Pathogenic Ischemic Stroke Phenotypes in the NINDS-Stroke Genetics Network

Hakan Ay, MD; Ethem Murat Arsava, MD; Gunnar Andsberg, MD; Thomas Benner, PhD; Robert D. Brown Jr, MD; Sherita N. Chapman, MD; John W. Cole, MD, MS; Hossein Delavaran, MD; Martin Dichgans, MD; Gunnar Engström, MD; Eva Giralt-Steinhauer, MD; Raji P. Grewal, MD; Katrina Gwinn, MD; Christina Jern, MD; Jordi Jimenez-Conde, MD; Katarina Jood, MD; Michael Katsnelson, MD; Brett Kissela, MD; Steven J. Kittner, MD; Dawn O. Kleindorfer, MD; Daniel L. Labovitz, MD; Silvia Lanfranconi, MD; Jin-Moo Lee, MD; Manuel Lehnh, BSc; Robin Lemmens, MD; Chris Levi, MD; Linxin Li, PhD; Arne Lindgren, MD; Hugh S. Markus, DM; Patrick F. Mc Ardle, PhD; Olle Melander, MD; Bo Norrving, MD; Leema Reddy Peddaredy gari, MD; Annie Pedersén, MD; Joanna Pera, MD; Kristina Rannikmäe, MD; Kathryn M. Rexrode, MD; David Rhodes, MPH; Stephen S. Rich, PhD; Jaume Roquer, MD, PhD; Jonathan Rosand, MD, MSc; Peter M. Rothwell, MD; Tatjana Rundek, MD, PhD; Ralph L. Sacco, MD, MS; Reinhold Schmidt, MD; Markus Schürks, MD; Stephan Seiler, MD; Pankaj Sharma, MD; Agnieszka Slowik, MD; Cathie Sudlow, MD; Vincent Thijs, MD; Rebecca Woodfield, MD; Bradford B. Worrall, MD, MSc*; James F. Meschia, MD*

Background and Purpose—NINDS (National Institute of Neurological Disorders and Stroke)-SiGN (Stroke Genetics Network) is an international consortium of ischemic stroke studies that aims to generate high-quality phenotype data to identify the genetic basis of pathogenic stroke subtypes. This analysis characterizes the etiopathogenetic basis of ischemic stroke and reliability of stroke classification in the consortium.

Received September 5, 2014; final revision received October 2, 2014; accepted October 3, 2014.
From the Department of Radiology, AA Martinos Center for Biomedical Imaging (H.A., E.M.A., T.B.), Stroke Service, Department of Neurology (H.A., J.R.), and Center for Human Genetic Research (J.R.), Massachusetts General Hospital, Harvard Medical School, Boston; Department of Neurology and Rehabilitation Medicine, Skåne University Hospital, Lund, Sweden (G.A., H.D., A.L., O.M., B.N.); Department of Neurology, Mayo Clinic Rochester, MN (R.D.B.); Department of Neurology (S.N.C., B.B.W.); Department of Neurology, Imperial College London, United Kingdom (P.S.); and Department of Neurology, Mayo Clinic Jacksonville, FL (J.F.M.).

Clinical Neurosciences, University of Cambridge, United Kingdom (H.S.M.); Department of Neurology, Jagiellonian University, Medical College, Krakow, Poland (A.P.); Department of Neurology, Bundaberg Hospital, Bundaberg, Australia (C.L.); Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford University, United Kingdom (J.R.C., S.J.K.); Department of Clinical Science, Lund University, Malmö, Sweden (G.E., B.N.); Department of Neurology, Neurovascular Surgery Group, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (K.G.); Institute of Biomedicine (C.J., A.P.) and Institute of Neuroscience and Physiology (K.J.), Sahlgrenska Academy at University of Gothenburg, Sweden; Department of Neurology, University of Miami Miller School of Medicine, FL (M.K., TR., R.L.S.); Department of Neurology, University of Cincinnati College of Medicine, OH (B.K., D.O.K.); Department of Neurology, Stern Stroke Center, Albert Einstein College of Medicine, Bronx, NY (D.L.L.); Department of Neuroscience and Sensory Organs, Policlinico Hospital Foundation IRCCS Cà Gandra, Milan, Italy (S.L.); Department of Neurology, Washington University, St. Louis, MO (J.-M.L.); Department of Neurology, University Hospitals Leuven, Belgium (R.L., V.T.); Department of Neurosciences, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), KU Leuven-University of Leuven, Belgium (R.L., V.T.); VIB, Vesalius Research Center, Laboratory of Neurobiology, Leuven, Belgium (R.L., V.T.); Department of Neurology, John Hunter Hospital, The University of Newcastle, New South Wales, Australia (C.L.); Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford University, United Kingdom (L.L., P.M.R.); Department of Clinical Neurosciences, University of Cambridge, United Kingdom (H.S.M.); Department of Neurology, Jagiellonian University, Medical College, Krakow, Poland (J.P., A.S.); Centre for Clinical Brain Sciences, University of Edinburgh, United Kingdom (K.R., C.S., R.W.); Division of Preventive Medicine, Department of Medicine, Brigham and Women’s Hospital, Boston, MA (K.M.R.); School of Public Health, University of Alabama, Birmingham (D.R.); Department of Neurology, Medical University Graz, Austria (R.S., S.S.); Department of Neurology, University Hospital Essen, Essen, Germany (M.S.); Cerebrovascular Research Unit, Department of Medicine, Imperial College London, United Kingdom (P.S.); and Department of Neurology, Mayo Clinic Jacksonville, FL (J.F.M.).

