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Identification of genetic regions associated with Alzheimer ‘s disease blood-based biomarkers in Mexican American families

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Sunday, July 16, 2023 : 12:00 AM - 4:55 PM

Monday, July 17, 2023 : 12:00 AM - 4:55 PM

Tuesday, July 18, 2023 : 12:00 AM - 4:55 PM

Wednesday, July 19, 2023 : 12:00 AM - 4:55 PM

Theme

Biomarkers

Abstract

Background:

Dementias are heterogeneous age-associated neurodegenerative disorders generally included in the broad term, Alzheimer’s disease (AD) and related dementias (ADRD). ADRD affects individuals of all ethnicities, but Hispanic individuals show a 1.5-fold higher risk when compared to non-Hispanic whites. Many AD risk biomarkers have been proposed but not much is known about how genetic elements control their expression. We used 2000 genome sequenced Mexican Americans from extended pedigrees to identify genetic regions associated with AD blood-based biomarkers.

Method:

A total of 70 Mexican American subjects were diagnosed as ADRD cases (h^2= 0.75, p = 2.6×10^{-5}). We quantified plasma concentrations, using a QuanterixÒ elisa assay, of four AD candidate biomarkers AB40, AB42, TAU and NFL. We identified genomic regions associated with these biomarkers using a linear mixed model as implemented in SOLAR on a set of 28 million SNPs. Our genetic variance decomposition model is tailored for relatively rare diseases where extended pedigrees are available. Candidate SNPs identified were extensively annotated and their individual eQTL contribution to the expression of flanking genes defined.

Result:

The heritability component of each AD biomarker was defined, and the most significant estimate observed for NFL (h^2= 0.33, p=6.96×10^{-17}). We tested the association between circulating tau and identified two genome-wide significant associations for SNPs rs242557 (3.11×10^{-14}) and rs242562 (1.34×10^{-13})(Figure 1). Both SNPs are common and located in the first and second introns of the gene *MAPT*, respectively, and are in a conserved region with chromatin accessibility for transcription factors, suggesting regulatory functions (Figure 2). We tested the association between both SNPs and flanking gene expression, identifying strong evidence of cis-regulation with the expression of the antisense-RNA (*KANSL1_AS1*) of the gene *KANSL1*.

Conclusion:

The identification of genetic variants associated with AD biomarkers is key to providing a reliable and cost-effective genetic test for AD risk for the Hispanic population. The gene *KANSL1* encodes a subunit of a histone acetylation enzyme and has been associated with Koolen-de Vries Syndrome and cognitive impairment. The genetic associations are promising, but demand an independent validation to confirm their impact for the AD risk estimation.

Presenting Author

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Figure2.png Download

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