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IL1RN VNTR Polymorphism in Ischemic Stroke:

Analysis in 3 Populations

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Abstract

Background and Purpose—Genetic factors influence risk for ischemic stroke and likely do so at multiple steps in the pathogenic process. Variants in genes related to inflammation contribute to risk of stroke. The purpose of this study was to confirm our earlier finding of an association between allele 2 of a variable number tandem repeat of the IL-1 receptor antagonist gene (*IL1RN*) and cerebrovascular disease.

Methods—An association study of the variable number tandem repeat genotype with ischemic stroke and stroke subtypes was performed on samples from a North American study of affected sibling pairs concordant for ischemic stroke and 2 North American cohorts of prospectively ascertained ischemic stroke cases and unrelated controls. DNA analysis was performed on cases and controls, stratified by race.

Results—After adjustment for age, sex, and stroke risk factors, the odds ratio for association of allele 2 and ischemic stroke was 2.80 (95% confidence interval, 1.29 to 6.11; P=0.03) for the white participants. The effect of allele 2 of *IL1RN* on stroke risk most closely fits a recessive genetic model (P=0.009). For the smaller sample of nonwhite participants, the results were not significant.

Conclusions—Allele 2 of *IL1RN*, present in nearly one-quarter of stroke patients, may contribute to genetic risk for ischemic stroke and confirm the previously identified association with cerebrovascular disease. These results are driven by the association in the white participants. Further exploration in a larger nonwhite sample is warranted.

Keywords

atherosclerosis; genetics; IL-1 receptor antagonist; ischemia; stroke

Genetic determinants of ischemic stroke risk have not yet been fully characterized. Ischemic stroke is undoubtedly an oligogenic (genes of large and small effect on risk) and multifactorial (genetic and environmental effects) disease. Genes coding for inflammatory mediators hold

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*Members of the SWISS, ISGS, and MSGD Study Groups are listed in the Appendix.

Disclosures
None.

promise as candidates for determining risk for both cerebrovascular atherosclerosis and ischemic stroke.[1,2]

IL-1 receptor antagonist (IL-1ra) is a counter-inflammatory cytokine implicated in a number of inflammatory diseases, including atherosclerosis. The IL-1ra gene (*IL1RN*) contains an 86-basepair variable number tandem repeat (VNTR) polymorphism in intron 2.[3] Allele 2 of that polymorphism (*IL1RN*2*) is the shortest of the 5 alleles, with only 2 repeats. Carriage of *IL1RN*2* is increased in carotid atherosclerosis,[4] and an *IL1RN* point mutation that is in strong linkage disequilibrium with this VNTR polymorphism has been reported in association with carotid wall thickness in a cohort of black patients.[5] Similar data support an association of *IL1RN*2* with coronary atherosclerosis.[6,7]

Animal and cell culture data suggest a biological effect of this genetic variant that is plausibly linked to vascular disease through unchecked inflammation. IL-1ra has been found to be downregulated in microarray analyses of endothelial cells under continuous shear stress, which mimics conditions in atherosclerosis-resistant long straight segments.[8] Human endothelial cells from homozygotes for *IL1RN*2* have 2- to 3-fold lower IL-1ra production than homozygotes for *IL1RN*1*, with heterozygotes producing an intermediate level.[9] Laboratory analyses of endothelial cells from individuals homozygous for allele 2 show lower IL-1ra production and a shorter time for cell division compared with those from allele 1 homozygotes. Treating with exogenous IL-1ra slows division to the wild-type rate.[10]

Knockout mice lacking IL-1ra develop lethal inflammatory vascular lesions; hemizygous mice develop fibrotic lesions at vascular branch points[11] and have excessive neointimal formation and inflammation after injury.[12] IL-1ra depletion increases foam cell burden, whereas overexpression suppresses atherosclerosis in susceptible mice.[13] Pigs subjected to vessel wall injury and then treated with exogenous IL-1ra have a marked reduction in neointimal formation compared with untreated animals.[14]

In an earlier case-control study, we identified an association between carotid atherosclerosis and allele 2, the short variant of the VNTR polymorphism of *IL1RN*.[4] In that study, carriers of allele 2 had >13-fold increase in the risk of carotid disease (adjusted odds ratio [OR], 13.78; 95% confidence interval [CI], 1.94 to 97.9) after adjusting for stroke risk factors; however, there was no significant association between *IL1RN*2* and cerebrovascular symptoms. In the current analysis, we sought to replicate and expand on these earlier findings by determining whether the *IL1RN* genotype is associated with ischemic stroke risk or symptomatic large vessel atherosclerosis using samples from 3 independent sources.

