

Genetic Associations With Tau-PET Braak Staging: An ADSP Neuroimaging Study



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Introduction

Tau pathology is one of the defining features of Alzheimer's disease. Tau-PET derived Braak staging provides an *in vivo* measure of the spatial progression of tau pathology in the brain. Genetic factors underlying tau accumulation are not yet fully understood. Toward that aim, we conducted a genome-wide association study (GWAS) and gene-level analysis of tau-PET derived Braak staging.

Methods

The Alzheimer's Disease Sequencing Project (ADSP) collected and harmonized whole genome sequencing (WGS) data and tau-PET derived Braak staging in N=1,549 samples (Age=70.9±8.3 years, Sex=58.1% female). PLINK was used to perform GWAS on the quality-controlled WGS data of over 8.7 million variants, correcting for the first 6 principal components, age, and sex. MAGMA implemented in FUMA was used to perform gene-level analyses, which aggregates SNP-level association results into gene-level units. Significant independent GWAS loci were then mapped to genes using GTEx v8 eQTLs, and the resulting gene set was evaluated for maximum Combined Annotation Dependent Depletion (CADD) score to prioritize potentially deleterious genetic variants. That gene set was then further evaluated for tissue-specific enrichment.

Results

We identified 44 genetic variants that reached the genome-wide significance ($p < 5E-8$) (Fig 1), and 8 genes that reached gene-level significance ($p < 4.39E-6$) (Fig 2), including *ZNF285*. The gene set with 25 genes derived from eQTL mapping included 4 genes *ZNF233*, *ZNF235*, *ZNF223*, and *ZNF222* with maximum CADD score (>10). This gene set showed significant enrichment in the GTEx cerebellar hemisphere and cerebellum brain tissues, with 18 and 16 genes expressed, respectively (FDR-adjusted- $p = 2.3E-5$ and $p = 5.7E-4$, respectively).

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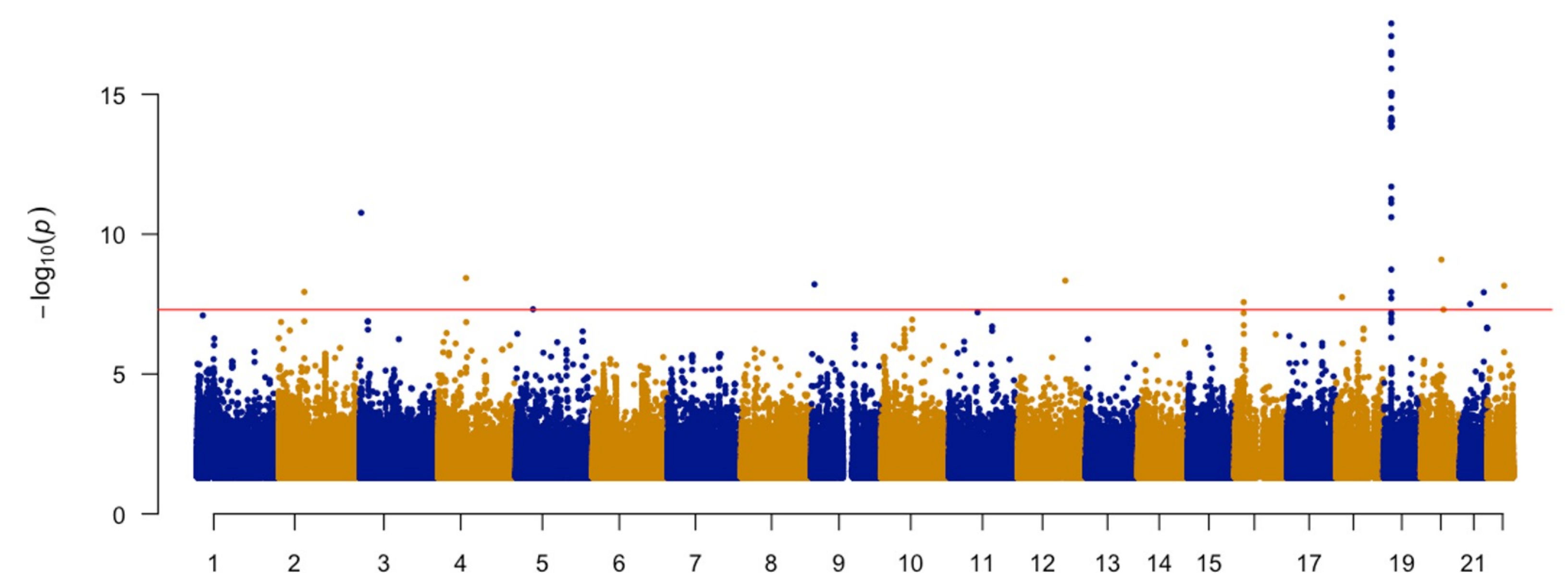


