Replication Study of Chr17q25 With Cerebral White Matter Lesion Volume

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Background and Purpose—Recently, the first genomewide association study on cerebral white matter lesion burden identified chr17q25 to be significantly associated with white matter lesions. We report on the first independent replication study of this genetic association.

Methods—In a population-based cohort study, we investigated the association between the 6 genomewide significant single nucleotide polymorphisms at that locus and cerebral white matter lesion volume on MRI, measured quantitatively, adjusted for age, sex, and intracranial volume. Adjustments for ApoE4 carriership and cardiovascular risk factors were evaluated separately. Finally, we performed a meta-analysis of all published data for the single most significant single nucleotide polymorphism, rs3744028.

Results—The risk alleles of all the 6 single nucleotide polymorphisms were significantly associated with white matter lesion volume with $P = 1.1 \times 10^{-3}$ for rs3744028, adjusted for age, sex, and intracranial volume. Additional adjustments only had minor influence on these associations. A meta-analysis with all published data for rs3744028 resulted in a probability value of $5.3 \times 10^{-17}$.

Conclusions—This study further establishes chr17q25 as a novel genetic locus for WML volume. (Stroke. 2011;42:3297-3299.)

Key Words: epidemiology ■ genetic association ■ risk ■ WML

Cerebral white matter lesion (WML) burden is associated with an increased risk of stroke and dementia.1 Unraveling the genetics of WMLs can identify potential targets for prevention and therapy. Recently, 6 single nucleotide polymorphisms mapping to 1 locus on chromosome 17q25 showed genomewide significance ($P < 5 \times 10^{-8}$) in the first genomewide association study on WML burden.2 Although this association was replicated in 2 replication samples in the discovery report, further independent replication is needed to accumulate more evidence and thus strengthen the association. Here, we report on the first replication of the association of chr17q25 with WML burden after the discovery report.

Methods

Study Population

This study is based on Rotterdam Study III, the second expansion of the Rotterdam Study.3 No overlap exists between Rotterdam Study III and the samples from Rotterdam Study I and II, which were reported on in the original report.2

In total, Rotterdam Study III comprised 3932 persons, of whom 2082 random persons were white and had good-quality genotype data. Of these, 1724 had MRI data available with good-quality brain segmentations. After excluding persons with cortical infarcts (n=45) and persons with dementia (n=2), 1677 persons were included in the analysis. Persons with cortical infarcts were excluded, because WMLs concomitant to cortical infarcts were considered to reflect a different pathology than the WMLs under study.

Genotyping

Genotyping and imputation were performed as part of a large project and are described in the Supplemental Methods (http://stroke.ahajournals.org). For this report, we extracted data on rs3744028, rs9894383, rs11869977, rs936393, rs3744017, and rs1055129. The quality of imputation of those single nucleotide polymorphisms was $>0.97$. APOE genotyping was performed on coded samples as described elsewhere.4

MRI Measurements

MRI was performed on a 1.5-Tesla scanner (GE Healthcare) with an 8-channel head coil and included T1-weighted, proton density-weighted and fluid-attenuated inversion recovery sequences.5 The
Table 1. Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>n=1677</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.1 (5.3)</td>
</tr>
<tr>
<td>Female sex</td>
<td>55%</td>
</tr>
<tr>
<td>ApoE4 carriership</td>
<td>31%</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.5 (4.4)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82.3 (10.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>131.9 (18.1)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.6 (1.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>22%</td>
</tr>
<tr>
<td>White matter lesion volume, mL</td>
<td>3.0 (3.9)</td>
</tr>
</tbody>
</table>

Values are means (SD) or percentages.

Table 2. Association of Chr17q25 With White Matter Lesion Volume*

<table>
<thead>
<tr>
<th>Single Nucleotide Polymorphism</th>
<th>Chr: Position</th>
<th>Imputed</th>
<th>R²</th>
<th>MA</th>
<th>MAF</th>
<th>Model I</th>
<th>Model II</th>
<th>Model III</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3744028</td>
<td>17:71400267</td>
<td>Yes</td>
<td>C</td>
<td>0.17</td>
<td>1.1*10^{-3}</td>
<td>0.10 (0.04–0.16)</td>
<td>3.9*10^{-3}</td>
<td>0.09 (0.03–0.15)</td>
</tr>
<tr>
<td>rs9894383</td>
<td>17:71377252</td>
<td>Yes</td>
<td>G</td>
<td>0.18</td>
<td>1.9*10^{-3}</td>
<td>0.10 (0.04–0.16)</td>
<td>2.7*10^{-3}</td>
<td>0.09 (0.03–0.16)</td>
</tr>
<tr>
<td>rs11869977</td>
<td>17:71368977</td>
<td>Yes</td>
<td>G</td>
<td>0.18</td>
<td>2.0*10^{-3}</td>
<td>0.10 (0.04–0.16)</td>
<td>2.8*10^{-3}</td>
<td>0.09 (0.03–0.16)</td>
</tr>
<tr>
<td>rs9363933</td>
<td>17:71395208</td>
<td>Yes</td>
<td>G</td>
<td>0.18</td>
<td>2.3*10^{-3}</td>
<td>0.09 (0.03–0.15)</td>
<td>3.0*10^{-3}</td>
<td>0.09 (0.03–0.16)</td>
</tr>
<tr>
<td>rs3744017</td>
<td>17:71383062</td>
<td>No</td>
<td>A</td>
<td>0.17</td>
<td>6.1*10^{-4}</td>
<td>0.11 (0.05–0.17)</td>
<td>1.5*10^{-3}</td>
<td>0.10 (0.04–0.16)</td>
</tr>
<tr>
<td>rs1055129</td>
<td>17:71384543</td>
<td>Yes</td>
<td>G</td>
<td>0.28</td>
<td>5.7*10^{-5}</td>
<td>0.10 (0.05–0.16)</td>
<td>2.0*10^{-4}</td>
<td>0.10 (0.05–0.15)</td>
</tr>
</tbody>
</table>

Model I, adjusted for age, sex, and intracranial volume; Model II, same as in I, additionally adjusted for apoE4 carriership and cardiovascular risk factors; Model III, white matter lesion volume expressed as percentage of intracranial volume adjusted for age and sex.

Values are differences (95% CI) in white matter lesion volume per additional risk allele.

Chr indicates chromosome; $R^2$, R-squared as a measure of linkage disequilibrium with rs3744028; MA, minor allele=risk allele; MAF, minor allele frequency; CI, confidence interval.

*Log-transformed.
the associations, any small residual effect cannot be ruled out
entirely.

Together with the replication samples described in the original report, this is the third sample replicating the original findings. In a small sample of blacks in the original report, findings were not replicated. Studies investigating this locus in larger samples of blacks, and in other ethnicities such as Hispanics and Chinese, are therefore needed. This will further increase generalizability and contribute to pinpointing of the causative polymorphism. Alternatively, deep sequencing and expression studies can identify and unravel possible causative mechanisms. Furthermore, research is required to elucidate the potential role of this locus in diseases associated with WML volume such as stroke and dementia.

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**Disclosures**

None.

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