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:

Objectives of the Proposed Research:

The goal of the proposed research is to identify new genes or SNPs that are probably causative factors to AD.

Study Design:

We hypothesize that distributions of predispositional SNP alleles may be distinct between differential characteristics of AD. GWAS meta-analysis will be conducted by grouping the participants with some factors. Also specific co-expression modules will be identified in these subgroups by employing weighted gene coexpression network analysis (WGCNA).

Analysis Plan:

For sub-group GWAS meta-analysis, all participants will be subdivided based on demographic characteristics or certain SNPs. Proper strategies such PCA and MDS will be used to check the homogeneity of different GWAS studies and exclude outliers. After quality control, homogenous GWAS studies were combined using Plink or METAL to identify these susceptible SNPs through Chi-square test in each subgroup. Then post-GWAS analysis will be conducted. Significant genes will be used to perform Gene Set Enrichment Analysis and hypergeometric test will be carried out to identify signaling pathways related to AD and related biological processes in each sub-group will be identified. Then similar sub-networks which indicate similar molecular functions or biological processes between two sub-groups were distinguished. If genes in a subnetwork are enriched in a certain pathway verified formerly, and the sub-network can only be observed in one sub-group, but not the other, then we could be convinced that the sub-network is subgroup-specific, and the hub gene in the sub-network can be a potential drug target.
For WGCNA analysis, the transcriptomic datasets deposited in NIAGADS will be subdivided into several subtypes according to individuals' demographic characteristics, and then WGCNA would be carried out on these sub-datasets to study the disease-specific co-expression modules. This analysis may be combined with our recent WGCNA analysis using GSE15222 dataset downloaded from Gene Expression Ominibus (GEO) or be used to replicate our analysis with GSE15222.

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.

Alzheimer's Disease is confirmed to be a highly heritable (with heritability of up to 76%) and polygenic disease. It may be a way to search for new therapeutic targets by identifying susceptible genes and altered signaling pathways of Alzheimer's disease. GWAS and eGWAS data may be the ideal resources for identification of these targets. Distributions of predispositional SNP alleles may be distinct between different ages and genders. Pathological and some other characteristics of Alzheimer's Disease can be differentiated by demographic characteristics, such as age and gender,

and genes. We hypothesize that distributions of predispositional SNP alleles may be distinct between differential characteristics. Thus, in this study, participants will be divided by the differential characteristics and then GWAS metaanalysis co-expression gene analysis will be conducted in these subgroups to identify specific genes or pathological processes.