The role of aging in LRRK2-associated Parkinsons disease

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Country

USA

Title of project or programme

The role of aging in LRRK2-associated Parkinsons disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 593,256.88

Start date of award

30/09/2014

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

LRRK2 gene, Parkinson Disease, Aging, dopaminergic neuron, mouse LRRK2 protein

Research Abstract

DESCRIPTION (provided by applicant): The role of aging in LRRK2-associated Parkinson’s disease Project Summary Parkinson’s disease (PD) is recognized as the second most common age-related neurodegenerative disorder after Alzheimer’s disease. The cardinal symptoms of

PD are caused by the progressive degeneration of midbrain dopaminergic (DA) neurons with aging in substantia nigra pars compacta (SNpc). It is believed that aging is the greatest risk factor for the development of PD. However, how advanced aging contributes to PD is poorly understood, largely due to the lack of a robust mouse aging model exhibiting progressive degeneration of DA neurons with aging that mimics PD pathogenesis. While the majority of PD cases are sporadic, investigations in the past decade have led to the identification of a number of genes linked to familial forms of PD, including a newly identified gene known as leucine-rich repeat kinase 2 (LRRK2). Mutations in LRRK2 gene are the most frequent genetic causes of PD and LRRK2 is the strongest genetic factor in sporadic PD known to date. Importantly, the penetrance of LRRK2 is greatly increased with age. The importance of LRRK2 suggests that using LRRK2 as a model is warranted in order to study how normal aging contributes to the disease pathogenesis of PD. The proposed project here is aimed to develop novel and robust LRRK2 transgenic mouse aging models with a progressive loss of DA neurons in SNpc to mimic PD pathogenesis, and to determine the role of aging in LRRK2-associated PD. My hypothesis is that specific changes during normal aging are responsible for aberrant LRRK2 enzymatic activities which in turn cause the disease pathogenesis of LRRK2-associated PD. To test this hypothesis, I will first examine whether selective expression of LRRK2 in the nigrostriatal pathway develops progressive DA neuron degeneration and associated cellular and behavioral deficits with aging that mimics PD pathogenesis. I will further examine whether specific aging-related changes contribute to the disease pathogenesis in LRRK2 mouse aging models of PD. Finally, I will determine the effects of aging on LRRK2 enzymatic activities in LRRK2-associated PD. This study will be the first to establish a robust LRRK2 transgenic mouse aging model with progressive degeneration of DA neurons that mimics PD pathogenesis. The study will directly determine the role of aging in PD and will provide robust tools for understanding the mechanisms of LRRK2-induced DA neurotoxicity in vivo, as well as a valuable platform for disease analysis and drug development. Importantly, during the award period, I will obtain extensive training in developing and characterizing mouse aging model of PD, the aging study, proteomics, and as well as oral presentation skills and scientific writing. This training will enabe me to establish a successful laboratory and launch an independent research career.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson’s disease (PD) is recognized as the second most common age-related neurodegenerative disorder after Alzheimer’s disease, affecting up to 1% of the population above the age of 60 and 4-5% above the age of 85 (1). According to the National Institute of Health, 1 million people in the United States are suffering from PD. The LRRK2 transgenic mouse aging model established in this study will directly determine the role of aging in PD and provide robust tools for understanding the mechanisms of LRRK2-induced DA neurotoxicity in vivo and a valuable platform for disease analysis and drug development.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

Database Tags:
N/A