	1.95E-01	1.05 [0.97-1.12]	2.25E-01
rs72794386	SLC12A2	1.67 [1.39-2.00]	4.37E-08	0.97 [0.89-1.06]	5.09E-01	1.09 [0.87-1.37]	4.61E-01	0.95 [0.56-1.62]	8.52E-01	0.78 [0.54-1.14]	1.81E-01	0.96 [0.90-1.03]	2.69E-01	1.06 [0.99-1.14]	1.18E-01
rs3805608	SLC12A2	1.57 [1.32-1.86]	2.11E-07	0.98 [0.90-1.07]	6.90E-01	1.04 [0.83-1.29]	7.41E-01	0.92 [0.55-1.55]	7.63E-01	0.73 [0.51-1.06]	8.43E-02	0.96 [0.90-1.03]	2.81E-01	1.06 [0.99-1.13]	1.20E-01
rs3828656	SLC12A2	1.55 [1.31-1.84]	5.13E-07	0.97 [0.89-1.05]	4.42E-01	1.03 [0.83-1.29]	7.64E-01	0.92 [0.55-1.56]	7.67E-01	0.73 [0.51-1.05]	7.78E-02	0.95 [0.89-1.02]	1.66E-01	1.04 [0.97-1.12]	2.55E-01
rs3805610	SLC12A2	1.59 [1.33-1.89]	1.89E-07	0.99 [0.90-1.08]	7.52E-01	1.05 [0.84-1.32]	6.73E-01	0.96 [0.57-1.63]	8.80E-01	0.73 [0.50-1.05]	7.93E-02	0.96 [0.90-1.03]	2.99E-01	1.06 [0.99-1.14]	9.16E-02
rs2913884	GLRA1	1.28 [1.16-1.43]	3.67E-06	0.97 [0.92-1.03]	3.02E-01	0.94 [0.82-1.08]	3.89E-01	0.91 [0.66-1.25]	5.45E-01	1.03 [0.84-1.26]	7.73E-01	0.99 [0.95-1.03]	6.37E-01	1.02 [0.97-1.07]	3.90E-01
rs1428155	GLRA1	1.28 [1.16-1.43]	3.10E-06	0.97 [0.92-1.03]	3.31E-01	0.95 [0.83-1.08]	4.41E-01	0.90 [0.66-1.24]	5.15E-01	0.99 [0.81-1.21]	9.43E-01	0.99 [0.95-1.03]	6.39E-01	1.02 [0.98-1.07]	3.84E-01
rs1361696	HDGFL1	1.56 [1.29-1.88]	3.71E-06	1.01 [0.92-1.11]	8.57E-01	0.88 [0.70-1.10]	2.67E-01	1.27 [0.78-2.06]	3.40E-01	1.18 [0.87-1.59]	2.97E-01	1.00 [0.93-1.08]	9.70E-01	1.08 [1.00-1.17]	4.08E-02
rs16886284	HDGFL1	1.51 [1.27-1.80]	3.74E-06	0.99 [0.90-1.09]	8.70E-01	0.86 [0.69-1.08]	1.94E-01	1.27 [0.80-2.02]	3.10E-01	1.20 [0.89-1.62]	2.38E-01	0.99 [0.92-1.06]	7.56E-01	1.07 [1.00-1.16]	6.05E-02

rs7771564	HDGFL1	1.53 [1.28-1.82]	2.10E-06	1.01 [0.92-1.10]	8.74E-01	0.88 [0.70-1.10]	2.47E-01	1.23 [0.77-1.96]	3.95E-01	1.20 [0.89-1.62]	2.43E-01	1.00 [0.93-1.07]	9.73E-01	1.08 [1.01-1.17]	3.10E-02
rs112552146	HDGFL1	1.47 [1.25-1.73]	3.48E-06	1.03 [0.94-1.12]	5.16E-01	1.02 [0.83-1.24]	8.66E-01	1.08 [0.69-1.70]	7.21E-01	1.12 [0.85-1.49]	4.28E-01	1.03 [0.96-1.10]	4.38E-01	1.10 [1.03-1.18]	5.30E-03
rs1495081	TUSC3	1.48 [1.25-1.74]	3.09E-06	1.05 [0.98-1.14]	1.84E-01	0.89 [0.72-1.09]	2.53E-01	1.35 [0.84-2.16]	2.15E-01	1.05 [0.79-1.40]	7.26E-01	1.04 [0.98-1.10]	2.40E-01	1.10 [1.03-1.17]	5.07E-03
rs2393938	ZNF239	1.45 [1.24-1.70]	3.47E-06	1.02 [0.94-1.10]	6.85E-01	1.01 [0.84-1.22]	8.85E-01	0.95 [0.60-1.52]	8.39E-01	0.96 [0.71-1.29]	7.65E-01	1.00 [0.94-1.07]	9.53E-01	1.07 [1.01-1.15]	2.93E-02
rs11021485	MAML2	1.60 [1.32-1.94]	1.24E-06	0.94 [0.86-1.03]	1.75E-01	0.77 [0.63-0.95]	1.49E-02	0.51 [0.25-1.04]	6.29E-02	1.06 [0.78-1.43]	7.27E-01	0.92 [0.86-0.99]	1.69E-02	0.99 [0.92-1.07]	8.21E-01
rs710011	DACT1	1.41 [1.22-1.63]	4.04E-06	1.00 [0.92-1.07]	9.27E-01	0.97 [0.81-1.17]	7.69E-01	1.21 [0.80-1.83]	3.71E-01	1.11 [0.85-1.45]	4.48E-01	1.00 [0.95-1.06]	9.49E-01	1.06 [1.00-1.13]	4.21E-02
rs856288	DACT1	1.41 [1.22-1.64]	3.62E-06	1.00 [0.92-1.08]	9.39E-01	0.98 [0.82-1.18]	8.48E-01	1.21 [0.80-1.83]	3.72E-01	1.10 [0.84-1.43]	5.09E-01	1.00 [0.95-1.06]	9.02E-01	1.07 [1.00-1.13]	3.88E-02
rs710009	DACT1	1.41 [1.22-1.64]	3.62E-06	1.00 [0.92-1.07]	9.26E-01	0.96 [0.80-1.15]	6.78E-01	1.21 [0.80-1.83]	3.71E-01	1.10 [0.84-1.43]	5.04E-01	1.00 [0.94-1.06]	9.57E-01	1.06 [1.00-1.13]	4.76E-02
rs710008	DACT1	1.41 [1.22-1.63]	4.07E-06	0.99 [0.92-1.07]	8.91E-01	0.96 [0.80-1.15]	6.37E-01	1.20 [0.79-1.81]	3.96E-01	1.10 [0.84-1.43]	5.07E-01	1.00 [0.94-1.06]	9.82E-01	1.06 [1.00-1.13]	5.65E-02
Non-cardioembolic stroke§															
rs77858481	SPRY2	1.46 [1.27-1.69]	2.92E-07	1.00 [0.87-1.15]	9.89E-01	0.67 [0.48-0.95]	2.44E-02	1.84 [0.93-3.63]	7.92E-02	0.73 [0.33-1.64]	4.27E-01	0.99 [0.89-1.10]	8.14E-01	1.15 [1.05-1.27]	3.60E-03
rs77858481	SPRY2	1.46 [1.27-1.69]	2.92E-07	1.07 [0.94-1.21]	3.14E-01	0.89 [0.63-1.25]	4.94E-01	0.97 [0.57-1.65]	9.13E-01	0.39 [0.08-1.93]	1.90E-01	1.05 [0.95-1.16]	3.48E-01	1.18 [1.08-1.29]	2.70E-04

