

## Mapping the effects of TOMM40 and APOE4 on hippocampal atrophy in cognitively normal elderly and MCI

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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 AD risk. TOMM40 polyT polymorphism has been implicated in modulating AD age of onset among ApoE4 negative subjects.

### Objective

To examine the effects of TOMM40 rs157580 and TOMM40 polyT polymorphism on hippocampal atrophy.

### Methods

44 normal controls (NC) and 48 mild cognitive impairment (MCI) subjects underwent T1-weighted MRI, ApoE and TOMM40 genotyping and TOMM40 polyT analyses. Using the radial distance mapping technique and multiple linear regression we investigated the independent effects of TOMM40 and APOE4 on hippocampal radial distance. PolyT analyses were performed in APOE4 noncarriers (N=59) who had either short (S,  $\leq 20$ ) or very long (VL,  $\geq 30$ ) polyT repeat. There were 10 S/S, 28 S/VL and 21 VL/VL carriers. S/S, S/VL and VL/VL groups were compared. Effects of S and VL repeats on hippocampal atrophy were investigated with multiple linear regression.

### Results

TOMM40 showed significant correlations with hippocampal radial distance after controlling for APOE4 genotype (right  $p=0.035$ , left  $p=0.066$ ). VL polymorphism was associated with greater right hippocampal radial distance ( $p=0.02$ ). APOE4 and polymorphism S failed to show significant associations with hippocampal radial distance. In the direct group comparisons S/VL carriers showed significantly larger right hippocampal radial distance relative to S/S carriers ( $p=0.028$ ). VL/VL carriers showed a trend for larger hippocampal radial distance relative to S/S carriers ( $p=0.084$ ). The VL effects localized mainly to the CA1 and subiculum. There were no significant differences in hippocampal atrophy between VL/VL and S/VL.

### Conclusion

Our data suggests that TOMM40 has an APOE4-independent effect on hippocampal atrophy. Contrary to our expectations, VL carriers showed larger hippocampi suggesting that the VL polymorphism effect on AD age of onset is perhaps mediated by extrahippocampal mechanism.