Understanding the role of MAPT in Parkinsonian disorders

https://www.neurodegenerationresearch.eu/survey/understanding-the-role-of-mapt-in-parkinsonian-disorders/

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Country

USA

Title of project or programme

Understanding the role of MAPT in Parkinsonian disorders

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,541,337.61

Start date of award

01/04/2012

Total duration of award in years

5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders|Neurodegenerative disease in general

Keywords

Progressive Supranuclear Palsy, Parkinsonian Disorders, Parkinson Disease, MAPT gene, rare variant

Research Abstract
DESCRIPTION (provided by applicant): Mutations within the MAPT gene encoding the microtubule-associated protein tau result in the clinical phenotype of frontotemporal dementia

with parkinsonism or progressive supranuclear palsy (PSP) both displaying predominant tau pathology at autopsy. Common variants at the MAPT locus further define two non- recombining MAPT haplotypes (MAPT H1 and H2) resulting from an ancient inversion. Recent genome-wide association studies have implicated MAPT H1 as a significant risk factor for both Parkinson’s disease (PD) and PSP; however preliminary sub-haplotype analyses suggest that different genetic variants on the MAPT H1 haplotype associate with each of these parkinsonian disorders. It currently remains unclear which variation at the MAPT locus is responsible for the risk and what is the underlying pathomechanism of disease. This project sets out to resolve the disease-associated genetic variation within the MAPT locus for both PD and PSP patients, to characterize the prevalence and effect size and to determine the functional consequence. The Specific Aims are focused on 1) identification of genetic variants in the MAPT genomic region through next-generation sequencing of 350 PD, 350 PSP and 350 controls using a DNA pooling strategy; 2) genetic association analyses of common and rare variants in MAPT in extensive PD and PSP case-control populations; and 3) study of the effect of MAPT variants on MAPT transcription, translation and alternative splicing in vitro and in human brain. The proposed studies are relevant to fully appreciate the contribution of common and rare variants in MAPT to the development of parkinsonian disorders and will contribute to a better understanding of the disease mechanism associated with tau dysfunction in PD and PSP.

Lay Summary
PROJECT NARRATIVE This proposal is designed to determine the full contribution of common and rare variants in MAPT to the development of the two most common parkinsonian disorders, PD and PSP. The proposed studies will contribute to our understanding of and our ability to treat patients with parkinsonism through improved patient diagnosis, the ability to develop novel etiologic disease models and an increased understanding of the MAPT associated pathomechanism(s), which may ultimately inform possible therapeutic strategies.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Neurodegenerative disease in general, Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
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