EAF: Effect allele frequency; EA: Efective allele; HR: Hazards ratio; CI: confidence interval; OR: Odds ratio; Effect estimates presented are with respect to the minor allele also the effect allele here.

*Follow-up results are from association analyses of ischemic stroke for SiGN, METASTROKE and CADISP, and of all stroke for HVH1; †follow-up results are from association analyses of ischemic stroke for SiGN, METASTROKE, HVH1, and CADISP; ‡follow-up results are from association analyses of cardioembolic ischemic stroke for SiGN, METASTROKE, HVH1 and CADISP (TOAST subtyping); §follow-up results are from association analyses of large artery ischemic stroke (first line) and small artery ischemic stroke (second line) for SiGN, METASTROKE, HVH1, and CADISP (TOAST subtyping)

Supplementary Table 8: Association of the top locus (chr6p25) with the small artery occlusion ischemic stroke subtype in follow-up samples

				TOAST		CCS-causative		CCS-phenotypic	
SNP	**RA**	**RAF**	**Dir**	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**	**OR (95%CI)**	**P**
rs12197982	G	0.19	++++	1.07 (1.01-1.13)	0.028	1.11 (1.04-1.18)	0.00083	1.09 (1.02-1.15)	0.0054
rs12198803	G	0.20	++++	1.07 (1.01-1.13)	0.017	1.11 (1.04-1.17)	0.00072	1.09 (1.03-1.15)	0.0046
rs12200309	G	0.20	++++	1.08 (1.02-1.14)	0.0093	1.11 (1.05-1.18)	0.00029	1.09 (1.03-1.16)	0.0022
rs12204590	A	0.19	++++	1.07 (1.01-1.13)	0.022	1.11 (1.04-1.18)	0.00062	1.09 (1.03-1.16)	0.0042
rs12211303	C	0.19	++++	1.07 (1.01-1.13)	0.025	1.11 (1.04-1.18)	0.00067	1.09 (1.04-1.16)	0.0045
rs12212982	A	0.19	++++	1.07 (1.01-1.13)	0.026	1.11 (1.04-1.18)	0.00068	1.09 (1.05-1.16)	0.0046

Dir: Direction of association in each of the four follow-up studies with respect to the risk allele; RA: Risk Allele; RAF: Risk Allele Frequency; OR: Odds raio; CI: Confidence interval

Supplementary Table 9: Association of the top locus (chr6p25) with white matter hyperintensity burden in the CHARGE consortium [88]

			All ethnicities		Europeans	
SNP	**RA**	**RAF**	**Z-score**	**P**	**Z-score**	**P**
rs12197982	G	0.19	2.994	0.0027	2.974	0.0029
rs12198803	G	0.20	2.998	0.0027	2.987	0.0028
rs12200309	G	0.20	2.992	0.0028	2.982	0.0029
rs12204590	A	0.18	2.709	0.0067	2.913	0.0036
rs12211303	C	0.19	2.980	0.0029	2.960	0.0031
rs12212982	A	0.19	3.019	0.0025	3.001	0.0027

RA: Risk Allele; RAF: Risk Allele Frequency; Z-score: association statistic from effective sample size weighted meta-analysis [88]

Supplementary Table 10: Sample size per study for analyses of 1-month stroke fatality

Study	Fatal all stroke	Non-fatal all stroke	Fatal ischemic stroke	Non-fatal ischemic stroke	Controls
AGES	12	87	18	96	2882
ARIC	51	459	36	416	8568
CHS	117	446	63	384	3268
FHS	59	178	35	165	4148
FINRISK_COREEXOME	20	74	n.a.	n.a.	5202
FINRISK_COROGENE	10	50	n.a.	n.a.	1887
FINRISK_PREDICTCVD	42	304	24	270	1265
PROSPER	26	215	n.a.	n.a.	4470
RS1	205	735	69	468	5097
RS2	19	117	n.a.	n.a.	1938
3C-Bordeaux-Montpellier	21	61	n.a.	n.a.	2071
3C-Dijon	32	124	13	112	3605
ULSAM	27	189	n.a.	n.a.	464
WGHS	46	453	13	389	22795
TOTAL	687	3492	271	2300	67660

Stroke was defined as fatal if death occurred within one month after stroke onset. Only studies with >10 participants with “fatal” stroke (or ischemic stroke) and >10 participants with “non-fatal” stroke (or ischemic stroke) were included in the analysis.

Supplementary Table 11: Associations of suggestive risk variants for incident all stroke and ischemic stroke with fatal and non-fatal stroke

