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

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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.

Abstract

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.

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. Multiple linear regression with a permutations threshold of $p<0.01$ was used to measure the effect of TOMM40 rs2075650 and TOMM40 rs157580 on ventricular radial distance while correcting for APOE4 genotype. We also analyzed associations between the short ($S \leq 20$) and very long ($VL \geq 30$) polyT repeat length, and ventricular enlargement in our 59 APOE4-negative individuals: 10 were S/S, 28 were S/VL and 21 were VL/VL carriers. The S/S, S/VL and VL/VL groups were compared.

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 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 $p_{corrected}=0.015$).

Conclusion: Among APOE4-negative subjects, presence of VL repeats associates with smaller lateral ventricles. These data are in agreement with our previous report of VL repeat being associated with larger hippocampi.

Figure: 3D statistical maps show the effect of VL repeats on ventricular radial distance (*left*), and the S/VL vs. S/S group comparison (*right*).