Association of integrin *α*2 gene variants with ischemic stroke

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Abstract

Genetic variants in the gene encoding integrin *α*2 (*ITGA2*) have been reported to be associated with an increased risk for ischemic stroke. The purpose of this study was to investigate the association between haplotype-tagging single-nucleotide polymorphisms (tSNPs) in *ITGA2* and risk of ischemic stroke in a collection of North American stroke cases and controls. The study included 484 cases and 263 controls. Thirteen tSNPs were genotyped. Association tests at and across each tSNP were performed, including haplotype association analysis. Secondary analyses considered stroke subtypes on the basis of Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. We observed significant association between tSNP rs3756541 (additive model, odds ratio (OR), 1.49; 95% confidence interval (CI), 1.11 to 2.04; *P* = 0.009) and disease and a trend toward association at rs2303124 (recessive model, OR, 1.56; 95% CI, 1.05 to 2.33; *P*= 0.03). These associations remained significant in the haplotype analyses. The associated tSNPs did not distinguish stroke etiology after application of TOAST criteria. Our results suggest that genetic variability within *ITGA2* may confer risk for ischemic stroke independent of conventional risk factors. These results provide additional support for a role for platelet receptor genes in the pathogenesis of ischemic stroke of diverse subtypes.

Keywords

atherosclerosis; cerebral infarction; genetics; integrin *α*2; stroke

Introduction

Platelet receptor genes are good candidates for stroke susceptibility studies, given the key role that platelet–collagen interactions play in mechanisms of ischemic stroke. Integrins are heterodimeric cell surface glycoproteins (GPs) consisting of *α* and *β* subunits. The platelet

integrin $\alpha2\beta1$, also known as GP Ia-IIa (where GP Ia represents the $\alpha2$ component and GP IIa represents the $\beta1$ common subunit), is one of the major platelet collagen receptors (Santoro and Zutter, 1995; Santoro, 1999; Clemetson and Clemetson, 2001; Kunicki, 2002). Via GP Ia-IIa, platelets adhere to collagen exposed in subendothelial structures and subsequently become activated (Nieuwenhuis *et al*, 1985; Kehrel *et al*, 1988; Handa *et al*, 1995), leading to thrombus formation (Santoro and Zutter, 1995). In addition to adhesion, integrins are thought to participate in cell surface-mediated signaling (Inoue *et al*, 2003). The gene for the integrin $\alpha2$ component, *ITGA2*, is located on chromosome 5q23-31, contains 30 exons, and spans approximately 110 kb.

This study comprised three groups of ischemic stroke cases and controls—probands from the Siblings With Ischemic Stroke Study (SWISS) and cases and controls from the Ischemic Stroke Genetics Study (ISGS) and the Mayo Stroke Genetics Databank (MSGD). We have characterized the *ITGA2* gene, including the pattern of linkage disequilibrium (LD) across this locus, and examined the role of haplotype-tagging single-nucleotide polymorphisms (tSNPs) in *ITGA2* with respect to ischemic stroke susceptibility, demonstrating that variation in *ITGA2* is linked to ischemic stroke risk, independent of known stroke risk factors.

Subjects and methods

Study Populations

We evaluated the role of *ITGA2* tSNPs and haplotypes in three distinct groups of patients: unrelated probands from SWISS (Meschia *et al*, 2006) (a sib-pair linkage study) and cases and controls from two case–control association studies, ISGS (Meschia *et al*, 2003) and MSGD. Eligibility criteria for cases and controls in MSGD and ISGS were identical, except that in MSGD cases included individuals with incident or recurrent ischemic stroke, whereas ISGS limited cases to individuals with incident ischemic stroke. There were 107 probands (from 107 families) used from the SWISS study, 329 cases and 215 controls from ISGS, and 48 cases and 48 controls from MSGD. All study subjects (cases and controls) were collected prospectively under protocols approved by the institutional review boards at participating institutions. All participants gave their written informed consent. Qualifying ischemic stroke events were diagnosed on the basis of medical history, neurologic examination, and imaging (computed tomography or magnetic resonance imaging scan) by experienced neurologists in the participating centers. Stroke was defined according to the World Health Organization criteria (WHO MONICA Project Principal Investigators, 1988). Each case was classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (Adams *et al*, 1993).

