ADSP Follow-up in Multi-Ethnic Cohorts via Endophenotypes, Omics & Model Systems

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Country

USA

Title of project or programme

ADSP Follow-up in Multi-Ethnic Cohorts via Endophenotypes, Omics & Model Systems

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,738,241.28

Start date of award

01/09/2016

Total duration of award in years

1

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... Minority Health for IC Use... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): The ADSP discovery phase will identify putative novel AD genes/variants. Nevertheless, to convincingly establish new late-onset AD (LOAD) loci, replication is essential and NHGRI will fund replication sequencing in 14,000 to 30,000 persons. Sample selection and analytical strategies will be determined by the ADSP Steering Committee in conjunction with grant awardees of RFA http://grants.nih.gov/grants/guide/rfa-files/RFA- AG-16-002.html. Here, we propose a cost-effective strategy to leverage phenotypic, endophenotypic, genomic and multi-dimensional omics data available through the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) and its large network of collaborators. In Aim 1, we will perform harmonization of phenotypic and genetic data from discovery and replication phases for validation of variant- and gene-level AD associations, and for novel gene discovery, supplementing U54 efforts. Samples will be drawn from community-based cohorts of African, Hispanic, Asian, and European ancestry (>15,000 cases & 100,000 controls, of whom >60,000 are over age 65). One quarter of the sample already has sequence data (whole exome, whole genome) available; the others will be eligible for the NHGRI replication sequencing. Genome- wide array data are available in >65,000 and we propose to use the Illumina Multi-Ethnic Genotype Array (MEGA) chip, with custom AD content, to genotype an additional ~10,000 richly phenotyped samples, selected for being non-European or European but with unique measures (e.g., with amyloid PET scans). We will integrate array- and sequence data to perform imputation of common and moderately rare variants using improved reference panels that represent the ancestral diversity of the study samples. In Aim 2, we will leverage fine-scale population structure in multi-ethnic and admixed samples to validate and fine-map discovery phase loci, and also identify novel AD loci through trans-ethnic meta-analyses and admixture mapping. In addition, we will identify novel AD-relevant associations and interrogate biological pathways by studying previously-harmonized and new, sensitive endophenotypes including (1) Brain MRI: hippocampal volumes, white matter microstructural injuries and `AD signature' patterns of cortical atrophy; (2) Cognition: general cognitive performance and verbal memory; (3) Biomarker: PET amyloid burden and circulating beta-amyloid levels. In Aim 3, we will gain additional insight into biology and prioritize loci for experimental follow-up and drug development. Specifically, we will utilize bioinformatic tools and ""omics"" data, including available DNA methylation, gene expression, miRNA and metabolomics from CHARGE and through the Accelerated Medicine Partnerships-AD (AMP-AD) project to create and validate an AD-specific Combined Annotation Dependent Depletion tool (AD-CADD), finally, we will parse the most promising loci for further functional exploration using Drosophila knockdown models.

Lay Summary

PUBLIC HEALTH RELEVANCE: We propose to utilize GWAS and next generation sequencing data and novel MRI, PET and cognition phenotypes already available in the CHARGE consortium and it's collaborators, to validate associations found in the ADSP discovery phase and also to identify additional novel AD-related loci. We propose to bring ~15,000 additional AD

cases and 60,000 additional controls of African, Hispanic, Asian and European ancestry to this replication effort. Finally, we will create a new AD specific version of a widely acclaimed annotation tool (CADD-AD) and also study the most promising loci using fruit fly models.

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