Family History in Ischemic Stroke Before 70 Years of Age
The Sahlgrenska Academy Study on Ischemic Stroke

Katarina Jood, MD; Claes Ladenvall, MSc; Annika Rosengren, MD, PhD; Christian Blomstrand, MD, PhD; Christina Jern, MD, PhD

Background and Purpose—Results from twin and family history studies of ischemic stroke suggest that future molecular genetic studies should focus on strictly defined stroke subtypes and younger cases. Accordingly, we investigated stroke subtypes, vascular risk factors, and family history in a large study of patients with ischemic stroke onset before age 70 years.

Methods—Six hundred consecutive white participants with ischemic stroke (18 to 69 years) and 600 age- and sex-matched controls were examined for vascular risk factors and family history of stroke and myocardial infarction (MI). Stroke subtype was defined using Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.

Results—Family history of stroke was associated with overall ischemic stroke (multivariate odds ratio [OR], 1.75; 95% confidence interval [CI], 1.26 to 2.43), large-vessel disease (LVD) (OR, 1.88; 95% CI, 1.02 to 3.44), small-vessel disease (SVD, OR, 1.79; 95% CI, 1.13 to 2.84), and cryptogenic stroke (OR, 1.70; 95% CI, 1.13 to 2.56), but not with cardioembolic stroke. Family history of MI was strongly associated with LVD (OR, 3.25; 95% CI, 1.74 to 6.07), whereas no significant association were observed for other subtypes. We also found an independent association between family history of stroke and a favorable outcome after 3 months.

Conclusion—Family history of stroke is an independent risk factor for ischemic stroke with onset before age 70 years. For the first time to our knowledge, we report this association not only for LVD and SVD but also for cryptogenic stroke, implying that future studies of the genetics of ischemic stroke should target these 3 subtypes. (Stroke. 2005;36:1383-1387.)

Key Words: genetics • heredity • stroke classification • stroke, ischemic • risk factors

Twin, family, and animal studies support a role for genetic factors in stroke.1-2 However, candidate gene studies have been inconclusive.2 In part, this could be explained by the heterogeneous pathophysiology of stroke. Because etiological subtyping requires considerable work-up, few studies have had sufficient power for analysis of the different subtypes.

One way to proceed is to design targeted molecular genetic studies based on a better understanding of the genetic epidemiology of stroke. Floßman et al recently conducted a systematic review of all published twin studies on stroke and studies measuring family history of stroke.3 This meta-analysis confirmed a genetic contribution to stroke, but concluded that major heterogeneity, insufficient detail, and potential publication bias undermine reliable interpretation of published family history studies. With respect to heterogeneity, many studies did not differentiate between ischemic and hemorrhagic stroke and only 2 studies assessed etiological subtypes of ischemic stroke in detail.3-5 Interestingly, these 2 case-control studies found an association between family history and large- and small-vessel disease, but not with cardioembolic or undetermined stroke. Similar findings were observed in the Oxfordshire case–case studies.6

The meta-analysis suggested a stronger genetic influence in younger age groups.3 Similar findings were recently reported from the Oxfordshire studies.6 However, few studies have investigated family history in patients with ischemic stroke at younger ages, and most of those are small and have not assessed stroke subtypes in detail.7-10

The Sahlgrenska Academy Study of Ischemic Stroke (SAHL-SIS) was designed to include patients with ischemic stroke before the age of 70 years with careful assessment of etiological subtypes. In this first report, we investigate the association between ischemic stroke subtypes and vascular risk factors including family history of stroke and myocardial infarction (MI).

Subjects and Methods

Study Population

White patients presenting with new or recurrent acute ischemic stroke before the age of 70 years were consecutively recruited from 4 Stroke Units in Western Sweden. Recruitment began in August 1998 and continued until 600 patients had been enrolled in December 2003. Of 645 eligible stroke patients, 29 were unwilling to participate and 16 died before the patient or a next-of-kin could give detailed informed consent.

