Mapping the interaction between *APOE*-epsilon4 and *TOMM40* SNPs and Brain Atrophy: An N=705 ADNI study

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INTRODUCTION

The epsilon 4 allele of the ApolipoproteinE gene (*APOE4*) is a prevalent risk factor for Alzheimer's disease (AD) and is associated with greater brain atrophy, specifically in temporo-parietal regions[1]. The 'G' allele of the SNP rs2075650[2], located in intron 2 of the *TOMM40* gene, is also a risk factor for Alzheimer's disease and carriers of this risk allele show hippocampal and temporal lobe atrophy[3]. However, so far, it is not known how *APOE4* and *TOMM40* SNPs might interact to influence regional brain volumes; interactions are likely as *TOMM40* lies close to *APOE4* gene on chromosome 19 and the two alleles are in linkage disequilibrium. We created a 3D map of structural brain differences associated with the interaction between the 2 risk alleles in 705 elderly Caucasian subjects scanned and genotyped as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI). We hypothesized that the interaction of the 2 risk alleles would be associated with lower regional brain volumes, than the individual alleles acting independently, in this elderly cohort. Our goal was to understand how *TOMM40* variants affect brain atrophy, and whether their effect depends on the adjacent *APOE* genotype.

Table1a. Baseline demographic and clinical characteristics, split by diagnosis

Mean (Standard deviation)	AD	MCI	Controls
Sample size (n)	158	348	199
Age (years)	75.4 (7.6)	75.0 (7.3)	76.1 (5.0)
Sex (Men, Women)	83, 75	224, 124	107, 92
Education (years)	15.2 (2.8)	15.3 (2.7)	15.8 (2.6)
MMSE[δ]	23.3 (2.0)	27.1 (1.8)	29.2 (1.0)
Global CDR[ε]	4.4 (1.5)	1.6 (0.8)	0.03 (0.1)

[δ]mini-mental status examination (maximum score: 30), [ε]clinical dementia rating

METHODS

Of the 842 subjects who received an MRI at 1.5 Tesla and were genotyped as part of the ADNI, 705 (199 controls (107M/92F), 348 with mild cognitive impairment (224M/124F), 158 with AD (83M/75F); mean age: 75·4±6·8 years) were of Caucasian origin and had *APOE4* and rs2075650 genotype data, mini-mental status exam scores (MMSE), and clinical dementia ratings (CDR) when they were first scanned. Subcortical brain volume measures were downloaded from the ADNI website. Using tensor-based morphometry (TBM)[4], 3D maps were created to show regions of volume deficit or excess relative to a brain template based on 40 healthy elderly subjects. At each brain voxel, the following multiple regression model was fitted: $y = \beta_0 + \beta_{Predictors} Predictors + \beta_{Confounders} Confounders + \varepsilon$
Here y represents cognitive scores (MMSE, CDR), generalized and voxel-wise regional brain volumes or sub-cortical brain volumes, respectively. 'Predictors' represent *APOE4* and *TOMM40*, each coded as 0,1,2 and their interaction term coded as 0,1,2,4; 'Confounders' considered were age and sex.
We created 3D maps to show regions of volume deficit or excess relative to the brain template, reflecting, in part, profiles of neurodegeneration associated with the genotypes. We used a standard false discovery rate (FDR) correction for multiple statistical comparisons across all brain voxels, at the conventionally accepted level of $q = 0.05$.

RESULTS

In line with our hypotheses, voxelwise regression analysis using TBM revealed significantly lower brain volumes, of up to 6% bilaterally in the frontal brain regions, as risk scores increased in the interaction term (from 0 to 4), which was not found when considering either of the gene-variants independently, as shown in prior studies[5,6]. Temporal brain regions showed significant brain volume deficits of up to 2, 4 and 6% associated with *TOMM40*, *APOE4* and their interaction term respectively.

CONCLUSION

The interaction between two well-known genetic variants appeared to promote brain atrophy – especially frontal lobe atrophy - beyond that explainable by the independent effect of each allele. This is the first study to reveal a 3D pattern of brain volume differences on MRI associated with the interaction of *APOE4* and *TOMM40* SNP. These atrophy profiles may help to empower drug trials using various biomarkers to offer an insight into the efficacy of interventions for Alzheimer's Disease.

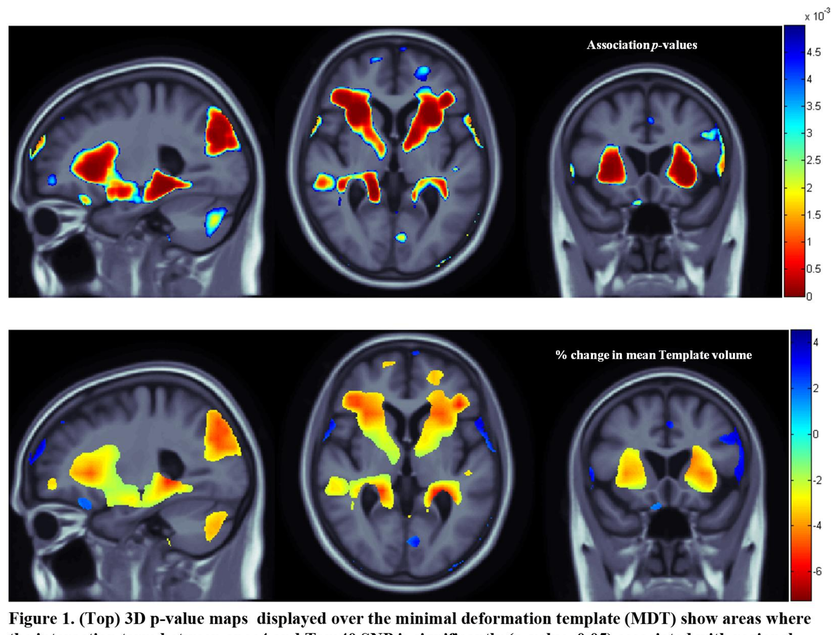

Figure 1. (Top) 3D p-value maps displayed over the minimal deformation template (MDT) show areas where the interaction term between apoe4 and Tom40 SNP is significantly (p-value 0.05) associated with regional brain volume differences in baseline ADNI subjects (n = 705) after covarying for age and sex. (Bottom) In the significant brain regions, 3D Beta-value maps show the estimated regional brain volume excess or deficit (percentage relative to MDT) at each voxel per 1unit change in the term, in the same subjects.

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