Alzheimer Disease Genetic Architecture in African Americans

https://neurodegenerationresearch.eu/survey/alzheimer-disease-genetic-architecture-in-african-americans/

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Country

USA

Title of project or programme

Alzheimer Disease Genetic Architecture in African Americans

Source of funding information

NIH (NIA)

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Total duration of award in years

2

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... Genetics... Human Genome... Minority Health for IC Use... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): A portion of the genetic component of Alzheimer disease (AD) is explained genes identified by positional cloning, targeted gene analysis and genome-wide association studies. With few notable exceptions, the functional variants in these genes and precise pathogenic mechanisms by which these variants lead to AD are unknown. We propose to direct our efforts to understanding AD genetic risk factors in African Americans (AAs), a group with a high incidence of dementia but with a different genetic architecture for AD than European Americans (EAs). Most notably, in AAs common variants in ABCA7 has an effect on AD risk comparable to that of APOE. Our recent discovery of two rare pathogenic AKAP9 mutations that are significantly enriched in AA AD cases, but absent in EAs altogether, suggests it is likely that there are population-specific AD-causing variants. We propose to use extensive clinical and genetic resources assembled by us and the AD Genetics Consortium to identify functional variants in AKAP9, ABCA7 and previously identified AD-associated genes that contribute directly to AD risk in AAs. To accomplish this goal we will resequence the coding and regulatory regions of these genes in 500 AA AD probands and 500 AA age-matched cognitively normal controls. Data will be evaluated using bioinformatic tools to identify functional variants that may directly influence AD pathogenesis. Potentially important functional variants will be tested for association in the discovery AA cohort and a replication AA cohort containing 1000 cases and 2000 controls. We will attempt to generalize these findings in EAs by evaluating top-ranked variants using publically available data to determine if variants identified in AAs are also important in EAs. Gene expression and RNA-Seq experiments will be performed in brain tissue from AA and EA cases and controls to identify variants that may regulate transcription of alternative isoforms. The most promising variants in ABCA7 and AKAP9 will be introduced into neuronal cells to evaluate their effects on expression and processing of APP, tau and other important AD markers. Finally, we will confirm the importance of these genes by demonstrating altered expression in neuropathologically confirmed brain specimens from AD cases and controls.

Lay Summary

PUBLIC HEALTH RELEVANCE: The collective findings from this project will permit us to develop new hypotheses about pathogenic mechanisms leading to AD, identify proteins as targets for development of drugs to treat AD, and provide genetic markers for use in AD risk assessment and profiling subjects for clinical trials.

Further information available at:

Types:
Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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