Identification of Functional Genomic Variants in Alzheimers Disease

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Contact information of lead PI
Country

USA

Title of project or programme

Identification of Functional Genomic Variants in Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 3,659,124.77

Start date of award

01/05/1999

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

functional genomics, genetic variant, whole genome, Alzheimer's Disease, National Institute of Mental Health

Research Abstract

DESCRIPTION (provided by applicant): This project began in 1994 as a NIMH U01 in which we initially completed whole-genome linkage analysis on 437 uniformly ascertained and evaluated

Alzheimer’s disease families comprising the NIMH AD Genetics Initiative Family Sample (NIMH sample). This led to novel loci chromosomes 9, 10 and 12. In 1998, the U01 was transformed into an R01, and in 2003, became a Merit Award (R37). Since 1998, the project was aimed at the identification and characterization of novel familial AD genes using family-based association analyses. In 2005, we initiated genome-wide association studies (GWAS) using Affymetrix 500K genotyping arrays and in 2008, we reported genome-wide significant results from this screen, focusing on CD33, and ATXN1. In 2009, we reported two rare, pathogenic AD mutations in the a-secretase gene, ADAM10. Over the past three years, we completed additional GWAS on the NIMH sample and another AD family sample (NCRAD), using the Affymetrix 6.0 (~900K single nucleotide polymorphisms [SNPs] and ~900K single copy probes) and Affymetrix 25K Coding SNP genotyping arrays. In addition, we carried out GWAS on four AD clinical-, pathological-, imaging-, and biomarker-based quantitative endophenotype samples. These GWAS data are being analyzed separately and as part of a meta-analysis using several imputed AD case-control GWAS datasets. In addition to the initial description of CD33 as a genome-wide significant AD risk gene, later confirmed independently in case-control samples, we identified SNPs in several other candidate genes exhibiting significant results by meta-analysis (see Preliminary Data). In the renewal of this project, we propose to analyze, validate, and follow-up the results of whole genome sequencing (WGS) of the entire NIMH sample (1510 subjects in 437 AD families) using the Illumina HiSeq 2000 platform. WGS sequencing costs will be covered by the Cure Alzheimer’s Fund. We will employ state-of-the-art statistical and bioinformatic approaches to identify functional genomic variants influencing AD risk and time-to-onset. In Aim 1, we will analyze WGS data from the NIMH sample to identify functional variants that are either linked to Mendelian forms of early-onset AD (EOAD) or associated with risk for late-onset AD (LOAD). We will also carry out various association analyses i.e. gene- based, multi-marker framework, and extreme discordant sib-pair, to identify common variants that influence risk for LOAD. In Aim 2, we will set out to replicate novel variants discovered in Aim 1 using two independent AD family-based cohorts. We will also impute rare variants and conduct association analyses on four case- control samples (NIA-LOAD, TGEN2, GenADA, and ADNI). We will also sequence candidate loci in African- Americans and Pacific Islanders, and compare our results from AD families to those obtained in various psychiatric disorders. In Aim 3, we will carry out preliminary functional studies on select functional variants, assessing effects on gene function and expression and AD-related pathogenicity, e.g. Ab metabolism and tauopathy. For promising variants, in vivo validation will be performed in independently funded future studies.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is the most common cause of dementia in the elderly and poses a huge economic burden on the healthcare system. In this project, we focus on the identification of novel genes underlying risk for AD, using a state-of-the art whole genome sequencing approach in AD pedigrees. Identification and characterization of novel AD genes will provide new therapeutic targets for the prevention and treatment of this devastating disease.

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

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