Materials and Methods

Two multicenter stroke genetics studies and a single-center stroke genetics database were the source of the DNA samples used in this study. Institutional review board approval was obtained at all participating institutions. In addition, the current analysis was reviewed and approved by the University of Virginia Human Investigations Committee. In all instances, subjects were enrolled after they or their surrogate provided written informed consent. The 2 larger studies used the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria for stroke subtyping, blinded to genotypic information.[15]

Ischemic Stroke Genetics Study

The Ischemic Stroke Genetics Study (ISGS), an ongoing 5-center, case-control study of first-ever ischemic stroke that began enrolling in December 2002, was designed to investigate candidate genes from the thrombosis and hemostasis cascade. Details of the protocol have been published elsewhere.[16] Potential case subjects are invited to participate in ISGS if they have

had a stroke radiologically confirmed to be ischemic within the preceding 30 days and have no history of ischemic stroke. Subjects with iatrogenic stroke and stroke caused by septic embolism, vasospasm, or certain monogenetic disorders are excluded. Controls are concurrently enrolled and individually matched for age, sex, and recruitment center. Once eligibility is confirmed, blood samples are obtained for DNA extraction, analysis, and storage.

Mayo Stroke Genetics Database

The Mayo Stroke Genetics Database (MSGD) was derived from 50 cases and 50 unrelated controls prospectively enrolled at Mayo Clinic and St. Luke's Hospital, Jacksonville, Florida, from November 15, 2000 to November 2, 2001. MSGD established the feasibility of ISGS. The inclusion and exclusion criteria for cases and controls matched those of ISGS with the exception that MSGD allowed recurrent stroke for entry. Age- and sex-matched controls were concurrently enrolled with cases at each site. The MSGD was developed with approval from the Mayo Foundation Institutional Review Board.

Siblings With Ischemic Stroke Study

The Siblings With Ischemic Stroke Study (SWISS), a multicenter family study, was designed to identify genetic risk factors through a genome-wide linkage screen in sibling pairs concordant and discordant for ischemic stroke. Details of the protocol have been previously published.[17] SWISS comprised 49 enrolling centers across the United States and Canada. Potential probands were invited to participate in SWISS if they had a stroke radiologically confirmed to be ischemic and reported having at least 1 living sibling with a history of ischemic stroke. Once concordance was verified by medical record review, blood samples were obtained from proband, concordant sibling, and, if applicable, discordant sibling, for DNA extraction, analysis, and storage.

Molecular Genetic Analyses

Immortalized lymphoblastoid cell line creation and DNA extraction were performed at Coriell Institute for Medical Research (Camden, New Jersey) using methods described elsewhere.[16,17] Briefly, DNA samples were delivered to the Laboratory of Neurogenetics of the National Institute on Aging, where all genetic analyses were performed. All samples were analyzed blinded to clinical status. Polymer-ase chain reaction amplification was performed on ≈25 ng of genomic DNA with 10 pmol of forward (ACTCATGGCCTTGTTCATT) and reverse (AAAACTAAAATCCCGAGGTC) primers, according to manufacturer's specifications (Thermo-Start PCR Master Mix, ABgene). Polymerase chain reaction products were run on a 2% agarose gel. Allele calling for the 86-basepair VNTR of *IL1RN* was based on sample migration on the gel versus a 100-basepair ladder. Data were dually and independently entered for quality assurance.

Quality control was performed on the entire batch of 886 samples, including samples from the 145 affected and unaffected siblings not used for the genetic analyses. Every plate had negative controls, and the call rate for negative controls was 100%. Replicates were both concurrent and sequential. The sample plates are designed with 148 samples, where multiple wells were filled with the same DNA as concurrent replicates. An additional 157 samples were randomly chosen for replicate analysis. A total of 389 samples (44% of total) were run more than once. Ninety-one percent (802/886) yielded usable results on the first run. The 84 samples that did not yield usable results on the first run were rerun a minimum of 2 times. The majority of these yielded replicated results immediately (2 additional runs). However, for a small number, including the 3 samples that never yielded usable results, we returned to the master plate and reamplified the DNA. A single pair of genotyping errors was found in the concurrent replicates. These were subsequently identified as a known mislabeling of wells on the master plate. All

results were consistent when the wells were correctly labeled. Only 3 samples failed to yield results; thus, genotyping success was 99.7%.

Statistical Methods

To describe the study group, categorical data were reported as frequencies and percentages, and continuous data were reported as means with standard deviations. A 2-sample test for binomial proportions between cases and controls was reported using a χ^2 test of independence. The Fisher exact test was used where appropriate. A 2-sample *t* test for independent samples was used to compare age among groups.

Although the distribution of genotypes is similar within all 3 studies, there are significant differences by race. Therefore, all analyses were performed stratified by race (white/nonwhite) to minimize population stratification.

Results were examined for Hardy-Weinberg equilibrium assumptions using the methods described by Wigginton et al.[18] Association analyses were performed to estimate ORs for the *IL1RN* VNTR polymorphism with case-control status. Genotype frequencies of *IL1RN* were compared by case-control and symptom status using contingency tables and logistic regression models. For the primary analysis, individuals with rare alleles (3, 4, and 5) were excluded from the analyses. Two secondary analyses were run including the rare alleles but pooling them with allele 1 and allele 2.

