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TREM2 Risk Variant and Loss of Brain Tissue

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We were intrigued by reports of a discovery of a rare variant in *TREM2* (1–3) that roughly triples the lifetime risk of Alzheimer's disease (AD). The frequency of this risk variant was reported as 0.63% in the Icelandic population (1) and is somewhat variable across populations **(see** Supplement). Here we aimed to understand how the gene variant affects AD risk by mapping its effects on brain in 478 subjects (mean age: 75.5±6.5 years; 283M/195F; 100 with AD, 221 with mild cognitive impairment and 157 healthy controls) from the Alzheimer's Disease Neuroimaging Initiative, scanned with brain MRI every year for 2 years (4). Using tensor-based morphometry, we computed the rates of brain tissue loss, per year, over 24 months from the baseline MRI in a statistically-defined region of interest, based on voxels with significant atrophic rates over time within the temporal lobes in AD (4). We then tested the hypothesis that annual brain loss rates, over time, in this region are associated with carrying the risk allele of rs9394721, a close proxy for the newly discovered risk variant, rs75932628, in *TREM2* (r^2=0.492; **see** Supplement). We report that *TREM2* mutation carriers annually lose brain tissue up to 1.4–3.3% faster than non-carriers, in a pattern that mirrors the profile of AD pathology in the brain (Figure 1). Mutation carriers lose brain tissue twice as fast as healthy elderly people (Table 2S). After adjusting for age and sex, the risk allele was also significantly associated with smaller hippocampal volumes, elevated levels of cerebrospinal fluid (CSF) biomarker p-tau181p, which are usually observed in AD (5), and poorer cognitive performance **(see** Supplement) based on the standard clinical dementia rating scale (CDR) and Alzheimer's Disease Assessment Scale (ADAS-cog), assessed at baseline MRI scan and after 24 months' follow-up (Table 1S). The *TREM2* risk variant may affect signaling by TREM2 receptors expressed on microglial cells in the brain, perhaps interfering with the anti-inflammatory functions of these cells and their removal of apoptotic tissue. This may affect brain amyloid clearance, leading to AD-like neurodegeneration and accelerated cognitive decline (2). Selection of carriers of this risk variant and probably other *TREM2* risk variants for enrollment in trials of interventions to treat persons with Alzheimer's disease, in which MRI scans are used in obtaining outcomes, should increase the power of such trials.

Supplementary Material

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Financial disclosure
The authors have no competing financial interests to declare.

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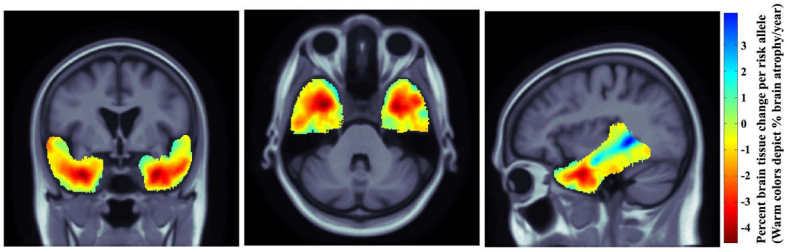

Figure 1.

At a 24-month follow-up scan, these 3D regression coefficient maps show brain volume differences in the temporal lobe associated with carrying the *TREM2* risk allele. The risk allele carriers showed significantly accelerated brain atrophy from 1.4–3.3% in the statistical region of interest (FDR critical $p = 0.0036$; $q = 0.05$). Statistical tests were performed using permutation tests, which are robust in the presence of outliers and small sample sizes **(see** Supplement). The figure is shown in the radiological convention (left side of the image is the right hemisphere).