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GENETICS

Novel sex-specific candidate loci associated with Alzheimer disease identified through sex-aware multi-ancestry genome-wide meta-analysis

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Abstract

Background: Sex differences in progression and pathology of Alzheimer's disease (AD) suggest sex-specific factors influencing its development. While studies have established *APOE*-genotype as contributing to AD risk differently in men and women, few have searched for additional genetic sex differences in AD. To identify sex-specific AD genetic associations, we conducted genome-wide sex-aware meta-analyses in the Alzheimer's Disease Genetics Consortium (ADGC) and Alzheimer's Disease Sequencing Project (ADSP) datasets.

Method: Sex-interaction and sex-stratified analyses were performed in multi-ancestry genome-wide imputed AD datasets from the ADGC ($N = 25,284$ cases, 60% female and 33,455 controls, 63% female; ancestry/ethnicity distribution: 63.7% European, 15.6% African, 15.2% Hispanic/Latino, 5.5% Asian). STAAR aggregation-based rare-variant testing was also conducted in coding and non-coding genomic regions on an ancestrally diverse sample of 8,697 AD cases and 14,758 controls with whole-genome sequencing from the ADSP.

Result: Cross-ancestry sex-stratified analyses identified several loci with evidence of interaction ($p < 0.05$) and suggestive significance in one sex ($p < 5x10-6$) and not the

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other (p >0.05). These include male specific variants in *STXBP6*, *MAP4K5* and the known AD locus *PICALM*. Genetic loci associated in females and not males include *NPAS3*, *ZNF438* and a genome-wide result in *NECTIN2* near the *APOE* locus. Top ancestry-specific results include associations at *COL4A2* in Asian-ancestry males and *C16orf96* in African-ancestry females.

Cross-ancestry rare-variant aggregation-based testing revealed four novel genome-wide significant associations in females including with missense variants in *SH3BP1*. Five population specific associations were also discovered including with missense variants in *SERTAD4* in a genetically-defined Hispanic/Amerindian/African ancestral population cluster and promoter variants of *PSMA5* in a European population cluster. Seven male-specific effects were also discovered including genome-wide significant cross-ancestry associations with an enhancer region of *MORC1* and a promoter of *ITPKA*.

Conclusion: We identified sex-specific AD associations at loci with AD-relevant genes including *STXBP6* (involved in AD relevant processes such as endolysosomal transport and synaptic transmission), *NPAS3* (neurogenesis), *COL4A2* (cerebral vasculature), *ITPKA* (learning/memory processes), *PAQR3* (cholesterol homeostatis and neuronal function), and *MORC1* (recently associated in a UK Biobank exome-wide sequencing study of dementia (Zhang et al. Alz & Dementia 2024). Understanding the nature of these associations could help explain sex differences in risk and progression for AD.