Guest Editor for this article was Anthony J. Furlan, MD.

*Drss Worrall and Meschia are joint co-senior authors and co-chairs of the SiGN Phenotype Committee.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/supp/dji:10.1161/STROKEAHA.114.007362/DC1.

Correspondence to Hakan Ay, MD, AA Martinos Center for Biomedical Imaging and Stroke Service, Departments of Neurology and Radiology, Massachusetts General Hospital, Harvard Medical School, 149 13th St, Room 2301, Charlestown, MA 02129. E-mail hay@mgh.harvard.edu.

© 2014 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.114.007362

3589
**Methods**—Fifty-two trained and certified adjudicators determined both phenotypic (abnormal test findings categorized in major pathogenic groups without weighting toward the most likely cause) and causative ischemic stroke subtypes in 16954 subjects with imaging-confirmed ischemic stroke from 12 US studies and 11 studies from 8 European countries using the web-based Causative Classification of Stroke System. Classification reliability was assessed with blinded readjudication of 1509 randomly selected cases.

**Results**—The distribution of pathogenic categories varied by study, age, sex, and race (P<0.001 for each). Overall, only 40% to 54% of cases with a given major ischemic stroke pathogenesis (phenotypic subtype) were classified into the same final causative category with high confidence. There was good agreement for both causative (κ 0.72; 95% confidence interval, 0.69–0.75) and phenotypic classifications (κ 0.73; 95% confidence interval, 0.70–0.75).

**Conclusions**—This study demonstrates that pathogenic subtypes can be determined with good reliability in studies that include investigators with different expertise and background, institutions with different stroke evaluation protocols and geographic location, and patient populations with different epidemiological characteristics. The discordance between phenotypic and causative stroke subtypes highlights the fact that the presence of an abnormality in a patient with stroke does not necessarily mean that it is the cause of stroke. *(Stroke. 2014;45:3589-3596.)*

Key Words: classification ■ pathogenesis ■ phenotype

Successful identification of genes that modify ischemic stroke risk relies on accurate delineation of pathogenic stroke phenotypes. Determination of pathogenic stroke subtypes requires integration of several clinical, diagnostic, and imaging features and, therefore, is inherently subject to variability. Reproducible data on frequency of pathogenic stroke subtypes based on large multicenter data sets using well-defined and evidence-based criteria do not exist. Published studies on pathogenic stroke subtypes are largely constrained by poor to moderate reliability of the classification system. suboptimal or uncertain diagnostic workup, small sample size, single center design, and use of stringent selection criteria.

This analysis sought to better understand the pathogenic basis of ischemic stroke. We prospectively identified pathogenic stroke subtypes using the rule- and evidence-based Causative Classification of Stroke (CCS) system within the context of the NINDS (National Institute of Neurological Disorders and Stroke)-Stroke Genetics Network (SiGN). CCS automatically provides both phenotypic and causative stroke subtypes in each case. The former is a summary of positive test findings, whereas the latter requires integration of clinical, laboratory, and imaging stroke features and diagnostic test results to identify a single most likely causative subtype for each case. Hence, they provide different information. Here, we report distribution characteristics of various CCS-defined ischemic stroke subtypes and inter-rater reliability of pathogenic subtype assignments in the SiGN data set.

### Methods

**Contributing Studies and Patient Population**

SiGN is a large international consortium of ischemic stroke studies aiming to generate high-quality phenotype data to assist in the identification of the genetic basis of ischemic stroke subtypes. This analysis included ischemic stroke cases from the initial 12 US and 11 European ischemic stroke studies in SiGN from 9 countries. Imaging confirmation of the absence of hemorrhagic stroke was required in each subject. Details about the individual contributing studies have published previously in a separate publication. Seventeen studies recruited consenting cases without using any selection criteria. In contrast, 6 studies were conducted in selected populations based on age, sex, and family history.

Recruitment to contributing studies occurred during a 23-year period between 1989 and 2012.

