Familial Clustering of Stroke According to Proband Age at Onset of Presenting Ischemic Stroke

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Background and Purpose—The magnitude of inherited risk of stroke may lessen with age, and this would have implications for optimizing genomic approaches to identifying genetic risk factors for stroke. We investigated the relationship between age and inherited risk of stroke.

Methods—Family histories of stroke were obtained in systematic interviews with 310 adult men and women with recent CT- or MR-confirmed ischemic stroke. Probability of stroke in first-degree relatives was analyzed by logistic regression, adjusting for sibship size.

Results—The probability of having a sibling with stroke increased as proband age at stroke presentation increased. Per decade increase in proband age, the odds ratio was 1.65 (95% confidence interval [CI], 1.20 to 2.28; \( P = 0.002 \)) for a concordant sibling and 1.69 (95% CI, 1.15 to 2.49; \( P = 0.008 \)) for \( \geq 2 \) first-degree relatives with a history of stroke.

Conclusions—Clustering of stroke was not greater in families with probands manifesting symptoms of stroke in earlier than later adulthood. The relationship between proband age and positive family history of stroke does not suggest an upper age-limit cutoff for genomewide linkage studies. (Stroke. 2003;34:e89-e91.)

Key Words: age of onset | genetics | history | stroke, ischemic
were retained in the model only if they were significant at the 0.05 level. To visualize the associations, graphs showing the estimated probability of concordance as a function of age and number of siblings were prepared by using generalized additive models. A test for a heterogeneous association between concordance and age was carried out with the generalized rank-sum test. 

Results

A total of 310 probands (median age, 75 years; mean ± SD, 72 ± 12 years; range, 26 to 97 years; 48% women) were enrolled between January 1999 and August 2000; 188 (61%) were enrolled in Rochester and 122 (39%) in Jacksonville. Of the total, 251 (81%) of probands were incident cases of ischemic stroke. Proband age distribution at stroke presentation was nearly gaussian; 292 probands (94.2%) were older than age 50 years. Median time from stroke onset to enrollment was 5 days.

The probability of having a concordant sibling increased monotonically with sibship size (Fig. 1A). The probability of having a concordant parent was not affected by sibship size (Fig. 1B). Because of the relationship between the probability of having a concordant sibling and sibship size, all other analyses were adjusted for number of siblings per pedigree. Only probands who had at least 1 sibling were included in the subsequent analyses (n=283).

Regression analyses (Table) showed that increases in proband age significantly increased the probability of having a concordant sibling but not the probability of having a living concordant sibling or the probability of having a concordant parent. Increases in proband age also significantly increased the probability of having at least 2 first-degree relatives, either siblings or parents, with a history of stroke.

When the models were fit with only probands 50 years of age or older, results were virtually identical except in the model for risk of having a concordant sibling or parent, in which the odds ratio for age by decade was 1.11 (95% confidence interval [CI], 0.86 to 1.43; P=0.445). Figure 2 illustrates the relationship between proband age and probability of a concordant sibling for probands with stroke onset at age 50 years or older.

Attempts at modeling the relationship using a quadratic function or a 2-stage linear function did not explain the probability of having an affected sibling any better than the simple linear model. We also examined the possibility that clustering of stroke in siblings occurs at younger ages (reflecting a genetic etiology) as well as at older ages (reflecting an age-driven etiology). The generalized rank-sum test for a heterogeneous association between concordance of stroke among siblings and proband age was not significant.

Discussion

In this family history study of adult men and women presenting with a recent ischemic stroke, we found that the probability of stroke clustering within a sibship showed a roughly monotonic rise with proband age at stroke onset. The same pattern of clustering within sibships may not apply to children or young adults. A general tendency for sibling stroke rates to rise with proband age is expected because siblings and probands age concurrently. However, our purpose was to investigate whether the age effect might be overwhelmed by a genetic predisposition to stroke that might play a greater role in younger than in older patients. We did not find greater clustering of stroke within younger sibships.
reported stroke histories in first-degree relatives, it was reassuring to find that the probability of having a stroke-affected sibling increased linearly as a function of sibship size. This finding serves as a positive control for the validity of proband-reported sibling stroke histories. Absence of a relationship between parental history of stroke and sibship size serves as a negative control.

We conclude that it would be inappropriate at present to target only younger adults in genomic studies that assess possible ischemic stroke risk factors or polymorphisms. The ongoing Siblings With Ischemic Stroke Study does not specify an upper age limit for proband eligibility. Investigators from the deCODE Genetics group have successfully identified a stroke susceptibility locus on 5q12 at D5S2080 (designated STRK1; LOD score, 4.86 for ischemic stroke and TIA) without limiting their genomewide search to any one particular age group.15 Once risk factor genes are identified, it would be of interest to assess relative risk for stroke as a function of age.

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References
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