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:

Genome-wide association studies (GWAS) have identified about 40 reliable risk loci for Alzheimer's disease (AD), while the functional variants responsible for the pathogenesis of AD in each locus are still unknown. In the proposed study, we conducted functional genomic annotations on variants targeted by AD GWAS loci by using multi-omics data, and identified a number of potentially functional variants. Considering that most functional variants are in complex linkage blocks and their association signals may be contributed by variants in linkage disequilibrium (LD) with them, therefore, the reliability of these functional variants should be confirmed by testing whether the association signals of these variants were still significant after adjusting for genotypes of variants in LD with them. ADGC dataset provided genotype and phenotype data for a relatively large cohort of AD patients and controls, thus is the best resource for us to perform aforementioned analysis. Genotypes, diagnosis, age at onset, gender, and other available covariate information from the ADGC dataset will be used in our analysis. We plan to perform two different analyses on these data to validate the reliability of our functional variants. Firstly, logistic regression model will be used to test the association of target variants with AD conditioning for genotypes of their linked variants. Secondly, polygenic risk scores will be computed for each individual based on different sets of variants and area under the receiver operating characteristic curve (AUC) will be used to assess their performance. We assume that if our functional variants are reliable, the association between these functional variants and AD will still be significant after conditioning for genotypes of their linked variants, and PRS based on functional variants will outperform PRS based on other sets of variants.

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.

In the proposed study, genotype and phenotype data for AD patients and controls from the ADGC dataset will be used to validate the reliability of functional variants in each AD GWAS loci identified by functional annotations based on multi-omics data.