Integrating Neuropathology to Refine Genetic Risk in Alzheimer's Disease

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BACKGROUND: Alzheimer's disease (AD) is a heterogeneous disorder with a substantial genetic component. Traditional genome-wide association studies (GWAS) rely on clinical diagnoses of large cohorts, which are compromised by phenotypic heterogeneity. We conducted GWAS in a novel European neuropathological cohort (n=414) with detailed neuropathological characterization to identify genetic associations with specific AD-related lesions.

METHODS: AVITI low-coverage whole-genome sequencing was performed at 1x coverage. SNPs and indels were imputed using GLIMPSE2, referencing the 1000 Genomes Project panel. Association testing was conducted in PLINK2. Variants reaching genome-wide significance ($p < 5 \times 10^{-8}$) and notable subthreshold loci were evaluated for potential roles as quantitative trait loci (QTLs).

RESULTS: We identified genome-wide significant and suggestive loci contributing to the heterogeneity of AD risk. In addition to APOE, we discovered an intronic variant in GYPE and a variant upstream of ADAMTS16, both showed nominal associations with ABC score, reflecting AD pathology. Both were significantly linked to Braak staging (Tau neuropathological score), suggesting a potential role in tau-related lesions. Significant associations with co-morbidities were found, like granulovacuolar degeneration (necroptotic cell death), with an intronic variant in XAF1, and an intronic variant in NRF1 associated with Hirano body scores (actin aggregates).

CONCLUSIONS: Despite sample size constraints, we identified genome-wide significant associations with AD-related lesions by controlling for phenotypic heterogeneity. Results from QTL analyses highlight the molecular relevance of several loci and suggest potential novel risk genes. Moving forward, we will prioritize replication and meta-analysis in independent cohorts, functional validation and targeted resequencing.