For the case-control data, a series of generalized estimating equations[19] was computed that included relevant covariates (age, sex, hypertension, atrial fibrillation, myocardial infarction, smoking status, diabetes mellitus, and family history of stroke). All modeling was performed in a hierarchical manner, with a baseline model that included only the single nucleotide polymorphism as the predictor. Additional models were tested with age and sex; further models were then tested by adding an individual stroke risk factor variable as a covariate. A final, fully saturated model that included stroke risk factors was also used. Probability values were computed using the 2 degree-of-freedom generalized test of association. A series of genetic models was tested (dominant, additive, recessive) for estimation of best fit for risk. Results were examined only when the generalized test reached statistical significance.

Differences in the distribution of *IL1RN* genotypes within cases according to TOAST subtype versus controls were determined using χ^2 tests. Comparisons were made for cases according to large vessel subtype for the index stroke and any evidence of large vessel cerebrovascular atherosclerotic disease, including history of carotid procedures.

Results

DNA from 328 cases and 213 controls from ISGS and 48 cases and 48 controls from MGSD were available; samples from 104 probands, 104 affected siblings, and 41 unaffected siblings from SWISS were available (Table 1). Among those used for the case-control analyses, 158 (21.3%) of 741 subjects were non-white. Allele frequencies for the 3 study groups were 72.5% (allele 1), 24.9% (allele 2), 2.4% (allele 3), 0.28% (allele 4), and 0% (allele 5), which are findings consistent with other published estimates in North American populations.[20] The allelic and genotypic frequencies overall and stratified by race (Table 2) were consistent with Hardy-Weinberg expectations (data not shown). Furthermore, the genotype distribution among the 3 groups (together and pairwise) in cases was not significantly different. This result was true also for the controls in ISGS and MSGD. Thus, all cases were pooled for the primary analysis, as were the 2 control groups.

As shown in Table 2, the *IL1RN* 1/1 genotype was present in 262 (54.8%) of 478 cases/probands and 149 (57.1%) of 261 controls. The *IL1RN* 1/2 genotype occurred in 151 (31.6%) of 478 cases/probands and 85 (32.6%) of 261 controls. The frequency of the *IL1RN* 2/2 genotype was 42 (8.8%) of 478 cases/probands and 13 (5.0%) of 261 controls. The frequency of *IL1RN* genotypes containing at least one of the rare alleles (3, 4, or 5) was 25 (5.2%) of 478 cases/probands and 14 (5.4%) of 261 controls. The allele frequency for *IL1RN*2* in the nonwhite participants was 9.6% (29/302), much lower than that observed in the white participants, which was 28.8% (317/1102).

Among white participants, the unadjusted association model demonstrated a nonsignificant increase in risk associated with the *IL1RN* 2/2 genotype (OR, 1.95; 95% CI, 0.98 to 3.90; *P*=0.16). Adjustment for age, sex, and stroke risk factors (hypertension, diabetes mellitus, atrial fibrillation, coronary disease, smoking status, and family history) strengthened the independent association of the *IL1RN* 2/2 genotype with ischemic stroke risk in white participants (OR, 2.8; *P*=0.03, for the fully adjusted general association; *P*=0.009 for a recessive mode of inheritance; Table 3).

For nonwhite participants, the genotype distributions were not significantly different between cases and controls in either the unadjusted model (OR, 1.50; 95% CI, 0.15 to 14.86; *P*=0.94) or the fully adjusted model (OR, 1.54; 95% CI, 0.10 to 24.67; *P*=0.95; Table 3).

Including rare alleles and their genotypes did alter the results. For the white participants, grouping the rare alleles with *IL1RN*1* increased the adjusted OR to 2.71 (95% CI, 1.23 to 5.98; *P*=0.04); the general association strongly supported the recessive mode of inheritance (*P*=0.01) of risk. When the rare alleles were grouped with *IL1RN*2*, the adjusted OR of 2.09 (95% CI, 1.02 to 4.28; *P*=0.13) was no longer significant for general association. The recessive model of inheritance remained marginally significant (*P*=0.05).

