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:

Identifying risk factors that predispose individuals to Alzheimer's Disease (AD) is valuable for understanding its pathophysiology. Knowledge of risk factors can be used to predict who is most likely to develop AD and identify factors that promote *resilience* to AD.

Polygenic risk scoring can be used to distinguish affected cases from unaffected comparison subjects for a disease phenotype. We developed a novel method that capitalizes on the predictive power of polygenic risk scores to identify variants that foster resilience to disease. Allele frequencies for unaffected controls in the upper tail of the distribution for risk are contrasted with affected cases with equivalent risk scores by GWAS. Higher allele frequencies found in the high-risk unaffected control group are putatively associated with resilience.

The specific steps for our analysis are:

1. Compile available GWAS data sets on AD cases and cognitive normal comparison subjects (CNs).

2. Split the data into training and validation samples, with an equivalent ratio of cases to controls.

3. Perform a GWAS meta-analysis of AD and CNs in the discovery cohort to train a 'polygenic risk score' formula.

4. Compute polygenic risk scores in the discovery cohort and pick the top 10% (or 1%, 5%, or others) of CNs along with AD cases with similar risk score.

5. Perform a GWAS meta-analysis using the subset of CNs and AD cases picked in step 4.

6. Remove variants associated with AD risk found in step 1 along with variants in linkage disequilibrium (R^2>0.2).

7. Examine the remaining SNPs to see if there is a significant genome-wide association result for resilience to AD, then construct a polygenic resilience score (i.e., sum of resilience alleles across top AD-resilience SNPs weighted by their effect size). Estimate the amount of variance in resilience status (i.e., high risk CNs versus high risk AD cases) explained by polygenic resilience scores.

8. Repeat step 7 in the validation set. If signal for polygenic resilience scores is robust and sample size for validation cohort is sufficiently large, then the variance explained by polygenic

resilience scores should be significant.

Lastly, perform a second iteration of steps 5 – 8 wherein we condition association tests on *APOE*-ε2 status.

Expected outcomes of this process are:

a. Uncover markers separate from the protective *APOE*-e2 allele that promotes resilience to AD in high risk CNs.
b. Identify resilience variants that offset the contribution of risk variants in the same gene.
c. Identify resilience genes that offset the contribution of risk genes in the same pathway.

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.

Substantial scientific progress has been made in the past decade for Alzheimer's Disease (AD), a devastating form of dementia characterized by brain shrinkage, drastic memory loss, and sharp cognitive decline. A recent large-scale genetics study identified several genes contributing to risk for AD, which has enabled researchers to predict who is at high risk for developing AD according to the number of risk genes that a person carries. Our study will build on these efforts by attempting to identify genetic factors that contribute to *resilience* to AD. More specifically, we suspect that there are genetic variants that occur more frequently in healthy elderly individuals who carry many risk genes for AD, thereby promoting resilience in those individuals. This proposed work could have significant implications for our understanding AD pathophysiology, and potentially offer useful targets for interventions that foster resilience among at-risk individuals.