Clinical Sciences

Genetic Epidemiology of Spontaneous Subarachnoid Hemorrhage
Nordic Twin Study

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Background and Purpose—It would be essential to clinicians, familial aneurysm study groups, and aneurysm families to understand the genetic basis of subarachnoid hemorrhage (SAH), but there are no large population-based heritability estimates assessing the relative contribution of genetic and environmental factors to SAH.

Methods—We constructed the largest twin cohort to date, the population-based Nordic Twin Cohort, which comprised 79 644 complete twin pairs of Danish, Finnish, and Swedish origin. The Nordic Twin Cohort was followed up for 6.01 million person-years using nationwide cause-of-death and hospitalization registries.

Results—One hundred eighty-eight fatal and 321 nonfatal SAH cases were recorded in the Nordic Twin Cohort. Thus, SAH incidence was 8.47 cases per 100 000 follow-up years. Data for pairwise analyses were available for a total of 504 SAH cases, of which 6 were concordant (5 monozygotic and 1 opposite sex) and 492 discordant twin pairs for SAH. The concordance for SAH in monozygotic twins was 3.1% compared with 0.27% in dizygotic twins, suggesting at most a modest role for genetic factors in the etiology of SAH. The population-based probability estimate for SAH in dizygotic siblings of a patient with SAH is 0.54%, and only 1 of 185 full siblings experience familial SAH. The corresponding risk of SAH in monozygotic twins is 5.9%. Model-fitting, which was based on the comparison of the few monozygotic and dizygotic pairs, suggested that the estimated heritability of SAH is 41%.

Conclusions—SAH appears to be mainly of nongenetic origin, and familial SAHs can mostly be attributed to environmental risk factors. (Stroke. 2010;41:2458-2462.)

Key Words: familial • intracranial aneurysm • SAH • twin • genetics

The incidence of subarachnoid hemorrhage (SAH) of approximately 7.8 cases per 100 000 person-years in non-Finnish countries1 together with a 30-day mortality rate of 40% to 60% ranks SAH among the deadliest vascular emergencies. Compared with most Western countries, the risk of SAH is nearly 3 times as high (incidence 21.4 per 100 000 person-years) in Finland,1 the reason for which remains unclear. Up to 90% of spontaneous SAH cases are due to rupture of an intracranial aneurysm.2 Important modifiable risk factors for SAH include cigarette smoking (relative risk, 2.2 to 3.1), high blood pressure (relative risk, 2.5 to 2.6), and heavy (>150 g/week) alcohol consumption (relative risk, 1.5 to 2.1).3 It has been estimated that the population-attributable risk of cigarette smoking is 20% for SAH, whereas high blood pressure accounts for 17% and alcohol abuse for 11% to 21% of SAHs.4

Familial risk is defined as the probability of a healthy family member being affected by the same disease, which has already affected at least 1 other family member. Familial risk of SAH depends on a number of factors, including especially genetic and environmental factors as well as the number and ages of relatives at risk. In general, any population-based heritability estimate value of <50% indicates that environmental variance is greater than genetic variance. Given the
Table 1. Characteristics of the Nordic Twin Cohort

<table>
<thead>
<tr>
<th></th>
<th>Danish Same-Sex Cohort</th>
<th>Danish Opposite-Sex Cohort</th>
<th>Finnish Cohort</th>
<th>Swedish Older Cohort</th>
<th>Swedish Younger Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline data collection</td>
<td>Varies</td>
<td>Varies</td>
<td>1975</td>
<td>1963</td>
<td>1972</td>
</tr>
<tr>
<td>Mean age in years at baseline (range)</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>36 (18–95)</td>
<td>49 (36–75)</td>
<td>28 (14–46)</td>
</tr>
<tr>
<td>No. twin individuals</td>
<td>52,386</td>
<td>27,530</td>
<td>26,326</td>
<td>21,163</td>
<td>32,495</td>
</tr>
<tr>
<td>No. complete pairs</td>
<td>26,184</td>
<td>13,765</td>
<td>12,898</td>
<td>10,581</td>
<td>16,236</td>
</tr>
<tr>
<td>Females, %</td>
<td>48</td>
<td>50</td>
<td>51</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>Monozygotic twins, %</td>
<td>35</td>
<td>0</td>
<td>31</td>
<td>35</td>
<td>39</td>
</tr>
</tbody>
</table>

*Hospitalized cases of SAH.

Determination of Zygosity
For all 3 national cohorts, zygosity was determined by standardized questionnaire methods. The questionnaire methods have been validated, and they correctly classify >95% of twin pairs as monozygotic (MZ) or dizygotic (DZ).

