Genetic Epidemiology of Early-Onset Alzheimers disease in Caribbean Hispanics and non-Hispanic Whites

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USA

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Genetic Epidemiology of Early-Onset Alzheimers disease in Caribbean Hispanics and non-Hispanic Whites

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NIH (NIA)

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Biotechnology... Brain Disorders...

Clinical Research... Clinical Research - Extramural... Dementia... Epidemiology And Longitudinal Studies... Genetics... Human Genome... Minority Health for IC Use... Neurodegenerative... Neurosciences... Prevention

Research Abstract
Project Summary To further disentangle the molecular mechanisms underlying Alzheimer's disease (AD) and to foster the mapping of therapeutic targets, we propose an extreme phenotype design: a whole-genome sequencing (WGS) study of early-onset AD (EOAD) in a large set of multiply affected, well-phenotyped Caribbean Hispanic (CH) and non-Hispanic White (NHW) families. Extreme phenotype designs (e.g., early age-at-onset–AAO, fast vs. slow progressors, very high vs. very low biomarker levels, etc) increase statistical power by creating more homogeneous and genetically loaded populations, and have the potential to reveal genetic risk factors and mechanisms that are difficult to identify in more heterogeneous datasets. This is critical for clarifying AD etiology and developing more effective therapeutic targets. Early studies in AD focused on EOAD and identified a limited number of highly penetrant risk variants: APP, PSEN1, and PSEN2. These genes increase the generation and/or aggregation of the amyloid ß peptide, an observation that underlies current therapeutic strategies. However, these known mutations account for less than half of the genetic basis of EOAD. Many of the EOAD families do not carry known mutations, and among known mutation carriers AAO is often highly variable. This unexplained genetic component to EOAD represents a critical gap in our understanding of AD etiology—a gap not filled by the ongoing AD sequencing studies, which largely focus on the more heterogeneous late-onset form of AD (LOAD). Additionally, this proposal includes both Hispanic and non-Hispanic white samples. The inclusion of minority populations allows us to examine EOAD risk in an understudied but fast-growing population and to map AD risk loci that are unique to this ethnic group, giving further insight into the etiologic mechanisms underlying the disease. To accomplish these goals, we propose the following Aims: (SA1) Identification of novel genetic risk factors for EOAD by whole genome and targeted sequencing. We will perform WGS in 87 multiplex EOAD families, followed by bioinformatics annotation and prioritization based on segregation and function. Highest priority genes/regions will be validated in the family and then will become targets for custom sequencing in a set of EOAD singletons to maximize variant identification. (SA2) Putative functional loci resulting from SA1 will be validated in independent EOAD samples using custom genotyping arrays and (SA3) evaluated for generalizability to late-onset AD using existing LOAD resources such as the ADSP, ADGC, and WHICAP datasets. Finally (4), the most interesting variants will be subject to rapid, biological screening procedures to determine their molecular effects.

Lay Summary
Project Narrative The current generation of genomic studies of Alzheimer's disease (AD) largely focuses on subjects over the age of 65 with affecteds showing variable phenotypic expressions and age at onset, hampering the identification of causative genetic variants. To identify novel genetic risk factors we will perform a whole- genome sequencing study of early onset AD, capitalizing on two unique, richly phenotyped sets of multi- generational Caribbean Hispanic and non-Hispanic white families multiply affected by early onset AD. Studies of extreme phenotypes such as early onset, especially when performed in highly loaded families, are a powerful tool to reveal genetic risk factors, and unique insights into the disease etiology.

Further information available at:

Types:

Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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