							Fatal all stroke (N=687/67,660)		Non-fatal all stroke (N=3,492/67,660)		Fatal ischemic stroke (N=271/51,628)		Non-fatal ischemic stroke (N=2,300/51,628)		Heterogeneity	
SNP	Chr	Position	Pheno	Gene	EA	EAF	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	P (All stroke)	P (Ischemic stroke)
rs10189949	2	182132131	AS	*UBE2E3/MIR4437*	C	0.08	1.23 [1.02-1.50]	3.49E-02	1.22 [1.12-1.32]	5.26E-06	1.14 [0.83-1.56]	4.36E-01	1.25 [1.12-1.38]	3.09E-05	0.8339	0.8970
rs6433905	2	182138150	AS	*UBE2E3/MIR4437*	C	0.08	1.22 [1.00-1.48]	4.70E-02	1.21 [1.11-1.31]	1.28E-05	1.14 [0.83-1.58]	4.13E-01	1.23 [1.11-1.37]	9.29E-05	0.9088	0.9959
rs62262077	3	105014929	IS	*ALCAM*	A	0.27	1.05 [0.93-1.19]	4.02E-01	1.11 [1.05-1.17]	3.04E-04	1.24 [1.02-1.51]	3.00E-02	1.13 [1.05-1.21]	7.33E-04	0.1890	0.6615
rs7649869	3	105021917	IS	*ALCAM*	G	0.3	1.05 [0.93-1.18]	4.45E-01	1.10 [1.04-1.16]	6.30E-04	1.23 [1.01-1.48]	3.52E-02	1.11 [1.04-1.19]	2.46E-03	0.2368	0.8043
rs12152354	3	105045025	IS	*ALCAM*	A	0.29	1.05 [0.93-1.18]	4.62E-01	1.09 [1.04-1.15]	9.80E-04	1.24 [1.03-1.49]	2.11E-02	1.10 [1.03-1.18]	3.19E-03	0.2085	0.8701
rs7633149	3	105045248	IS	*ALCAM*	A	0.29	1.05 [0.93-1.18]	4.61E-01	1.09 [1.04-1.15]	9.78E-04	1.24 [1.03-1.49]	2.11E-02	1.10 [1.03-1.18]	3.18E-03	0.2086	0.8704
rs4894921	3	105070826	IS	*ALCAM*	C	0.29	1.05 [0.93-1.18]	4.56E-01	1.09 [1.04-1.15]	9.23E-04	1.24 [1.03-1.50]	2.03E-02	1.10 [1.03-1.18]	3.12E-03	0.2195	0.9260
rs10037362	5	31110857	IS	*CDH6*	A	0.07	1.02 [0.83-1.27]	8.37E-01	1.21 [1.11-1.33]	2.72E-05	1.22 [0.88-1.70]	2.40E-01	1.22 [1.09-1.36]	4.57E-04	0.2622	0.9723
rs35470188	5	31111255	IS	*CDH6*	G	0.07	1.02 [0.83-1.27]	8.30E-01	1.21 [1.11-1.33]	3.32E-05	1.22 [0.88-1.70]	2.31E-01	1.22 [1.09-1.36]	5.60E-04	0.2759	0.9405
rs12204590	6	1337393	AS	*FOXQ1/FOXF2*	A	0.21	1.15 [1.01-1.31]	3.62E-02	1.13 [1.07-1.20]	1.93E-05	1.21 [0.99-1.50]	6.84E-02	1.14 [1.06-1.22]	4.90E-04	0.3338	0.6166
rs12197982	6	1338196	AS	*FOXQ1/FOXF2*	G	0.21	1.15 [1.01-1.31]	3.64E-02	1.13 [1.07-1.20]	2.04E-05	1.22 [0.99-1.50]	6.79E-02	1.14 [1.06-1.22]	4.98E-04	0.3300	0.6116
rs12211303	6	1338655	AS	*FOXQ1/FOXF2*	C	0.21	1.15 [1.01-1.31]	3.65E-02	1.13 [1.07-1.20]	2.06E-05	1.22 [0.99-1.50]	6.79E-02	1.14 [1.06-1.22]	4.96E-04	0.3288	0.6105
rs12212982	6	1339188	AS	*FOXQ1/FOXF2*	A	0.21	1.15 [1.01-1.31]	3.62E-02	1.13 [1.07-1.20]	2.14E-05	1.22 [0.99-1.50]	6.67E-02	1.14 [1.06-1.22]	4.98E-04	0.3251	0.6051
rs12198803	6	1340473	AS	*FOXQ1/FOXF2*	G	0.21	1.15 [1.01-1.30]	3.89E-02	1.13 [1.07-1.20]	2.78E-05	1.21 [0.98-1.49]	7.16E-02	1.13 [1.06-1.22]	5.94E-04	0.3215	0.6082
rs12200309	6	1340548	AS	*FOXQ1/FOXF2*	G	0.21	1.14 [1.00-1.30]	4.54E-02	1.13 [1.07-1.20]	2.92E-05	1.21 [0.98-1.50]	7.03E-02	1.13 [1.06-1.22]	5.89E-04	0.3237	0.5936
rs712241	6	154293180	AS	*OPRM1*	G	0.45	1.11 [1.00-1.24]	5.98E-02	1.11 [1.05-1.16]	5.90E-05	1.02 [0.85-1.22]	8.30E-01	1.10 [1.04-1.17]	1.63E-03	0.9519	0.6445
rs790919	6	154298875	AS	*OPRM1*	A	0.44	1.12 [1.00-1.24]	5.12E-02	1.11 [1.06-1.17]	3.94E-05	1.03 [0.86-1.23]	7.75E-01	1.11 [1.04-1.18]	1.13E-03	0.9316	0.6713
rs10961053	9	13444573	AS	*FLJ41200/LINC00583*	G	0.34	1.24 [1.11-1.39]	2.29E-04	1.10 [1.05-1.16]	1.87E-04	1.27 [1.05-1.53]	1.22E-02	1.11 [1.04-1.18]	2.02E-03	0.0782	0.0622
rs10491751	9	13444932	AS	*FLJ41200/LINC00583*	A	0.33	1.23 [1.10-1.38]	4.35E-04	1.11 [1.05-1.16]	1.64E-04	1.25 [1.04-1.51]	1.82E-02	1.11 [1.04-1.18]	2.11E-03	0.1134	0.0685
rs11788315	9	13445680	AS	*FLJ41200/LINC00583*	T	0.28	1.23 [1.09-1.39]	7.10E-04	1.12 [1.06-1.19]	2.63E-05	1.26 [1.03-1.53]	2.33E-02	1.13 [1.06-1.21]	3.61E-04	0.2084	0.1099
rs11788316	9	13445687	AS	*FLJ41200/LINC00583*	T	0.28	1.23 [1.09-1.39]	7.10E-04	1.12 [1.06-1.19]	2.76E-05	1.26 [1.03-1.53]	2.31E-02	1.13 [1.06-1.21]	3.56E-04	0.2061	0.1080
rs2209804	10	21651654	IS	*NEBL-AS1/C10orf114*	C	0.14	0.97 [0.82-1.14]	7.19E-01	0.85 [0.79-0.92]	3.12E-05	0.98 [0.75-1.29]	9.01E-01	0.80 [0.73-0.89]	9.04E-06	0.2013	0.5285
rs58809874	10	21651981	IS	*NEBL-AS1/C10orf114*	A	0.14	0.96 [0.82-1.13]	6.33E-01	0.87 [0.80-0.93]	2.00E-04	1.01 [0.77-1.31]	9.66E-01	0.83 [0.75-0.91]	9.44E-05	0.2873	0.5455
rs7068408	10	21652235	IS	*NEBL-AS1/C10orf114*	A	0.14	0.98 [0.83-1.15]	7.86E-01	0.85 [0.79-0.92]	3.27E-05	0.98 [0.75-1.29]	9.10E-01	0.80 [0.73-0.89]	9.90E-06	0.1701	0.5296
rs7086407	10	21661336	IS	*NEBL-AS1/C10orf114*	C	0.14	0.96 [0.81-1.13]	6.07E-01	0.85 [0.78-0.92]	2.58E-05	0.97 [0.74-1.28]	8.40E-01	0.80 [0.73-0.89]	1.07E-05	0.2604	0.6108
rs11012681	10	21664505	IS	*NEBL-AS1/C10orf114*	A	0.14	0.95 [0.80-1.12]	5.23E-01	0.86 [0.80-0.93]	1.53E-04	0.98 [0.75-1.29]	9.02E-01	0.83 [0.75-0.91]	1.00E-04	0.3257	0.6428
rs4448595	10	21666138	IS	*NEBL-AS1/C10orf114*	G	0.16	0.94 [0.80-1.09]	3.90E-01	0.88 [0.82-0.94]	2.36E-04	0.92 [0.71-1.20]	5.53E-01	0.84 [0.77-0.92]	1.02E-04	0.4077	0.7850
rs12245880	10	21668199	IS	*NEBL-AS1/C10orf114*	T	0.16	0.93 [0.80-1.09]	3.84E-01	0.88 [0.82-0.94]	3.46E-04	0.93 [0.71-1.20]	5.58E-01	0.84 [0.77-0.92]	1.44E-04	0.4419	0.8018
rs1243181	10	21916468	IS	*MLLT10*	T	0.48	1.05 [0.94-1.17]	3.75E-01	1.10 [1.05-1.16]	6.90E-05	1.18 [0.99-1.41]	6.79E-02	1.16 [1.09-1.23]	3.61E-06	0.6823	0.8618
rs11833579	12	775199	IS	*NINJ2*	A	0.25	1.07 [0.94-1.22]	3.05E-01	1.11 [1.05-1.18]	3.89E-04	1.45 [1.18-1.77]	3.40E-04	1.17 [1.09-1.26]	2.88E-05	0.7143	0.0826
rs12425791	12	783484	IS	*NINJ2*	A	0.2	1.08 [0.94-1.25]	2.73E-01	1.12 [1.05-1.20]	3.60E-04	1.40 [1.12-1.74]	2.97E-03	1.18 [1.09-1.27]	5.57E-05	0.9678	0.1825

