Mouse model studies of TMEM230-linked Parkinsons disease

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USA

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Mouse model studies of TMEM230-linked Parkinsons disease

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5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract

Through our previous work funded by the American Parkinson Disease Association and NINDS, we have discovered a new genetic locus on the short arm of chromosome 20, and identified a new PD gene, TMEM230. TMEM230-linked PD shows clinical and pathological features compatible with those in sporadic PD. TMEM230, also known as C20orf30, is an uncharacterized gene. We performed extensive genetic and cellular studies on this new PD

gene in vitro. We found that TMEM230 encodes a transmembrane protein of secretory and recycling vesicles, including synaptic vesicles in neurons. We also found that TMEM230 is a component of Lewy bodies and Lewy neurites. We further performed functional studies and found that PD-linked TMEM230 mutants identified in our study impair synaptic vesicle trafficking and alpha-synuclein clearance in vitro. TMEM230 is the first transmembrane protein of synaptic vesicles identified in PD to date. Our findings, therefore, directly point to the dysfunction of synaptic vesicles in the pathogenesis of PD. The precise functions of TMEM230, and pathogenic mechanism of the TMEM230-mediated PD remain unclear. Based on the molecular features of TMEM230, and its relationship with synaptic vesicle and endosomal markers tested in our study, we hypothesize that TMEM230 is a trafficking protein of secretory/recycling vesicles, primarily involved in synaptic vesicle exocytosis, endocytosis and recycling, and synaptic transmission in neurons; and dysfunction of the synaptic vesicles, such as impaired trafficking, recycling and synaptic transmission, underlies the pathogenesis of the TMEM230-linked PD, and possibly other forms of PD as well. Although our preliminary data in vitro are consistent with this hypothesis, in vivo data are lacking. Appropriate animal models relevant to testing potential pathogenic mechanisms have not been developed. In this application, we propose three closely interactive specific aims to generate relevant mouse models and test this hypothesis in vivo. In Specific Aim1, we will develop all three representative types of mouse models, including knockout, knockin and transgenic models. These models will provide unique and essential resources for mechanistic studies in Specific Aims 2 and 3. In Specific Aim 2, we will test the effects of different types of TMEM230 genetic modifications on alpha-synuclein clearance, motor and non-motor phenotypes, and PD-related pathology in the mouse models. To further provide insights into the molecular underpinning of PD phenotype and pathology caused by TMEM230-related mutations, we will use a combination of electrophysiological and cell biological approaches to study synaptic vesicle trafficking and synaptic transmission in the mouse models in Specific Aim 3. Successful completion of the proposed studies of this new PD-linked gene in mouse models should provide essential information for understanding the physiological functions of TMEM230, and the role of the mutant TMEM230 in the pathogenesis underlying PD. The positive outcomes from this application may also provide a mechanistic basis for PD therapeutic development.

Lay Summary

Through our efforts over 20 years, we have established a new genetic locus on chromosome 20 and identified a new PD-causative gene. This project is designed to develop TMEM230-linked PD mouse models and to understand the molecular basis by which mutations in this new PD gene cause PD. Understanding the molecular mechanism may provide a pathophysiological basis for design of rational therapies for PD.

Further information available at:

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Investments > €500k

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United States of America

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