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

Single nucleotide polymorphisms (SNPs) in the complement receptor 1 (*CR1*) gene have been consistently associated with AD risk in multiple genome-wide association studies (GWAS). Our research seeks to evaluate how and which of the various *CR1* SNPs affect the primary function of CR1: erythrocyte clearance of circulating pathogens, including Aβ. Under NIA grant RO1AG039750 to the PI, we collected blood samples from 256 well-annotated, well-matched AD, MCI and non-demented control patients at the NIA Arizona AD Center. The subjects were genotyped for 28 SNPs in the *CR1* gene that had either previously been associated with AD risk or that enabled us to map the entire *CR1* region based on linkage disequilibrium data. Genomic data were phased and additional SNPs within the CR1 region were imputed using IMPUTE2 and reference data from the 1000 genomes database, generating patient haplotypes for the CR1 region. We then evaluated association of *CR1* SNPs/haplotypes with erythrocyte CR1 structure, levels, and ability to clear Aβ. Using the much larger datasets available from NIAGADS, we now seek to assess the association of AD risk with the CR1 SNPs and/or haplotypes that significantly influenced erythrocyte CR1 structure, expression, and function in our study (target *CR1* SNPs/haplotypes).

Study design and analysis plan

In collaboration with an experienced biostatistician at SRI, Dr. Harold Javitz, we will employ logistic regression to assess the effects of our target *CR1* SNPs/haplotypes on AD risk in 15 relevant NIAGADS databases (see appended file “SRI Supplemental Information Document.pdf”). Since the databases also contain *ApoE*, gender, and age status, we will additionally evaluate their contributions to AD risk as covariates. Overall, we will apply QC controls and use meta-analysis and joint analysis strategies similar to those described in detail by Naj et al. (Nature Genetics, 43:436-39, 2011), including their extended model of covariate adjustment and the use of a Discovery and a Replication cohort. Unlike Naj et al., we will evaluate both dominant and additive models, as our preliminary data indicate that the effect of some *CR1* SNPs on CR1 structure, expression, or function may differ with respect to model depending on the SNP and the outcome measure.

Non-Technical Summary for Application for Genomic Data from NIAGADS

Subtle variations in the complement receptor 1(*CR1*) gene have been consistently

associated with risk for developing Alzheimer's disease. Exactly which variations and how they might impact the disease process remain unclear. Because CR1 is difficult to find in the brain, and because almost all of the body's CR1 is found on peripheral red blood cells, we have investigated a well-established mechanism in which red cells use CR1 to clear pathogens from the circulation. Our research shows that a critical molecule in Alzheimer's disease, amyloid β peptide (Aβ), is subject to this mechanism, and that its removal from blood is significantly deficient in Alzheimer's patients. Using blood samples from Alzheimer's and normal elderly control patients, we have found several variations in the *CR1* gene that influence red cell-mediated clearance of Aβ, but we do not have gene data on enough patients to track these variants to risk for Alzheimer's. The very large datasets provided by NIAGADS will substantially improve such an analysis.