Estrogen Receptor α Gene Variation and the Risk of Stroke

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Background—Estrogen receptor α (ESR1) gene variation is associated with a range of important estrogen-dependent characteristics, including responses of lipid profile and atherosclerotic severity to hormone replacement therapy, coronary heart disease risk, and migraine. The roles that reproductive steroids play in cerebrovascular pathophysiology and ischemia are an important area of investigation. Given that there is a significantly higher risk of myocardial infarction among men with the CC genotype (PP of PvulI) of c.454-397T>C (rs2234693), we asked whether this genotype is associated with a higher risk of stroke.

Methods—Relative risk of stroke by genotype was determined in 2709 participants of the Second Northwick Park Heart Study, white males with a mean baseline age 56 years and follow up 10.5 years.

Results—Compared with participants with the ESR1 c.454-397CT or TT genotype, those with the CC genotype had a relative risk of stroke of 1.92 (95% confidence interval, 1.06 to 3.48, P=0.03) after adjustment for age, primary care practice; additional adjustment for body mass index, serum cholesterol and triglyceride levels, hypertension, diabetes, and smoking status. Exclusion of stroke cases with coronary heart disease gave results that were essentially unchanged.

Conclusions—in this study, subjects with the common ESR1 c.454-397CC genotype have a substantial increase in risk of stroke. In another publication, other ESR1 variation was associated with migraine. We thus hypothesize that estrogen receptor variation may provide a basis for the established relationship among estrogens, migraine, and stroke. (Stroke. 2005;36:2281-2282.)

Key Words: genetics ■ risk factors ■ stroke

There is recent evidence for a role of estrogen receptor α (ESR1) gene variation in determining a range of important estrogen-dependent characteristics, including responses of lipid profile and atherosclerotic severity to hormone replacement therapy, coronary reactivity, and coronary heart disease (CHD) risk.1–6 The roles that reproductive steroids play in cerebrovascular pathophysiology and ischemia are an important area of ongoing investigation. Given that there is a significantly higher risk of myocardial infarction among men with the CC genotype (PP of PvulI)6 of c.454-397T>C (rs2234693), we tested the hypothesis that the CC genotype is associated with a higher risk of stroke.

Materials and Methods
We studied white men from the prospective population-based Second Northwick Park Heart Study in the United Kingdom.7 Follow up is ongoing with a current median duration of 10.5 years. Strokes were categorized according to the International Classification of Diseases, Ninth Edition (ICD-9): cerebral artery occlusion (434.9, n=31), unspecified cerebrovascular accident (436.0, n=18), intracerebral hemorrhage (431.0, n=6), subarachnoid hemorrhage (430.0, n=0), and cerebral embolism (434.1, n=0) on the basis of clinical presentation, computed tomography (CT), lumbar puncture, or autopsy findings. Genotype data from 2709 men were included in the current study. (Please see additional information in the online only Appendix to this article available at http://www.strokeaha.org.)

Results
Individuals with stroke had higher baseline means or frequencies of the nonlipid-established cardiovascular disease risk factors (Table). In a model with adjustment for age and primary care practice, compared with men with the ESR1 c.454-397CT or TT genotype, those with the CC genotype had a relative risk of 1.92 (95% confidence interval [CI], 1.06 to 3.48, P=0.03). This result was essentially unchanged, at 1.84 (95% CI, 1.01 to 3.35, P=0.045), after additional adjustment for body mass index, serum cholesterol and triglyceride levels, hypertension, diabetes, and smoking status. Further adjustment of the model for CHD, or exclusion of participants with CHD, gave similar results. Survival curves were calculated for stroke by genotype (Figure).

Apart from diabetes, baseline characteristics (Table), high-density lipoprotein cholesterol, and Apo-A1 levels gave no evidence of association with genotype.

Received May 11, 2005; accepted May 12, 2005.
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Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000181088.76518.ec

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Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No Stroke Subjects (n=2654)</th>
<th>Stroke Subjects (n=55)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.0 (3.4)</td>
<td>57.5 (3.1)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Body mass index,* kg/m²</td>
<td>26.2 (3.4)</td>
<td>27.1 (4.1)</td>
<td>0.04‡</td>
</tr>
<tr>
<td>Smoking</td>
<td>28.1% (746)</td>
<td>34.6% (19)</td>
<td>0.07‡</td>
</tr>
<tr>
<td>Cholesterol level, mmol/L</td>
<td>5.73 (1.01)</td>
<td>5.72 (0.93)</td>
<td>0.91†</td>
</tr>
<tr>
<td>Triglyceride level,* mmol/L</td>
<td>1.79 (0.95)</td>
<td>1.84 (0.89)</td>
<td>0.73†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52.4% (1390)</td>
<td>74.6% (41)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.3% (61)</td>
<td>3.6% (2)</td>
<td>0.37§</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>7.8% (206)</td>
<td>21.8% (12)</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td>Genotype TT/TT/CC, no.</td>
<td>777/1346/531</td>
<td>13/25/17</td>
<td>0.13‡</td>
</tr>
</tbody>
</table>

*Geometric mean (approximate standard deviation). †Two-sample t test. ‡χ² test. §Fisher exact test.

Discussion

Estrogen receptors are required for normal vascular physiology in males, and in animal models, estrogen receptor α plays a role in estradiol-mediated cerebral injury protection. The mechanisms that underlie the association seen here with stroke are not clear, although there is evidence from 2 groups that the ESR1 c.454-397CC allele results in a relatively high level of ESR1 transcription. Other polymorphisms in linkage disequilibrium with ESR1 c.454-397TT>C may nevertheless be responsible for some or all of the observed association. Our coincidental support for an association of genotype with diabetes is consistent with a report of impaired glucose tolerance and hyperinsulinemia in a man with a premature stop codon in both copies of the ESR1 gene. However, this result may be because of multiple testing, and a much larger study found no such evidence of association with diabetes.

Importantly, the association of genotype with risk of stroke was independent of established cardiovascular risk factors, including diabetes, and was essentially unchanged after exclusion of stroke cases with CHD.

These results require replication in other studies of stroke among both ethnically similar and disparate subjects. We do not currently have access to such data, but our findings are strengthened by the fact that they resemble previous results for myocardial infarction in a Finnish Study and the Framingham Heart Study. A common mechanism based on ESR1 variation may determine risk of both CHD and stroke. A recent report of association between another ESR1 polymorphism and migraine susceptibility makes variation in this gene a potential basis for the close but complex relationship among estrogens, migraine, and stroke. In men, the common ESR1 c.454-397CC genotype, present in approximately 20% of individuals, may be a risk factor for stroke and, if confirmed in replicate studies, may be useful for identifying at-risk subjects.

References

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Stroke. 2005;36:2281-2282; originally published online September 22, 2005;
doi: 10.1161/01.STR.0000181088.76518.ec
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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