Data Analysis
Nonfatal and fatal SAHs were recorded during the follow-up time, which was different for every cohort (Table 1). Twin pairs were defined as discordant twin pairs for SAH if only 1 twin had an SAH during the follow-up time regardless of whether the cotwin had died from another cause. Twin pairs were discordant for SAH if both twins had an SAH. Sex, zygosity, and age effects on the incidence of SAH were tested by a Cox proportional hazard model, for which the follow-up time was calculated from the time point of the baseline measurement to the date of SAH, death from other causes, emigration, or the end of the follow-up period. The effect of the twin pair sample design was taken into account using the cluster option of the Stata statistical package (Version 9.2). The analyses were adjusted for birth date, study cohort and sex in the pooled analyses for men and women were included as a stratum variable, that is, allowing its sample design to be taken into account using the cluster option of the Stata statistical package (Version 9.2).

Risk and Genetics of SAH
Two different estimators of the familial risk of SAH were used. To estimate the risk that a twin is affected given an affected cotwin, probandwise concordance was computed by dividing the number of cases among concordant twin pairs by the total number of cases.

Incident cases of SAH as well as all deaths with the underlying cause of death coded as an SAH or hospitalization for an SAH (the main cause) were classified as cases. After an SAH (fatal or nonfatal) in a twin, the median follow-up time for the cotwin was computed as the time until an SAH (fatal or nonfatal) occurred, emigration, or end of follow-up. Characteristics of the twin cohorts are presented in Table 1.

Results
The total number of twin subjects with SAH in the Nordic Twin Cohort was 509, but the follow-up data of cotwins were not available for 5 patients, and they were thus excluded from all pairwise analyses. The follow-up time was 6.01 million person-years for all individuals (Table 2). Of 509 twins with an SAH, 295 (58%) were female and 214 (42%) were male. SAH incidence in the Nordic Twin Cohort was 8.47 cases per 100,000 follow-up years (26.74, 12.43, 15.56, and 4.27 cases...
per 100,000 follow-up years in the Finnish, Swedish younger, Swedish older, and Danish cohorts, respectively; if the follow-up for the Danish cohort is started after the age of 20 years, the incidence is 7.16 cases per 100,000 follow-up years; see the Figure). The hazard ratio for women compared with men was 1.36 (95% CI, 1.10 to 1.69) for SAH incidence, whereas no difference in age- and sex-adjusted SAH incidence and mortality was found between MZ and DZ twin individuals in the pooled data (P = 0.09 and P = 0.24, respectively). The median age at SAH diagnosis was 53.6 years (interquartile range, 43.0 to 65.5 years; Table 2).

We identified only 6 twin pairs (12 twin subjects) concordant for SAH, and 5 of these were MZ twin pairs (Table 2). Patient characteristics for the concordant twin pairs are depicted in Table 3. In the 6 concordant pairs, the median time between the onset of SAH in both twin siblings was 3.5 years (range, 0 to 13 years). In comparison, the median follow-up time for all cotwins after SAH in the other twin (index case) was nearly 3-fold (9.7 years; interquartile range, 3.5 to 16.3 years; Table 2), which implies that a longer follow-up would unlikely show more concordant pairs. The probandwise concordance for all cases was 5.9% in MZ pairs. Furthermore, the tetrachoric correlation in liability was 0.42 (95% CI, 0.24 to 0.56). For DZ pairs, the probandwise concordance was 0.54%, and the tetrachoric correlation in liability was 0.054 (95% CI, 0.0 to 0.26). Of the 492 discordant twin pairs (147 MZ and 345 DZ pairs), 184 (55 MZ and 129 DZ pairs) were discordant for fatal SAH (Table 2). Based on the comparison of the few MZ and DZ pairs, model-fitting estimate of heritability was 41% (95% CI, 23.7% to 55.5%).

### Discussion

In this first and only large population-based heritability study assessing the relative contribution of genetic factors to SAH, we identified only 6 (1.2%) concordant pairs (5 MZ and opposite sex) of 498 twin pairs with SAH. Only 1 discordant MZ pair was relatively young at the time of SAH. The probandwise concordance value of 0.54% for DZ twins depicts the probability (recurrence risk) of SAH in full (same father and mother) singleton siblings, who, like DZ twins, share 50% of their segregating genes. This means that in families with 1 SAH patient, only 1 of 185 siblings experiences SAH. For MZ twins, who share, in addition to the genetic sequence, numerous environmental exposures and experiences, the probandwise concordance value was 5.9%, which means that every 17th MZ twin will experience an SAH after an occurrence of an SAH in the cotwin. The MZ tetrachoric correlation value (42%) implies a moderate size

