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Proband Race/Ethnicity Affects Pedigree Completion Rate in a Genetic Study of Ischemic Stroke

Brett M. Kissela, MD^{*}, Thomas G. Brott, MD[†], Robert D. Brown Jr, MD[‡], Scott L. Silliman, MD[§], W. Mark Brown, MA^{//}, Stephen S. Rich, PhD[¶], and James F. Meschia, MD[†]

^{*}Department of Neurology, University of Cincinnati, Ohio

[†]Department of Neurology, Mayo Clinic, Jacksonville, Florida

[‡]Department of Neurology, Mayo Clinic, Rochester, Minnesota

[§]Department of Neurology, University of Florida, Shands Hospital, Jacksonville

^{//}Department of Biostatistics, Wake Forest University, Winston-Salem, North Carolina

[¶]Department of Public Health Sciences, University of Virginia, Charlottesville

Abstract

Background—A recent meta-analysis suggested that racial/ethnic status is not a major determinant of willingness to participate in observational studies or treatment trials. However, little is known about the predictors of enrollment in family-based observational genetic studies. We tested the hypothesis that proband race/ethnicity is a significant predictor of enrolling a pedigree.

Methods—Univariable and multivariable logistic regression modeling was used to determine proband characteristics that predict DNA donation from both members of an affected sibling pair. A total of 619 adult male and female probands with first-time or recurrent ischemic stroke and a positive sibling history of stroke enrolled across 53 hospitals and clinics in the United States and Canada into the Siblings with Ischemic Stroke Study, a family based prospective genomics study.

Results—In univariable analysis, probands with siblings who agreed to a blood draw for DNA analyses were more likely to be male and less likely to be nonwhite. In multivariable analysis, only race/ethnicity was significantly associated with likelihood of a proband's having a sibling who agreed to a blood draw.

Conclusions—Contrary to observational studies that are not family based, the willingness of family members to participate in observational genetics studies may be influenced by race/ethnicity. This result reinforces the need for improving methods for recruiting diverse populations into genetic studies of stroke.

Keywords

Ethnicity; genetics; pedigree research; race; siblings; stroke

Genetic studies of stroke may help identify heritable biologic factors that increase the risk of stroke in the presence of environmental (nonheritable) factors. These genetic factors may be novel targets for pharmacotherapy or may identify novel therapeutic pathways. Genomewide linkage studies^{1,2} and case-control candidate gene association studies^{3,4} have previously identified putative ischemic stroke susceptibility genes, such as phosphodiesterase 4D and 5-lipoxygenase-activating protein. The genome-wide association method is being applied to ischemic stroke as well.⁵ An important aspect of genetic studies using a classic positional cloning approach (linkage) is collection of DNA samples from family members. Many studies suggest that non-Hispanic whites are more likely to participate in medical research than

minority groups. However, a recent meta-analysis cast doubt on this assumption.⁶ Our hypothesis was that proband race/ethnicity is a significant predictor of pedigree completion. We report an analysis of proband factors that predict pedigree completion in the Siblings with Ischemic Stroke Study (SWISS).

Methods

SWISS is an affected sibling pair, genome-wide linkage study. Study methods have been reported previously.⁷ The first proband was enrolled on August 30, 1999, and recruitment is ongoing. This report is limited to 619 individuals enrolled across 53 sites as of October 1, 2005. The study has institutional review board approval at all institutions contributing data. For these 619 probands, 208 concordant siblings (34%) agreed to participate, had a previously diagnosed ischemic stroke fulfilling the inclusion criteria, and completed the pedigree (as evidenced by blood draws to obtain a genetic sample for the probands' siblings). Demographic and health information about probands and siblings was collected by interview, including self-reported race/ethnicity.

The SWISS design calls for recruiting concordant sibling pairs and discordant siblings. For purposes of the genome-wide linkage scan, however, the primary focus of recruitment has been on the affected sibling. We have used active proband recruitment, but institutional review boards have generally required passive methods for recruitment of affected siblings to complete the concordant affected sibling pair. Thus, the proband, once enrolled and providing informed consent, must permit and direct subsequent efforts to recruit the sibling and complete the sibling pair. Study personnel provide letters that may be sent to the sibling, and information about the study. A proband is encouraged to contact the sibling by telephone. At most centers, no direct contact is allowed between the sibling and study personnel unless requested by the sibling.

Proband factors potentially relevant to pedigree completion were analyzed in univariable fashion. Factors in univariable analysis at P less than .10 were entered into a multivariable logistic regression model to determine the significance of independent predictors of recruitment completion. Specific comparisons were made between non-Hispanic white and nonwhite groups, given the small sample size in the "other" category.

Results

The 619 probands had a mean age of 66.1 years, and 291 (47%) were male. A total of 473 probands were white (76%), 106 (17%) were African American, 38 (6%) were categorized as "other," and 2 (<1%) did not report race.

Results of univariable analyses are displayed in Table 1. Male and white probands were significantly more likely to complete the pedigree than female or nonwhite probands. Although not achieving statistical significance, other predictors of completion included older ages, a history of left carotid endarterectomy, and "other" causes of stroke. In multivariable analysis, only white race/ethnicity predicted pedigree completion ($P < .001$).

Discussion

To our knowledge, this is the first study to show that nonwhite race/ethnicity (particularly being African American, given the high proportion of African Americans relative to other nonwhite minority groups) predicts lower likelihood of participating in a genetic study of stroke. These data are consistent with our previous findings that reported logistical challenges of completing pedigrees for a genetic study using passive recruitment of affected and unaffected siblings.⁸ Passive recruitment is a challenge for many reasons, including the proband's lack of initiative,

sibling estrangement, incorrect medical histories (siblings thought to have had a stroke but who had not), fear of phlebotomy, and concerns regarding use of DNA in genetic studies.

