

**Abstract Title:**

Neuroinflammatory pathways associated with Alzheimer's disease

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**Introduction:**

Growing evidence suggests inflammation contributes to Alzheimer's disease (AD). Activated microglia cluster around amyloid and correlate with disease symptoms. Many inflammatory genes are associated with AD, including rare variants in the TREM2 gene. We sought to establish whether there are additional rare variants in any of the 112 genes which make up a brain co-expression module which includes TREM2 and CD33. We also investigated the effects of TREM2 variants on microglia activation in post-mortem human brain to establish whether microglia respond similarly in AD patients with or without a TREM2 risk variant.

**Materials and Methods:**

Using a custom capture assay (Agilent), we sequenced the exons of 144 genes in 950 DNA samples from AD, MCI and control individuals. After de-multiplexing, alignment and quality control, we tested for association of variants with AD. We also investigated microglia activation using the established markers CD68, Iba-1 and, HLA. We compared the abundance of microglia with each marker in the CA1 and CA4 hippocampal regions between AD cases with risk TREM2 variants (TREM2+) and AD and Control cases without these variants (TREM2-).

**Results:**

A number of rare variants were found to be associated with AD. Validation of these findings in independent cohorts is underway. 80% of bases were covered at  $\geq 12$  x read depth in the majority of samples and all cases previously found to have a TREM2 risk variant were verified. AD/TREM2+ cases were found to have significantly fewer HLA and CD68-stained microglia compared to AD and control TREM2- cases. The numbers of Iba-1-stained microglia were not different between groups.

**Conclusions:**

Rare genetic variants associated with AD may cluster in functionally related pathways, although further validation will be necessary to confirm these results. While greater numbers of activated microglia are found in AD patients without a TREM2 risk variant this is significantly attenuated in AD patients who have a TREM2 risk variant, suggesting some aspects of pathology may not be common to all AD patients. These results have implications for strategies which target neuroinflammation to treat AD.