Identifying Alzheimers disease genes using genomic and family data

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Contact information of lead PI
Country

USA

Title of project or programme

Identifying Alzheimers disease genes using genomic and family data

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 849,155.05

Start date of award

01/09/2013

Total duration of award in years

5

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... Genetics... Human Genome... Neurodegenerative... Neurosciences

Research Abstract

Project Summary/Abstract The goals of this K99/R00 Pathway to Independence award are to 1) teach Dr. Marchani how to identify genetic variants influencing age-at-onset of Alzheimer's disease within a specific genomic region of interest, so that she may, 2) develop an independent research program to prioritize other genomic regions of interest and discover other such genetic variants in other data sets. Dr. Marchani's graduate education established her ability to detect population structure, measure genetic diversity and construct and test hypotheses to explain that variation. As a postdoctoral fellow, she has recently published evidence that several genes in addition to APP, PSEN1, PSEN2, and APOE influence Alzheimer's disease. She has the skills to find genomic regions likely to harbor variants influencing Alzheimer's disease risk, but requires additional training to determine which genetic variants are in fact responsible. During the mentored K99 phase of this award, she and her mentors will 1) refine these regions of interest by high-resolution mapping, and 2) identify candidate genetic variants by DNA resequencing the narrowed regions. During the independent R00 phase of this award, Dr. Marchani will validate the contribution of the discovered variants (and the genes they modify) influence variation in age-at- onset of Alzheimer's disease, and write and submit a new grant proposal to further interrogate those genes. It is well-established that Alzheimer disease (AD) has a strong genetic basis. Rare mutations in the APP, PSEN1 and PSEN2 genes lead to early onset AD (EOAD), and common variation in APOE contributes to risk and age-at-onset (AAO) in both early and late onset AD (LOAD). Other than APOE, it has been difficult to identify relevant genes for LOAD. However, a small number of genomic regions have provided consistent evidence for linkage with LOAD across multiple independent pedigree-based samples, including three regions that we identified in a unique cohort. Given the current understanding of complex traits, it is likely these regions harbor genes or control regions with rare or uncommon alleles that have considerable effects on penetrance and age-at-onset. The goal of this proposal is to apply novel analytic and next generation sequencing technologies to find some of these genes or control regions. The University of Washington (UW) AD collection contains a cohort of large families a unique historical background and strong evidence for AD AAO in regions with strong evidence of linkage in multiple samples. Additional available samples that also support these same regions include a cohort within the NIMH and NIA LOAD samples. We will use samples from these collections, coupled with genomic resequencing, to identify the underlying age-at-onset variants. We will use dense SNP genotypes for UW samples to refine the regions of interest. Within at least one of these narrowed regions, we will use targeted DNA sequencing to identify candidate genes/regions. Finally, we will follow-up the most promising findings with direct genotyping, functional studies, and/or genotyping subjects in other sample collections. The identification of novel genes with variants modifying AD AAO would be a significant step towards understanding AD biology. Examination of molecular pathways implicated by the genes or control regions found will likely lead to additional therapeutic targets. In addition, this study will provide important information about the genetic architecture of AD and approaches to identifying the associated risk variants, which will be useful for design of complex-trait studies.

Lay Summary

There is no known cure or effective prevention for Alzheimer's disease (AD), the most common cause of dementia in the US, and the few medications that slow the progression of disease have limited efficacy. The goal of this proposal is to discover novel genes that have a strong influence on age-at-onset of AD. Identification of new genes affecting AD age-at-onset will facilitate an understanding of the etiology of AD, lead to better diagnostic methods, and

improved therapeutic and preventative measures.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A