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For each case, one white control without clinical atherothrombotic disease, matched for age (±1 year), sex, and geographical residence area was randomly selected from participants in a population-based health survey11 (Gothenburg residents) or the Swedish Population Register (Skövde and Borås residents, and controls younger than 30 years). If a selected control did not respond, refused to participate, or was ineligible because of previous cardiovascular disease, a second and then a third matched control was invited. Of the 1107 selected controls, 208 did not respond, 191 were unwilling to participate, and 108 were excluded because of a history of stroke, coronary or peripheral artery disease, or signs of ischemic heart disease on resting electrocardiogram according to the Minnesota code (1982).

The study was approved by the Ethics Committee of Göteborg University, and data handling procedures were approved by the National Computer Data Inspection Board. All participants gave their written informed consent. Next-of-kin consented for those participants who were unable to communicate.

Data Collection and Risk Factor Definition
All patients were examined by a physician trained in stroke medicine. Examinations were performed during the acute stage and at a follow-up visit after 3 months. Controls were examined once. Among all participants, information on demographic characteristics and risk factors was collected using a structured questionnaire. Weight and height were measured. Blood pressure was measured after 10 minutes at rest in the supine position. Blood samples were drawn after an overnight fast of >8 hours. Hypertension was defined by pharmacological treatment for hypertension, systolic blood pressure ≥160 mm Hg, and/or diastolic blood pressure ≥90 mm Hg. Diabetes was defined by diet or pharmacological treatment, fasting plasma glucose ≥7.0 mmol/L, or fasting blood glucose ≥6.1 mmol/L. Hyperlipidemia was defined by pharmacological treatment, total fasting serum cholesterol >5.0 mmol/L, and/or low-density lipoprotein >3.0 mmol/L. Among cases measurements performed at 3-month follow-up were used to define hypertension, diabetes, and hyperlipidemia. Body mass index was calculated as kg/m², and among cases, weights and heights measured in the acute stage were used. Smoking history was coded as current versus never or former (smoking cessation at least 1 year before inclusion in the study). Occupational class was coded according to the Swedish socioeconomic classification system. The score was dichotomized, and employed and self-employed professionals, higher civil servants, executives, and intermediate nonmanual employees formed one category (corresponding to higher education) and all others formed a second category (corresponding to lower education). Among cases, stroke outcome was evaluated after 3 months using the modified Rankin Scale (score 0 to 6). The score was dichotomized for death or dependency (score of 3 to 6) versus a favorable outcome (score of 0 to 2).

A complete first-degree family history of stroke and MI was obtained using a written questionnaire and structured interview. Cases were interviewed 3 months after stroke onset and controls at the time of their examination. Participants were asked whether parents and siblings were alive or dead, whether they had been affected by stroke or MI, and at what age. When a participant was unable to provide an adequate family history, a collateral history from a relative was sought. A positive family history was defined as history of stroke or MI in a first-degree relative. We did not distinguish hemorrhagic and ischemic stroke in first-degree relatives because of difficulty differentiating these by history alone. When the cause of death or disease in a family member was unknown, family history in this subject was defined as negative.

Stroke Subtyping
All cases underwent ECG and neuroimaging with CT, and 62% underwent MRI. Extracranial and vertebral duplex ultrasound (82%), MR angiography (31%), cerebral angiography (7%), transcranial Doppler ultrasound (24%), and transhoracic and/or transesophageal echocardiography (78%) were performed when clinically indicated. Each case was classified according to Trial of Org 10172 in Acute Treatment (TOAST) criteria13 into the etiological categories large-vessel disease (LVD), small-vessel disease (SVD), and cardioembolic (CE) stroke, other determined cause, cryptogenic stroke, and undetermined stroke. Cryptogenic stroke was defined when no cause was identified despite an extensive evaluation. Undetermined stroke included cases for which more than one cause was identified or when the evaluation was cursory. Adjudication of subtype was centralized and performed by 2 neurologists (K.J., C.B.). The analysis by subtypes was confined to the 4 major subtypes: LVD, SVD, CE, and cryptogenic stroke.