Prespecified subgroup analyses of the cases from ISGS and affected individuals from SWISS (MSGD did not include TOAST subtyping) were performed to compare genotypes and allele frequencies for those with large vessel atherosclerotic mechanism and controls among white and nonwhite participants. In the white cohort, the *IL1RN* 1/1 genotype was present in 38 (47.5%) of 80 subjects with large vessel atherosclerosis and 117 (47.4%) of 247 with other mechanisms. *IL1RN* 1/2 occurred in 31 (38.8%) of 80 with large vessel atherosclerosis and 91 (36.8%) of the 247 others. The frequency of *IL1RN* 2/2 was 8 (10.0%) of 80 with large vessel atherosclerosis, and 23 (9.3%) in the 247 others. The frequency of *IL1RN* genotypes containing at least one of the rare alleles (3, 4, or 5) was 3 (3.8%) of 80 with large vessel atherosclerosis, and 16 (6.5%) in the 247 others. Neither the genotype (*P*=0.43) nor the allele (*P*=0.27) frequencies for those with large vessel atherosclerotic mechanism differed from controls among white participants (Table 4). When individuals with a documented history of carotid atherosclerosis were included (identified by history of carotid endarterectomy, angioplasty, or stent), the genotype and allele distributions were similar. Carriage of *IL1RN*2* (having a genotype with at least 1 copy of allele 2) was observed in 39 of 80 subjects with large vessel atherosclerotic stroke compared with 90 of 208 controls (*P*=0.62).

In the nonwhite cohort, the *IL1RN* 1/1 genotype was present in 12 (92.3%) of 13 subjects with large vessel atherosclerosis, and 72 (78.3%) of 92 with other mechanisms. *IL1RN* 1/2 occurred in 1 (7.7%) of 13 with large vessel atherosclerosis, and 13 (14.1%) of the 92 others. The frequency of *IL1RN* 2/2 was 0 (0.0%) of 13 with large vessel atherosclerosis, and 3 (3.3%) in the 92 others. The frequency of *IL1RN* genotypes containing at least one of the rare alleles (3, 4, or 5) was 0 (0.0%) of 13 with large vessel atherosclerosis, and 4 (4.3%) in the 92 others. Among nonwhite participants, the genotype frequencies for those with large vessel atherosclerotic mechanism did not differ from controls (*P*=0.72). When individuals with a

documented history of carotid atherosclerosis were included (identified by history of carotid endarterectomy or angioplasty and stent), the genotype distributions were similar. Carriage of *IL1RN*2* was observed in 1 of 13 subjects with large vessel atherosclerotic stroke compared with 8 of 53 controls (P=0.99).

Discussion

Our results indicate that variation within the *IL1RN* locus, previously implicated as a genetic risk factor for carotid atherosclerosis[4] and symptomatic coronary disease,[6] is associated with ischemic stroke risk in our white participants. Homozygotes for allele 2, the short variant of the VNTR polymorphism, appear to be at greater risk for ischemic stroke. Because of small sample numbers, the data on our nonwhite participants are inconclusive. The current study did not demonstrate a specific association with large vessel atherosclerosis as the mechanism of stroke.

Homozygous carriers of *IL1RN*2* have been shown to have more prolonged and more intense inflammatory responses than those with other genotypes.[3] The complexity of cytokine interactions and genetic regulatory mechanisms make it likely that polymorphisms in other genes influence the overall inflammatory phenotype. Composite genotype profiles of the IL-1 gene family are associated with increased risk for either severe periodontal infection (profile 1) or angiographically confirmed coronary atherosclerosis (profile 2).[21] Similar interactions between the IL-1ra and IL-1α genotypes have been observed in ischemic stroke.[22] Variations in *IL1RN* and other related genes may have other effects such as lowering the threshold for susceptibility for ischemic stroke.[23] Chlamydial infection may confer greater risk for symptomatic atherosclerotic disease among carriers of *IL1RN* and *IL1B* gene mutations out of proportion to the risk conferred by either these mutations or the infection alone;[24] not all data support this association.[25]

Our results contrast with those reported in an earlier Italian study that found a higher frequency of both carriage of the *IL1RN*1* allele and homozygosity for *IL1RN*1* among stroke survivors than in a control group.[26] However, the impact of survival bias must be considered. *IL1RN*2* is associated with increased susceptibility to cerebral ischemia,[23] which may impact stroke severity and survival. Furthermore, the impact of *IL1RN*2* in inflammatory response[3] may also affect stroke severity and survival.[27]

Our association study may have yielded false-positive results because of the stratification of the study groups. Racial and ethnic differences in IL-1 gene family genotype distributions are well-recognized.[3] We are reassured that our findings are not an artifact of this stratification, because a significant association remained for *IL1RN*2* homozygosity among white subjects in the race-stratified analysis. The failure to find a relationship in the nonwhite population likely reflects both a lack of statistical power to detect a difference and the difference in the allele frequencies noted. Furthermore, the nonwhite group is a heterogeneous mix of subjects. The differences observed in these racial categories should be viewed with caution. Further analyses in larger nonwhite and non-North American populations are warranted.

