Research Use Statement for Application for Genomic Data from NIAGADS

We are seeking access to NIAGADS data to pursue the specific aims listed in our funded NIH project, " Gender, Imaging Genetics (GIG)," which will leverage existing longitudinal cohorts from NACC, ADNI, AIBL, and BAI/Mayo. While the focus of this project is to examine the effects of gender and APOE4 on brain, cognition, and clinical progression, our third aim is to explore and discover new genetic associations with sex-specific risk for AD.

Using the NIAGADS datasets, we plan to extract a small subset of GWAS data from the NACC subjects (~950 individuals), for which we already have imaging and clinical data, to increase our study's sample size and the statistical power of our downstream analyses. With the remaining samples, we intend to produce summary statistics that will be used to construct polygenic risk scores for our study's subjects who we have whole genome sequencing data. This will require a large training dataset of ancestry-matched subjects with AD diagnosis information, which will be provided by the NIAGADS datasets we are requesting. The autosomal and chromosome X GWAS data will be ran through the University of Michigan Imputation server (using the Haplotype Reference Consortium dataset as a reference) to produce a larger set of overlapping markers. Additionally our collaborators have constructed an Imputation pipeline for Mitochondrial and Chromosome Y genomes (manuscript pending). We will use the software LDpred to account for linkage disequilibrium during the construction of our study's PRS. These risk scores will be used as covariates in our downstream analyses to control for the effect of non-APOE genetic markers, account for the total proportion of observed AD heritability explained by the available genetic data, and also to tease apart the genetic factors that contribute to the Sex-based differences in AD prevalence and inheritance.

Non-Technical Summary for Application for Genomic Data from NIAGADS

The Gender, Imaging Genetics (GIG) Project will examine the effects of gender and genetic markers on brain, cognition, and clinical progression towards Alzheimer's dementia. We will be using existing longitudinal cohorts from NACC, ADNI, AIBL, and BAI/Mayo, and additionally NIAGADS as a reference database. Using neuroimaging analyses and statistical models of cognition and clinical conversion, we will evaluate genetic associations, hippocampal shapes, along with other AD-specific brain regions, in relation to cognitive function and clinical progression in our cohort of ~2800 cognitively normal, MCI, and AD and how these relationships differ by gender. For assessment of cognition, we will harmonize the cognitive variables across cohorts to examine tests of global cognition, episodic memory and executive function. This project will provide new, critical information on how gender, a commonly overlooked and underpowered variable in AD research, interacts with APOE4 and other genetic risk to confer brain deformation, cognitive decline, and clinical progression.