### Table 2. Follow-Up Times of the Cohorts, Concordant Twin Pairs for SAH, the Median Age at Diagnosis of Nonfatal SAH, and the Median Age of Death From SAH Among the 79,664 Twin Pairs

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. fatal SAH cases</th>
<th>No. concordant fatal pairs</th>
<th>No. all SAH cases</th>
<th>No. concordant pairs</th>
<th>Age of death from SAH in years and IQR†</th>
<th>Age at diagnosis of all SAHs in years and IQR†</th>
<th>Cotwin follow-up time in years and IQR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same-Sex Cohort</td>
<td>29</td>
<td>0</td>
<td>96</td>
<td>2</td>
<td>57.9 (47.5–72.1)</td>
<td>54.5 (41.8–66.8)</td>
<td>7.9 (4.3–13.5)</td>
</tr>
<tr>
<td>Opposite-Sex Cohort</td>
<td>19</td>
<td>1</td>
<td>67</td>
<td>1</td>
<td>46.0 (41.3–51.6)</td>
<td>46.0 (38.3–52.3)</td>
<td>8.9 (3.8–16.3)</td>
</tr>
<tr>
<td>Finnish Cohort</td>
<td>60</td>
<td>0</td>
<td>137</td>
<td>0</td>
<td>56.1 (46.7–68.2)</td>
<td>51.9 (41.0–64.9)</td>
<td>8.6 (5.6–19.0)</td>
</tr>
<tr>
<td>Swedish Older Cohort</td>
<td>49</td>
<td>1</td>
<td>93</td>
<td>2</td>
<td>69.5 (62.8–78.1)</td>
<td>69.8 (63.5–77.4)</td>
<td>12.6 (6.7–18.0)</td>
</tr>
<tr>
<td>Swedish Younger Cohort</td>
<td>31</td>
<td>1</td>
<td>116</td>
<td>1</td>
<td>50.0 (39.7–54.3)</td>
<td>50.0 (41.0–56.9)</td>
<td>10.2 (3.8–19.8)</td>
</tr>
</tbody>
</table>

*Hospitalized cases of SAH.
†Median together with interquartile range (IQR) (ie, lower [25th percentile] and upper [75th percentile] quartiles).

### Table 3. Patient Characteristics of Concordant Twin Pairs

<table>
<thead>
<tr>
<th>Nationality</th>
<th>Zygosity</th>
<th>Sex</th>
<th>Age at Death</th>
<th>Age at SAH Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>DZ</td>
<td>M/F</td>
<td>53/52</td>
<td>53/52</td>
</tr>
<tr>
<td>Denmark</td>
<td>MZ</td>
<td>M/M</td>
<td>49/48</td>
<td>48/48</td>
</tr>
<tr>
<td>Denmark</td>
<td>MZ</td>
<td>M/M</td>
<td>…/…</td>
<td>72/68</td>
</tr>
<tr>
<td>Finland</td>
<td>MZ</td>
<td>F/F</td>
<td>65/77</td>
<td>64/72</td>
</tr>
<tr>
<td>Finland</td>
<td>MZ</td>
<td>F/F</td>
<td>85/87</td>
<td>85/82</td>
</tr>
<tr>
<td>Swedish young</td>
<td>MZ</td>
<td>F/F</td>
<td>34/21</td>
<td>34/21</td>
</tr>
</tbody>
</table>

M indicates male; F, female.
broad-sense heritability (additive and nonadditive factors), which can result from additive genetic effects, genetic effects due to dominance, and genome–environment interaction effects shared by the twins. If the heritability was due only to additive genetic effects, the tetrachoric correlation in the DZ pairs should be 0.21. However, it was considerably lower (0.054), which implies the presence of effects due to dominance or the combination of genes at multiple loci. Model-fitting based on the comparison of the few MZ and DZ pairs showed that the estimated heritability was 41% (95% CI, 23.7% to 55.5%), which is very similar to the MZ tetrachoric correlation value. Previously, we have reported that the estimated heritability for prostate cancer, colorectal cancer, and breast cancer is 42%, 35%, and 27%, respectively.10

The strengths of our study include: (1) the population-based study cohorts with both fatal and nonfatal SAH cases; (2) the exceptionally large number of twins surveyed; (3) the satisfactory number of SAH events found among twins; (4) the reliable estimate of the incidence rate of SAH (8.47 cases per 100 000 follow-up years) in comparison with previous reports; 5) the long-term (almost lifetime) prospective follow-up of unaffected cotwins; 6) the similar centralized and high-quality cause-of-death and hospitalization registers, which have been widely used in thousands of previous studies in Nordic countries; and 7) the presence of the middle-aged large birth cohort. Because being a sibling of an affected relative has been reported to increase the risk of having an aneurysm or SAH more than being a parent or child,18–20 the strength of evidence from our study of twin siblings is even more significant. The fact that twins are siblings of the same age eliminates the possibility of large phenotypic differences related to age differences, which complicate the analyses of genetic studies in singleton siblings and nuclear families. In addition, the systematic ignoring of extramarital paternity in genetic studies in singleton siblings and nuclear families. In addition, the systematic ignoring of extramarital paternity in family-based studies of heritability may result in some bias, whereas twin siblings rarely have different fathers.