We found an association of *IL1RN*2* with ischemic stroke generally not with specific stroke subtypes. Our previous work demonstrated an association between carotid atherosclerosis but not symptomatic status.[4] There are several important differences between these 2 studies. The current study included 93 individuals (21.5%) with large vessel atherosclerosis as the putative mechanism of stroke among a total of 432 individuals with subtyping data with a corresponding reduction in power. Furthermore, we compared cases with and without large vessel atherosclerosis. An association of *IL1RN*2* with large vessel atherosclerosis may have been more difficult to detect in this case-only analysis. Similarly, the case-control analysis did not

identify subtype-specific associations. In this study, the control population was clinically free of stroke, whereas the earlier study used a stroke-free control group with ultrasound verification of disease-free status. Genetic variation at the *IL1RN* may play >1 role in the progression of cerebrovascular atherosclerosis to a symptomatic state.

Clearly, *IL1RN* has potential as a pharmacological target.[28] A phase 2 trial of recombinant human IL-1ra (rhIL-1ra) recently demonstrated IL-1ra is safe and well-tolerated in patients with acute stroke.[29] Furthermore, active treatment was associated with a less inflammatory serum profile. Exploratory analyses suggest improved outcome for those treated with rhIL-1ra. Unfortunately, the report does not include an analysis of outcome by *IL1RN* genotype. This kind of pharmacogenomic consideration is prudent given that carriage of *IL1RN*2* is associated with both increased risk of hemorrhage and better clinical outcome in other neurologic diseases.[30] Further research into this potential treatment is planned.

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Appendix

Siblings With Ischemic Stroke Study Centers and Investigators Listed by Proband Enrollment as of January 31, 2006

Study Centers

Mayo Clinic, Rochester, Minnesota (probands enrolled, 56): principal investigator (PI): Robert D. Brown, Jr, MD; coordinator: Colleen S. Albers, RN; subinvestigators (SI): George W. Petty, MD, Eelco F. M. Wijdicks, MD, Irene Meissner, MD, Bruce A. Evans, MD, Kelly D. Flemming, MD, Edward M. Manno, MD, Jimmy R. Fulgham, MD, David O. Wiebers, MD.

University of Cincinnati, Cincinnati, Ohio (43): PI: Brett Kissela, MD; coordinator: Kathleen Alwell, RN; SI: Joseph Broderick, MD, Daniel Woo, MD, Daniel Kanter, MD, Dawn Kleindorfer, Alexander Schneider, MD, Matthew Flaherty, MD, Pooja Khatri, MD, Brian A. Stettler, MD.

University of Virginia, Charlottesville, Virginia (43): PI: Bradford Worrall, MD, MSc; coordinator: Helen Roehl; SI: E. Clarke Haley, Jr, MD, Karen Johnston, MD, MSc, Jaclyn van Wingerden.

University of Florida/Shands Jacksonville, Jacksonville, Florida (42): PI: Scott Silliman, MD; coordinators: Barbara Quinn, RN, Cicely Bryant.

Mayo Clinic, Jacksonville, Florida (42): PI: Thomas G. Brott, MD; coordinators: Dale M. Gamble, Alexa N. Richie; SI: James F. Meschia, MD, Frank A. Rubino, MD, Benjamin H. Eidelman, MD.

Mercy Ruan Neurology Clinic and Clinical Research Center, Des Moines, Iowa (34): PI: Michael Jacoby, MD; coordinator: Judi Greene, RN; SI: Bruce Hughes, MD, Randall Hamilton, MD, Paul Babikian, MD, Mark Puricelli, DO.

Neurological Associates, Inc, Richmond, Virginia (31): PI: Francis McGee, Jr, MD; coordinator: Janet McGee, CCRC; SI: Stephen Thurston, MD, Thomas Smith, MD, Robert White, MD, Philip Davenport, MD, John Brush, MD, Susanna Mathe, MD, Robert Cohen, MD, J. Kim Harris, MD, John O'Bannon III, MD, John Blevins, MD, John Wittman, MD, Michael Mareska, MD, Daniel Hardy, MD.

Mercy General Hospital, Sacramento, California (19): PI: Paul Akins, MD, PhD; coordinators: Deidre Wentworth, RN, Laura Newman, BSN, RN.

Maine Line Health—Stroke Program, Bryn Mawr, Pennsylvania (18): PI: Gary Friday, MD; coordinator: Angela Whittington-Smith, RN.

Centre Hospitalier Affilie Universitaire de Quebec, Quebec City, Province of Quebec (14): PI: Ariane Mackey, MD; coordinators: Annette Hache, RN, Sophie Dube, RN; SI: Steve Veireault, MD.

Luther-Midelfort Clinic, Eau Claire, Wisconsin (14): PI: Felix Chukwudelunzu, MD; coordinator: Karen Snobl, RN; SI: James Bounds, MD, Rae Hanson, MD, David Nye, MD, Donn Dexter, MD.

Kaleida Stroke Center—Millard Fillmore Hospital, Buffalo, New York (14): PI: Richard Ferguson, MD; coordinator: Kathleen Wrest, MLS; SI: F. E. Munschauer, MD, E. Mark Hekler, MD.

University of Maryland, Baltimore, Maryland (14): PI: Steven Kittner, MD; coordinator: Mary J. Sparks; SI: John Cole, MD.