Molecular Genetic Analysis

Thirteen tSNPs across *ITGA2* were chosen from the International HapMap Project database (http://www.hapmap.org) with use of TagIT version 2.03 (Weale *et al*, 2003). Median spacing of the tSNPs was 7,500 bp, with a range of 1,645 to 25,566 bp. A total of 13 tSNPs were used to 'tag' the LD that was characterized by the HapMap data for *ITGA2*. For 10 tSNPs, single-tube reagent-based genotyping assays (TaqMan; Applied Biosystems, Foster City, CA, USA) were used (assay details available on request). The tSNP rs3756541 was genotyped by direct DNA sequencing using a genetic analyzer (ABI Prism 3100; Applied Biosystems). Two tSNPs (rs1862639 and rs989073) were analyzed by pyrosequencing (Pyrosequencing Inc., Westborough, MA, USA). (Primers are available on request.) The tSNPs studied and details of probes and primers used are provided in Supplementary Table 1; all genotype assignments were performed masked to clinical data, including stroke-affected status.

Statistical Analysis

Descriptive statistics were reported as frequencies and percentages (categorical data) and means with standard deviations (continuous data). Tests of statistical significance between cases and controls were performed using two-sample tests for binomial proportions (with a χ^2 test of independence). The Fisher exact test was used when appropriate. For comparison of age (continuous variable) among case–control groups, a two-sample *t*-test for independent samples was performed.

Hardy–Weinberg Equilibrium and Linkage Disequilibrium

For each tSNP, tests of deviations from Hardy–Weinberg equilibrium expectations were performed using the methods described by Wigginton *et al* (2005), with significance considered $P < 0.05$ under a χ^2 goodness-of-fit test. The degree of tSNP–tSNP LD was estimated using the *D′* statistic and visualized by haplotype analysis software (Haploview; Broad Institute of MIT and Harvard, Cambridge, MA, USA). Individual tSNP allele frequencies were computed, and differences in allele frequencies were tested by permutation ($n = 1000$) of the likelihood ratio statistic.

Statistical Genetic Analysis—Haplotype-Tagging Single-Nucleotide Polymorphisms

For tests of association with individual tSNPs between cases and controls, a series of generalized estimating equations (GEEs) were used that permitted inclusion of recognized stroke risk factors as covariates (age, sex, race, hypertension status, presence of atrial fibrillation, history of myocardial infarction, smoking status, presence of diabetes mellitus, and family history of stroke). All GEE models and testing were performed in a hierarchical manner, with a baseline risk model that included only the tSNP of interest as the predictor of outcome (stroke/no stroke). Additional models were tested, with age, sex (age + sex), and race (age + sex + race); additional 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. *P* values were computed using the 2-degree-of-freedom generalized test of association. When the generalized test of association was significant ($P < 0.05$), additional models were tested that assumed an underlying mode of inheritance of risk (dominant, additive, recessive) with a 1-degree-of-freedom test. Differences in the distribution of *ITGA2* within cases according to TOAST subtype versus control subjects were determined using χ^2 tests. Comparisons were made for cases according to large-vessel, cardioembolic, or smallvessel disease and combined phenotype (large-vessel and cardioembolic) categories.

Statistical Genetic Analysis—Haplotypes

Haplotype frequencies and tests for association with stroke risk were computed using the expectation-maximization algorithm. Statistical significance was assessed using a permutation test of the likelihood ratio statistic. For all 2-, 3-, 4-, and 5-tSNP haplotypes, frequencies in cases and controls were estimated by the expectation-maximization algorithm and tested (for all haplotypes with frequencies greater than 10%) by permutation methods. For computation of tests in which stroke risk factors were included, all haplotype–genotype (haplotype pairs) probabilities were determined and used as weights in a weighted GEE1 regression analysis. For both unadjusted and adjusted analyses, the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were computed for each haplotype relative to all other haplotypes.

LD calculations, haplotype block determination, and statistical genetic analysis were performed for white and nonwhite patient groups separately.

