Lewy body neuropathologies and SNCA gene: variants expression and splicing

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Country

USA

Title of project or programme

Lewy body neuropathologies and SNCA gene: variants expression and splicing

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NIH (NINDS)

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25/09/2013

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2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

SNCA gene, Lewy Bodies, alpha synuclein, neuropathology, RNA Splicing

Research Abstract

DESCRIPTION (provided by applicant): A neuropathological hallmark of a group of neurodegenerative diseases, known as human ‘synucleinopathies’, is the presence of

intracellular protein aggregates, Lewy bodies (LB), upon postmortem brain examination. The alpha-synuclein protein is a major component of LB. Parkinson’s disease (PD) is the prototype of human ‘synucleinopathies’ and has been studied extensively. Genome-wide association studies (GWAS) have implicated the alpha-synuclein (SNCA) gene as a central player in the pathogenesis of PD. Several studies in cell-cultures and animal models reported that over expression of wild-type SNCA can be toxic and may lead to cell death. Moreover, previously we documented elevated SNCA expression in sporadic-PD patients. Describing the molecular mechanisms underlying the regulation of SNCA expression, and any genetic variability that impinges on this regulation, is highly important for understanding the pathogenesis of LB related diseases. The overarching goal of this proposal is to understand the genetic elements controlling SNCA expression. We will further investigate whether any genetic variants in SNCA locus and/or changes in gene expression are associated with a broad-spectrum of LB diseases, focusing on autopsy-confirmed cases of dementia with Lewy bodies (DLB) and LB presentation in Alzheimer’s disease (AD). To accomplish our goals, we will address the following specific aims: 1. Determine whether SNCA variants are associated with LB neuropathology in neurodegenerative diseases, specifically in AD and DLB. 2. Determine whether genetic variability in the SNCA locus alters SNCA-mRNA and protein expression in different anatomic areas of neuropathologically normal and LB-affected human brains; 3. Explore in depth candidate sub-regions within the SNCA locus to identify novel variants that contribute to the risk to develop LB pathology, and evaluate their effect on SNCA expression. The fulfillment of these aims will enrich our understanding of the genetic basis of variability in SNCA expression and the general relevance of these variants to LB pathology. Moreover, the proposed studies will enhance our understanding of the genetic risk factors and molecular mechanisms that contribute to LB diseases including PD and provide valuable information for developing therapies targeting SNCA expression levels.

Lay Summary

PUBLIC HEALTH RELEVANCE: NARRATIVE Human ‘synucleinopathies’ including Parkinson’s disease (PD), are common neurodegenerative diseases worldwide and poses an enormous health burden on the society. Currently, there is no method to prevent these diseases or to slow their progression. This group of diseases is characterized by neuropathology of Lewy bodies that consist of alpha-synuclein aggregates. Alpha-synuclein (SNCA) is implicated in the genetics and pathogenesis of PD. The proposed project aims to investigate the genetic basis underlying the regulation of SNCA expression in relation to susceptibility to the spectrum of Lewy body neuropathologies. The results will provide a better understanding of the genetic factors and molecular mechanisms underlying ‘synucleinopathies’ and will advance the identification of valuable pathways for developing therapies targeting SNCA expression.

Further information available at:

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Investments > €500k

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United States of America

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Parkinson's disease & PD-related disorders

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