Research Use Statement for Application for Genomic Data from NIAGADS

Research Use Statement:
In a pathologically defined cohort we will test the hypothesis that the Alzheimer's disease (AD) polygenic hazard score (PHS), a dementia with Lewy bodies (DLB) polygenic risk score (PRS), and a Parkinson's disease (PD) PRS can differentiate individuals with DLB from those who have AD.

Inclusion will be limited to NACC participants who had undergone genotyping and a neuropathological assessment at autopsy. Genetic data will be incorporated into that collected through the NACC uniform data set, minimum data set, or neuropathology data set and available through NACC.

The AD PHS will be calculated for each participant as the vector product of that individual's genotype for the 31 SNPs and the corresponding parameter estimates from the ADGC phase 1 Cox proportional hazard model, choosing the effect allele to be consistent with the direction of the beta in the IGAP summary statistics, in addition to the APOE effects (Desikan et al., 2017).

The PD PRS will be calculated for each participant as the vector product of that individual's genotype for the 90 independent genome-wide significant variants identified by the most recent meta-analysis of PD genome-wide association study (GWAS) data and the corresponding parameter estimates using data from all available studies (Nalls et al., 2019).

The DLB PRS will be calculated as the vector product of that individual's genotype for the 5 independent genome-wide significant variants identified by the first DLB GWAS and the corresponding parameter estimates from the discovery stage (Guerreiro et al., 2018).

Logistic regression models will be used to examine the relationship between the AD PHS, PD PRS, or DLB PRS and pathological variables.

Non-Technical Summary for Application for Genomic Data from NIAGADS

Investigators will provide a non-technical summary of their proposed research. If the project is approved, this statement will be publicly available for lay audiences to read the purpose and objectives of the research. Please limit to 1,100 characters.

Accurate distinctions between Alzheimer's disease (AD) and related dementias may improve precision in care delivery and thus lead to better outcomes. In the diagnosis of Dementia with Lewy bodies (DLB), distinction from AD is suboptimal. Incorporating information about genetic risk into a difficult differential diagnosis may improve clinical-pathological correlations. This is complicated by the frequent co-occurrence of AD pathology with Lewy bodies (LBs) and the fact that DLB has both clinical features and genetic risk factors that overlap with both AD and Parkinson's disease (PD). We will test the hypothesis that genetic risk for AD, DLB, and PD can be used to differentiate individuals with DLB from those who have AD.