**Stroke Subtyping**

Pathogenic stroke classification in SiGN started in July 2010. The current study included 16954 cases for whom pathogenic subtype information was available in the SiGN database as of March 2014. SiGN used the web-based CCS system for stroke subtyping (available at https://ccs.mgh.harvard.edu/). The details of CCS were published elsewhere. For the purpose of SiGN, we customized CCS by generating a confidential, password-protected data collection platform. We also made a modification in the online CCS form by separating the single data entry field for small artery occlusion (SAO) in the original CCS into 2 separate data entry fields: one to indicate whether there is a typical lacunar infarct on neuroimaging and the second one to rule out whether there is an accompanying parent artery disease at the origin of the penetrating artery supplying the site of the lacunar infarct. Thus, it became possible to collect phenotypic data on lacunar infarcts for which vascular imaging for parent artery disease was not available. No modification was made in the decision-making code of the CCS; both customized and original CCS algorithms provided the same subtype for each given test condition.

We determined phenotypic subtypes in each subject. Phenotypic subtypes referred to abnormal test findings categorized in major pathogenic groups without weighting toward the most likely cause in the presence of multiple causes. There were 4 main phenotypic categories: large artery atherosclerosis (LAA), cardiac embolism (CE), lacunar infarction, and other uncommon causes. There were 4 possible states for LAA and CE (major, minor, absent, and incomplete evaluation), 3 for lacunar infarction (major, absent, and incomplete evaluation), and 2 for other uncommon causes (major and absent), giving rise to a total of 96 phenotypic categories. We collapsed these categories into the following 7 subtypes: LAA-major, CE-major, lacunar infarction-major, other-major, no major pathogenesis, multiple competing major pathogeneses, and incomplete investigation. We further collapsed the last 3 categories into undetermined category and generated a 5-subtype phenotypic categorization.

We also recorded causative subtypes in each case. In contrast to phenotypic subtypes, causative subtyping requires integration of multiple aspects of ischemic stroke evaluation in a probabilistic and objective manner. The causative subtype differs from the phenotypic subtype in certain occasions. For instance, in a patient with internal carotid artery stenosis, ipsilateral internal borderzone infarcts, and atrial fibrillation, the causative subtype is LAA, whereas the phenotypic subtype is multiple competing pathogeneses because of coexistence of LAA and CE. Major causative categories included LAA, CE, SAO, other uncommon causes, and undetermined causes. The undetermined group was further divided into 4 subcategories as...
cryptogenic embolism, cryptogenic-other, incomplete evaluation, and multiple competing causes (unclassified). We grouped cardiac pathologies with uncertain risk of stroke (minor sources) into the undetermined cryptogenic-other category. This allowed us to generate a more refined cardioembolic category (CE-major). Each causative category in CCS (except for undetermined category) was subdivided based on the weight of available data as evident, probable, or possible to identify the level of confidence in assigning a pathogenesis. Overall, CCS generated 17 causative subtypes.

CCS did not require a minimum level of investigations. In cases with missing tests, the system still assigned a subtype based on results of available tests but with a lower level of confidence. For instance, in a patient with typical lacunar infarct in the internal capsule and missing intracranial vascular imaging to rule out a parent artery disease, the level of confidence in attributing lacunar infarct to SAO was reduced from evident to possible. A subtype (both causative and phenotypic) was considered to be incomplete evaluation only when brain imaging, vascular imaging, or cardiac evaluation was not performed in the absence of an identified pathogenesis.

### Data Adjudication and Quality Control

A total of 52 adjudicators (13 stroke neurologists, 17 stroke fellows, 13 neurology residents, and 9 non-neurologists) performed stroke subtyping. A centralized Phenotype Committee of 4 expert stroke neurologists met weekly to monitor data quality and site performance. The same committee blindly readjudicated a randomly selected 10% of cases recruited from the US studies for quality control. Similarly, 10% of cases from European studies were readjudicated by blinded European investigators (n=20). Each adjudicator and readjudicator had to complete an interactive online training module. The Phenotype Committee members provided training to adjudicators/readjudicators on data entry, data submission, and archiving at scheduled study meetings and via webinars. Every investigator was required to pass an online certification examination available at the CCS website.

### Data Source

Study-specific case report forms and unabridged medical records served as data source for subtyping. Readjudicators used the same data source available to adjudicators to determine the CCS subtypes. Data sources varied in length and detail among the study sites. Subtype assignments were done based on data available at the time of discharge in the majority. Prolonged ambulatory cardiac monitoring was obtained after discharge in 14% of the subjects. In such cases, we used postdischarge cardiac monitoring findings for stroke subtyping. All data entered into CCS and the system output were saved in a confidential SIGN database. In addition to subtype-related data, each study site provided baseline variables such as age, sex, race, and vascular risk factors, using a structured data collection form.

