AD Gene Discovery: Exome Chip, New Endophenotypes & Functional Studies in CHARGE

https://neurodegenerationresearch.eu/survey/ad-gene-discovery-exome-chip-new-endophenotypes-functional-studies-in-charge/

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Country

USA

Title of project or programme

AD Gene Discovery: Exome Chip, New Endophenotypes & Functional Studies in CHARGE

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,504,228.44

Start date of award

01/02/2009

Total duration of award in years

7

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... Neurodegenerative... Neurosciences... Prevention

Research Abstract
DESCRIPTION (provided by applicant): This competitive renewal grant application seeks to continue a collaboration that used genome-wide association data in large, prospective epidemiological cohorts, the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), with >2-6 decades of risk factor, dementia, AD, MRI and cognitive endophenotype data in >30,000 persons to identify new genes/loci underlying the risk of Alzheimer's disease (AD). It produced >50 publications, helped identify 9 novel loci for AD (BIN1 & EPHA1 first reached genome-wide significance in a CHARGE-lead publication), and 8 for AD endophenotypes. CHARGE helped found the International Genomics of Alzheimer Project (IGAP) and established collaborations with >25 cohorts/ consortia such as the Enhancing Neuro Imaging through Meta-Analysis (ENIGMA) consortium. However, genes identified to date collectively explain < 35% of the observed AD heritability of 60-80%. The missing heritability could be partly explained by multiple low-frequency or rare genetic variants that can be detected cost-effectively via analysis of exome chip (EC) data now available in the original CHARGE and in 4 additional cohorts (the CHARGE-Plus sample: n=45,910, ~4058 with AD). In this application we propose the following: Aim 1: To use EC data to search for rare genetic variants related to incident clinical AD, and to AD endophenotypes. We have shown that GWAS of AD endophenotypes, e.g. hippocampal & total brain volumes, verbal memory can identify novel loci implicated in brain aging, and biological pathways underlying AD. We propose to use EC data to search for rare variants related to these established AD endophenotypes. Aim 2: To understand preclinical AD, the stage of early pathological changes 1-2 decades before clinical AD, during which AD is likely most amenable to intervention, we propose GWAS and EC analyses of emerging novel, sensitive MRI endophenotypes, cognitive and circulating biomarker (plasma ?-amyloid and clusterin) data in the entire CHARGE-Plus and in younger cohorts aged 30-65 years. Aim 3: To better understand the biology, epidemiological and public health significance of the identified genes we will study gene-gene interactions between known and novel loci, and gene-environment interactions both targeted (interaction of loci from Aims 1&2 with midlife cholesterol and BMI), and genome-wide. The CHARGE cohorts, with premorbid data on mid-life exposure to a wide-range of environmental covariates, are uniquely positioned to study such interactions and permit analyses of other covariates when indicated. Aim 4: Finally, we will explore the biology of the identified variants using bio-informatics annotation databases created in CHARGE, available systemic and brain mRNA, miRNA, methylation data (n~8000 & 750, respectively), hippocampal neuronal expression in autopsy brains and in Drosophila tau & ?-amyloid models. We seek modest analytic resources to leverage existing phenotypic and genotypic data worth millions, to discover new AD genes and potentially novel prevention and treatment approaches for AD.

Lay Summary
PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) is a major public health burden with no known prevention or treatment, but identifying new AD genes can uncover new biological pathways leading to novel treatments. We assembled an international collaboration of cohort studies and searched for common genetic variants causing AD leading to the identification of 9 novel genes for AD, 8 for MRI and cognitive function markers of AD; we propose to expand our studies to seek rare genetic variants for AD using exome chip data on 45,000 persons, 4000 with AD. We will also explore the genetics of preclinical AD in the 40,000 without clinical disease

by studying newer, sensitive MRI markers and gene-environment interactions and study the expression in humans and function in Drosophila for the novel genes we find.

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