Maine Medical Center, Portland, Maine (12): PI: John Belden, MD; coordinator: Diane Diconzo-Fanning, RN; SI: Paul Muscat, MD.

University of Pennsylvania Medical Center, Philadelphia, Pennsylvania (12): PI: Scott Kasner, MD; coordinator: Sue Heppler; SI: David S. Liebeskind, MD, Brett L. Cucchiara, MD, Michael L. McGarvey, MD, Steven R. Messe, MD, Robert A. Taylor, MD.

Ohio State University, Columbus, Ohio (12): PI: Andrew Slivka, MD; coordinator: Peggy Notestine, CCRC; SI: Yousef Mohammad, MD.

Mayo Clinic, Scottsdale, Arizona (12): PI: David W. Dodick, MD; coordinators: Erica L. Boyd, RN, Rebecca J. Rush, RN, Gail R. LeBrun, RN, Nadine F. Lendzion, RN, Barbara B. Cleary, RN; SI: Bart M. Demaerschalk, MD.

Wake Forest University School of Medicine, Winston-Salem, North Carolina (11): PI: David Lefkowitz, MD; coordinators: Jean Satterfield, RN, Elizabeth Westerberg, CCRC; SI: Charles Tegeler IV, MD, Patrick Reynolds, MD.

Metro Health Medical Center, Cleveland, Ohio (11): PI: Joseph Hanna, MD; coordinators: Alice Liskay, RN, Joan Kappler, RN, Dana Simcox, RN; SI: Marc D. Winkelman, MD, Nimish Thakore, MD, DM.

University of South Alabama, Mobile, Alabama (11): PI: Richard Zweifler, MD; coordinator: Kelli Boots; SI: Ivan Lopez, MD, M. Asim Mahmood, MD.

Cleveland Clinic Florida, Weston, Florida (10): PI: Virgilio Salanga, MD; coordinator: Anupama Podichetty, MD; SI: Jose Alvarez, MD, Eduardo Locatelli, MD, Nestor Galvez-Jimenez, MD, Efrain Salgado, MD.

Stroke Prevention and Atherosclerosis Research Centre (SPARC), London, Ontario (10): PI: David Spence, MD; coordinator: Rose Freitas; SI: Claudio Munoz, MD.

Hospital Charles Le Moyne, Greenfield Park, Province of Quebec (10): PI: Leo Berger, MD; coordinators: Denise Racicot, Johanne Pontbriand.

University of Iowa Hospital, Iowa City, Iowa (9): PI: Patricia Davis, MD; coordinator: Jeri Sieren, RN; SI: Harold P. Adams, Jr, MD, Enrique C. Leira, MD.

University of Texas Southwestern Medical Center at Dallas, Dallas, Texas (9) PI: Mark Johnson, MD; coordinator: J. Greggory Wright, BS; SI: Dion Graybeal, MD.

Washington University School of Medicine, St. Louis, Missouri (8): PI: Jin-Moo Lee, MD, PhD; coordinator: Denise Shearrer, RMA, BS; SI: Abdullah Nassief, MD.

Helen Hayes Hospital, West Haverstraw, New York (8): PI: Laura Lennihan, MD; coordinator: Laura Tenteromano, RN.

Emory University School of Medicine, Atlanta, Georgia (7): PI: Barney Stern, MD; coordinator: Betty Jo Shipp, RN; SI: Michael Frankel, MD, Marc Chimowitz, MD, Owen Samuels, MD.

University of Wisconsin, Madison, Wisconsin (7): PI: Robert Dempsey, MD; coordinator: Pam Winne; SI: George Newman, MD, Douglas Dulli, MD, Madeleine Geraghty, MD.

Indiana University School of Medicine, Indianapolis, Indiana (7): PI: Linda Williams, MD; coordinator: Kelley Faber; SI: Askiel Bruno, MD, William Jones, MD, James Fleck, MD.

University of California, Davis School of Medicine, Sacramento, California (7): PI: Piero Verro, MD; coordinator: Lisa Wilson.

Marshfield Clinic, Marshfield, Wisconsin (7): PI: Percy Karanjia, MD; coordinator: Kathy Mancl, CCRC; SI: Kenneth Madden, MD.

Inova Fairfax Hospital, Falls Church, Virginia (7): PI: Paul Nyquist, MD; coordinator: Barbara Farmer, RN, MSN.

East Bay Region Associates in Neurology, Berkeley, California (6): PI: Brian Richardson, MD; coordinator: Lauren McCormick.

University of California Los Angeles Stroke Center, Los Angeles, California (6): PI: Jeffery Saver, MD; coordinator: Jill Haines; SI: Bruce Ovbiagele, MD, Scott Selco, MD, Venkatakrishna Rajajee, MD.