### Statistics

Our primary objective was to determine the distribution of CCS subtypes within the SIGN cohort. We also determined pathogenic subtype distribution in a subset with complete diagnostic investigation. We defined complete investigation as the presence of brain imaging, intracranial and extracranial vascular imaging, and cardiac evaluation with echocardiography if ECG and clinical assessment did not reveal a source. We assessed the heterogeneity among centers in utilization of diagnostic tests using the \( \chi^2 \) test. We used \( \chi^2 \) test and Student \( t \) test to evaluate differences between cohorts with and without complete investigation for categorical and continuous variables, respectively. We assessed the correlation between causative and phenotypic subtypes by calculating how often CCS classified a given major abnormal evaluation finding (phenotypic subtype) as the causative stroke mechanism (causative subtype). We performed multinomial logistic regression to evaluate associations between causative CCS subtypes and age, sex, and race. In regression models, undetermined category served as the reference. We assessed the concordance between paired ratings by adjudicators and readjudicators by calculating crude agreement rates and unweighted \( \chi^2 \) values for both 5-subtype causative and phenotypic classification. We expressed associations as odds ratios and 95% confidence intervals (CIs). We considered \( P \) values <0.05 as statistically significant.

### Results

#### Stroke Subtypes

Figure 1 shows the distribution of phenotypic and causative subtypes. Compared with the overall population, subtype distribution differed in the cohorts with complete investigation (Figure 1; \( P<0.001 \)) and after exclusion of the 6 studies that used selection rules (Figure 1 in the online-only Data Supplement; \( P<0.001 \)).

Vascular investigations revealed an atherosclerotic lesion causing ≥50% stenosis (LAA-major phenotype) in 3392 of the 16954 cases (20%); among these, 2093 (62%) had extracranial stenosis, 962 (28%) had intracranial stenosis, and 337 (10%) had both extra- and intracranial stenoses. LAA-major was an isolated finding in 2536 (75%); in the remaining 856 (25%), there was another major pathogenesis such as a major cardioembolic source. Diagnostic tests for other pathogeneses were missing in 972 (29%). Overall, 1719 (51%) cases with a major LAA had either a missing test or another competing pathogenesis. The final causative subtype was LAA-evident in only 1815 (54%) cases (Figure 2A). The remaining individuals were either classified into the category of LAA but with a

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall Study Population (n=16954)</th>
<th>Complete Investigation (n=7748)</th>
<th>Incomplete Investigation (n=9206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>67.1 (14.9)</td>
<td>64.7 (15.7)</td>
<td>69.1 (13.9)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>48.8</td>
<td>44.5</td>
<td>52.3</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>9.7</td>
<td>11.0</td>
<td>8.7</td>
</tr>
<tr>
<td>White</td>
<td>79.3</td>
<td>77.5</td>
<td>80.7</td>
</tr>
<tr>
<td>Other</td>
<td>11.0</td>
<td>11.5</td>
<td>10.6</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>67.8</td>
<td>66.0</td>
<td>69.3</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>25.0</td>
<td>25.7</td>
<td>24.4</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>21.4</td>
<td>23.2</td>
<td>19.9</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>22.9</td>
<td>21.3</td>
<td>24.3</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>24.1</td>
<td>24.4</td>
<td>23.8</td>
</tr>
</tbody>
</table>

Complete investigation is defined as the presence of brain imaging, cardiac evaluation with electrocardiography, echocardiography if other investigations did not reveal a source, and intracranial and extracranial vascular evaluation.
lower level of confidence (either probable or possible) or into another category.

There was a major cardiac source in 4496 of the 16 954 (27%) cases. Atrial fibrillation accounted for the largest proportion of the major cardiac source of embolism (3735; 83%). There was another competing major vascular or systemic abnormality in 816 (18%) cases. Diagnostic investigations were incomplete in 2229 (50%) cases. The final causative subtype was CE-evident in 992 (40%) cases with a typical lacunar infarct on neuroimaging (Figure 2C).

Diagnostic investigations revealed a major uncommon pathogenesis in 1109 (7%) cases. The most frequent uncommon pathogenesis was acute arterial dissection (397 cases, 36%). Overall, incomplete evaluation and completing major pathogenesis rate was 53% in this category. The final causative subtype was evident other uncommon causes in 526 (47%) patients with a major uncommon pathogenesis (Figure 2D).

The largest pathogenic category was undetermined pathogenesis (7272 cases; 43%). This category included 3947 (55%) with incomplete evaluation, 1333 (18%) with minor cardiac emboli sources, 655 (9%) with multiple competing pathogeneses, 1118 (15%) with cryptogenic-other, and 219 (3%) with cryptogenic embolism. Of note, there were a total of 3257 (19%) cases in the entire study cohort with multiple competing pathogeneses (major or minor). Nevertheless, the final causative subtype was unclassified in only 655 (4%), suggesting that the CCS algorithm was able to identify a probable pathogenesis in the vast majority of patients with overlapping pathogeneses.

