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Weighted burden analysis of exome-sequenced late onset alzheimer's cases and controls provides further evidence for involvement of psen1 and demonstrates role for pi3k/akt/gsk-3β signalling pathway

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Introduction: Previous studies have implicated common and rare genetic variants as risk factors for late onset Alzheimer's disease (LOAD).
Objectives: To analyse a sample of exome sequenced LOAD cases and controls in order to identify genes in which variants predicted to be functional were associated with increased or decreased risk.
Methods: Weighted burden analysis was applied to over 10,000 exome sequenced subjects from the Alzheimer's Disease Sequencing Project. Weighted burden analyses were carried out to investigate whether rare genetic variants predicted to have a functional effect were more commonly seen in cases or in controls. Population principal components were included as covariates.
Results: Confirmatory results were obtained for the previously identified genes TREM2, ABCA7 and SORL1. Additional support was provided for PSEN1 ($p = 0.0002$), which previously had been only weakly implicated in LOAD. There was suggestive evidence that functional variants in PIK3R1, C1R and EXOC5 might increase risk and that variants in TIAF1, GFRAL and GADD45G might have a protective effect. Overall, there was strong evidence ($p = 5 \times 10^{-6}$) that variants in tyrosine phosphatase genes reduce the risk of developing LOAD.
Conclusions: The results provide further evidence that disruption of the PI3K/Akt/GSK-3β signalling pathway can increase risk of LOAD while enhancement of signalling through reduction of tyrosine phosphatase inhibition can reduce risk. Variants in C1R might increase risk via a direct effect of complement activity in the brain or indirectly mediated through encouraging periodontitis and P. gingivalis infection.

Conflict of interest: No
Keywords: Alzheimer's disease; PSEN1; PI3K/Akt/GSK-3β signalling; C1R