Investigation of the Tau Gene Network and Quantitative Alzheimers Disease Biomarker Phenotypes

https://www.neurodegenerationresearch.eu/survey/investigation-of-the-tau-gene-network-and-quantitative-alzheimers-disease-biomarker-phenotypes/

Principal Investigators

DETERS, KACIE

Institution

INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS

Contact information of lead PI
Country

USA

Title of project or programme

Investigation of the Tau Gene Network and Quantitative Alzheimers Disease Biomarker Phenotypes

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

124706.422

Start date of award

01/09/2016

Total duration of award in years

1

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Biotechnology... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences... Prevention

Research Abstract

Abstract One of the key hallmarks of Alzheimer’s disease (AD) is intracellular aggregates of

hyperphosphorylated tau protein. Mutations in the tau gene, microtubule-associated protein tau (MAPT), result in significant abnormal tau pathology post mortem and are known to be causative for neurodegenerative disorders similar to AD. This suggests tau dysfunction is sufficient to cause neurodegeneration and dementia. Pathological tau protein can undergo abnormal modification that leads to increased phosphorylation, aggregation, and ultimately neurodegeneration. Despite some appreciation of the role of MAPT and tau in AD-like dementias, there is an important knowledge gap regarding the mechanisms by which tau-related genetic factors influence AD pathophysiology and progression. Thus, an in-depth investigation of the gene network responsible for regulating proteins involved in the abnormal processing of tau is warranted to help explain the molecular mechanisms governing tau aggregation and potentially identify novel drug targets. Preliminary data of common MAPT variants has already identified a single nucleotide polymorphism (SNP) associated with cerebrospinal fluid (CSF) total-tau levels, rs117199550 (see Research Plan), in participants diagnosed with AD or mild cognitive impairment (MCI) in the Alzheimer Disease Neuroimaging Initiative (ADNI) cohort. This work will be extended using whole-genome sequencing (WGS) data in ADNI, allowing investigation of low frequency (minor allele frequency < 5%) variants which cannot be identified in SNP studies. I hypothesize that variation in MAPT and other genes in the tau gene network are associated, directly or indirectly, with established biomarkers of AD pathophysiology (grey matter atrophy, cognitive decline, and changes in CSF levels of tau and amyloid- beta) in participants diagnosed with AD or MCI. To achieve these goals, I will investigate the following Aims: [1] Investigate the impact of low frequency MAPT genetic variants on AD biomarkers. MAPT variants will be extracted from WGS data and the impact of these variants on key quantitative AD biomarkers will be examined; [2] Develop a tau gene network using a curated gene list from literature searches and databases. Then, I will determine if common and/or low frequency genetic variation within the tau gene network involved in the pathological processing of tau will have a deleterious or protective effect on AD biomarkers using independent, additive, and interactive associations at the gene and SNP level; [3] Functionally characterize rs117199550 and novel SNPs identified in Aims 1 and 2 using CRISPR/Cas9. RT-PCR analysis will be used to quantify changes in MAPT gene expression and ELISA to quantify changes in tau phosphorylation. Together, the proposed Aims provide a unique investigation of MAPT by combining advanced genetic, statistic, and functional techniques. The results of this study will increase our understanding of how genetic variation in MAPT and the tau gene network contribute to AD pathophysiology and potentially identify novel diagnostic and therapeutic targets, which would have direct implications for early detection and treatment of AD.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:

N/A

Database Tags:
N/A