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# MECHANISMS CONTRIBUTING TO DIFFERENTIAL GENETIC RISKS IN TREM2 R47H AND R62H VARIANTS IN ALZHEIMER'S DISEASE

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## Aims

Coding variants in the microglial TREM2 ectodomain differentially (R47H> R62H) increase the risk of Alzheimer's disease (AD). To define mechanisms responsible, we aimed to characterise neuropathology and transcriptomic responses in heterozygotes for these *TREM2* variant alleles (*TREM2var*) and for common allele homozygotes (*CV*) in non-diseased (n=16) and AD (n=42) brain cortical tissue from 58 donors.

## Methods

Using immunohistochemistry (IHC) and imaging mass cytometry (IMC), we characterised neocortical β-amyloid and AT8/PHF1 pTau pathology with *CV* (*n*=30) and the *R47H* (*n*=11) or *R62H* (*n*=17) *TREM2var*. We performed single nuclear RNA sequencing to test for differences in cell-type proportions and for the differential gene expression (DGE) in *TREM2var* and *CV* cortical tissues with greater 4G8$^+$ β-amyloid- or PHF1$^+$ pTau-immunostaining.

## Results

There was a two-fold increase in 4G8$^+$, a three-fold reduction in AT8$^+$ but no change in PHF1$^+$ immunostaining, and reductions in neuronal nuclei proportions with AD in *TREM2var* versus *CV* . We found a partial loss of gene expression associated with *TREM2* function with variant alleles (*R47H>R62H*) relative to CV. Increased neurodegeneration in the *TREM2var* AD cortex was associated with genotype-dependent reductions in expression of Disease Associated Microglia genes (*R47H>R62H*) and increased expression of complement and Type I and II interferon pathways in microglia. The risk variants were associated with increased gene expression in astrocytes particularly of Disease Associated Astrocyte genes (*R47H>R62H*). Neuronal gene expression changes were evident in both variants, however enhanced in R47H, in response to 4G8$^+$ β-amyloid- and PHF1$^+$ pTau with changes in growth factor, ubiquitination and apoptotic pathways.

## Conclusions

This analysis identified novel disease-associated transcriptomic differences in microglia, associated astrocytic responses and secondary neuronal responses that can explain differences in the genetic AD risk conferred by these two *TREM2* risk variants.