Statistical Methods
Descriptive statistics are presented as frequencies or mean values and standard deviations. Differences between groups were examined with the χ² test for proportions and with Student t test for continuous variables. Multivariate odds ratios (ORs) and 95% confidence intervals (CIs) for family history variables and risk factors in cases versus controls were calculated using conditional logistic regression analysis. The multivariate model included age, sex, smoking status, occupational class, hypertension, diabetes, hyperlipidemia, and family history variables. Body mass index was not significantly associated with ischemic stroke or family history variables and therefore not included in the multivariate model. ORs were calculated for overall ischemic stroke and for the 4 major subtypes. Each subtype was compared with the whole control group, and unconditional logistic regression analysis was therefore applied for calculation of ORs among subtypes. Differences between risk factor subtype associations were assessed through analysis of the generalized logits for the subtypes versus controls. Associations between functional outcome and family history variables were examined in cases. Adjustment for multiple testing was not made. Data were analyzed using SPSS 12.0 and SAS 8.2 package. Statistical testing was performed at a 2-tailed P<0.05 level.

Missing Values
Information about diabetes was missing in 2 participants, hypertension in 9, smoking habits in 3, hyperlipidemia in 56, and occupational class in 36. All controls provided a family history. In 38 cases it was not possible to obtain a family history because of intervening death (n=8), being adopted (n=1), dysphasia, and no collateral history available (n=4), or the patient refused to take part in the follow-up examination or was unwilling to provide a family history (n=25). In the logistic regression, dummy variables were introduced for missing values for categorized variables.

Results
The distribution of stroke subtypes was as follows: LVD (n=73, 12%); SVD (n=124, 21%); CE (n=98, 16%); cryptogenic stroke (n=162, 27%); other determined cause (n=51, 9%); and undetermined stroke (n=92, 15%). Demographic and risk factor profiles according to the 4 major stroke subtypes are given in Table 1. There were no significant differences with regard to number of siblings between cases and controls or between subtypes. Hypertension, diabetes mellitus, hyperlipidemia, smoking, family history of stroke, and occupation classified as lower education were all significantly more common in cases than in controls.

Demographic characteristics and risk factor profiles according to family history status are given in Table 2. Among participants reporting a positive family history, 162 (25%) had a family history of both stroke and MI, 229 (35%) had a family history of stroke only, and 255 (40%) had a family history of MI only. The risk factor distribution between the 2 latter groups did not differ significantly (data not shown).

The multiple adjusted ORs for overall ischemic stroke and the major etiological subtypes according to vascular risk factors and family history variables are presented in Table 3.
Notably, risk factor–stroke associations differed by subtype (P < 0.001 for hypertension, diabetes, and smoking; P < 0.05 for family history of stroke; and P < 0.01 for family history of MI). Family history of stroke was significantly associated with overall ischemic stroke. Exclusion of cases who reported history of coronary and/or peripheral artery disease (n = 109) did not influence this result.

Analysis by stroke subtypes showed that family history of stroke was associated with LVD, SVD, and cryptogenic stroke, but not with CE stroke. Family history of MI was strongly associated with LVD, whereas no other significant independent association was observed.

Functional outcome after 3 months follow-up varied by stroke subtype. Death or dependency occurred in 22% of patients with overall ischemic stroke, 27% in LVD, 9% in SVD, 31% in CE, and 20% in cryptogenic stroke. Stroke subtype was therefore entered into multivariate models examining the influence of vascular risk factors and family history variables on outcome. Patients reporting a positive family history of stroke had a lower risk of an unfavorable outcome (modified Rankin Scale score ≥3; multivariate OR, 0.53; 95% CI, 0.34 to 0.84; P < 0.01). Family history of MI and vascular risk factors were not significantly associated with functional outcome (data not shown). Family history was not available for 38 cases. To examine a possible bias caused by difficulties to obtain family history from the most severe cases, we performed an analysis in which the dead and dependent cases with missing family history (n = 14) were assigned positive family history, and cases with favorable outcome and missing family history (n = 7) were assigned negative family history. In this analysis, the OR of death and dependency for family history of stroke was 0.65 (95% CI, 0.42 to 1.00; P = 0.05).