There was a significant relationship between stroke subtypes and age, sex, and race (P<0.001 for each; Figure II in the online-only Data Supplement). The association was most obvious for age. Subjects ≥50 years were 4× more likely to have cardioembolic stroke and 6× less likely to have stroke because of other uncommon causes as compared with those <50 years. In a further analysis where age was classified by decades, we found a continuous increase in LAA and SAO with increasing age with peak values in the age ≥50 to 70 years (Figure 3). There was no such age peak in major CE; instead, the probability of major CE continuously increased by increasing age. In contrast, there was a steady decrease in cryptogenic and other uncommon strokes by increasing age.

Reliability

There were 1509 paired ratings by 52 adjudicators and 24 readjudicators. The crude agreement for 5-subtype causative system was 80% (Table I in the online-only Data Supplement). The corresponding κ value was 0.72 (95% CI, 0.69–0.75). The crude agreement rate for 5-subtype phenotypic system was 81% with a corresponding κ value of 0.73 (95% CI, 0.70–0.75; Table II in the online-only Data Supplement). Crude agreements rates for causative system varied between 65% and 99% across the study sites except for 1 site where the agreement rate was 40% (Figure III in the online-only Data Supplement). After excluding that one outlier, the κ value increased to 0.75 (95% CI, 0.72–0.77) for causative and 0.75 (95% CI, 0.72–0.78) for phenotypic classifications.

Discussion

This is a large study of systematic ischemic stroke subtyping using an evidence- and rule-based system. Because of its size, patterns of subtype distribution across age groups are more readily discernible. It is also the largest study of the inter-rater reliability of ischemic stroke subtyping published thus far, based on 1509 paired ratings by a total of 76 trained and certified adjudicators and readjudicators. There was simultaneous
assessment of phenotypic and causative subtypes allowing examination of subtype distribution and reliability separately for these 2 types of classification. Our finding of discordance between the causative and phenotypic classifications is expected and reflects the fact that the presence of a phenotypic characteristic in a given patient, such as a vascular or cardiac abnormality, does not necessarily mean that it is the cause of stroke in that patient.

The extent of diagnostic evaluation was heterogeneous for a variety of reasons. Some studies used single site recruitment where strokes were evaluated at tertiary medical centers by vascular neurologists with a highly consistent diagnostic approach, whereas other studies were regional or national in scope with strokes evaluated primarily at community hospitals by physicians with diverse backgrounds with a less consistent diagnostic approach. This variation in extent of diagnostic evaluation motivated us to provide data separately for the subset with complete vascular and cardiac investigations. The results in this subset are the highest quality data available in the literature on the distribution of stroke subtypes. Of note, the subset with complete investigations resembled the overall study population with respect to the majority of baseline characteristics, suggesting no substantial selection bias.

In the present study, inter-rater reliability was slightly lower (κ=0.72) than previously reported for CCS (κ≥0.80). Prior studies had smaller number of raters (n=2–20) and smaller number of cases (n=50). As the number of cases and the number of raters increase, the variance introduced to stroke classification also increases and hence the reliability decreases. In contrast to prior studies that used abstracted case summaries, reliability analysis in this study was based on reviews of unabstracted case report forms and patient charts. Differences in raters’ ability to pinpoint the medical record data that is critical for subtyping, ambiguities in the source data (for instance, inconsistencies in interpretation of test findings between physician notes), variance in raters’ interpretation of the diagnostic data, and lack of data or incomplete data.
Several limitations merit further discussion. We did not include a specific minimum standard for quality of source data used for phenotyping. The 23 studies included in this analysis represent a broad range of methodologies (hospital-based case-control, pedigree-based, observational cohorts, and population-based studies) and using a broad range of criteria for inclusion ranging from no restriction to targeted recruitment by age, sex, family history, etc. Source documents varied from secondary notes of test results to computerized data repositories where access to source data such as radiographic images was possible. This diversity strengthens the confidence in our findings by capturing the vagaries that may occur in the real world as opposed to the rigors of a structured clinical research setting. Moreover, CCS provides refined subtypes by integrating quality and completeness of source data into level of confidence for each subtype, minimizing the impact of diversity in source data on validity of classifications. Insufficient representation of certain racial and ethnic groups (for instance, Asian population) in SiGN may have caused underestimation of certain mechanisms such as intracranial atherosclerosis. Finally, because majority of studies were hospital-based, the study population was vulnerable to survival, severity, or consent bias in addition to the impact of specific inclusion and exclusion criteria.

A major strength of this study was systematic adjudication of stroke subtypes using a rule- and evidence-based system. CCS offers several advantages such as good to excellent reliability and web-based interface. In addition, CCS retains and standardizes individual data points such as atrial fibrillation or arterial dissection that underlie subtype classification. Furthermore, its ability to provide both phenotypic and causative subtypes would allow one to separately explore the genetic basis of the presence of a potential pathogenesis (phenotypic subtype) and the presence of a causative pathogenesis (causative subtype). A gene for LAA could be different from a gene that makes an atherosclerotic plaque rupture and cause

**Figure 2.** Correlation between causative and phenotypic subtypes. Segments in each circle indicate proportion of causative subtypes in each major phenotypic category (circles). CE indicates cardiac embolism; LAA, large artery atherosclerosis; LI, lacunar infarction; and SAO, small artery occlusion.

