Genetic Variant on Chromosome 12p13 Does Not Show Association to Ischemic Stroke in 3 Swedish Case-Control Studies

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Background and Purpose—In a genome-wide association study and subsequent case-control studies, the single-nucleotide polymorphism rs12425791 on chromosome 12p13 was reported to be associated with ischemic stroke, but this could not be validated in a recent well-powered study. We therefore investigated whether an association between ischemic stroke and rs12425791 could be detected in 3 different case-control studies from the southwest of Sweden.

Methods—We examined 3606 patients with ischemic stroke and 2528 controls from 3 independent case-controls studies.

Results—No significant association between ischemic stroke and the single-nucleotide polymorphism rs12425791 was detected in any of the 3 case-control samples or in the samples combined. The odds ratio for ischemic stroke for the minor allele in the combined sample was 1.02 (95% CI, 0.93 to 1.13).

Conclusions—The single-nucleotide polymorphism rs12425791 does not confer a substantial risk for ischemic stroke in our population. Our results support a recent large study including other European populations. (Stroke. 2011;42:214-216.)

Key Words: stroke ■ single-nucleotide polymorphism ■ genetic association studies

Materials and Methods

All 3 study populations, the Lund Stroke Register, the Malmö Diet and Cancer study, and the Sahlgrenska Academy Study on Ischemic Stroke, were from the southwest of Sweden. Sample characteristics, data collection, and clinical definitions including those for risk factors have been described elsewhere.5–7

In brief, the Lund Stroke Register is a prospective, epidemiologic study that consecutively includes patients with first-ever stroke from the local area of Lund. Controls without stroke are randomly selected from the same geographic region.6 The Malmö Diet and Cancer study is a prospective, population-based cohort study that includes 28 449 randomly selected men (born between 1923 and 1945) and women (born between 1923 and 1950) with baseline examinations between 1991 and 1996.6 The Sahlgrenska Academy Study on Ischemic Stroke comprises patients who presented with first-ever or recurrent acute IS before reaching the age of 70 years and who were recruited consecutively between 1998 and 2008 at 4 stroke units in western Sweden.7 Controls without cardiovascular disease were randomly selected from the same geographic region as the patients.7

In all 3 studies, the diagnosis of IS was ascertained in accordance with World Health Organization criteria and verified by computed tomography or autopsy. The study was approved by the ethics committee of the University of Gothenburg or by the ethics committee of Lund University. All participants provided informed consent before enrolment. For participants who were unable to communicate, consent was obtained from their next of kin.

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Matsushita et al could not be replicated. On the contrary, results from the present study support the results from the controls. Thus, the association reported by Ikram et al and or in the combined sample of 3606 patients with IS and 2528 SNP rs12425791 and IS in any of the 3 case-control samples separately or in the combined sample (Table). The odds ratio for IS for the minor allele in the combined sample was 1.02 (95% CI, 0.93 to 1.10). Because stroke subtyping has not been performed in all samples, we did not investigate the etiologic subtypes separately.

The present study did not detect an association between the analyzed SNP and IS. In addition, the minor allele frequency detected in our study (0.17) is similar to that reported in the genome-wide association study by ISGC and WTCCC2.2 Our results further underscore the importance of black ancestry or in samples from Chinese and Pakistani subjects.2 In conclusion, no association between the SNP rs12425791 and IS could be detected in 3 large, independent samples from the southwest of Sweden, which supports findings from the recent meta-analysis by ISGC and WTCCC2.2

In conclusion, no association between the SNP rs12425791 on chromosome 12p13 and IS could be detected in 3 large, independent samples from the southwest of Sweden, which supports findings from the recent meta-analysis by ISGC and WTCCC2.2 Our results further underscore the importance of independent replication of novel genetic findings.

### Table. Baseline Characteristics for the 3 Case-Control Samples as Well as Genotype Frequencies and Odds Ratios for the SNP rs12425791

<table>
<thead>
<tr>
<th></th>
<th>LSR</th>
<th>MDC</th>
<th>SAHLSS</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>IS</td>
<td>Control</td>
<td>IS</td>
</tr>
<tr>
<td></td>
<td>n=960 n=1865</td>
<td>n=900 n=897</td>
<td>n=668 n=844</td>
<td>n=2528 n=3606</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>74 (12)</td>
<td>74 (12)</td>
<td>63 (7)</td>
<td>63 (7)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>546 (57)</td>
<td>993 (53)</td>
<td>485 (54)</td>
<td>496 (55)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>452 (47)</td>
<td>1202 (66)</td>
<td>520 (59)</td>
<td>661 (74)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>70 (7)</td>
<td>454 (25)</td>
<td>25 (3)</td>
<td>87 (10)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>95 (10)</td>
<td>352 (19)</td>
<td>191 (21)</td>
<td>293 (33)</td>
</tr>
<tr>
<td>Genotype frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GG</strong> n (%)</td>
<td>647 (67)</td>
<td>1294 (70)</td>
<td>611 (70)</td>
<td>596 (68)</td>
</tr>
<tr>
<td><strong>AG</strong> n (%)</td>
<td>267 (30)</td>
<td>499 (27)</td>
<td>237 (27)</td>
<td>250 (29)</td>
</tr>
<tr>
<td><strong>AA</strong> n (%)</td>
<td>26 (3)</td>
<td>50 (3)</td>
<td>24 (3)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>Minor allele frequency</td>
<td>0.17</td>
<td>0.16</td>
<td>0.16</td>
<td>0.17</td>
</tr>
<tr>
<td>Odds ratio for the A allele</td>
<td>Ref</td>
<td>0.95</td>
<td>Ref</td>
<td>1.07</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.81–1.10</td>
<td>0.90–1.28</td>
<td>0.90–1.30</td>
<td>0.93–1.13</td>
</tr>
<tr>
<td>P value</td>
<td>P=0.46</td>
<td>P=0.46</td>
<td>P=0.42</td>
<td>P=0.64</td>
</tr>
</tbody>
</table>

LSR indicates Lund Stroke Register; MDC, the Malmö Diet and Cancer study; SAHLSS, the Sahlgrenska Academy Study on Ischemic Stroke; and Ref, reference. Odds ratios were calculated with an additive model adjusted for age and sex.
Acknowledgments
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Disclosures
None.

References
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