Research Use Statement:

Objectives of the proposed research

The objective of this proposal is to investigate whether known genetic risk factors for dementia are correlated with maternal and paternal family histories of Alzheimer's disease (AD) in an individual's risk for mild cognitive impairment (MCI) for Apolipoprotein E (APOE) ε3/ε3 carriers.

Study design

We have identified 616 APOE ε3/ε3 participants in the Wisconsin Registry for Alzheimer's Prevention (WRAP) and National Alzheimer's Coordinating Center (NACC) studies with self-reported parental histories of AD. Individuals were 89% Caucasian and between the ages of 55 and 85 years. A parent was considered cognitively normal if the parent did not have an MCI or AD diagnosis before the age of 80. Prevalence of MCI was retrospectively calculated for different groups of maternal and paternal histories of AD. The prevalence of MCI was 3 times smaller for the group with paternal histories of AD compared to groups with maternal histories of AD, both maternal and paternal histories of AD, and no maternal or paternal histories of AD. This result was unchanged when the WRAP and NACC data sets were independently considered, but was reduced when the threshold age used to define the minimum age of a cognitively normal mother was lowered.

Analysis plan

We propose to analyze genetic factors from NACC participants in the Alzheimer's Disease Centers (ADC) sets to determine if single nucleotide polymorphisms (SNPs) that are known to be associated with dementia (e.g., AD, cardiovascular disease), along with polymorphisms in the linkage disequilibrium block containing the APOE, TOMM40, and APOC1 genes, are correlated with MCI risk and family history of AD. Additional NACC participants with APOE ε3/ε3 and ε3/ε4 genotypes with cognitively normal and AD diagnoses will be identified to model as parental groups. Logistic regressions will be used to test SNP variant interactions with sex for risk of MCI along with cumulative genetic risk scores. If genetic factors are identified, we then propose to use mixed-effects regression models to analyze continuous cognitive outcomes using scores from cognitive tests (e.g., MMSE, CDR) that were administered to NACC participants. A separate request for collaboration has been sent to the WRAP genetics core.

Non-Technical Summary for Application for Genomic Data from NIAGADS:

For individuals with two copies of the "neutral" variant of the Apolipoprotein E (APOE) gene, having a father who developed Alzheimer's disease statistically appears to reduce one's chance of developing cognitive problems later in life

(even compared to having a father and mother who did not develop Alzheimer's disease). We are proposing to look at known genetic risk factors for Alzheimer's disease and dementia in order to determine if there are possible inheritance scenarios for these individuals that may offer an explanation.