**Figure 3.** The relationship between age and causative stroke subtypes. CE indicates cardiac embolism; LAA, large artery atherosclerosis; and SAO, small artery occlusion.
stroke. The ability to study such differential genetic associations would facilitate our understanding of the pathophysiological basis of ischemic stroke.

Sources of Funding

The Stroke Genetics Network (SiGN) study was funded by a cooperative agreement grant from the National Institute of Neurological Disorders and Stroke (NINDS) U01 NS069208. The Base de Datos de Ictus del Hospital del Mar (BASICMAR) Genetic Study was supported by the Ministerio de Sanidad and Consumo de España, Instituto de Salud Carlos III (ISC III) with the grants: Registro BASICMAR Funding for Research in Health (PI051737); GWA Study of Leukoaraiosis (GWALA) project from Fondos de Investigación Sanitaria ISC III (P10/02064) and (P11/01238); and Fondos European Regional Development Fund (FEDER/ERDF) Red de Investigación Cardiovascular (RD12/0042/0200). Additional support was provided by the Fundació la Marató TV3 with the grant GOD’s project. Genestroke Consortium (76/C/2011) Recercaixa’13 (JJ086116). Assistance with data cleaning was provided by the Research in Cardiovascular and Inflammatory Diseases Program of Institute of Neurology at the Mar of Medicine, Investigations, Hospital del Mar, and, the Barcelona Biomedical Research Park. The BioRepository of DNA in Stroke (BRAIN5) was supported by the British Council (UKIERI), Henry Smith Charity, and the UK Stroke Research Network. Dr Sharma was supported by a Department of Health (United Kingdom) Senior Fellowship. Center for Inherited Disease Research (CIDR); genotyping services were provided by the Johns Hopkins University CIDR, which is fully funded through a federal contract from the National Institutes of Health (NIH) to the Johns Hopkins University (contract No. HHSN268200782096C). The Edinburgh Stroke Study was supported by the Wellcome Trust (clinician scientist award to Dr Sudlow) and the Binks Trust. Sample processing occurred in the Genetics Core Laboratory of the Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh. Much of the neuroimaging occurred in the Scottish Funding Council Brain Imaging Research Centre (www. sbirc.ed.ac.uk), Division of Clinical Neurosciences, University of Edinburgh, a core area of the Wellcome Trust Clinical Research Facility and part of the Scottish Imaging Network–A Platform for Scientific Excellence collaboration (www.sinapsc.ac.uk), funded by the Scottish Funding Council and the Chief Scientist Office. Genotyping was performed at the Wellcome Trust Sanger Institute in the United Kingdom and funded by the Wellcome Trust as part of the Wellcome Trust Case Control Consortium 2 project (085475/B/08/Z and 085475/Z/08/Z and WT084724/MA). The Massachusetts General Hospital Stroke Genetics Group was supported by the NIH Genes Affecting Stroke Risks and Outcomes Study grant K23 NS042720, the American Heart Association/Bugher Foundation Centers for Stroke Prevention Research 0775010N, and NINDS K23NS042695, R01NS059727, the Deane Institute for Integrative Research in Atrial Fibrillation and Stroke, and by the Keane Stroke Genetics Fund. Genotyping services were provided by the Broad Institute Center for Genotyping and Analysis, supported by grant U54 RR020278 from the National Center for Research Resources. The Greater Cincinnati/Northern Kentucky Stroke Study (GCNKS) was supported by the NIH (NS 030678). The Genetics of Early Onset Stroke (GEOS) Study was supported by the NIH Genes, Environment, and Health Initiative (GEI) grant U01 HG004436, as part of the Gene Environment Association Studies (GENEVA) consortium under GEI, with additional support provided by the Mid-Atlantic Nutrition and Obesity Research Center (P30 DK072488) and the Office of Research and Development, Medical Research Service, and the Baltimore Geriatrics Research, Education, and Clinical Center of the Department of Veterans Affairs. Genotyping services were provided by the Johns Hopkins University CIDR, which is fully funded through a federal contract from the NIH to the Johns Hopkins University (contract No. HHSN268200782096C). Assistance with data cleaning was provided by the GENEVA Coordinating Center (U01 HG 004446; PI Bruce S Weir). Study recruitment and assembly of data sets were supported by a Cooperative Agreement with the Division of Adult and Community Health, Centers for Disease Control and by grants from the NINDS and the NIH Office of Research on Women’s Health (R01 NS45012, U01 NS069208-01). GRAZ: The Austrian Stroke Prevention Study was supported by the Austrian Science Fund (FWF) grant Nos. P20545-P05 and P3180 and I1904-B13 (Era-Net). The Medical University of Graz supports the databases of the Stroke Study and of the Austrian Stroke Prevention Study. The Ischemic Stroke Genetics Study (ISGS) was supported by the NINDS (R01 NS42733; PI Dr Meschia). The Sibling with Ischemic Stroke Study (SWISS) was supported by the NINDS (R01 NS39987; PI Dr Meschia). Both SWISS and ISGS received additional support, in part, from the Intramural Research Program of the National Institute on Aging (Z01 AG000954-06; PI Andrew Singleton). SWISS and ISGS used stroke-free