Mistrust and fear of clinical research, especially genetic studies, may be especially relevant for nonwhite race/ethnic minority groups. Our findings are consistent with other study reports that minority groups such as African Americans are less likely to participate in genetic studies⁹⁻¹¹ and are contrary to the results of a recent meta-analysis.⁶ Postulated reasons for reluctance to participate in medical or genetic studies include mistrust of the medical system, mistrust of research, and lack of understanding about genetics.^{12,13} In our experience, minority subjects who are informed about the SWISS protocol in face-to-face interviews with study staff are more likely to appreciate the importance of research aims and be reassured of minimal risk of participation than are individuals first informed of the study by relatives. Proband-initiated contact may compound pre-existing reluctance among minority populations to participate in genetic research.

As noted by Wendler and Emanuel,¹⁴ the heterogeneity of the empirical data in their review argues against a simple relationship between race and willingness to participate in medical research. Racial difference in trust of scientists is only one of several potential explanations for our results. Several additional factors that may have contributed to lack of participation were not available for analysis, including siblings' geographic proximity. Presumably, pedigree completion would be more likely if siblings lived near each other and were in close communication. Similarly, we were not able to consider the quality of relationships among siblings in our analysis. There is no easy way to capture these data, but we are aware (anecdotally) that several pedigrees were not completed because siblings were estranged. Additional potential confounding variables not tested in our study include access to child care among screened individuals to permit study visits, reimbursement for travel expenses, and education and income levels of screened individuals. Facilitating participation in research in concrete and practical ways may be more effective in reducing racial disparities than attempts to change perceived attitudes of mistrust.¹⁵

Minority recruitment is a high priority in SWISS. Actions taken to improve minority recruitment include: (1) seminars during the annual SWISS Investigators' Meeting to address cultural sensitivity and improve recruitment; (2) release of human-interest stories to media that specifically target minority audiences; (3) participation in community health events (e.g., health fairs at churches, youth groups, skilled nursing facilities); (4) use of minority research or outreach office/programs at study sites where these services are available; and (5) identification of sites that have successfully recruited diverse populations into stroke studies when new study sites are needed.

Increased participation by nonwhite individuals in medical studies, and particularly in genetic studies, will broaden our knowledge of the basic mechanisms of stroke. Data collection among diverse racial/ethnic patient groups may affect future diagnosis and treatment of stroke. We have demonstrated that nonwhite race/ethnicity is the single factor most predictive of pedigree noncompletion in SWISS to date and have described actions being taken to enhance recruitment of minority pedigrees. It is essential that diverse populations be included in all current and future genetic studies to define potential racial/ethnic variation in these biologic factors.

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Table 1
Comparison of Probands With and Without Sibling Blood Draw*

	Sibling blood draw		
Characteristic	Yes (n=208)	No (n=411)	P value
Age, mean $\pm$ SD, y	67.2 $\pm$ 11.4	65.5 $\pm$ 11.5 [†]	.07
Male sex	112/208 (53.8)	179/410 (43.7)	.02
Non-Hispanic, White race/ethnicity	15/208 (7.2)	129/409 (31.5) [‡]	<.001
Total siblings			
2	159/208 (76.4)	314/409 (76.8)	.93
3	119/208 (57.2)	240/409 (58.7)	.73
4	79/208 (38.0)	163/409 (39.9)	.65
Risk factors			
Myocardial infarction	35/207 (16.9)	61/407 (15.0)	.54
Atrial fibrillation (AF)	21/206 (10.2)	44/406 (10.8)	.81
Chronic AF	15/206 (7.3)	28/406 (6.9)	.86
Paroxysmal AF	7/204 (3.4)	20/402 (5.0)	.38
Ever smoking	115/205 (56.1)	220/409 (53.8)	.59
Current smoker	38/205 (18.5)	102/409 (24.9)	.07
Former smoker	95/203 (46.8)	180/403 (44.7)	.62
Hypertension	151/208 (72.6)	302/407 (74.2)	.67
Carotid	17/208 (8.2)	20/409 (4.9)	.10
Left endarterectomy	10/208 (4.8)	9/409 (2.2)	.08
Right endarterectomy	9/208 (4.3)	9/409 (2.2)	.14
Left angioplasty/stent	1/207 (0.5)	2/407 (0.5)	.45 [§]
Right angioplasty/stent	2/207 (1.0)	5/408 (1.2)	.31 [§]
Deep vein thrombosis	13/207 (6.3)	19/407 (4.7)	.40
Pulmonary embolus	5/206 (2.4)	4/408 (1.0)	.16 [§]
Peripheral vascular disease	22/204 (10.8)	27/401 (6.7)	.08
Migraine headache	22/204 (10.8)	59/403 (14.6)	.19
Hyperlipidemia	127/207 (61.4)	242/401 (60.4)	.81
Congestive heart failure	13/207 (6.3)	25/408 (6.1)	.94
Diabetes mellitus	54/208 (26.0)	128/407 (31.5)	.16
TOAST ischemic stroke subtype ^{//}			.20
Large vessel	53/208 (25.5)	108/406 (26.6)	.77
Cardioembolism	24/208 (11.5)	40/406 (9.9)	.52
Small vessel	68/208 (32.7)	160/406 (39.4)	.10
Other determined etiology	11/208 (5.3)	10/406 (2.5)	.07
Undetermined etiology	52/208 (25.0)	88/406 (21.7)	.35

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

* Values are n/N (%) unless indicated otherwise.

[†] 1 proband with missing age.

[#]2 probands with missing race.

^{\$}Fisher exact test due to low cell counts.

// 5 probands without blood draw missing TOAST subtyping.