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

HLA-C variants as risk factors for neurocognitive diseases

Research Use Statement:

Background and Objectives
Viral infections and neuroinflammation are involved in neurodegenerative disorders and brain aging, but underlying molecular mechanisms are mostly unknown.
β2-microglobulin (β2m) is an important pro-aging factor that interferes with neurogenesis, alters cognitive functions and forms insoluble protein aggregates causing amyloidosis. High levels of β2m have been detected in patients with Alzheimer's disease.
Inflammation in the elders has been associated with polymorphisms of the MHC-I locus encoding HLA molecules that, by associating with β2m, intervene in cellular immunity. Studies conducted in our laboratory have shown that HLA-C variants more or less stably linked to β2m may modify viral infectivity. These observations led us to hypothesize that some variants of HLA-C, in the presence of viral infections, could promote the release and accumulation of β2m, which in turn may be involved in triggering neuroinflammatory processes, and facilitate neurodegeneration.
The aim of this study is to evaluate if HLA-C genetic variants with unstable binding to β2m are more frequent in patients with Alzheimer's disease.

Study Design
The study will be conducted as a case-control association study of HLA-C alleles (categorized as either stable or unstable according our previous results) with AD patients and their matched controls. Association model will be adjusted for the most important covariates that might include known candidate genes.

Analysis Plan
The analysis will be performed through the following steps:
- collecting the relevant clinical information along with the disease status for each individual to setup the association model to be investigated;
- downloading genetic data of HLA chromosomal region and candidate genes, and arranging them in the proper format for the following computations;
- estimating allele (and/or groups of haplotypes at different resolution levels) frequency of the HLA region and of known candidate genes, and preparing a summary statistics;

- genotype imputation and phasing haplotypes for the HLA and candidate gene regions. Position of the variant sites will be also remapped to the appropriate reference for the HLA region.
- Association of HLA gene variants with Alzheimer disease. The genetic factor to be to be included into the association model will be defined as allele, haplotype or genotype and, more importantly, as 'stable' or 'unstable' allele. The most important covariates will be included into the association model. Associations will be adjusted for multiple testing.

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.

The present project will explore whether the genetic variability of the major histocompatibility complex (MHC) is involved in the pathogenesis of Alzheimer's disease (AD).
MHC is a set of cell surface proteins that are essential for the acquired immune system to recognize foreign molecules in humans, and is involved in histocompatibility (e.g., in transplant rejection).
We hypothesize that some MHC variants (i.e., HLA-C variants) may facilitate interactions between viruses and the neurons in the brain, thus leading to chronic neuroinflammation, and in turn neurodegenerative changes of AD.
If our hypothesis was to be confirmed, exploring HLA-C variants may help stratify the risk of developing AD at elderly age, and design further studies aimed to reduce this risk.