**TABLE 1. Risk Factors and Family History Variables in Cases, Controls, and the Major Stroke Subtypes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=600)</th>
<th>Ischemic Stroke (n=600)</th>
<th>LVD (n=73)</th>
<th>SVD (n=124)</th>
<th>CE (n=98)</th>
<th>Cryptogenic Stroke (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>56 (10)</td>
<td>56 (10)</td>
<td>59 (8)*</td>
<td>58 (7)*</td>
<td>57 (10)</td>
<td>53 (12)†</td>
</tr>
<tr>
<td>Male sex, no. (%)</td>
<td>385 (64)</td>
<td>385 (64)</td>
<td>54 (74)</td>
<td>77 (62)</td>
<td>66 (67)</td>
<td>95 (59)</td>
</tr>
<tr>
<td>N of siblings, mean (SD)</td>
<td>2.1 (1.9)</td>
<td>2.3 (2.0)</td>
<td>2.3 (1.8)</td>
<td>2.3 (2.2)</td>
<td>2.1 (1.6)</td>
<td>2.3 (2.0)</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>224 (37)</td>
<td>354 (59)‡</td>
<td>44 (60)‡</td>
<td>89 (72)‡</td>
<td>50 (51)†</td>
<td>87 (54)‡</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>33 (6)</td>
<td>114 (19)‡</td>
<td>25 (34)‡</td>
<td>26 (21)†</td>
<td>19 (19)†</td>
<td>23 (14)‡</td>
</tr>
<tr>
<td>Hyperlipidemia, no. (%)</td>
<td>403 (67)</td>
<td>413 (76)†</td>
<td>53 (82)*</td>
<td>77 (71)</td>
<td>73 (82)†</td>
<td>107 (71)</td>
</tr>
<tr>
<td>Current smoking, no. (%)</td>
<td>109 (18)</td>
<td>233 (39)‡</td>
<td>39 (53)‡</td>
<td>54 (44)†</td>
<td>34 (35)†</td>
<td>60 (37)‡</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.5 (4.0)</td>
<td>26.5 (4.5)</td>
<td>26.7 (4.6)</td>
<td>26.8 (4.3)</td>
<td>26.8 (4.8)</td>
<td>26.1 (3.9)</td>
</tr>
<tr>
<td>Occupation, lower education, no. (%)</td>
<td>282 (52)</td>
<td>24 (62)‡</td>
<td>43 (67)*</td>
<td>64 (57)</td>
<td>50 (60)</td>
<td>94 (65)‡</td>
</tr>
<tr>
<td>Personal history of CAD and/or PAD</td>
<td>...</td>
<td>109 (18)</td>
<td>21 (29)</td>
<td>10 (8)</td>
<td>40 (41)</td>
<td>16 (10)</td>
</tr>
<tr>
<td>Family history of stroke, no. (%)</td>
<td>162 (27)</td>
<td>229 (41)†</td>
<td>31 (47)†</td>
<td>52 (43)†</td>
<td>30 (34)</td>
<td>61 (40)†</td>
</tr>
<tr>
<td>Family history of MI, no. (%)</td>
<td>202 (34)</td>
<td>215 (38)</td>
<td>41 (62)*</td>
<td>35 (29)</td>
<td>42 (47)*</td>
<td>52 (34)</td>
</tr>
</tbody>
</table>

LVD indicates large-vessel disease; SVD, small-vessel disease; CE, cardioembolic stroke; CAD, coronary artery disease; PAD, peripheral artery disease.

Differences between cases and controls were examined with the \( \chi^2 \) test for proportions and with Student t test for continuous variables.

\*P < 0.05.

†P < 0.01.

‡P < 0.001.

