Using Genealogical Pedigrees to Identify AD Modifier Genes

Type of Project: Exploratory Clinical Research
Methods: Neuropsychology and Genetics
Status: Seeking $250,000 in funding
Study Period: Undetermined; one year study
University of Utah Collaborative Units: Department of Human Genetics, Utah Population Database, Clinical Research Center
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Project Summary:

The overall goal of this project is to identify genes that modify the clinical effects of Alzheimer’s disease (AD) pathology using the unique resource of the Utah Population Database (UPDB). Genetic mutations that cause early-onset, familial AD already have been identified. However, the situation with late-onset familial AD is much different. It has been difficult to identify and obtain sufficient DNA samples from large families with a clear autosomal dominant pattern of inheritance of late-onset AD. We hypothesize that this is at least partly explained because late-onset, familial AD often masquerades as a sporadic condition, because of the inheritance of genes that influence disease expression. We suspect genetic alterations leading to late-onset familial AD cause only slight alterations in primary pathogenic pathways, such as amyloid processing, making mutations or polymorphisms in other genes sufficient to offset their effects. This would explain the difficulty in identifying genetic causes of familial late-onset AD.

We will identify patients with late-onset AD that have one or more family members who developed symptoms of dementia beginning at age 65 or older. We also will identify individuals from the community without a family history of late-onset dementia who will serve as controls. We will obtain blood samples from affected individuals and then extract DNA. Next, we will determine whether AD and control subjects are in the Utah Population Database (UPDB) and use the database to identify and characterize family clusters for these individuals. With the help of our subjects, we will collect DNA from relevant family members identified by the UPDB. The DNA samples will be used to perform genetic linkage analysis based upon the structures of pedigrees identified, and the number of affected individuals in each pedigree. We will generate maximum simulated LOD scores, using parametric and non-parametric models of linkage analysis to identify candidate genes that are associated with dementia-free survival in these family clusters using either a genome-wide microsatellite screen or a chip-based dense SNP approach.

Potential Benefits:

The discovery of protective genes could help explain the presence of asymptomatic AD pathology found at autopsy in some elderly. It also may identify genetic mutations causing late-onset AD that could be used for diagnosis and genetic counseling. In addition, these genes would be excellent new targets for therapies directed to preventing or slowing the progression of AD.