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Investigation of amyloid and microglial pathology in sporadic, familial and *TREM2* variant Alzheimer's disease cases

Introduction: TREM2 was discovered as a genetic risk factor for late onset Alzheimer's disease (AD) with a similar odds ratio to *APOE*. *TREM2* is expressed on microglia and is thought to play a role in clearing amyloid plaques via phagocytotic mechanisms. Phagocytotic microglia have an amoeboid morphology whereas other microglia are more ramified in appearance. Previous studies suggest that *TREM2*$^{-}$ mice have less dense amyloid plaques than TREM2^{+} mice when crossed with amyloid producing mice (5xFAD). Here we investigate the amyloid and microglial pathology in sporadic, familial and *TREM2* variant AD human post-mortem tissue.
Material and methods: Eight µm sections from human frontal cortex, temporal cortex, hippocampus, putamen and midbrain were cut from sporadic (n=8), familial with both *PSEN1* and *APP* variants (n=11) and *TREM2* variant (n=4) AD cases. Immunohistochemistry was performed using Aβ, Iba1, CD68 and CR3-43 antibodies. Regions of interest were selected and ten random squares were generated from each case using a Python script. Area density analysis was performed for all antibodies. Cases were blinded and the number of diffuse and dense core amyloid plaques were counted. ImageJ was used to assess the circularity of the microglia.
Results: The Aβ area density was reduced in *TREM2* variant cases compared to sporadic and familial cases in the CA1 region of the hippocampus, putamen and the midbrain whereas levels were similar in frontal and temporal cortices. There were more diffuse plaques compared to dense core plaques in all regions. There was a higher density of Iba1^{+} and CD68^{+} microglia in *TREM2* variant cases in the frontal cortex compared to sporadic AD cases with no TREM2 variant, whereas there were fewer CR3-43^{+} microglia. The circularity of microglia followed a similar pattern to the density of microglia.
Conclusions: This data highlights that *TREM2* variant AD cases do have a different pathological profile to sporadic and familial AD cases. A reduction in dense core plaques in some areas may suggest that TREM2 plays a role in amyloid plaque fibrillisation. Add to this the differences in microglial morphology between *TREM2* cases and other AD cases and we can hypothesise that TREM2 alters microglial morphology which in turn may alter their response to amyloid deposition.

References:
1. Wang *et al. J Exp Med* 2016; **213**:667-675