The major drawbacks include the following: (1) discordant cotwins were not traced (practically impossible) to check whether preventive treatments for SAH had been given; (2) the relatively small proportional representation of young (<25 years of age) individuals in the cohorts; (3) surviving discordant cotwins were not invited to have an MRI angiogram to estimate the familial prevalence of aneurysms (which was not the purpose of this study); and (4) register-based diagnoses may contain errors. It is very unlikely that a significant number of endo- or exovascular procedures had been conducted before the rupture of an aneurysm to prevent a SAH in a discordant cotwin because 62% of the SAH incidents happened before 1993 when screening of family members was not a routine procedure nor a recommendation in Nordic countries. We believe that it is highly unlikely that the possible ignoring of rare events of SAHs at young ages may have affected our conclusions drawn.

Due to inevitable difficulties in conducting epidemiological studies on a rare, dichotomous and complex disease trait, some methodological shortcomings may have influenced previous interpretations. It has been virtually impossible to conduct a large enough population-based familial SAH study containing multiple affected individuals and longitudinal (several decades of follow-up) family data. Such a study cannot be done either at present or in the future, because many unruptured familial and incidental intracranial aneurysms are currently treated. Previous reports suggest that familial (at least 1 first-degree relative with SAH) occurrence of SAH is an important nonmodifiable risk factor for SAH.5,20–22 Understandably, none of these studies have been able to control (1) risk factors (ie, confounding factors including cigarette smoking, high blood pressure, heavy alcohol consumption) among study and control subjects; (2) the number of full-sisters and other first-degree family members of the cases and control subjects when reporting incidence of SAH in families; and (3) consanguinity among family members. In accordance with our results, a recent large population-based (hospital-admitted, mainly nonfatal index cases) case–control (matched for age and sex, not for risk factors) study of the risk of familial SAH reported that only 10 (0.19%) of 5282 hospital-admitted patients with SAH have ≥2 first-degree relatives with an SAH (ie, ≥3 patients with SAH in the family), and 156 (2.95%) patients with SAH have 1 affected first-degree relative in the family.23 In total, only 166 (3.14%) of 5282 patients with SAH have ≥1 affected first-degree family members.23 The OR (not relative risk) of familial SAH for individuals with ≥1 affected first-degree relatives was 2.28 when compared with age- and sex-matched control subjects (ie, no adjustment for, for example, confounding risk factors), of which 1.41% had SAH cases in the family.23 If the lifetime relative risk of SAH of a family member was 2-fold or even 15-fold higher than in the general population, for which the lifetime risk has been estimated to be 0.7%,23 the absolute lifetime risk of SAH would be 1.4% and 10.5%, respectively. The recent population-based data suggest an absolute lifetime risk of SAH of 26% (OR, 51.0) for individuals with ≥2 first-degree relatives with SAH.23 This very high lifetime risk estimate surely warrants screening programs for these rare SAH families.

Our results with the heritability estimate of 41% suggest that there is a moderate role for genetic factors in the etiology of SAH, whereas environmental factors play a significant role in SAH susceptibility at the population level. This relatively low heritability estimate for a complex trait suggests that very large genomewide association studies, similar to recent studies of intracranial aneurysms,24,25 or whole genome linkage studies are necessary to identify genomic variants and candidate genes underlying the risk for SAH. Alternatively, genetic studies should focus on identifying rare variants in the families with multiple affected members.

**Summary**

In brief, our results together with the previous results23 suggest that a positive family history accounts for, at the most, only a small percentage of SAHs, not for 11% of the population-attributable risk for SAH.4 Of these rare familial SAH cases, possibly only a minority is due to the clustering of susceptibility genes. It is conceivable that familial clustering of confounding risk factors (eg, cigarette smoking, high blood pressure, and heavy alcohol consumption) makes a significant contribution to previously reported incidence rates
of familial SAHs. On the basis of current evidence, screening of familial aneurysms may be warranted at least for first-degree family members with $\geq 2$ SAHs in the family and to a monozygotic sibling of a MZ twin with a positive history of SAH.

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Disclosures

None.

References


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自然発症くも膜下出血の遺伝疫学 — 北欧双生児研究

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Abstract

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図 本研究コートのKaplan-Meier生存推定値。