rs77858481	13	81142325	IS	*SPRY2*	G	0.07	1.46 [1.17-1.82]	8.67E-04	1.21 [1.09-1.35]	3.87E-04	1.41 [0.98-2.03]	6.21E-02	1.32 [1.16-1.49]	1.90E-05	0.1735	0.6749
rs11627959	14	35160471	AS	*CFL2*	C	0.44	0.91 [0.81-1.01]	8.79E-02	0.91 [0.87-0.96]	3.91E-04	0.88 [0.73-1.06]	1.93E-01	0.88 [0.83-0.94]	1.10E-04	0.9774	0.9727
14:35163898:T_TA	14	35163898	AS	*CFL2*	I	0.47	0.91 [0.80-1.03]	1.25E-01	0.93 [0.88-0.98]	9.34E-03	0.86 [0.70-1.06]	1.50E-01	0.89 [0.83-0.96]	1.40E-03	0.7328	0.6882
rs8003414	14	35170800	AS	*CFL2*	C	0.44	0.91 [0.81-1.02]	9.28E-02	0.92 [0.87-0.96]	6.02E-04	0.89 [0.74-1.06]	1.96E-01	0.88 [0.83-0.94]	1.36E-04	0.9531	0.9970
rs12883300	14	35171218	AS	*CFL2*	G	0.43	0.91 [0.81-1.02]	9.26E-02	0.92 [0.87-0.97]	8.98E-04	0.89 [0.74-1.07]	2.12E-01	0.88 [0.83-0.94]	1.59E-04	0.9711	0.9677
rs4899120	14	64335447	AS	*SYNE2*	T	0.08	1.20 [0.99-1.46]	6.82E-02	1.16 [1.07-1.27]	5.37E-04	1.23 [0.90-1.67]	2.01E-01	1.14 [1.03-1.27]	1.57E-02	0.4593	0.7078

AS: all Stroke; IS: ischemic Stroke; EA: effect allele; EAF: effect allele frequency; HR=Hazard ratio; N=Number of cases and controls for the analysis; fatal stroke was defined as stroke leading to death within one month. Only variants which were significantly associated with all stroke and ischemic stroke in population based GWAS analysis (discovery) were their effects on stroke fatality

Supplementary Table 12: Heterogeneity analysis between Europeans, Africans and Hispanics for FOXF2 top SNPs

				Europeans			Africans			Hispanics			Meta-analysis (Eur+Afr+His)					
FOXF2-SNP	Allele1	Allele2	Freq1	beta	SE	P	beta	SE	P	beta	SE	P	beta	SE	P	Direction	HetISq	Het-P
all ischemic stroke																		
rs12212982	a	g	0.20	0.069	0.020	5.16E-04	0.015	0.127	9.03E-01	-0.059	0.087	4.96E-01	0.062	0.019	1.31E-03	++-	9.4	0.33
rs12197982	c	g	0.80	-0.069	0.020	5.66E-04	-0.029	0.127	8.19E-01	0.057	0.087	5.16E-01	-0.062	0.019	1.31E-03	--+	1.6	0.36
rs12204590	a	t	0.20	0.068	0.020	5.88E-04	0.113	0.134	4.00E-01	-0.058	0.088	5.06E-01	0.063	0.019	9.96E-04	++-	6.1	0.34
rs12211303	c	g	0.20	0.069	0.020	5.46E-04	0.022	0.127	8.63E-01	-0.058	0.087	5.09E-01	0.062	0.019	1.32E-03	++-	4.9	0.35
rs12198803	a	g	0.80	-0.069	0.020	5.36E-04	-0.011	0.072	8.81E-01	0.083	0.084	3.23E-01	-0.057	0.019	2.13E-03	--+	43.7	0.17
rs12200309	t	g	0.80	-0.068	0.020	5.88E-04	-0.012	0.072	8.66E-01	0.084	0.083	3.07E-01	-0.057	0.019	2.37E-03	--+	45.2	0.16
small artery IS (TOAST)																		
rs12212982	a	g	0.19	0.069	0.040	8.67E-02	0.082	0.216	7.04E-01	0.074	0.107	4.87E-01	0.070	0.037	5.93E-02	+++	0	0.99
rs12197982	c	g	0.81	-0.069	0.040	8.67E-02	-0.090	0.216	6.77E-01	-0.077	0.107	4.71E-01	-0.071	0.037	5.73E-02	---	0	0.99
rs12204590	a	t	0.19	0.069	0.040	8.67E-02	0.188	0.229	4.12E-01	0.085	0.107	4.26E-01	0.074	0.037	4.64E-02	+++	0	0.87
rs12211303	c	g	0.19	0.069	0.040	8.67E-02	0.087	0.216	6.87E-01	0.076	0.107	4.77E-01	0.071	0.037	5.80E-02	+++	0	0.99
rs12198803	a	g	0.81	-0.067	0.041	9.71E-02	-0.183	0.120	1.26E-01	-0.052	0.105	6.20E-01	-0.076	0.036	3.52E-02	---	0	0.64
rs12200309	t	g	0.81	-0.067	0.040	9.72E-02	-0.185	0.120	1.23E-01	-0.052	0.103	6.14E-01	-0.076	0.036	3.48E-02	---	0	0.63
small artery IS (CCS)																		
rs12212982	a	g	0.19	0.150	0.044	6.31E-04	-0.056	0.226	8.04E-01	0.101	0.109	3.55E-01	0.105	0.039	7.52E-03	+-+	0	0.50
rs12197982	c	g	0.81	-0.149	0.044	6.92E-04	0.048	0.226	8.32E-01	-0.104	0.109	3.40E-01	-0.105	0.039	7.64E-03	-+-	0	0.53
rs12204590	a	t	0.19	0.148	0.044	7.10E-04	0.039	0.240	8.73E-01	0.113	0.109	3.00E-01	0.108	0.039	5.75E-03	+-+	0	0.75
rs12211303	c	g	0.19	0.149	0.044	6.69E-04	-0.051	0.226	8.22E-01	0.103	0.109	3.46E-01	0.105	0.039	7.57E-03	+-+	0	0.52
rs12198803	a	g	0.81	-0.150	0.044	6.08E-04	-0.068	0.126	5.89E-01	-0.066	0.107	5.34E-01	-0.102	0.038	7.06E-03	---	0	0.57
rs12200309	t	g	0.81	-0.149	0.044	6.34E-04	-0.069	0.125	5.81E-01	-0.073	0.105	4.88E-01	-0.102	0.038	6.86E-03	---	0	0.60

