

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:

Introduction: Recently, we reported that a polymorphic variant (rs3846662) in the gene encoding 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) completely eliminates the risk of Alzheimer's Disease (AD) dementia onset otherwise associated with the presence of the APOE e4 allele in a population isolate from Eastern Canada. HMGCR regulates cholesterol synthesis in the CNS. In recent months, we have discovered novel polymorphisms in a nearby antisense CTD gene (5' of the HMGCR locus) that again affect both AD risk and HMGCR gene expression and regulation.

Objective: The overarching goal of this research program is to determine the relationship between HMGCR protective/risk variants, HMGCR gene expression and splicing, and HMG-CoA reductase activity in relation to A β and tau pathology, neurodegeneration and cognitive decline across the entire AD spectrum. While most of the work is done using brain samples from the Douglas Brain Bank in Montreal, Canada, we now wish to replicate some of our pathological findings linking certain HMGCR genotypes to senile plaque density and tangle accumulation in AD using the Neuropathology Data set of the National Alzheimer's Coordinating Center (NACC)

ADC/NACC pathological dataset (we have already obtained the dataset: proposal ID#894) and the NIAGADS genetic dataset of the corresponding NACC autopsied subjects.

Study Design and Analysis Plan: Using the NIAGADS databases, we wish to access the genechip data from ADC1-7 (NG00022-24 and NG-00068-71) to extract SNPs from the entire areas of the HMGCR gene locus on chromosome 5 (+/- 100 kb). We will then contrast the HMGCR variants with a) tangles and senile plaques densities of the autopsied AD and control cases from the NACC-neuropath dataset and b) CSF concentrations of t-tau, p-tau and BA42 in NACC-Neuropath subjects for which pre-mortem lumbar punctures were performed.

We use standardized quantitative traits analysis regression statistics to assess the association between protective/risk variants and biomarkers levels using PLINK v1.09 (Purcell et al., 2007). Correlations between allele dose and CSF protein levels and age at onset are obtained with IBM SPSS Statistics 22 using the general linear model analysis of variance.

Results obtained with the Montreal Bank Bank samples will be contrasted initially with the University of Washington dataset and then combined to created a larger samples size in order to assessed the role of risk and protective HMGCR alleles with lower population frequencies.

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.

This proposed study will use resources from the Centre for Studies in the Prevention of Alzheimer's Disease, NIAGADS datasets and the Douglas-Bell Brain Bank in Montreal to examine the neurobiology and the mode of action of a series of novel genetic variants in a gene called HMG CoA reductase, which were found to either accelerate or slow down the progression of the disease in the years prior to diagnosis. This gene which is either protective or detrimental, depending on its genetic make-up, regulates cholesterol production in the brain. It was shown to alter specific biomarkers of disease progression which are known to directly impact memory performance in humans. The novel information to be obtained via this research program is bound to be very significant at many levels: It will allow scientists a) to determine whether these variants are specific to AD pathological markers or, if they can be used as more general indicators of unhealthy/healthy brain aging; and b) to develop, on an individualized basis, a number of genetic and biochemical predictors of disease protection.