Identification of pathogenic mechanisms important in multiple system atrophy

https://neurodegenerationresearch.eu/survey/identification-of-pathogenic-mechanisms-important-in-multiple-system-atrophy/

Principal Investigators

HUENTELMAN, MATTHEW

Institution

TRANSLATIONAL GENOMICS RESEARCH INST

Contact information of lead PI
Country

USA

Title of project or programme

Identification of pathogenic mechanisms important in multiple system atrophy

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

498300

Start date of award

01/09/2015

Total duration of award in years

1

Keywords

Multiple System Atrophy, Cytoplasmic Inclusion, FYN gene, Rare Diseases, synucleinopathy

Research Abstract

? DESCRIPTION (provided by applicant): There are many examples where the study of rare disease has fundamentally changed our understanding of common diseases with similar phenotypic characteristics. This is true to a large extent because the rare disease represents a much clearer “”lens”” by which to understand the mechanisms of the disorder. This grant proposal focuses on the investigation of multiple system atrophy (MSA), a rare but severe neurodegenerative synucleinopathy with adult onset characterized by autonomic dysfunction

with parkinsonism and/or cerebellar symptoms. Of specific interest in MSA are the oligodendroglial and neuronal cytoplasmic inclusions (GCIs and NCIs) formed by fibrillar alpha-synuclein (a-SYN) proteins although the pathogenic mechanisms driving these accumulations are unclear. Currently, there are no disease preventing or modifying treatments for MSA, and a crucial need for research to identify pathways that can be targeted for therapy. Little research has been done to understand the etiology of this disease especially in the area of modern genomic sequencing even though such an approach has revolutionized the way rare childhood disorders are investigated. Our first goal is to use family-based genomics to uncover rare genetic variants associated with MSA. We will perform genomic sequencing on quads of MSA patients, parents, and one unaffected sibling. Identified genetic variants will be characterized in vitro by using CRISPR-Cas9 engineering of existing cell-lines. Our second goal is to identify the pathogenic mechanisms important to MSA a-SYN accumulation, by combining laser capture microdissection and next generation RNA-Seq in neuropath-confirmed MSA brains and matched controls. Both of these aims are designed to identify underlying disease mechanisms and key targets that could be exploited as potential future therapeutic options. Our findings may shed additional light on the mechanisms of disease in more common synucleinopathies like Parkinson’s disease and Lewy Body Dementia.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A