Folate gene associated with brain volumes: Replication in ADNI (N=740) and Queensland Twins (N=577)

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INTRODUCTION
Recently, a single nucleotide polymorphism (SNP), rs11754661, in the MTHFD1L folate gene encoding the monofunctional mitochondrial C1-tetrahydrofolate (THF) synthase was reported to be associated with late-onset Alzheimer's disease (AD), through a genome-wide association study. Because of its association with AD, this SNP in MTHFD1L becomes a good candidate for examining associations with brain structural variance. We were also interested in testing potentially functional SNPs in the MTHFD1 gene, the trifunctional C1-THF synthase, which is the cytosolic homolog of the MTHFD1L gene. We tested their associations with brain volume differences in an elderly population; for replication purposes, we also analyzed a young adult twins cohort.

RESULTS
Of the 3 SNPs studied, only rs1950902 with its commonly carried A allele (minor allele frequency 0.2) was associated with regional brain volume differences in the ADNI cohort. Carriers of at least one copy of the major G allele showed a maximum brain volume atrophy of 4.9% with ~2.9% atrophy in the left parieto-occipital region (critical cluster p-value = 0.006 as determined by the topological FDR at the level of q=0.017) versus non-carriers, and relative to the structure volumes in the MDT, after controlling for age, sex & diagnosis. We then carried forward rs1950902 for independent testing in the young healthy twins. We were able to detect partially overlapping brain volume reductions with a maximum of 2.9% atrophy in the left parieto-occipital region in the carriers of the G allele (critical cluster p-value = 0.007, corrected for the topological FDR at the level of q=0.05). Cluster sizes for association between SNPs and anatomy were larger than would be expected at random.

METHODS
Our testing data consisted of 740 unrelated Caucasian elderly subjects (173 AD, 361 MCI, 206 controls); mean age: 75.5+/−6.8 years). All subjects were scanned with brain MRI at 1.5T and genotyped as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI). Our replication data included 577 healthy young adult twins & siblings (222 M/355F; mean age: 23.8+/−2.2 years) of European descent imaged with anatomical MRI at 4T. Using tensor-based morphometry, we generated 3D maps of regional brain volume differences in each cohort, by mapping subjects to cohort-specific mean templates (MDT). We identified 6 non-synonymous functional SNPs (rs1950902, rs2236225, rs1803950, rs1803951, rs10137921, rs11551058) associated with the MTHFD1 gene of which 2 had been genotyped in the ADNI, in addition to rs11754661. For each of the 3 SNPs studied, we used univariate regression to associate the number of minor alleles (0,1, or 2) to the Jacobian values describing the amount of expansion or shrinkage obtained by TBM at each voxel in the brain, relative to the MDT, after covarying for age and sex. We used the topological false discovery rate (FDR) method to correct for multiple statistical comparisons across the brain, at the level of q = 0.05/3 (to account for testing 3 SNPs).

CONCLUSION
A commonly carried susceptibility allele in MTHFD1 (rs1950902) was found to be associated with regional brain volumes in young and old cohorts scanned on two different continents. Further tests are needed to determine whether this genetic variant may influence vulnerability to brain disease, with implications for public health.

### Table: Gene SNPs and Comments

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylene tetrahydrofolate dehydrogenase (MTHFD1)</td>
<td>rs11754661</td>
<td>MTHFD1L did not pass FDR</td>
</tr>
<tr>
<td>Methylene tetrahydrofolate dehydrogenase (MTHFD1)</td>
<td>rs1950902</td>
<td>passed FDR</td>
</tr>
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The 2 non-synonymous SNPs associated with the trifunctional cytosolic methylene tetrahydrofolate dehydrogenase 1 (MTHFD1) gene.

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**Gene**

| MTHFD1 | THF | 10-formyl-THF synthase
| 5,10-methylene-THF dehydrogenase
| 5,10-methylene-THF
| MTHFR

**MTHFD1** gene encodes a trifunctional cytosolic methylene tetrahydrofolate (THF) dehydrogenase gene where the mitochondrial MTHFD1L gene encodes for only the formyl THF reductase activity.