Gene discovery in PSP by transcriptome, neuropathology and sequence analysis

https://www.neurodegenerationresearch.eu/survey/gene-discovery-in-psp-by-transcriptome-neuropathology-and-sequence-analysis/

Principal Investigators

ERTEKIN-TANER, NILUFER

Institution

MAYO CLINIC JACKSONVILLE

Contact information of lead PI
Country

USA

Title of project or programme

Gene discovery in PSP by transcriptome, neuropathology and sequence analysis

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,639,033.94

Start date of award

15/07/2013

Total duration of award in years

5

The project/programme is most relevant to:

Neurodegenerative disease in general

Keywords

Progressive Supranuclear Palsy, transcriptome, gene discovery, Sequence Analysis, neuropathology

Research Abstract
DESCRIPTION (provided by applicant): Progressive supranuclear palsy (PSP) is a rapidly

progressive neurodegenerative disorder with clinicopathologic heterogeneity and without any therapies. Genetic studies can be instrumental in the identification of the molecular pathophysiology underlying PSP risk and its heterogeneity, which may enable discovery of therapeutic targets. Until recently, H1 haplotype of MAPT, encoding tau, was the strongest genetic risk factor for PSP. A new PSP genome-wide association study (GWAS) identified six additional loci. The effective translation of these findings to therapy requires identification of he disease gene, the functional variants and their mechanism of action. These goals cannot be achieved by the disease GWAS alone and require alternative, powerful and mechanistic approaches. The current proposal aims to close this knowledge gap by joint analysis of the whole transcriptome and quantitative neuropathology measures in a well- characterized autopsied PSP cohort with existing GWAS data. Our long-term goal is to uncover the pathophysiology of PSP and the molecular substrates of its subtypes that will ultimately lead to drug discoveries. Given the clinicopathological overlap between PSP and other tauopathies, our proposal is expected to impact a wide range of neurodegenerative disorders and generate novel therapeutic avenues. Our central hypothesis, is that many PSP variants confer risk by regulating brain gene expression. Further, differential transcriptional regulation may underlie the heterogeneity in PSP. Our preliminary data identified brain transcript associations for some of the top PSP GWAS variants supporting our hypothesis. In our Brain Bank, we have access to nearly 500 brain samples from autopsied PSP subjects with existing GWAS, ~400 of which have typical and ~100 with atypical clinicopathology. All subjects have clinical data and detailed quantitative neuropathology measures. Our objective is to obtain brain transcriptome measurements in this unique cohort, which will be analyzed jointly with quantitative neuropathology measures to identify functional variants underlying PSP risk, its clinicopathological heterogeneity and to discover the mechanism of action of these variants. The expected outcomes of our specific aims are: 1) To identify a) genetic variants that influence gene expression in PSP brains, b) transcript level differences between subtypes of PSP that are not simply due to aging; 2) To discover a) genetic factors that influence both neuropathology and gene expression in PSP; b) transcripts that correlate with neuropathology; 3) To uncover the mechanism of transcriptional regulation in PSP by a) next-generation RNA sequencing of 200 select PSP brain samples; b) translational in- vitro studies. Results from all aims will be compared with the PSP disease GWAS. The overall knowledge will nominate genes and their transcriptional changes as novel disease mechanisms in PSP. These molecular mechanisms will constitute modifiable drug targets, which will impact PSP and other related neurodegenerative diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: The proposed research is relevant to public health because uncovering the genetic risk factors of Progressive Supranuclear Palsy (PSP) is fundamental for the understanding of its formation, may provide progress in its prediction, prevention and potential drug targets for the cure of this rapidly progressive, currently incurable disease, and also possibly of other related neurodegenerative diseases. Our proposal is aimed at the discovery of functional PSP risk variants that influence gene expression and brain PSP pathology, by leveraging existing genome-wide association studies and highly informative autopsied cohorts with rich data. Thus, the proposed research is relevant to NIH’s mission to develop fundamental discoveries and resources to improve public health, as these studies are expected to have a significant impact in research on PSP risk and pathology and will constitute an important shared resource with significant utility for projects and researchers beyond the

scope of this proposal.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Neurodegenerative disease in general

Years:
2016

Database Categories:
N/A

Database Tags:
N/A