**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

**Identification of novel CSF endophenotypes and genetic variants for AD by Mendelian Randomization**

Large genome-wide association studies have identified several genetic variants in 20 loci associated with risk for Alzheimer’s disease (AD). However, the pathogenic mechanism associated with these variants remains unknown. Recent studies have identified very promising cerebrospinal fluid (CSF) and plasma biomarker for AD, but it is not clear whether this protein is really involved in the pathogenic pathway or just is a product of the disease. In this proposal, we will use innovative statistical methods including Mendelian randomization to analyze whether those novel biomakers are part of the causative pathway for AD and to determine whether they can be used as informative endophenotypes for genetic studies. We have recently used Mendelian randomization analysis to identify CSF APOE and fatty acid binding protein (FABP) as promising endophenotypes for AD. We have also successfully used CSF endophenotypes for genetic studies of AD to identify several novel genetic variants associated with age at onset, disease progression, and risk for AD. Our studies demonstrate that the CSF endophenotypes are a powerful and alternative approach to the classical case-control studies. We plan to use powerful analyses and methodologies to identify the effect of not only common genetic variants but also rare variants by incorporating whole-genome sequencing and exome-chip data on the endophenotype levels. The broad, long-term goal of our research is to dissect the complex genetic architecture of AD which will lead to better prediction and treatment of this devastating disease. Combining CSF endophenotypes and biomarkers discovery with genetics analysis will allow us to identify the complex relationships between genes, proteins, and disease which will help to identify novel and key proteins involved in disease pathogenesis and potential therapeutic targets.

**Research Use Statement:**

**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.

Recent genetic studies of complex traits and diseases have focused on the identification of common variants associated with risk through genome-wide association studies (GWAS). Other aspects such as rate of progression, age at onset and the effect of rare variants are generally not investigated. These studies have been very successful in identifying novel loci associated with many complex diseases. The current proposal focuses on these understudied aspects of disease etiology, namely the role of common and rare genetic variation on quantitative diagnostic and prognostic endophenotypes of Alzheimer’s disease (AD). We will use GWAS and exome-chip data to identify single variants, genes and pathways associated with cerebrospinal fluid (CSF) levels of known AD biomarkers (tau, ptau, Aβ, YKL40, VILIP1) and other AD-related proteins (CLU, APOE, TREM2). The integration of these endophenotypes will enable us to disentangle the genetic architecture of AD. With this insight, we will then determine whether those SNPs, genes or pathways are also associated with other AD phenotypes (risk, age at onset or progression), and whether we can use genetic information to increase the diagnostic or prognostic ability of these CSF biomarkers. Further, we will utilize Mendelian Randomization and a novel network-based approach to identify causal plasma and CSF proteins involved in AD and other complex traits.