TOMM40 rs2075650, TOMM40 rs157580 and TOMM40 PolyT Polymorphism Effects on Ventricular Enlargement in Individuals with and without Mild Cognitive Impairment

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Background:
Apolipoprotein E4 (APOE4) is the most established sporadic Alzheimer’s disease (AD) susceptibility gene. TOMM40, a gene adjacent to APOE4, has been postulated to increase one’s risk of AD. TOMM40 polyT polymorphism has been implicated in modulating AD age of onset among APOE4-negative subjects.

Objective:
To examine the effects of TOMM40 rs2075650, TOMM40 rs157580 and TOMM40 polyT polymorphism on lateral ventricular enlargement in normal aging and the mild cognitive impairment (MCI) state.

Methods:
Genotyping for APOE4, TOMM40 rs2075650 and rs157580, and TOMM40 polyT polymorphism analyses were performed on 44 cognitively normal elderly (NC) and 48 mild cognitive impairment (MCI) subjects. A novel automated ventricular segmentation technique and the radial distance mapping approach were applied to the subjects’ T1-weighted magnetic resonance imaging data (see Figure 1). Multiple linear regression was used to study the associations between TOMM40 rs2075650 and TOMM40 rs157580 and ventricular radial distance while correcting for APOE4 genotype. We also investigated the associations between the short (S≤20) and very long (VL ≥30) polyT repeat length, and ventricular enlargement in 59 APOE4-negative individuals. Of these 59 subjects, 10 were S/S, 28 S/VL and 21 VL/VL carriers (see Table 1). The S/S, S/VL and VL/VL groups were compared. Multiple comparison correction was conducted with permutation testing using a threshold p<0.01.

Results:
TOMM40 rs2075650 and TOMM40 rs157580 failed to show significant associations with ventricular radial distance. Presence of VL showed significant association with the right temporal (p_corrected=0.039) and left occipital lateral ventricle horns (p_corrected=0.014) in ApoE4-negative subjects. Trend level effects were detected in the right occipital (p_corrected=0.085) and frontal (p_corrected=0.094) horns. In between-group comparisons, S/VL carriers showed significantly smaller occipital horns than S/S carriers (left p_corrected=0.014; right p_corrected=0.015). Figure 2 shows all significant results and the corresponding beta-coefficient maps.

Conclusions:
Among APOE4-negative subjects, presence of VL repeats associates with smaller lateral ventricles. These data complement our previous report from the same cohort that the presence of VL repeat in APOE4 noncarriers is associated with larger hippocampi.

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Table 1. Demographic characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>S/S</th>
<th>S/VL</th>
<th>VL/VL</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>75.8 (7.1)</td>
<td>70.5 (8.3)</td>
<td>70.4 (6.6)</td>
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</tr>
<tr>
<td>Gender (F:M)</td>
<td>4:6</td>
<td>11:17</td>
<td>14:7</td>
<td>0.135</td>
</tr>
<tr>
<td>Education (years)</td>
<td>18.7 (1.8)</td>
<td>16.4 (2.4)</td>
<td>15.7 (2.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>NC:MCI</td>
<td>6:4</td>
<td>13:15</td>
<td>9:12</td>
<td>0.663</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.1 (2.3)</td>
<td>28.3 (1.5)</td>
<td>28.3 (1.5)</td>
<td>0.934</td>
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</tbody>
</table>