

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:

Alzheimer's Disease (AD) is the most common form of dementia with strong genetic etiology. This study is aimed at identifying some genetic variations that can regulate the expression of *APOE*, whose structural variant *APOE4* has been validated to be the most risk factor for AD, by combining genotype datasets from the National Institute on Aging Genetics of Alzheimer's Disease Data Storage (NIAGADS) Site.

Study Design:

We will retrieve brain *APOE* eQTLs from two publicly available databases and one database established by ourselves. We will extract genotype information of these brain *APOE* eQTLs from each GWAS dataset and assemble them together after quality control and imputation procedures. Further analyses would be implemented to identify AD-associated or *APOE* ϵ 4-interactive brain eQTLs for *APOE* gene.

Analysis Plan:

All datasets will be quality-controlled by PLINK, then imputation will be conducted for each dataset by using Liftover, Shapeit and Impute2. After quality control and imputation for each genotype dataset from NIAGADS, these datasets would be combined together. Genetic variations which can regulate the expression of *APOE* will be retrieved from some established eQTL databases (www.braineac.org and GTex) and an eQTL database established by ourselves. Genotype data for these genetic variations would be extracted from the combined genotype dataset. After correction for population stratification, further analyses would be carried out to determine if some brain eQTLs for *APOE* gene are AD-associated or if they can interact with *APOE* ϵ 4 after adjusting for covariances.

After identification of these AD-associated genetic variations around *APOE*, some molecular biological experiments would be implemented to illuminate the mechanisms behind it.

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 (AD) is the most common form of dementia with strong genetic etiology (with heritability of up to 76%). *APOE*, the widely investigated gene in AD research, its structural variant *APOE4* has been validated to be the most

risk factor for AD. We hypothesize that some SNPs can influence the expression level of *APOE* gene and can interact with *APOE* ϵ 4 simultaneously. In such case, these SNPs may regulate the expression of *APOE*4. In this study, all GWAS cohorts will be incorporated together to identify such kind of SNPs.