

## Introduction

The epsilon 4 allele of the apolipoprotein E gene (*APOE4*) is a well-established risk factor for Alzheimer's disease (AD). The 'G' allele of the SNP rs2075650, located in intron 2 of the *TOMM40* gene, is also a more recently discovered risk factor for AD. *TOMM40* lies close to the *APOE* gene on chromosome 19 and the two alleles are in linkage disequilibrium (they are correlated). Both alleles are associated with greater brain atrophy in carriers, specifically temporal lobe atrophy and ventricular expansion. However, so far, it is unknown how *APOE4* and *TOMM40* SNPs influence *rates* of ventricular expansion. This was tested in our study.

## Methods

We used 644 of the 738 Caucasian subjects (187 controls, 317 with mild cognitive impairment, 187 with AD; mean age:  $75.4 \pm 6.8$  years) who received a brain MRI at 1.5 Tesla at both baseline and 1-year follow-up and were genotyped as part of the ADNI cohort. All 644 subjects had *APOE4* genotype data; of these, 616 had rs2075650 genotype data. The following multiple regression model was fitted at each point on the ventricular surface:

$$y = \beta_0 + \beta_{Predictors} Predictors + \beta_{Confounders} Confounders + \varepsilon$$

*APOE4* and *TOMM40* were tested individually, each coded as 0,1,2 after adjusting for age, sex and diagnosis. After registering all ventricular models, we created 3D maps reflecting profiles of neurodegeneration (expansion) associated with the genotypes. Permutations tests were used to correct for multiple comparisons.

## Results

Both *APOE4* (Corrected *P*-value: Right-0.0004; Left <0.0004) and *TOMM40* (Corrected *P*-value: Right-0.0008 Left-0.0036) risk alleles are significantly associated with accelerated rate of ventricular expansion. 3D statistical maps show the associations predominantly in the body and occipital horn, stronger on the right than the left.

## Discussion

This is the first study to reveal a dynamic 3D pattern of ventricular expansion associated with carrying Alzheimer risk alleles in *APOE4* and *TOMM40* genes. These anatomical profiles may help to empower drug trials using various biomarkers to evaluate efficacy of interventions for Alzheimer's Disease.