Heterogeneity analysis in European, African and Hispanics samples for FOXF2 top SNPS in the SiGN follow-up samples. Het-P : Heterogeneity P-value

Supplementary Table 13: Enhancer enrichment analysis for *FOXF2*-rs12204590 and SNPs in LD with it

Cell type		All enhancers				Strongest enhancers			
ID	**Description**	**Obs**	**Exp**	**Fold**	**p**	**Obs**	**Exp**	**Fold**	**p**
HepG2	hepatocellular carcinoma	6	2.1	2.9	0.0179	2	0.7	2.9	0.153
NHLF	lung fibroblasts	14	2.6	5.4	0	8	1	8.1	6.00×10^{-6}
HMEC	mammary epithelial cells	9	3.4	2.7	0.00609	7	1.3	5.4	0.000303
NHEK	epidermal keratinocytes	9	2.9	3.1	0.00236	5	1.3	3.9	0.00917

Enhancer enrichment analysis was performed using HaploReg V2 (http://www.broadinstitute.org/mammals/haploreg/haploreg.php). The *FOXF2* variant rs12204590 and SNPs in LD with it (r2>0.5) were used as inputs for this analysis.

Supplementary Table 14: DNase enrichment analysis for *FOXF2*-rs12204590 and SNPs in LD with it

Cell type				DNase			
ID	**Description**	**Treatment**	**Production**	**Obs**	**Exp**	**Fold**	**p**
WI-38	embryonic lung fibroblast	None	UW	8	0.5	15.2	<1.00E-06
HPdLF	periodontal ligament	None	UW	6	0.5	11.4	1.50E-05
HCM	cardiac myocytes	None	UW	3	0.6	4.9	0.023762
AG09309	adult toe fibroblast	None	UW	5	0.6	7.9	0.000426
HCF	cardiac fibroblasts	None	UW	3	0.5	5.5	0.017439
NHDF-	neonatal dermal	None	UW	5	0.6	8.6	0.000303
AG09319	gum tissue fibroblasts	None	UW	6	0.4	13.7	5.00E-06
HPF	pulmonary fibroblasts	None	UW	6	0.5	12.4	9.00E-06
PANC-1	pancreatic carcinoma	None	UW	3	0.4	8.1	0.006239
AoAF	aortic adventitial	None	UW	5	0.5	9.2	0.000221
HeLa-S3	cervical carcinoma	None	AWG	6	0.6	9.5	4.00E-05
BJ	skin fibroblast	None	UW	3	0.5	6	0.014041
HeLa-S3	cervical carcinoma	IFNa4h	Duke	3	0.4	8.2	0.006057
HCPEpiC	choroid plexus epithelial	None	UW	4	0.7	6	0.004539
HRPEpiC	retinal pigment epithelial	None	UW	4	0.7	5.5	0.005991
WI-38	embryonic lung fibroblast	4OHTAM_20nM	UW	4	0.7	6.1	0.00434
HConF	conjunctival fibroblast	None	UW	6	0.5	12.5	9.00E-06
HAEpiC	amniotic epithelial cells	None	UW	3	0.7	4.6	0.027865
NB4	acute promyelocytic	None	UW	3	0.5	6.4	0.011685
H7-hESC	undifferentiated	None	UW	4	0.9	4.5	0.011826
NHDF-Ad	adult dermal fibroblasts	None	UW	5	0.7	6.9	0.000808
HAc	astrocytes-cerebellar	None	UW	5	0.6	8.7	0.000274
HGF	gingival fibroblasts	None	UW	5	0.5	11	9.30E-05
HIPEpiC	iris pigment epithelial	None	UW	4	0.7	5.6	0.005616

DNase enrichment analysis was performed using HaploReg V2 (http://www.broadinstitute.org/mammals/haploreg/haploreg.php). The *FOXF2* variant rs12204590 and SNPs in LD with it (r2>0.5) were used as inputs for this analysis.