participants from the Baltimore Longitudinal Study of Aging (BLSA) as controls with the permission of Dr Luigi Ferrucci. The inclusion of BLSA samples was supported, in part, by the Intramural Research Program of the National Institute on Aging (Z01 AG000015-50), human subject protocol No. 2003-078. This study used the high-performance computational capabilities of the Biowulf Linux cluster at the NIH (http://biowulf.nih.gov). Phenotypic data and genetic specimens collection were funded by the grant from the Polish Ministry of Science and Higher Education for Leading National Research Centers (KNOW) and by the grant from the Medical College, Jagiellonian University in Krakow, Poland: KZDS/002848. The Leuven Stroke genetics study was supported by personal research funds from the Department of Neurology of the University Hospitals Leuven. Dr Thijss is supported by a Fundamental Clinical Research grant from FWO Flanders (Nos. 1.8.009.08.N.00 and 1800913N). Dr Lemmens is a Senior Clinical Investigator of FWO Flanders (FWO 1841913N) and is supported through Fonds Annie Planckaert-Dewaele. The Lund Stroke Register was supported by the Swedish Research Council (K2010- 61X-20378-04-3), The Swedish Heart-Lung Foundation, Region Skåne, the Freemasons Lodge of Instruction EOS in Lund, King Gustaf V’s and Queen Victoria’s Foundation, Lund University, and the Swedish Stroke Association. Biobank services were provided by Region Skåne Competence Centre (RSK, Malmö), Skåne University Hospital, Malmö, Sweden, and Biobank, Labmedicin Skåne, University and Regional Laboratories Region Skåne, Sweden. The Middlesex County Ischemic Stroke Study was supported by intramural funding from the New Jersey Neuroscience Institute/JFK Medical Center, Edison, NJ, and The Neurogenetics Foundation, Cranbury, NJ. The Northern Manhattan Study was supported by grants from the NINDS (R37 NS029993, R01 NS27517), The Cerebrovascular Biorepository at University of Miami/Jackson Memorial Hospital (The Miami Stroke Registry, Institutional Review Board No. 20070386) was supported by the Department of Neurology at University of Miami Miller School of Medicine and Evelyn McKnight Brain Institute. Biorepository and DNA extraction services were provided by the Hussmann Institute for Human Genomics at the Miller School of Medicine. The MUNCH study was supported by the Vascular Dementia Research Foundation and the Jackstaedt Stiftung. The Nurses’ Health Study work on stroke is supported by grants from the NIH, including HL088521 and HL34594 from the National Heart, Lung, and Blood Institute, as well as grants from the National Cancer Institute funding the questionnaire follow-up and blood collection: CA87969 and CA49449. The Oxford Vascular Study was supported by the Stroke Association, Medical Research Council, Wellcome Trust, Dunhll Medical Trust, NIH Research (NIHR), and NIHR Oxford Biomedical Research Centre based at Oxford University Hospitals NHS Trust and University of Oxford. Dr Rothwell is in receipt of Senior Investigator Awards from the Wellcome Trust and the NIHR. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) was supported by a cooperative agreement U01 NS041558 from the NINDS, NIH, and Department of Health and Human Service. A full
list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org. The Sahlgrenska Academy Study of Ischemic Stroke was supported by the Swedish Research Council (K2011-65X-14605-09-6), the Swedish Heart and Lung Foundation (2010256), the Swedish state/Sahlgrenska University Hospital (ALFGBG-148861), the Swedish Stroke Association, the Swedish Society of Medicine, and the Rune and Ulla Arnlov Foundation. SPS3: The Secondary Prevention of Small Subcortical Strokes trial was funded by the US National Institute of Health and Neurological Disorders and Stroke and Grant No. U01NS38529-04A1 (principal investigator, Oscar R. Benavente; coprincipal investigator, Robert G. Hart). The SPS3 Genetic Substudy (SPS3-GENES) was funded by R01 NS073346 (coprincipal investigators, Julie A. Johnson, Oscar R. Benavente, and Alan R. Shuldiner). ST. GEORGE’S: The principal funding for this study was provided by the Wellcome Trust, as part of the Wellcome Trust Case Control Consortium 2 project (085475/B/08/Z and 085475/Z/08/Z and W084724/MA). Collection of some of the St George’s stroke cohort was supported by project grant support from the Stroke Association. The Women’s Health Initiatives program was funded by the National Heart, Lung, and Blood Institute, NIH, US Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118 to 32119, 32122, 42107-26, 42129-32, and 44221. The Hormones and Biomarkers Predicting Stroke was supported by a grant from the National Institutes of Neurological Disorders and Stroke (R01NS042618). Washington University St. Louis Stroke Study (WUSTL): The collection, extraction of DNA from blood, and storage of specimens were supported by 2 NINDS NIH grants (PSO NS055977 and R01 NS8549101). Basic demographic and clinical characterization of stroke phenotype was prospectively collected in the Cognitive Rehabilitation and Recovery Group registry. The Recovery Genomics after Ischemic Stroke study was supported by a grant from the Barnes-Jewish Hospital Foundation.