Results

There were no significant differences in demographic characteristics among the three cohorts. Thus, cases and controls were pooled across studies. The descriptive statistics associated with cases and controls are shown in Supplementary Table 2. Cases (65.6 ± 14.2 years) were significantly older than controls (60.0 ± 14.7 years; $P < 0.001$). There were more women in the control group (62.0%) than in the case group (46.7%; $P < 0.001$). As expected, cases had greater prevalence of risk factors than controls ($P < 0.001$), including myocardial infarction (17.0% versus 5.7%), atrial fibrillation (14.8% versus 6.9%), smoking history (66.1% versus 47.1%), hypertension (69.5% versus 38.9%), hyperlipidemia (49.7% versus 26.6%), diabetes mellitus (24.6% versus 12.9%), and a positive family history of stroke (52.4% versus 33.5%).

Thirteen tSNPs in *ITGA2* were examined with respect to Hardy–Weinberg equilibrium expectations. Significant deviations from expectation could be generated by many factors, but most notably population stratification, genotyping errors, or a true association. In these data, significant ($P < 0.05$) deviations from the Hardy–Weinberg equilibrium were observed for three tSNPs—rs3756541, rs3212460, and rs2303124—in the overall group (Table 1). The same three tSNPs failed within cases. In the controls, rs3212460 and rs2303124 failed, but rs3756541 did not fail. Two additional tSNPs failed only in the controls (rs1363192 and rs10513009). The tSNP rs3756541 had been assayed by direct sequencing, and reanalysis of these data revealed consistent results. The remaining two tSNPs (rs3212460 and rs2303124) were originally assayed by TaqMan. Dye terminator sequencing of 96 samples for both of these tSNPs showed a genotype discordance rate of 2% (2/96). Thus, errors in genotyping were not believed to be the cause of the deviation from the Hardy–Weinberg equilibrium or a significant confounder in the association analyses. The deviations from Hardy–Weinberg equilibrium were observed across all studies (SWISS, ISGS, MSGD), so the likelihood of population stratification is small. Although these tSNPs deviated from the Hardy–Weinberg equilibrium, they should not be completely eliminated from analyses (Wittke-Thompson *et al*, 2005).

Each tSNP was tested independently for association with ischemic stroke. After adjustment for stroke risk factors (i.e., age, sex, race, and other stroke risk factors), three tSNPs were significantly associated with ischemic stroke risk (Table 1). The tSNP rs1645761 was significantly associated with ischemic stroke (OR, 2.76; 95% CI, 1.17 to 6.50; $P = 0.05$, generalized 2-degree-of-freedom test). Adjacent tSNP rs3756541 showed significant association in the unadjusted model (OR, 1.89; 95% CI, 1.03 to 3.45; $P = 0.02$) with increased significance (OR, 2.27; 95% CI, 1.15 to 4.55; $P = 0.008$) after adjustment for covariates. The tSNP rs2303124 was also significantly associated with risk of ischemic stroke in the fully adjusted model (OR, 1.43; 95% CI, 0.84 to 2.44; $P = 0.03$). The tSNP rs1645761 showed a significant association in the dominant ($P = 0.03$) and additive ($P = 0.02$) fully adjusted models. The tSNP rs3756541 showed a significant association in the additive ($P = 0.002$) and recessive ($P = 0.003$) fully adjusted models. The tSNP rs2303124 showed a significant association in the recessive ($P = 0.01$) fully adjusted model.

The association between tSNPs rs3756541 and rs2303124 with disease in the total group was largely driven by association at these loci in the group of white patients (Supplementary Table 3). Analyzing white patients, we observed significant association between tSNP rs3756541 (additive model, OR, 1.49; 95% CI, 1.11 to 2.04; $P = 0.009$) and disease and a trend toward association at rs2303124 (recessive model, OR, 1.56; 95% CI, 1.05 to 2.33; $P = 0.03$). Comparisons in the nonwhite group did not reveal any significant differences (Supplementary Table 4).

Pairwise LD between the 13 polymorphisms was evaluated using study population data for white and nonwhite patients separately (Figure 1). There was variation across these two groups.