**TABLE 2. Risk Factors by Family History Status**

<table>
<thead>
<tr>
<th>Family History of Stroke and/or MI</th>
<th>No (n=516)</th>
<th>Yes (n=646)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>54 (12)</td>
<td>59 (8)*</td>
</tr>
<tr>
<td>Male sex, no. (%)</td>
<td>335 (65)</td>
<td>411 (64)</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>213 (41)</td>
<td>352 (54)*</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>49 (10)</td>
<td>89 (14)*</td>
</tr>
<tr>
<td>Hyperlipidemia, no. (%)</td>
<td>324 (63)</td>
<td>484 (75)*</td>
</tr>
<tr>
<td>Current smoking, no. (%)</td>
<td>145 (28)</td>
<td>181 (28)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.4 (4.2)</td>
<td>26.5 (4.1)</td>
</tr>
<tr>
<td>Occupation, lower education, no. (%)</td>
<td>261 (51)</td>
<td>386 (60)*</td>
</tr>
</tbody>
</table>

Differences between groups were examined with the \( \chi^2 \) test for proportions and with Student t test for continuous variables.

\*P < 0.05.

†P < 0.01.

‡P < 0.001.

**Discussion**

In this large case-control study of ischemic stroke with onset before age 70 years, we found a significant and independent association with positive family history of stroke, suggesting a genetic contribution. For the first time to our knowledge we report an association not only with LVD and SVD but also with cryptogenic stroke. We also found a significant and independent association between family history of stroke and functional outcome after 3 months.

As expected, established risk factors were related to overall ischemic stroke, but strength of the associations varied by stroke subtype. LVD was strongly associated with smoking and diabetes, and SVD was strongly associated with hyper-
tension. Similar patterns have been reported previously.4,14–16 However, the pronounced association between diabetes and LVD has not been reported before. This may indicate a more important role for diabetes in ischemic stroke caused by LVD in younger age groups.

Our results show a significant positive association between family history of stroke and risk of overall ischemic stroke, which was independent of established risk factors. This is in line with results from a few previous smaller studies on ischemic stroke with younger age at onset.7–10 Association between family history and subtypes has not been studied in detail before in this age group. However, our results on subtypes are in line with a few earlier studies, in which adult patients were included regardless of age and classified according to TOAST. In a large case-control study of ischemic stroke, Jerrard-Dunne et al found association with LVD and SVD, but not with CE or undetermined stroke.4 Similar results have also been reported from a Greek case-control study.5 Furthermore, a lower frequency of family history in CE stroke as compared with the other subtypes has been reported from the Oxfordshire population-based case-control study.6 In contrast, a smaller case–case study reported no subtype differences.17

For the first time to our knowledge we report that family history of stroke is also a risk factor for cryptogenic stroke. The diagnosis of cryptogenic stroke was made when no cause was identified despite an extensive evaluation. In previous studies, cryptogenic stroke has been classified together with cases defined as undetermined because of incomplete diagnostic work-up. This might explain the negative findings. The identification of a possible genetic influence in cryptogenic stroke, the most common subtype in our study, is particularly interesting, because it represents a group in whom factors other than those related to atherosclerosis, lipohyalinosis, and heart disease are of importance. In this group hemostasis and inflammation may have greater influence, and genetic variations in these systems may contribute. We also found a strong and independent positive association between family history of MI and stroke caused by LVD. This is consistent with results from 2 previous studies4,6 and may reflect a shared genetic susceptibility for atherosclerotic disease in coronary and precerebral large vessels.

Functional outcome after 3 months was dependent on TOAST subtype, with the best outcome observed for SVD and the worst for CE stroke. Other investigators15,16 have reported similar results. A novel finding in our study is that family history of stroke was associated with a favorable outcome at 3 months, independent of subtype and vascular risk factors. Thus, our result indicates a stronger genetic susceptibility for less severe ischemic stroke, or, alternatively, better neuroprotective capacity and recovery for genetically influenced ischemic stroke cases. In line with our results, influence of family history on nonfatal but not on fatal stroke18 and on subclinical but not clinical stroke19 has been reported.

