PATHOLOG-OMICS – ESSENTIAL TREMOR IN THE BROADER CONTEXT OF NEURODEGENERATION

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Title of project or programme

PATHOLOG-OMICS - ESSENTIAL TREMOR IN THE BROADER CONTEXT OF NEURODEGENERATION

Source of funding information

NIH (NINDS)

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05/05/2015

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Essential Tremor, Multiple System Atrophy, Purkinje Cells, Spinocerebellar Ataxias, Dystonia

Research Abstract

? DESCRIPTION (provided by applicant): Over the past 5 – 8 years, we have identified a cluster of morphological changes in the essential tremor (ET) cerebellum, predominantly centered in/around the Purkinje cell (PC). The discovery of ET-related pathology has generated great interest but it has also raised difficult questions. Several of these pathologies have also been observed in primary cerebellar neurodegenerative diseases such as spinocerebellar ataxias (SCAs) and multiple system atrophy (MSA), but the degree to which these changes occur has not been formally studied or compared with that in ET. Interestingly, the cerebellum is now increasingly being implicated in tremor generation in other diseases such as Parkinson's disease (PD) and dystonia, yet their cerebellar pathology is presently unexplored. Hence, there is a large morphologic data gap. On a more primary level, we recently performed laser-capture microdissection (LCM) to specifically target PCs, thereby facilitating a precise evaluation of cell specific molecular changes in ET. We obtained a highly novel differential gene expression profile by direct sequencing of RNA (RNA-seq) isolated from PCs of ET vs. control brains. We identified 47 differentially expressed transcripts, which code for proteins that regulate neuronal function. However, a parallel set of LCM-RNA-seq studies, exploring the molecular biology of PCs in PD, dystonia, MSA and SCA, have yet to be performed. This represents a second, large molecular, data gap. This five-year proposal, which uses postmortem tissue from patients with ET well as from patients with a range of other cerebellar disorders, has two aims. Specific Aim 1: To undertake detailed postmortem studies of the cerebellum, comparing morphological changes in the cerebellum of ET patients to those of patients with primary cerebellar degenerative diseases (SCA and MSA) as well as those of patients with neurological diseases with tremor and cerebellar involvement (PD and dystonia). We will assemble an initial discovery sample of 160 brains (50 ET, 25 SCA, 15 MSA, 30 PD, 15 dystonia, 25 controls) as well as a replicate sample of 160 brains, assessing pathological changes across several cerebellar compartments. Hierarchical cluster analysis of quantified variables will be used to determine whether there is a definable ""ET cluster"" as well as definable clusters for each of these other four diseases. Specific Aim 2: To explore the molecular biology of PCs across neurodegenerative diseases characterized by cerebellar involvement and/or tremor. Using a novel LCM-RNA-seq approach, we will determine whether molecular expression changes in PCs are the same or differ across these diseases. For these novel molecular studies, we propose to use 60 brains (10 each of ET, SCA, MSA, PD, dystonia, controls).

Lay Summary

PUBLIC HEALTH RELEVANCE: The cerebellum is a brain region that is thought to be involved in a number of neurodegenerative diseases, including essential tremor, spinocerebellar ataxias, multiple system atrophy, Parkinson's disease, and dystonia, yet detailed studies of the pathology of the cerebellum in many of these diseases are either very limited or have never been performed. On a more primary level, studies of the molecular biology of cerebellar Purkinje cells, which provide the sole neuronal output from cerebellar cortex, have not been performed in any of these diseases either. The proposed studies will use a series of techniques, ranging from basic morphological methods to laser capture microdissection of Purkinje cells followed by direct sequencing of RNA isolated from these cells, on a carefully assembled collection of human postmortem brain tissue to advance our understanding of cerebellar biology, and identify commonalities and/or differences in disease mechanisms in a range of neurodegenerative diseases.

Further information available at:

Types:
Investments > €500k

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United States of America

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Parkinson's disease & PD-related disorders

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2016

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