

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 interaction study of pathogenic protein in Alzheimer's disease”**

Objectives: A weak association between pathogenic protein, tau and A β deposition and neurodegeneration biomarkers, such as brain atrophy, has been repeatedly reported in a subset of patients with Alzheimer's disease (AD), suggesting individual differences in response to pathogenic protein deposition. Here, we investigated the single nucleotide polymorphism (SNP) that modifies the effect of pathogenic protein deposition on brain atrophy.

Study design: We conducted a genome-wide interaction analysis to identify genetic variants that modify the effect of pathogenic protein on brain atrophy using a total of 723 subjects (218 cognitively healthy, 301 with mild cognitive impairment, and 204 with AD) with magnetic resonance imaging, positron emission tomography, and genetic data from the Alzheimer's Disease Neuroimaging Initiative database (<http://adni.loni.usc.edu/>). We identified significant interaction for some SNPs, the greater dosage of which increased the association between pathogenic protein deposition and brain atrophy and cognitive decline.

Analysis plan: Furthermore, using longitudinal data of NACC and NIAGADS, we planned to evaluate whether aforementioned SNPs predict individual's prognosis in independent data set. From NACC, we obtained the data set with the following criteria; (i) subject has longitudinal data (at least 2 visits) [NACCAVST \geq 2], (ii) subject with either normal cognition or mild cognitive impairment at baseline [NACCUDSD=1,2,3 and NACCVNUM=1], and (iii) subject with primary AD etiology [NACCETPR=1] or normal cognition [NACCUDSD=1]. From NIAGADS, we planned

to obtain genetic data, which include aforementioned SNPs. For missing SNPs, we planned to impute genotype using Michigan Imputation Server (<http://imputationserver.sph.umich.edu/>). After obtaining the data, we planned to perform cox regression analysis with follow-up time as a time variable and progression to dementia as a status variable while controlling for baseline age, sex, and level of education.

We expected that identification of such variants would help in understanding neurodegeneration of AD and identify individuals who are susceptible or resistant to pathogenic protein deposition and further progression.

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), which is the main cause of dementia in the elderly, is recognized as one of the most burdensome conditions in the elderly. Estimates suggest that it will affect 106 million people worldwide by 2050. Tau and A β , key pathogenic protein in AD accumulate in the brain of patients prior to brain atrophy and cognitive decline. However, subset of patients with AD shows no or minimal cognitive decline with high pathogenic protein deposition. Here, we attributed this individual difference to common genetic variant and planned to identify common genetic variant that modifies the effect of pathogenic protein on brain atrophy by conducting a genome-wide interaction study. Furthermore, we planned evaluate the predictive value of such variants on individual's prognosis using the longitudinal data. We expected that identification of such variants would help in understanding neurodegeneration of AD and identify individuals who are susceptible or resistant to pathogenic protein deposition and future progression.