Our study has some limitations that need to be considered. First, this study is based on hospitalized cases. However, the stroke admission rate in Sweden is known to be high, with $>94\%$ of the cases in this age group admitted to hospitals.20 Second, case-control studies may be undermined by survival bias. In this study, patients were consecutively recruited at arrival to the hospital. Because the early case fatality rate in ischemic stroke is low, especially for the age group studied here, we do not believe that survival bias has had any major influence on our results. Third, a possible family information bias cannot be excluded, whereby cases are more likely to recall a relative affected by the same illness. However, our results on family history are in line with those reported in prospective studies18,21,22 and recall bias is not likely to explain differences between subtypes. Fourth, in this study, family history was used as a measure of genetic influence. Familial clustering of disease may also be explained by a shared environment. In our study, we considered potential confounding effects of hypertension, diabetes, hyperlipidemia, and lifestyle factors including body mass index, smoking habits, and occupation. However, an effect of some factor shared in families not registered in our study cannot be excluded.

A major strength of this study is the careful assessment of stroke subtypes based on an extensive diagnostic work-up in the majority of the cases. Another strength is that the control

### TABLE 3. Multivariate ORs with 95% CIs for Risk Factors and Family History Variables in Ischemic Stroke and the Major Stroke Subtypes

<table>
<thead>
<tr>
<th>Case/Control</th>
<th>Ischemic Stroke n=600/600</th>
<th>LVD n=73/600</th>
<th>SVD n=124/600</th>
<th>CE n=98/600</th>
<th>Cryptogenic Stroke n=162/600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.71 (1.97–3.74)†</td>
<td>2.11 (1.12–2.96)*</td>
<td>3.91 (2.40–6.39)‡</td>
<td>1.68 (1.03–2.74)*</td>
<td>2.08 (1.39–3.13)‡</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.78 (1.94–3.98)‡</td>
<td>8.30 (4.31–15.97)‡</td>
<td>3.97 (2.44–6.46)‡</td>
<td>2.59 (1.53–4.40)‡</td>
<td>2.62 (1.73–3.98)‡</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.67 (2.21–6.10)‡</td>
<td>11.61 (5.52–24.44)‡</td>
<td>3.76 (2.00–7.19)‡</td>
<td>3.41 (1.70–6.85)†</td>
<td>3.13 (1.65–5.96)†</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.70 (1.20–2.42)‡</td>
<td>1.75 (0.82–3.75)</td>
<td>0.88 (0.52–1.47)</td>
<td>1.85 (1.00–3.43)</td>
<td>1.55 (0.98–2.40)</td>
</tr>
<tr>
<td>Occupation, lower education</td>
<td>1.34 (0.99–1.81)</td>
<td>1.21 (0.64–2.29)</td>
<td>0.93 (0.59–1.58)</td>
<td>1.18 (0.72–1.94)</td>
<td>1.39 (0.92–2.08)</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>1.75 (1.26–2.43)‡</td>
<td>1.88 (1.02–3.44)*</td>
<td>1.79 (1.13–2.84)*</td>
<td>1.27 (0.76–2.12)</td>
<td>1.70 (1.13–2.56)*</td>
</tr>
<tr>
<td>Family history of MI</td>
<td>1.21 (0.88–1.65)</td>
<td>3.25 (1.74–6.07)‡</td>
<td>0.80 (0.49–1.30)</td>
<td>1.56 (0.96–2.53)</td>
<td>0.96 (0.63–1.46)</td>
</tr>
</tbody>
</table>

Variables included in the logistic regressions were age, sex, hypertension, diabetes mellitus, smoking status, hyperlipidemia, occupational class, and family history of stroke and family history of MI.

*P<0.05; †P<0.01; ‡P<0.001, all compared with controls.

Risk factor–stroke associations differed by subtype (generalized logits, see Methods section): P<0.001 for hypertension, diabetes, and smoking; P<0.05 for family history of stroke; and P<0.01 for family history of MI.
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