Supplementary Table 15: RegulomeDB scores for variants in LD (r^2>0.5) with lead SNP rs12204590 (chr6p25)

Chr	Position	SNP	r2 with rs12204590	distance from rs12204590	RegulomeDB score
6	1336867	rs7750826	0.77	526	2b
6	1316451	rs2006798	0.75	20942	2b
6	1338196	rs12197982	1.00	803	4
6	1340473	rs12198803	1.00	3080	4
6	1340548	rs12200309	0.99	3155	4
6	1335849	rs74564934	0.61	1544	4
6	1338265	rs78451852	0.56	872	4
6	1347118	rs6596812	0.56	9725	4
6	1316016	rs74536576	0.51	21377	4
6	1338570	rs114957082	0.56	1177	5
6	1341581	rs79565252	0.56	4188	5
6	1341652	rs17260983	0.56	4259	5
6	1341730	rs17261011	0.56	4337	5
6	1344549	rs79618067	0.56	7156	5
6	1346515	rs17261060	0.56	9122	5
6	1346541	rs17261109	0.56	9148	5
6	1346561	rs17201698	0.56	9168	5
6	1346989	rs6596811	0.55	9596	5
6	1327402	rs4959545	0.53	9991	5
6	1326826	rs78120638	0.53	10567	5
6	1326894	rs2015134	0.53	10499	5
6	1330230	rs115370942	0.53	7163	5
6	1318711	rs951318	0.52	18682	5
6	1338655	rs12211303	1.00	1262	6
6	1339188	rs12212982	1.00	1795	6
6	1341423	rs74484590	0.57	4030	6
6	1341463	rs75289435	0.56	4070	6
6	1342314	rs79368490	0.56	4921	6
6	1342508	rs75802256	0.56	5115	6
6	1342663	rs78252540	0.56	5270	6
6	1343031	rs4959546	0.56	5638	6
6	1343622	rs75586483	0.56	6229	6
6	1344000	rs79783857	0.56	6607	6
6	1345762	rs78460052	0.56	8369	6
6	1342334	rs77796590	0.55	4941	6
6	1329748	rs2317897	0.53	7645	6
6	1333266	rs149766397	0.53	4127	6
6	1334409	rs10498653	0.53	2984	6

RegulomeDB (http://www.regulomedb.org/) scores variants for their role in gene regulation. It is possible that some variants are not scored by this method; this includes the top variant of *FOXF2* rs12204590. The meanings of the various scores by RegulomeDB are presented below.

1a: eQTL + TF binding + matched TF motif + matched DNase Footprint + DNase peak
1b: eQTL + TF binding + any motif + DNase Footprint + DNase peak
1c: eQTL + TF binding + matched TF motif + DNase peak
1d: eQTL + TF binding + any motif + DNase peak

1e: eQTL + TF binding + matched TF motif
1f: eQTL + TF binding / DNase peak
2a: TF binding + matched TF motif + matched DNase Footprint + DNase peak
2b: TF binding + any motif + DNase Footprint + DNase peak
2c: TF binding + matched TF motif + DNase peak
3a: TF binding + any motif + DNase peak
3b: TF binding + matched TF motif
4: TF binding + DNase peak
5: TF binding or DNase peak
6: other

Supplementary Table 16: eQTL search for variants chosen for follow-up in non-brain tissues

SNP ‡	Chr	Position	Closest Gene	Gene expression	Cell type	Reference	P-value
rs17042088	4	111654814	PITX2	CHES1	Monocytes	Zeller T, PLoS One 2010 [89]	9.56E-06
rs17042121	4	111677101	PITX2	ACLY	Monocytes	Zeller T, PLoS One 2010 [89]	8.16E-06
rs17042121	4	111677101	PITX2	CHES1	Monocytes	Zeller T, PLoS One 2010 [89]	2.74E-06
rs17042121	4	111677101	PITX2	RNASE10	Monocytes	Zeller T, PLoS One 2010 [89]	5.17E-06
rs17042144	4	111689666	PITX2	ACLY	Monocytes	Zeller T, PLoS One 2010 [89]	6.05E-06
rs17042144	4	111689666	PITX2	CHES1	Monocytes	Zeller T, PLoS One 2010 [89]	2.19E-06
rs17042144	4	111689666	PITX2	RNASE10	Monocytes	Zeller T, PLoS One 2010 [89]	6.04E-06
rs12646447	4	111699326	PITX2	ACLY	Monocytes	Zeller T, PLoS One 2010 [89]	2.38E-06
rs12646447	4	111699326	PITX2	CHES1	Monocytes	Zeller T, PLoS One 2010 [89]	2.99E-06
rs12646447	4	111699326	PITX2	CS	Monocytes	Zeller T, PLoS One 2010 [89]	9.18E-06
rs12646447	4	111699326	PITX2	RNASE10	Monocytes	Zeller T, PLoS One 2010 [89]	8.29E-06
rs17042171	4	111708287	PITX2	ACLY	Monocytes	Zeller T, PLoS One 2010 [89]	6.44E-06
rs17042171	4	111708287	PITX2	CHES1	Monocytes	Zeller T, PLoS One 2010 [89]	4.94E-06
rs2200733	4	111710169	PITX2	RNASE10	Monocytes	Zeller T, PLoS One 2010 [89]	7.79E-06
rs4611994	4	111711041	PITX2	ACLY	Monocytes	Zeller T, PLoS One 2010 [89]	6.44E-06
rs4611994	4	111711041	PITX2	CHES1	Monocytes	Zeller T, PLoS One 2010 [89]	4.94E-06
rs12644625	4	111716513	PITX2	CHES1	Monocytes	Zeller T, PLoS One 2010 [89]	6.54E-06
rs2393938	10	44063812	ZNF239	ZNF239	Blood cells †	Fehrmann RS, PLoS Genet 2011 [90]	1.20E-11
rs2393938	10	44063812	ZNF239	ZNF239	CD4+ lymphocytes	Murphy A, Hum Mol Genet 2010 [91]	2.14E-11
rs710011	14	59183275	DACT1	CUEDC1	Monocytes	Zeller T, PLoS One 2010 [89]	8.07E-07
rs710011	14	59183275	DACT1	DYRK2	Monocytes	Zeller T, PLoS One 2010 [89]	3.37E-06
rs710011	14	59183275	DACT1	FUSIP1	Monocytes	Zeller T, PLoS One 2010 [89]	4.94E-07
rs710011	14	59183275	DACT1	NFIC	Monocytes	Zeller T, PLoS One 2010 [89]	6.60E-06
rs710011	14	59183275	DACT1	OPA3	Monocytes	Zeller T, PLoS One 2010 [89]	6.58E-06
rs710011	14	59183275	DACT1	PPP2R5E	Monocytes	Zeller T, PLoS One 2010 [89]	5.80E-06
rs710011	14	59183275	DACT1	UPF2	Monocytes	Zeller T, PLoS One 2010 [89]	7.98E-06
rs710011	14	59183275	DACT1	ZNF281	Monocytes	Zeller T, PLoS One 2010 [89]	2.98E-06

* Invasive breast carcinoma; † Whole peripheral blood cells; ‡ SNPs with MAF > 5%

We did not observe FOXF2 variants to act as eQTLs for nearby protein coding genes

Supplementary Table 17: mQTL search for variants chosen for follow-up using GENEVAR

