AAN 72nd ANNUAL MEETING ABSTRACT

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Abstract Title: Genome-Wide Association Study of Tau PET in the Mayo Clinic Study of Aging

Press Release Title: Researchers Find Gene Variants That May Increase Susceptibility to Alzheimer's Proteins

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Objective: To identify genetic factors associated with tau deposition in older adults.

Background: Tau deposition is a key biological feature of Alzheimer's disease, but the heritable influences on susceptibility and resistance to tau deposition are not well-understood. The recent availability of tau-PET provides an opportunity to test the hypothesis that common genetic variants would be associated with cerebral tau burden.

Design/Methods: Inclusion criteria included individuals over age 50 from the population-based Mayo Clinic Study of Aging with genome-wide genotype and regional tau-PET (AV-1451) data. Following genotyping with the Illumina GSA array and standard quality control, 515,206 single nucleotide polymorphisms (SNPs) were available for analysis. A genome-wide association study of an AD-signature composite for tau PET was performed using an additive genetic model and covarying for age and sex. Post-hoc stratified analyses utilized amyloid positivity (global PiB>1.48) as a discriminator.

Results: The study sample included 754 individuals (mean age 72.4 years, 54.6% men, 87.4% cognitively unimpaired). Genome-wide significant associations with higher tau were identified for rs76752255 (p=8.70x10^{-9}, β=0.20) in *PPP2R2B* (protein phosphatase 2 regulatory subunit B), and rs115862481 (p=2.31x10^{-8}, β=0.17), in an intergenic region on chromosome 1, with each minor allele (frequencies=1.5%/1.1%) displaying a stronger association in amyloid-positive (β=0.29/0.23) versus amyloid-negative (β=0.11/0.09) individuals. No associations with tau burden were identified for the SNPs defining *APOE* (apolipoprotein E) ε4 or for genotyped SNPs previously associated with AD in large case-control studies. Three SNPs within *MAPT* (microtubule-associated protein tau) displayed nominal associations to tau burden, including rs3785883 (p=0.04, β=0.07) which was previously associated with higher cerebrospinal fluid tau in an independent cohort.

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Conclusions: This study identified novel genetic associations with susceptibility to tau deposition in older adults. Our data also suggests that tau deposition may have a genetic architecture distinct from known AD risk genes, which may have implications for enhanced risk prediction and therapeutic targeting.

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