Disclosures
Drs Brown, Kittner, Markus, Rexrode, Sacco, and Meschia received research grant from National Institutes of Health (NIH). Dr Engström has an employment position in Astra Zeneca R&D. Dr Rosand received research grant from NIH and has a consultant or advisory relationship with Boehringer Ingelheim. Dr Worrall received research grant from National Institutes of Health (NIH). Drs Brown, Kittner, Markus, Rexrode, Sacco, and Meschia received research grant from National Institutes of Health (NIH). The other authors report no conflicts.

References
Pathogenic Ischemic Stroke Phenotypes in the NINDS-Stroke Genetics Network


Stroke. 2014;45:3589-3596; originally published online November 6, 2014;
doi: 10.1161/STROKEAHA.114.007362
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/12/3589

An erratum has been published regarding this article. Please see the attached page for:
/content/46/1/e17.full.pdf

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
The version of the article, “Pathogenic Ischemic Stroke Phenotypes in the NINDS-Stroke Genetics Network” by Ay et al that published online ahead-of-print on November 6, 2014, and appears in the December issue (Stroke. 2014;45:3589–3596) contained incomplete author affiliations. The following affiliations have been added for authors Robin Lemmens and Vincent Thijs:

KU Leuven - University of Leuven, Department of Neurosciences, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), B-3000 Leuven, Belgium (R.L., V.T.).

VIB, Vesalius Research Center, Laboratory of Neurobiology, B-3000 Leuven, Belgium (R.L., V.T.).

This correction has been made to the online version of the article, which is available at http://stroke.ahajournals.org/content/45/12/3589.
**Supplemental Table I:** Causative subtypes by adjudicators and readjudicators. The numbers indicate number of stroke cases evaluated.

<table>
<thead>
<tr>
<th>Adjudicator</th>
<th>LAA</th>
<th>CE</th>
<th>SAO</th>
<th>Other</th>
<th>Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA</td>
<td>186</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>CE</td>
<td>4</td>
<td>296</td>
<td>7</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>SAO</td>
<td>6</td>
<td>8</td>
<td>125</td>
<td>3</td>
<td>62</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>56</td>
<td>10</td>
</tr>
<tr>
<td>Undetermined</td>
<td>23</td>
<td>36</td>
<td>40</td>
<td>13</td>
<td>546</td>
</tr>
</tbody>
</table>
**Supplemental Table II:** Phenotypic subtypes by adjudicators and readjudicators. The numbers indicate number of stroke cases evaluated.

<table>
<thead>
<tr>
<th>Adjudicator</th>
<th>LAA-major</th>
<th>CE-major</th>
<th>LI-major</th>
<th>Other-major</th>
<th>Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA-major</td>
<td>177</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>CE-major</td>
<td>4</td>
<td>307</td>
<td>4</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>LI-major</td>
<td>5</td>
<td>3</td>
<td>108</td>
<td>3</td>
<td>56</td>
</tr>
<tr>
<td>Other-major</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td>Undetermined</td>
<td>28</td>
<td>45</td>
<td>40</td>
<td>15</td>
<td>579</td>
</tr>
</tbody>
</table>
Supplemental figure I:
Supplemental Figure II:

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td></td>
</tr>
<tr>
<td>SAO</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&lt;50 yr</th>
<th>≥50 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td></td>
</tr>
<tr>
<td>SAO</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Caucasian</th>
<th>Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td></td>
</tr>
<tr>
<td>SAO</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>
Supplemental Figure III:
Supplemental Figure Legends:

**Supplemental figure I:** Distribution of causative and phenotypic stroke subtypes in studies with unselected populations: 1(a), phenotypic subtypes in the entire population; 1(b), phenotypic subtypes in the subset with complete vascular and cardiac investigation; 1(c), causative subtypes in the entire population; 1(d), causative subtypes in the subset with complete vascular and cardiac investigation. Und: undetermined

**Supplemental figure II:** Association between causative stroke subtypes and patient characteristics. Multinomial logistic regression was used to calculate odds ratios and 95% CI with the “Undetermined” group as the reference category.

**Supplemental figure III:** Crude agreement rates for causative classification between adjudicators and readjudications across the contributing studies.