Deep Resequencing of Candidate Gene Regions in Late-onset Alzheimers Disease

https://neurodegenerationresearch.eu/survey/deep-resequencing-of-candidate-gene-regions-in-late-onset-alzheimers-disease/

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USA

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Deep Resequencing of Candidate Gene Regions in Late-onset Alzheimers Disease

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NIH (NIA)

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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)... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Genetics... Human Genome... Neurodegenerative... Neurosciences... Prevention

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD), especially late-onset (LOAD) is a complex multifactorial neurodegenerative disease with the possible involvement of several genes. Until 2010, APOE was the only established risk factor for LOAD. However, recent five large genomewide association studies (GWAS) have identified significant associations of LOAD with SNPs in nine additional loci, including, ABCA7, MS4A4, EPHA1, CLU, CR1, PICALM, BIN1, CD2AP and CD33 and all, but CR1 and CD2AP, have been replicated in our GWAS sample. Although GWAS have made significant contribution in uncovering additional genes for LOAD, they are unlikely to identify all the genetic contribution because the commercial GWAS arrays are designed to capture only the common variants with low penetrance to test common disease/common variant hypothesis. On the other hand, rare variants having a higher individual penetrance than common variants that are not captured by GWAS may account for 1/3 of the population attributable risk for common and complex diseases and multiple rare variants may account for many of the observed GWAS signals. Furthermore, GWAS arrays use an indirect approach of association that relies on linkage disequilibrium to detect association signals and rarely the identified significant variants are the causal variants. This may explain the small effect sizes associated with the observed GWAS signals. Here we propose to perform deep resequencing of the seven gene regions implicated in recent GWAS and replicated in our sample and selected additional genes involved in the networks of these seven genes using next-generation sequencing in 1,000 AD cases and controls to identify both common and rare SNPs and replicate them in independent samples. The identification of causal variants in these genes would make a significant contribution in understanding the underlying biological mechanism of LOAD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Late-onset Alzheimer’s disease (LOAD) is a complex multifactorial neurodegenerative disease and a leading cause of dementia among elderly people. Currently there are ~5 million AD cases in the U.S. and it is estimated that by 2050 the number of AD cases would reach to ~16 million, if no medical breakthroughs are found. Thus LOAD is a major public health problem and it is essential to understand the underlying causes so that effective preventative measures could be devised. Recent genome-wide association studies (GWAS) have identified nine new gene regions and seven of them have been replicated in our sample. However, the identified common variants do not seem to be functional. In addition to the common variants these genes may also harbor rare functional variants which were not identified in GWAS. The objective of this study is to resequence the seven gene regions replicated in our large case-control sample and selected additional genes involved in the networks of these seven genes in order to identify causal rare and common variants. The identification of causal variants in these genes would make a significant contribution in understanding the underlying biological mechanism of the disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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2016

Database Categories:
N/A

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N/A