Thomas Jefferson University Hospital, Philadelphia, Pennsylvania (6): PI: Rodney Bell, MD; coordinator: Mary-Kathleen Nilson-Whitten, BA; SI: David G. Brock, MD, Carissa Pineda, MD, Kiwon Lee, MD.

Florida Neurovascular Institute, Tampa, Florida (5): PI: Erfan Albakri, MD; coordinator: Judy Jackson, Mary Katherine Taylor, ARNP.

University of Kentucky, Lexington, Kentucky (5): PI: L. Creed Pettigrew, MD; coordinator: Deborah Taylor, MS; SI: Stephen Ryan, MD, Anand G. Vaishnav, MD.

Yale University School of Medicine, New Haven, Connecticut (5): PI: Lawrence Brass, MD; coordinators: Janet Halliday, RN, BS, Karin Nystrom; SI: Mark Gorman, MD.

Scripps Clinic, La Jolla, California (4): PI: Mary Kalafut, MD; coordinator: Krista Greiner, BS, CCRC.

University of California San Diego Stroke Center, San Diego, California (3): PI: Patrick Lyden, MD; coordinators: Nancy Kelly, RN, Janet Werner, RN; SI: Christy Jackson, MD, Thomas Hemmen, MD, Brett Meyer, MD.

Rush-Presbyterian-St Luke's Medical Center, Chicago, Illinois (3): PI: Sean Ruland, DO, MD; coordinator: Karen Whited, RN; SI: Michael Schneck, MD, Michael Sloan, MD, Phillip Gorelick, MD, MPH.

University of Illinois at Chicago, Chicago, Illinois (3): PI: Cathy Helgason, MD; coordinator: Joan N. Martellotto, RN, PhD.

Johns Hopkins Bayview Medical Center, Baltimore, Maryland (3): PI: Rafael Llinas, MD; coordinator: Janice Alt; SI: Christopher Earley, MD.

Field Neurosciences Institute, Saginaw, Michigan (3): PI: Faith Abbott, MD; coordinator: Richard Herm, RN, BSN, CEN; SI: Malcolm Field, MD, Debasish Mridha, MD.

Medical University of South Carolina, Charleston, South Carolina (3): PI: Timothy Carter, MD; coordinator: Feng Liu, MSN.

Royal University Hospital, Saskatoon, Saskatchewan (3): PI: Ali Rajput, MD; coordinator: Theresa Shirley, RN; SI: Alexander Rajput, MD.

Chattanooga Neurology Associates, Chattanooga, Tennessee (2): PI: Thomas Devlin, MD; coordinators: Patty Wade-Hardie, RN, Tammy Owens, RN; SI: Adele Ackell, MD, Sharon Farber, MD, Ravi Chander, MD, G. Hagan Jackson, MD, Kadrie Hytham, MD, Bruce Kaplan, MD, David Rankine, MD.

Morton Plant Hospital, Clearwater, Florida (2): PI: Ajay Arora, MD; coordinators: Jo Simpson, RN, Teresa Jones, RN, Victoria Bernsee, RN.

Charles R. Drew University of Medicine and Science, Los Angeles, California (1): PI: Lowell Nelson, MD; coordinator: Marcia Montenegro, RN; SI: Derek Knight, MD.

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Mayo Stroke Genetics Databank

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TABLE 1

Demographic, Stroke Risk Factor, and Subtype Characteristics of the Study Population

	ISGS		MSGD		SWISS		
	Cases* **(n=328)**	**Controls†** **(n=213)**	**Cases*** **(n=48)**	**Controls†** **(n=48)**	**Probands*** **(n=104)**	**Affected (n=104)**	**Unaffected (n=41)**
Age, mean±SD, y	64.1±15.0	58.3±14.4	69.9±13.8	67.3±14.4	68.4±11.0	70.3±11.0	66.5±11.6
Male, n (%)	177 (54.0)	82 (38.5)	24 (50.0)	17 (35.4)	54 (51.9)	56 (53.8)	9 (22.0)
Nonwhite, n (%)	98 (29.9)	52 (24.4)	0 (0.0)	1 (2.1)	7 (6.7)	7 (6.7)	2 (4.9)
Risk factors, n/N							
Hypertension	277/326	82/128	29/48	19/48	76/104	75/103	22/41
Diabetes	79/328	29/213	11/48	4/48	28/104	29/103	1/41
Ever smoker	232/328	103/213	24/48	20/48	60/101	68/101	20/41
Atrial fibrillation	48/324	11/213	10/48	7/48	13/104	26/102	7/41
Myocardial infarction	51/327	13/213	8/48	1/48	22/103	28/102	6/41
CABG	31/328	9/213	6/48	1/48	NA	NA	NA
PVD	14/326	3/213	4/48	1/48	11/102	26/103	3/41
Dyslipidemia	146/325	56/209	NA	NA	67/104	69/103	19/41
Family history	127/325	70/213	18/48	17/48	104/104	104/104	41/41
TOAST type							
Large vessel atherosclerosis	64		NA		29	29	
Cardioembolic	82		NA		9	5	
Small vessel	56		NA		33	37	
Other	14		NA		6	3	
Undetermined	112		NA		27	30	

CABG indicates coronary artery bypass graft; NA, not available; PVD, peripheral vascular disease.