SNP †	Chr	Position	Closest Gene	CpG probeID	Probe position *	CpG probe start	Distance (SNP-CpG probe)	P-value
rs12152354	3	105045025	ALCAM	cg03376719	ALCAM	105086940	41915	2.22E-26
rs12152354	3	105045025	ALCAM	cg03416645	ALCAM	105087206	42181	1.72E-22
rs12152354	3	105045025	ALCAM	cg05645404	ALCAM	105087242	42217	1.47E-20
rs12152354	3	105045025	ALCAM	cg15054274	3q13.11	105072683	27658	1.54E-08
rs12152354	3	105045025	ALCAM	cg23058405	3q13.11	105072537	27512	1.77E-12
rs7633149	3	105045248	ALCAM	cg03376719	ALCAM	105086940	41692	2.44E-26
rs7633149	3	105045248	ALCAM	cg03416645	ALCAM	105087206	41958	1.49E-22
rs7633149	3	105045248	ALCAM	cg05645404	ALCAM	105087242	41994	1.10E-20
rs7633149	3	105045248	ALCAM	cg15054274	3q13.11	105072683	27435	1.49E-08
rs7633149	3	105045248	ALCAM	cg23058405	3q13.11	105072537	27289	1.82E-12
rs17042059	4	111641186	PITX2	cg03587884	4q25	111642146	960	4.78E-13
rs4529121	4	111645555	PITX2	cg03587884	4q25	111642146	3409	5.35E-13
rs4543199	4	111648140	PITX2	cg03587884	4q25	111642146	5994	5.52E-13
rs12647316	4	111649251	PITX2	cg03587884	4q25	111642146	7105	5.49E-13
rs10019689	4	111649869	PITX2	cg03587884	4q25	111642146	7723	3.76E-13
rs4626276	4	111649989	PITX2	cg03587884	4q25	111642146	7843	2.66E-13
rs17042076	4	111652338	PITX2	cg03587884	4q25	111642146	10192	3.83E-13
rs11098089	4	111654226	PITX2	cg03587884	4q25	111642146	12080	5.47E-13
rs17042088	4	111654814	PITX2	cg03587884	4q25	111642146	12668	5.46E-13
rs11930528	4	111660194	PITX2	cg03587884	4q25	111642146	18048	2.95E-13
rs17042098	4	111664158	PITX2	cg03587884	4q25	111642146	22012	5.03E-13
rs17042121	4	111677101	PITX2	cg03587884	4q25	111642146	34955	7.18E-13
rs10516563	4	111677722	PITX2	cg03587884	4q25	111642146	35576	6.93E-13
rs4605724	4	111685081	PITX2	cg03587884	4q25	111642146	42935	9.01E-13
rs2350269	4	111687124	PITX2	cg03587884	4q25	111642146	44978	9.81E-13
rs6533527	4	111687514	PITX2	cg03587884	4q25	111642146	45368	3.20E-12
rs17042144	4	111689666	PITX2	cg03587884	4q25	111642146	47520	2.06E-12
rs1906617	4	111695814	PITX2	cg03587884	4q25	111642146	53668	4.79E-12
rs12646447	4	111699326	PITX2	cg03587884	4q25	111642146	57180	6.95E-12
rs12646754	4	111703572	PITX2	cg03587884	4q25	111642146	61426	7.77E-12
rs2129981	4	111704199	PITX2	cg03587884	4q25	111642146	62053	8.97E-12
rs12639654	4	111705295	PITX2	cg03587884	4q25	111642146	63149	1.05E-11
rs6817105	4	111705768	PITX2	cg03587884	4q25	111642146	63622	9.84E-12
rs17042171	4	111708287	PITX2	cg03587884	4q25	111642146	66141	1.10E-11
rs1906591	4	111708889	PITX2	cg03587884	4q25	111642146	66743	1.11E-11
rs1906592	4	111709004	PITX2	cg03587884	4q25	111642146	66858	1.12E-11
rs2200732	4	111710042	PITX2	cg03587884	4q25	111642146	67896	1.18E-11
rs2200733	4	111710169	PITX2	cg03587884	4q25	111642146	68023	1.20E-11
rs4611994	4	111711041	PITX2	cg03587884	4q25	111642146	68895	1.18E-11
rs4540107	4	111711102	PITX2	cg03587884	4q25	111642146	68956	1.18E-11
rs1906593	4	111711922	PITX2	cg03587884	4q25	111642146	69776	1.15E-11
rs1906596	4	111712236	PITX2	cg03587884	4q25	111642146	70090	1.81E-11
rs2220427	4	111714889	PITX2	cg03587884	4q25	111642146	72743	1.20E-11
rs2913884	5	151277143	GLRA1	cg01997606	5q33.1	151308141	30998	5.72E-10
rs2913884	5	151277143	GLRA1	cg05422647	GLRA1	151304811	27668	8.15E-05
rs2913884	5	151277143	GLRA1	cg07012926	GLRA1	151304488	27345	6.89E-06
rs2913884	5	151277143	GLRA1	cg08316825	GLRA1	151304547	27404	1.17E-06
rs2913884	5	151277143	GLRA1	cg14319409	GLRA1	151304409	27266	6.99E-39
rs2913884	5	151277143	GLRA1	cg20702419	GLRA1	151304770	27627	2.80E-07
rs1428155	5	151281633	GLRA1	cg01997606	5q33.1	151308141	26508	3.19E-10
rs1428155	5	151281633	GLRA1	cg05422647	GLRA1	151304811	23178	8.39E-05
rs1428155	5	151281633	GLRA1	cg07012926	GLRA1	151304488	22855	5.67E-06
rs1428155	5	151281633	GLRA1	cg08316825	GLRA1	151304547	22914	8.02E-07
rs1428155	5	151281633	GLRA1	cg14319409	GLRA1	151304409	22776	3.41E-39

rs1428155	5	151281633	GLRA1	cg20702419	GLRA1	151304770	23137	2.70E-07
rs10961053	9	13444573	FLJ41200	cg13593562	9p23	13432483	12090	4.88E-05
rs10491751	9	13444932	FLJ41200	cg13593562	9p23	13432483	12449	4.55E-05
rs11788316	9	13445687	FLJ41200	cg13593562	9p23	13432483	13204	8.02E-05
rs1243181	10	21916468	MLLT10	cg04231319	MLLT10	21824447	92021	2.88E-06
rs2393938	10	44063812	ZNF239	cg04825431	ZNF239	44063899	87	1.77E-07
rs2393938	10	44063812	ZNF239	cg05050592	ZNF239	44069309	5497	1.91E-04
rs2393938	10	44063812	ZNF239	cg07541020	ZNF239	44068714	4902	4.96E-14
rs710011	14	59183275	DACT1	cg02899011	14q23.1	59223051	39776	1.11E-16
rs710011	14	59183275	DACT1	cg13972423	14q23.1	59183596	321	2.37E-15
rs856288	14	59184103	DACT1	cg02899011	14q23.1	59223051	38948	6.49E-17
rs856288	14	59184103	DACT1	cg13972423	14q23.1	59183596	507	2.16E-15
rs710009	14	59184500	DACT1	cg02899011	14q23.1	59223051	38551	5.39E-17
rs710009	14	59184500	DACT1	cg13972423	14q23.1	59183596	904	2.65E-15
rs710008	14	59184596	DACT1	cg02899011	14q23.1	59223051	38455	4.90E-17
rs710008	14	59184596	DACT1	cg13972423	14q23.1	59183596	1000	2.44E-15

