Genetics of Early-Onset Alzheimer's Disease: Investigation of Rare Variants in the LEADS Cohort

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Introduction: Early-Onset Alzheimer's Disease (EOAD) is a neurodegenerative disease (NDD) with marked heritability, the majority of which is unexplained by known pathogenic variants. We hypothesize that a portion of the genetic etiology of EOAD may be due to rare pathogenic variants in genes associated with other NDDs, including Parkinson Disease (PD), Frontotemporal Dementia (FTD), and Amyotrophic Lateral Sclerosis (ALS).

Methods: First, we constructed a gene set comprised of 31 loci commercially screened for both dementia and another NDD, captured by ten commercial dementia and four commercial NDD genetic test panels. We performed gene ontology analysis of this 31-gene set. We then conducted SKAT-O testing for pathway-level enrichment of rare functional variants in whole exome sequencing (WES) data from participants in the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) (n = 303) and age-matched controls from the Parkinson's Progression Markers Initiative (n = 193), with pathways defined by NDD gene panel. We performed *post-hoc* gene-set tests for individual genes in significant pathway results.

Results: SKAT-O analysis showed LEADS participants were enriched in functional SNPs compared to controls within genes in panels for PD and Parkinsonism (p=0.0003) and FTD (p=0.0119). *Post-hoc* testing revealed significant enrichment in *FUS* (p = 0.0098), from the FTD panel, and *ATP7B* (p = 0.0002), from the PD and Parkinsonism panel. Ontology analysis revealed that numerous neurodegeneration-associated biological processes, including mitochondrial organization and function, autophagy, proteasomal catabolism, and oxidative stress were statistically enriched in the original 31-gene set.

Conclusion and Scientific Impact: Functional SNP enrichment in PD- and FTD-associated genes in the LEADS cohort suggests shared etiology amongst NDDs. Future directions include analysis of effect direction for SNPs in the genes driving significance of pathways. The genes and pathways identified are promising for targeted research capable of detection of specific

variants responsible for the missing heritability of clinical EOAD, which would improve diagnostic timeliness and accuracy.