* Individuals used as cases in the primary analysis.

† Individuals used as controls in the primary analysis.

TABLE 2

Genotypes of the Study Population and Race

	ISGS		MSGD		SWISS			White		Nonwhite[§]	
	Cases[*] (n=328)	Controls[†] (n=213)	Cases[*] (n=48)	Controls[†] (n=48)	Probands[*] (n=104)	Affected Siblings (n=104)	Unaffected Siblings (n=41)	Cases (n=375)	Controls (n=208)	Cases (n=105)	Controls (n=53)
IL1RN genotype											
1/1	183	126	23	23	56	49	18	178	107	84	42
1/2	101	66	15	19	35	40	19	137	78	14	7
2/2	25	9	8	4	9	9	3	39	12	3	1
Rare[‡]	19	12	2	2	4	6	1	21	11	4	3

[*] Individuals used as cases in the primary analysis.

[†] Individuals used as controls in the primary analysis.

[‡] Rare genotypes contain alleles 3, 4, or 5.

[§] The nonwhite participants were predominantly black individuals.

TABLE 3

Models: Cases From 3 Cohorts (SWISS, ISGS, and MSGD) and Controls From ISGS and MSGD Cohorts Stratified by Race

	IL1RN			*P*			
Model*	**Genotype†**	**Count**	**OR (95% CI)**	**General Association**	**Dominant**	**Additive**	**Recessive**
White							
a	2/2	51	1.95 (0.98–3.90)	0.16	0.36	0.12	0.06
	1/2	215	1.06 (0.73–1.52)				
	1/1	285	1.00 (1–1)				
b	2/2	51	2.11 (1.05–4.27)	0.11	0.40	0.11	0.04
	1/2	215	1.03 (0.71–1.49)				
	1/1	285	1.00 (1–1)				
c	2/2	51	1.99 (0.99–4.01)	0.15	0.30	0.10	0.06
	1/2	215	1.09 (0.75–1.58)				
	1/1	285	1.00 (1–1)				
d	2/2	51	2.17 (1.06–4.45)	0.10	0.33	0.09	0.03
	1/2	215	1.05 (0.72–1.54)				
	1/1	285	1.00 (1–1)				
e	2/2	51	2.80 (1.29–6.11)	0.03	0.27	0.04	0.009
	1/2	215	1.05 (0.69–1.60)				
	1/1	285	1.00 (1–1)				
Nonwhite							
a	2/2	4	1.50 (0.15–14.86)	0.94	0.90	0.82	0.73
	1/2	21	1.00 (0.38–2.66)				
	1/1	126	1.00 (1–1)				
b	2/2	4	1.63 (0.16–16.83)	0.92	0.89	0.80	0.68
	1/2	21	0.99 (0.36–2.71)				
	1/1	126	1.00 (1–1)				
c	2/2	4	1.38 (0.14–13.85)	0.96	0.90	0.85	0.78
	1/2	21	1.01 (0.38–2.70)				
	1/1	126	1.00 (1–1)				
d	2/2	4	1.45 (0.14–15)	0.95	0.91	0.84	0.76
	1/2	21	1.00 (0.36–2.75)				
	1/1	126	1.00 (1–1)				
e	2/2	4	1.54 (0.10–24.67)	0.95	0.87	0.81	0.76
	1/2	21	1.04 (0.34–3.17)				
	1/1	126	1.00 (1–1)				

CI indicates confidence interval.

*Models: a, unadjusted; b, age; c, sex; d, age and sex; e, age, sex, atrial fibrillation, myocardial infarction, smoking, family history, and diabetes mellitus.

†Excludes genotypes with one of the rare alleles (3, 4, or 5).

TABLE 4

Large Vessel Atherosclerosis

	TOAST Subtype		Any Cerebrovascular LVA*		
	LVA† (n=93)	No LVA (n=339)	Yes (n=101)	No (n=331)	Controls (n=261)
IL1RN genotype					
White					
1/1	38	117	41	114	107
1/2	31	91	35	87	78
2/2	8	23	9	22	12
Rare‡	3	16	3	16	11
Nonwhite					
1/1	12	72	12	72	42
1/2	1	13	1	13	7
2/2	0	3	0	3	1
Rare‡	0	4	0	4	3

LVA indicates large vessel atherosclerosis.

*Any cerebrovascular LVA, LVA stroke, or history of endarterectomy, stent, or angioplasty of either carotid artery.

†Stroke categorized as LVA using the TOAST classification system (15).

‡Rare genotypes contain alleles 3, 4, or 5.