Regulation of tau expression in Alzheimer disease and aging

https://neurodegenerationresearch.eu/survey/regulation-of-tau-expression-in-alzheimer-disease-and-aging/

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Country

USA

Title of project or programme

Regulation of tau expression in Alzheimer disease and aging

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NIH (NIA)

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15/07/2016

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 Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Biotechnology... Brain Disorders... Dementia... Frontotemporal Dementia (FTD)... Genetics... Neurodegenerative... Neurosciences

Research Abstract

The 17q21.31 MAPT locus is associated with Alzheimer’s disease (AD) and sporadic primary tauopathies in the absence of a tau gene coding region mutation, but the causative variants remain unknown. Our long-term goal is to understand the pathogenesis of tauopathies and pave the way towards novel diagnostics and therapeutics. The objective here is to use new diagnostic criteria to better stratify subjects for a molecular genetic study of tauopathy. Using high-resolution fine mapping and long-read single molecule real time (SMRT) DNA sequencing that employs phospholinked nucleotides to produce very long reads (>70,000 bp) to overcome structural complexity at the locus and pinpoint functional alleles. Further, we will use long-read mRNA isoform sequencing (IsoSeq) to assess mRNA levels, splicing and alternative 3? untranslated regions (UTRs) that might influence post-transcriptional regulation, including RNA binding proteins and microRNAs. We will validate our findings using biochemical, histopathological and cellular techniques. Our central hypothesis is that distinct subhaplotypes confer risk for different MAPT-associated diseases through dysregulation of the expression of toxic tau species leading to unique higher order degenerative phenotypes. Our rationale is that understanding these changes will be crucial for diagnostic stratification and further clinical and mechanistic studies. We will test our hypothesis by pursuing the following specific aims: Aim 1. To identify functional risk alleles associated with tauopathy, we will generate a high density genetic map of the 17q21.31 locus using high-coverage genotyping and targeted SMRT sequencing to characterize the locus and correlate novel variation with AD, primary age-related tauopathy, progressive supranuclear palsy, corticobasal degeneration, Parkinson disease and other tauopathies to pinpoint functional risk alleles; Aim 2. To discover and validate novel mRNA splicing events in tauopathy, we will perform a genome wide computational analysis using brains from subjects with AD and other tauopathies to discover novel splicing events in tau and other genes as well as changes in splicing factors then validate these findings using biochemical, histopathological and cellular approaches; and Aim 3. To uncover novel post-transcriptional regulators of tauopathy, we will discover and validate both protein and RNA post-transcriptional regulators of tau and tauopathy and characterize their networks and validate these changes using biochemical, histopathological and cellular approaches. This contribution will be significant because it will provide a foundation for further mechanistic studies that will elucidate the drivers of disease and pave the way for future clinical studies. This proposal is innovative because by studying AD in the context of the tauopathies there is the possibility that it will lead to a harmonized classification system.

Lay Summary
This research is relevant to public health because we will transform the way clinicians and scientists diagnose individuals with Alzheimer’s disease neuropathologic change. Understanding the mechanism whereby the tau gene influences neurodegeneration will lay the groundwork for clinical and mechanistic studies that will elucidate disease burden, pathogenesis and progression.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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2016

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N/A

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