Research Use Statement for Application for Genomic Data from NIAGADS

Please limit to 2,200 characters max. The statement should include the following components:

- Objectives of the proposed research;
- Study design;
- Analysis plan, including the phenotypic characteristics that will be evaluated in association with genetic variants

Research Use Statement:

Alzheimer's Disease (AD) has a complex genetic component. Several loci of interest have been discovered using genome-wide association studies (GWAS) for AD, notably APOE, which remains the greatest genetic indicator of AD development to date. While efforts have discerned key contributors to the disease, much of the genetic heritability of AD remains unexplained. Thus far, genetic heritability of AD has been understood using GWAS, which have been conducted with the assumption that the effects of alleles in genes are linearly additive. However, this is not always an accurate representation of the underlying biology. We aim to explore the genetics of AD by utilizing a non-additive genetic model in our GWAS. This method will allow us to find novel genes associated with increased or reduced risk of AD that interact via a previously unexamined, biologically-informed way. By inspecting the biological interplay of AD genes, we hope to find variants of functional importance in AD.

Study Design:

We will assemble for analysis 15 GWAS datasets (ADNI, GenADA, and the 13 sets requested in this present application). A genome wide association study (GWAS) will be performed in a case-control setting, analyzing each dataset independently and combining the results by metaanalysis.
The GWAS will use a different model of allelic association based on biological phenophenomena.
We will also test the association of MCI subjects with CSF markers (beta-amyloid, phospho-tau and total-tau) in the ADNI data set. We will further validate genetic results through the RNA expression level dataset from the AD case-control study of ROSMAP.

Analysis Plan:

For each dataset, we will apply a stringent quality-control pipeline to the data before and after the imputation using IMPUTE2 software. The association testing will be carried out by logistic regression (or linear regression using CSF biomarker levels as a quantitative trait), adjusting for age, sex, APOE4 status, and population structure using PLINK(v1.7). The analysis will be be conducted using biologically-informed models of genetics in humans, as opposed to the usual methodology commonly observed in GWAS studies, such as the additive allele model or the dominant allele model. The results will be combined in a meta-analysis using the method implemented in the GWAMA software tool, after applying genomic control within each individual study. Finally, we wish to further validate any SNP findings with gene expression data, which will help discern the functional importance of our results.

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.

We aim to identify additional genetic factors contributing to the development of AD through the use of biologically-informed, non-additive genetic models in our GWAS to test for significant association. The use of novel models to understand and characterize AD may illuminate novel gene candidates that function via underexplored mechanisms that are closer in accuracy to the underlying molecular biology.