In white patients, these analyses showed two LD blocks in *ITGA2*. The first LD block (block 1) contained two tSNPs (rs152088, rs3212418) of 7 kb. The second LD block (block 2) contained two tSNPs (rs984966, rs10513009) of 2 kb. The tSNP that was associated with ischemic stroke in the adjusted model (rs3756541) does not reside in either of the LD blocks. Analysis of the nonwhite group showed an LD block containing two tSNPs (rs152088, rs3212418).

Haplotype analyses were undertaken across the 13 tSNP panels using a 2-, 3-, 4-, and 5-tSNP moving window. Empirical *P* values were calculated using permutation testing. In the overall group, a majority of the 2-, 3-, and 4-tSNP haplotypes that included the first six tSNPs showed a significant difference between the distributions seen between cases and controls. We saw a similar pattern in the nonwhite group with the first four tSNPs. For the white group, we saw only two 2-tSNP haplotypes that had a significant empirical *P* value. Haplotype analysis in white and nonwhite subjects separately are summarized in Supplementary Tables 5 and 6.

With the empirical analyses indicating haplotypic differences between cases and controls, specific haplotypes were examined for significance and risk. The overall group had significant haplotypes and ORs evident in all haplotype windows through the first six tSNPs, even when removing tSNP rs3756541 (not in Hardy–Weinberg equilibrium). The white group had significance in a couple of four-marker haplotypes, one involving tSNPs 1 through 4 and the other involving tSNPs 10 through 13. Both of these were not evident when tSNPs not in Hardy–Weinberg equilibrium were removed. In the nonwhite group, significance was seen only after removing the tSNPs not in Hardy–Weinberg equilibrium. This evidence was seen in haplotypes involving the first six tSNPs. In both the white and nonwhite groups, the ORs maintained a significant consistent risk comparable to the overall group. Using weighted GEE1 analyses, almost all the analyses involving a significant haplotype using the full model showed a significant result in both the additive and dominant models. Results for significant individual haplotypes and ORs are listed in Supplementary Tables 7, 8, and 9.

Finally, there was no differential association of any individual tSNP or haplotype with ischemic stroke by TOAST subtype (data not shown), which suggests that the effect of *ITGA2* variation may apply to a broad range of ischemic stroke etiologies.

Discussion

The aim of this study was to determine, using a tSNP polymorphism approach, whether common variability in *ITGA2* alters risk for ischemic stroke in a large number of North American subjects. Association studies addressing the relationship between *ITGA2* polymorphisms and risk of cerebrovascular disease have been performed, with many evaluating only three tSNPs (C807T, G873A, and A1648G) that define three major *ITGA2* haplotypes. In particular, the T807 and A873 alleles within exons 8 and 9 have been associated with increased GPIa-IIa expression (Kunicki *et al*, 1997) and with risk for arterial thrombosis in younger men with a history of myocardial infarction (Santoso *et al*, 1999), women who smoke cigarettes (Roest *et al*, 2000), men and women with diabetic retinopathy (Matsubara *et al*, 2000), and younger men and women with stroke (Carlsson *et al*, 1999; Reiner *et al*, 2000). Also the C807T polymorphism has been involved in modeling individual response to antithrombotic treatment (Angiolillo *et al*, 2005). Another polymorphism, G1649A (Glu534Lys) at codon 534, exon 14, has also been associated with coronary artery disease (Kroll *et al*, 2000).

Several studies that have evaluated the relationship between the C807T polymorphism and ischemic stroke do not support a genetic association. The results of these studies may be inconsistent because the evaluated tSNPs may not be causal but rather in LD with disease-

causing tSNPs and the level of LD across *ITGA2* may vary by population. Alternatively, an interaction with another risk factor—genetic or environmental—may be required to lead to an increased risk of stroke. The independence shown in our study of the various *ITGA2* tSNPs indicates that selection of only one tSNP as a marker for the entire gene is inadequate to tag diversity across the locus.

Our cohort exhibited racial diversity. Haplotype patterns are known to vary by race, especially in populations with marked genetic diversity. This makes the study of nonhomogenous populations problematic. However, we designed our model to take racial and ethnic diversity into account. To strengthen the generalizability of our results, thereby contributing to the biologic plausibility of our findings, and to provide additional statistical power, we pooled all races in our analysis, but we then adjusted for race. Additionally, we specifically looked for genetic associations in each ethnic group.