Figure 1. SNP-level GWAS for Tau-PET Braak Staging in ADSP. Red horizontal lines indicate the genome-wide significant threshold (p -value=5E-8).

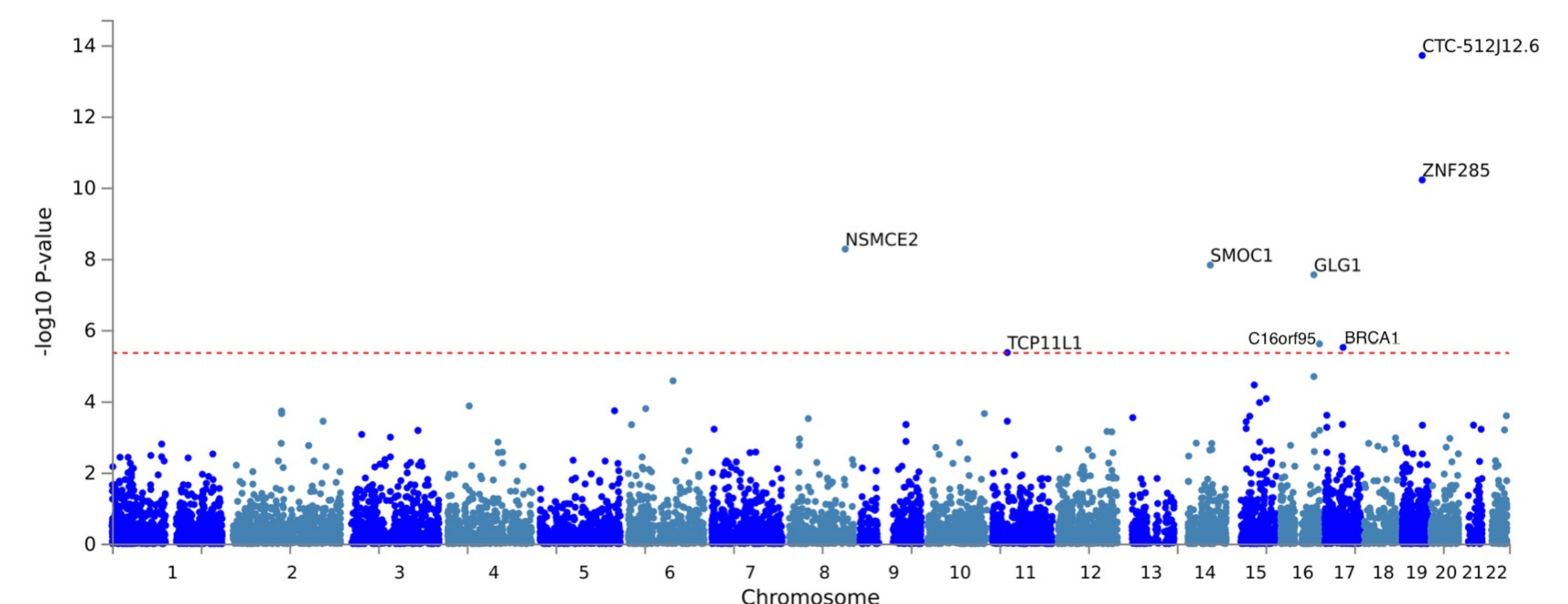


Figure 2. Gene-level GWAS for Tau-PET Braak Staging in ADSP. Red dashed horizontal lines indicate the genome-wide significant threshold (p -value=5.7E-4).

Conclusion

These results provide additional evidence supporting genetic contributions to risk of tau pathology, specifically reinforcing the association between variants of the zinc finger proteins and the accumulation of tau tangles. Integration of genetic data with tau-PET derived biomarkers provides insights into identifying genetic risk factors for individuals with early tau accumulation.