Pleiotropic and Interaction Effects on Alzheimers disease Risk and Progression

https://www.neurodegenerationresearch.eu/survey/pleiotropic-and-interaction-effects-on-alzheimers-disease-risk-and-progression/

Principal Investigators

KAUWE, JOHN SAI KEONG

Institution

BRIGHAM YOUNG UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Pleiotropic and Interaction Effects on Alzheimers disease Risk and Progression

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,367,674.31

Start date of award

01/09/2012

Total duration of award in years

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... Prevention

Research Abstract

DESCRIPTION (provided by applicant): Recent observations in Alzheimer’s disease suggest that factors, which influence the relationship between pathological features in the brain and clinical symptoms, play a significant role in the disease process. First, more than 25% of non-demented, elderly individuals have brain pathology that is indistinguishable from known Alzheimer’s disease individuals. Second, among those with a clinical diagnosis of disease there are clearly “”fast progressors”” and “”slow progressors””. We will perform a genome-wide screen for relationship loci (rQTL) that modify the known relationship (correlation) between cerebrospinal fluid A¿42 levels and case/control status, thus screening for loci that explain the observation of non-demented individuals with Alzheimer’s disease pathology. With slight adjustments to our models we can also screen for loci, which modify the known relationship between cerebrospinal fluid A¿42 levels and tau levels, and may explain the variation in the rate of progression of disease. For these analyses we have assembled over 2,000 samples with cerebrospinal fluid biomarker measurements, clinical evaluations, and whole-genome marker data for discovery and nearly 1000 samples with cerebrospinal fluid biomarker measurements and clinical evaluations for replication (genotyping to be completed as part of this proposal). We will then test the replicated variants for association with risk and rate of progression of Alzheimer’s disease in approximately 20,000 cases and 30,000 controls (over 1900 of which have longitudinal measurements of disease progression). As demonstrated by our preliminary analyses, this promising approach will leverage the largest sample of its kind to identify genetic variation that is associated with Alzheimer’s disease and Alzheimer’s disease biomarkers via pleiotropic and interaction effects. This will provide insight into variation in important disease related processes such as protein aggregation and inflammatory and immune response. These findings are likely to be important for other protein aggregation and/or protein misfolding diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: The broad, long-term goal of our research is to solve the complex genetic architecture of Alzheimer’s Disease, which will lead to better strategies for treatment and prevention of this devastating disease. In this proposal we will test hypotheses that genetic factors influence important clinical observations, such as the observation of Pleiotropic effects of APOE e4 on cerebrospinal fluid A? and tau levels, non-demented individuals with Alzheimer’s disease pathology and variation in the rate of progression in clinically diagnosed Alzheimer’s disease cases. We will use genome-wide marker data to detect loci that simultaneously affect cerebrospinal fluid amyloid beta and tau levels (pleiotropy), the relationships between Alzheimer’s disease biomarkers (cerebrospinal fluid amyloid beta and tau) and Alzheimer’s disease (referred to as rQTL), and gene-by-gene interactions. Identified loci are likely to affect both risk and/or progression of AD and will shed light on pathways connecting cerebrospinal fluid amyloid beta, tau, and Alzheimer’s 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

Database Tags:
N/A