The adjusted analysis showed three tSNPs associated with ischemic stroke risk in the total group. Among the white group, only the tSNP rs3756541 was significantly associated with the disease, whereas no tSNP was associated with ischemic stroke in the nonwhite group. Although we cannot ignore the possibility that these discrepancies could be caused by differences in population genetic structure, it is also likely that these differences and our failure to find association in nonwhite patients were affected by the sample size of the nonwhite group. Only 21% of our subjects were nonwhite.

We also need to consider the possibility that the positive findings we obtained in the entire study group were spurious or the result of type I error. However, even considering only white patients, the association with tSNP rs3756541 suggests that this tSNP could be associated with ischemic stroke.

Another factor to take into account is patient age. Although most positive associations have been obtained from studies of younger cohorts (Carlsson *et al*, 1999; Reiner *et al*, 2000; Sacchi *et al*, 2000), in our study, the age of patients and other known risk factors were also used as covariates, suggesting that these are unlikely to significantly modulate the genetic risk associated with *ITGA2*.

It should be noted that the associated tSNPs identify potential regions in the genome that contribute to genetic risk of ischemic stroke. As these tSNPs account for the majority, but not all, of the information within a haplotype block, any association should be considered as preliminary and serve as a rationale for more in-depth analysis of the region. Thus, association of a tSNP would warrant denser genotyping of tSNPs and other variants within the identified haplotype block as well as consideration of both common and rare variants as they relate to the genetic risk of ischemic stroke.

To date, many of the polymorphisms associated with increased risk of complex disorders are not amino-acid polymorphisms, and several lines of evidence support the functional importance of intronic polymorphisms in the etiology of complex disorders (Cox *et al*, 2004). In this study, significant association was observed for tSNPs rs1645761 and rs3756541 within intron 1 and rs2303124 within intron 26. According to FastSNP (http://fastsnp.ibms.sinica.edu.tw), a Web server that allows identification and prioritization of high-risk tSNPs, the tSNP 230324 could have a possible functional effect as intronic enhancer, whereas the functions of the other two intronic tSNPs are not known. Very little is known about the function that specific intronic sequences have with regard to the secondary structure, protein binding, stability, and splicing efficiency of heterogeneous nuclear RNA. Thus, any of these associated tSNPs may affect expression, which could be investigated directly in future studies by testing for case–control differences in transcript structures, quantity, spatial distribution, and developmental distribution.

In conclusion, our results suggest that *ITGA2* may be a susceptibility region for ischemic stroke in the North American population and can be equally important in all forms of ischemic stroke. Further studies with larger samples, different patient groups, and tSNPs that capture a reasonable amount of variation are needed to corroborate these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Helen Hayes Hospital, West Haverstraw, New York (probands enrolled, 8): PI: Jason P Greenberg, MD; coordinator: Laura Tenteromano, RN.

Washington University School of Medicine, St. Louis, Missouri (probands enrolled, 8): PI: Jin-Moo Lee, MD, PhD; coordinators: Denise Shearrer, RMA, BS, Julie Ruckmann.

University of Wisconsin, Madison, Wisconsin (probands enrolled, 7): PI: Robert Dempsey, MD; coordinator: MJ Washburn, RRT, BSRT.

Marshfield Clinic, Marshfield, Wisconsin (probands enrolled, 7): PI: Percy Karanjia, MD; coordinator: Kathy Mancl, CCRC, Rob Bohl, NP.

Thomas Jefferson University Hospital, Philadelphia, Pennsylvania (probands enrolled, 6): PI: Rodney Bell, MD; coordinator: Lisa Bowman.

University of California Los Angeles Stroke Center, Los Angeles, California (probands enrolled, 6): PI: Jeffery Saver, MD; coordinator: Jill Haines.

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

University of Utah Medical Center, Salt Lake City, Utah (probands enrolled, 5). PI: Elaine J Skalabrin, MD; coordinator: Jolee Mougey, MPH.

University of Kentucky, Lexington, Kentucky (probands enrolled, 5): PI: L Creed Pettigrew, MD; coordinator: Deborah Taylor, MS.