* Position of CpG probe, Intergenic probes are expressed with corresponding chromosome band; † SNPs with MAF > 5%

Supplementary Table 18: White matter hyperintensity distribution in patients with FOXC1 and FOXC1/FOXF2 deletions

Patient Age	Deletion	WMH Volume (cm^3)
15	*FOXC1*	0.08
17	*FOXC1*	0.07
2	*FOXC1/FOXF2*	2.05
32	*FOXC1/FOXF2*	1.23

WMH: White matter hyperintensities

Supplementary Table 19: Association of published risk loci for ischemic stroke or intracerebral hemorrhage (from cross-sectional case-control studies) with incident stroke in the population based GWAS (discovery stage)

			Original Study					CHARGE AS (N=4348/84961)		IS (N=3100/84961)		CE-IS (N=602/84961)		non-CE-IS (N=1770/84961)		ICH (N=277/42840)	
SNP	**Chr**	**Gene**	**Phenotype**	**RA**	**N***	**OR**	**P**	**HR**	**P**	**HR**	**P**	**HR**	**P**	**HR**	**P**	**HR**	**P**
Published risk loci for ischemic stroke																	
rs6843082	4	*PITX2* [53]	CE-IS	G	2365/12389	1.36	7.80E-16	**1.07**	**0.010**	1.06	0.072	**1.30**	**7.82E-5**	0.96	0.39	**1.35**	**0.0031**
rs556621	6	*CDC5L* [72]	LAA-IS	A	400/1172	1.62	3.92E-8	0.97	0.22	0.97	0.36	1.08	0.19	0.96	0.25	0.90	0.31
rs2107595	7	*HDAC9* [53]	LAA-IS	A	2167/12389	1.39	2.03E-16	**1.08**	**0.0090**	**1.12**	**0.0016**	1.11	0.19	**1.15**	**0.0024**	**1.31**	**0.034**
rs2383207	9	*CDKN2B-AS1* [53]	LAA-IS	G	2167/12389	1.15	3.30E-5	**1.05**	**0.022**	**1.06**	**0.019**	**1.12**	**0.036**	1.01	0.72	1.07	0.40
rs505922	9	*ABO* [92]	LAA-IS	C	2167/12389	1.13	<1.00E-4	1.02	0.47	**1.06**	**0.035**	**1.13**	**0.026**	1.03	0.41	1.05	0.57
			CE-IS	C	2365/12389	1.23	<1.00E-4										
rs660599	11	*MMP12* [73]	LAA-IS	A	3197/62912	1.18	2.60E-8	**1.06**	**0.037**	**1.09**	**0.0082**	1.11	0.16	**1.09**	**0.042**	1.03	0.82
rs10744777	12	*ALDH2* [75 †]	IS	T	17970/70764	1.1	7.12E-11	1.02	0.48	1.06	**0.047**	1.06	0.29	1.03	0.50	1.01	0.95
rs879324	16	*ZFHX3* [53]	CE-IS	A	2365/12389	1.25	2.28E-8	**1.09**	**0.0022**	**1.08**	**0.030**	1.15	0.076	1.00	0.96	1.11	0.40
Published risk loci for intracerebral hemorrhage																	
rs2984613	1	*PMF1-BGLAP* [76]	non-lobar ICH	C	881/1481	1.44	1.60E-8	**1.08**	**0.0011**	**1.10**	**0.00064**	1.08	0.15	**1.10**	**0.011**	1.00	0.98
rs11179580	12	*TRHDE* [71]	lobar ICH	C	664/1481	1.56	7.00E-8	1.03	0.24	1.04	0.23	1.08	0.29	1.04	0.34	1.00	0.99

*N cases / N controls; † this study used an age-informed analysis; AS: All Stroke; IS: Ischemic Stroke; CE-IS: Cardio-Embolic Ischemic Stroke; non-CE IS: non Cardio-Embolic Ischemic Stroke; ICH: Intra-Cerebral Hemorrhage

A genetic risk score combining all 10 established stroke risk variants (for IS and ICH) was associated with incident all stroke (HR=1.04[1.03-1.06], $p=7.44\times10^{-8}$) and IS (HR=1.06[1.04-1.08], $p=2.68\times10^{-10}$)

Supplementary Table 20: Association of chr6p25 risk variants with intracerebral hemorrhage

SNP	Effect Allele	CHARGE (N=262/40498)		ISGC (N=1576/1303)		Meta-analysis (CHARGE +ISGC)		
		HR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P	Heterogeneity-P
rs12197982	G	1.06 [0.85 - 1.31]	0.60	1.05 [0.92 - 1.20]	0.46	1.05 [0.94 - 1.18]	0.37	0.95
rs12198803	G	1.05 [0.85 - 1.30]	0.66	1.04 [0.92 - 1.19]	0.51	1.04 [0.94 - 1.16]	0.45	0.94
rs12200309	G	1.05 [0.84 - 1.30]	0.68	1.04 [0.92 - 1.19]	0.52	1.04 [0.94 - 1.16]	0.46	0.97
rs12204590	A	1.06 [0.86 - 1.31]	0.59	1.05 [0.92 - 1.19]	0.46	1.05 [0.94 - 1.18]	0.37	0.93
rs12211303	C	1.06 [0.85 - 1.31]	0.61	1.05 [0.92 - 1.20]	0.46	1.05 [0.94 - 1.18]	0.38	0.96
rs12212982	A	1.05 [0.85 - 1.31]	0.63	1.05 [0.92 - 1.20]	0.46	1.05 [0.94 - 1.18]	0.38	0.98

HR: Hazards ratio; OR: Odds ratio; CI: Confidence interval; Heterogeneity-P is for difference in effect size across studies as measured by the Cochran's Q test

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Discovery genetic association studies

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Follow-up genetic association studies

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https://www.whi.org/researchers/_layouts/15/WopiFrame.aspx?sourcedoc=/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf&action=default.

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eQTL analysis in dorsolateral prefrontal cortex of post-mortem tissue

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