IDENTIFYING RARE VARIANTS THAT INCREASE RISK FOR ALZHEIMERS DISEASE

https://neurodegenerationresearch.eu/survey/identifying-rare-variants-that-increase-risk-for-alzheimers-disease/

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Country

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Title of project or programme

IDENTIFYING RARE VARIANTS THAT INCREASE RISK FOR ALZHEIMERS DISEASE

Source of funding information

NIH (NIA)

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€ 2,493,674.31

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15/08/2013

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4

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

Research Abstract

DESCRIPTION (provided by applicant): The aim of this research is to identify rare functional

variants with large effect size on risk for Alzheimer’s disease (AD). In a recent study published in the New England Journal of Medicine, we identified a novel rare variant in TREM2 with large effect size on risk for AD by using exome-sequencing and follow-up sequencing/genotyping in a large case-control series. The TREM2 R47H variant exhibits an odds ratio similar to that of the apolipoprotein e4 allele, confirming that additional rare variants with large effect sizes are yet o be discovered. We hypothesize that families with extensive history of dementia are enriched for genetic risk factors and that by sequencing those families, we will identify rare variants with large effect size. In this project, we will combine sequencing data in families with late-onset AD and genotyping data in large case-control series. We will analyze 69 previously generated whole-exomes from 27 families with three or more affected individuals each and no mutations in APP, PSEN1, PSEN2, MAPT, GRN and C9ORF72. Sequencing data for additional 20 families will be included. The most promising variants identified using sequencing data and the subsequent segregation analysis will be followed-up by exome-chip genotyping in more than 26,000 samples and by targeted-genotype/sequencing in more than 8,562 cases and controls. We will have access to exome-sequencing data from an additional 2,189 cases and controls through our collaborators and through public resources. Our previous work has confirmed the feasibility of this study design and strongly suggests that additional variants with large effect size will be identified. Preliminary data for 5 of these 27 families have already identified severa variants that segregate with disease status and exhibit an odds ratio> 2. The identification of functional variants with large effect size on risk for Alzheimer’s disease would be a significant step towards an increased understanding of the genetic architecture of AD. These variants/genes will provide novel insight into the biology of the disease and expand or identify new molecular pathways involved in AD which will lead to better prediction of this devastating disease. This study will also establish new approaches to combine and maximize results from exome-sequencing and exome-chip data.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is a very common neurodegenerative disease with no effective means of prevention or treatment. Recent studies indicate that there are rare coding variants with large effect size for risk for AD, that are not identified by genome-wide association analysis or the exome-chip. In this study we propose an innovative and powerful study design to identify rare coding variants with large effect size. We will use the last advances in sequencing (whole-exome sequencing) and genotyping (exome-chip and custom genotyping) to identify such variants and genes. As in the case of the mutations in APP, PSEN1 or PSEN2 we do not expect that the mutation/s identified will explain a big proportion of AD cases, but the knowledge of the biology we will acquire will be very valuable, identifying new molecular pathways involved in AD, which will lead to better prediction 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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