Florida Neurovascular Institute, Tampa, Florida (probands enrolled, 5): PI: Erfan Albakri, MD; coordinators: Mary Katherine Taylor, ARNP; Anessa Hohns.

Mercy Hospital, Sioux City, Iowa (probands enrolled, 5): PI: Jennifer Pary, MD; coordinator: Deb Motz.

Rochester General Hospital, Rochester, New York (probands enrolled, 5): PI: Joshua Hollander, MD: coordinator: Cheryl Weber.

OSF Stroke Center, Peoria, Illinois (probands enrolled, 4): PI: David Wang, DO; coordinator: Mary Buttice.

Scripps Clinic, La Jolla, California (probands enrolled, 4): PI: Mary Kalafut, MD; coordinators: Krista Greiner, CCRC; Ileanna Iedelson, RN, BSN.

Morton Plant Hospital–Neuroscience Institute, Clearwater, Florida (probands enrolled, 3): PI: Ajay Arora, MD; coordinators: Jo Simpson, Teresa Jones, Victoria Bernsee.

Massachusetts General Hospital, Boston, Massachusetts (probands enrolled, 3): PI: Karen Furie, MD; coordinator: Donna Defilippo.

Vanderbilt University Medical Center, Nashville, Tennessee (probands enrolled, 2): PI: Anne E O'Duffy, MD; coordinator: Diane Brown.

Tri-State Neurology, Huntington, West Virginia (probands enrolled, 1): PI: Carl McComas, MD; coordinators: Jenny Edwards, RN, Christy Franklin, RN.

The Stroke Center at Hartford Hospital, Hartford, Connecticut (probands enrolled, 1): PI: Isaac Silverman, MD; coordinator: Martha Ahlquist, LPN, CCRP.

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

Virginia MasonMedical Center, Seattle, Washington (probands enrolled, 1): PI: Michael Elliott, MD; coordinator: Allison Singer.

ISGS Investigative Team

Study principal investigator (PI): James F Meschia, MD.

Executive committee: James F Meschia, chair; Thomas G Brott, Robert D Brown, Jr, Michael Frankel, John Hardy, Stephen S Rich, Scott Silliman, and Bradford B Worrall.

Data Management Center: Wake Forest University Medical Center: L Douglas Case, director; Laurie Russell, Carolyn Bell, Darrin Harris, and Wes Roberson.

Clinical Coordinating Center: Mayo Clinic, Jacksonville, Florida: James F Meschia, Alexa Richie, Dale Gamble, and Sothear Luke.

DNA Repository: Coriell Institute for Medical Research, Camden, New Jersey: Roderick A Corriveau, PhD.

Genetics Laboratory: National Institute on Aging, Bethesda, Maryland: John Hardy and Andrew Singleton.

Statistical Genetics Core: University of Virginia, Charlottesville, Virginia: Stephen S Rich; Wake Forest University Medical Center, Winston-Salem, North Carolina: W Mark Brown.

ISGS Sites and Investigators as of September 26, 2006

Mayo Clinic, Jacksonville, Florida (subjects enrolled, 271)—PI: James F Meschia, MD; coordinators: Alexa Richie, CRC, Dale Gamble, CRC, Sothear Luke, CRC; subinvestigators (SI): Thomas G Brott, MD, Benjamin H Eidelman, MD.

University of Florida/Shands Hospital, Jacksonville, Florida (subjects enrolled, 216)—PI: Scott Silliman, MD; coordinators: Yvonne Douglas, Rahm Sambandam; SI: Nader Antonios, MD.

Emory University School of Medicine, Atlanta, Georgia (subjects enrolled, 237)—PI: Michael Frankel, MD, MSc; coordinator: Sharion Sailor- Smith, RN.

Mayo Clinic, Rochester, Minnesota (subjects enrolled, 266)—PI: Robert D Brown, Jr, MD; coordinator: Colleen S Albers, RN.

University of Virginia, Charlottesville, Virginia (subjects enrolled, 231)—PI: Bradford Worrall, MD, MSc; coordinator: Daniel Chernavvsky.

The MSGD Investigative Team

PI: James F Meschia, MD

Clinical investigator: Thomas G Brott, MD

Clinical coordinator: Marc Lojacono

Data management and statistics: Elizabeth J

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Geneticists: Richard Crook, John Hardy, PhD
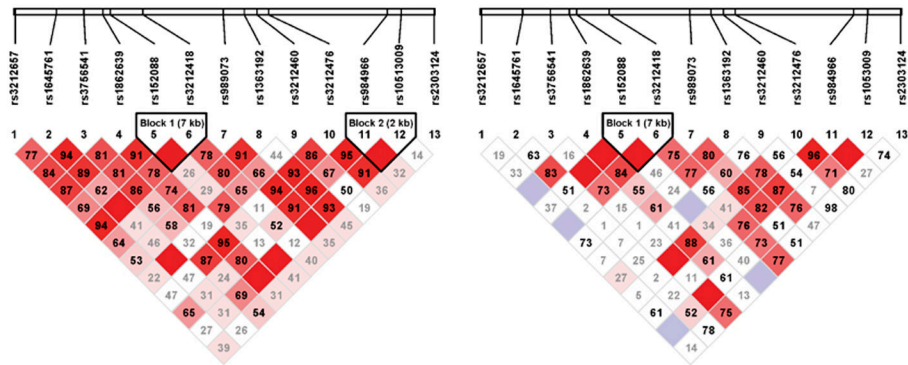
Figure 1.
Linkage equilibrium blocks in the white (left) and nonwhite (right) patient groups. Numbers within the diamonds are D′ values for the respective SNP pairs. Solid red diamonds represent absolute LD (D′ =1), blue diamonds represent strong LD with low level of significance. Numbers in gray within white diamonds represent a high probability or evidence of historical recombination.

Table 1

tSNP association analysis for ischemic stroke adjusted for age, sex, race, myocardial infarction, atrial fibrillation, cigarette smoking, family history, and diabetes status

tSNP major/minor	Location	Group	No. of genotypes[a]			Association (P-value)			
			11	12	22	General	Dominant	Additive	Recessive
rs3212657 T/C	52324239	Total	595	135	14	0.15	0.07	0.12	0.25
		Case	395	82	6				
		Control	200	53	8				
rs1645761 A/G	52332999	Total	518	198	30	0.05	0.03	0.02	0.07
		Case	346	123	15				
		Control	172	75	15				
rs3756541[b] C/T	52338852	Total	409	237	62	0.008	0.06	0.002	0.003
		Case	247	164	46				
		Control	162	73	16				
rs1862639 C/T	52343127	Total	463	252	30	0.35	0.16	0.25	0.44
		Case	306	162	15				
		Control	157	90	15				
rs152088 C/T	52344772	Total	499	210	34	0.35	0.19	0.19	0.31
		Case	335	131	17				
		Control	164	79	17				
rs3212418 T/C	52351929	Total	213	343	184	0.12	0.05	0.04	0.17
		Case	150	224	106				
		Control	63	119	78				
rs989073 C/A	52369177	Total	328	306	85	0.80	0.72	0.90	0.69
		Case	217	199	53				
		Control	111	107	32				
rs1363192 A/C	52373840	Total	380	299	66	0.10	0.04	0.33	0.95
		Case	245	207	32				
		Control	135	92	34				
rs3212460[b] C/T	52376431	Total	687	33	26	0.31	0.14	0.14	0.21
		Case	442	23	19				
		Control	245	10	7				
rs3212476 C/G	52379113	Total	379	302	63	0.51	0.62	0.27	0.25
		Case	251	194	38				
		Control	128	108	25				
rs984966 T/A	52404679	Total	274	355	116	0.94	0.78	0.71	0.76
		Case	180	232	71				
		Control	94	123	45				
rs10513009 C/T	52407631	Total	600	132	13	0.16	0.06	0.39	0.75
		Case	386	92	5				
		Control	214	40	8				
rs2303124[b] C/T	52414713	Total	359	245	114	0.03	0.68	0.06	0.01
		Case	222	169	76				
		Control	137	76	38				

tSNP, haplotype-tagging single-nucleotide polymorphism.

[a] Genotype 11 indicates the presence of both major alleles; genotype 12, one major allele and one minor allele; and genotype 22, both minor alleles.

[b] Not in Hardy–Weinberg equilibrium.