Analysis and characterization of a cohort of familial Parkinsons disease exomes

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Country

USA

Title of project or programme

Analysis and characterization of a cohort of familial Parkinsons disease exomes

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NIH (NINDS)

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01/05/2016

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

exome, Parkinson Disease, cohort, Rest Tremor, genetic pedigree

Research Abstract

? DESCRIPTION (provided by applicant) Parkinson’s disease (PD) is an adult-onset neurodegenerative disease of the substantia nigra characterized by resting tremor,

bradykinesia, muscular rigidity and postural instability and represents the second most common cause of neurodegenerative disease. Unfortunately, it is estimated that only ~30-40% of the underlying genetic causes of familial form of PD have been explained to date. The identification of causative mutations for Mendelian disorders is critical fo our understanding of their pathogenesis. As part of a NIH High Priority, Short-Term Project Award (R56NS082349), we are currently performing at the Center for Inherited Disease Research (CIDR) exome sequencing of 1,567 familial PD cases. These PD patients are from 1,089 familial PD pedigrees, including multiple PD cases from 440 pedigrees. We propose a series of aims that will leverage the information gained from these exomes to identify novel genes contributing to PD and then explore the functional effect of the genes/variants identified through functional studies. The Specific Aims of this proposal are: (1.) Discovery of Novel Genes Associated with Familial PD. We will employ two complementary approaches to identify novel genes associated with familial PD. (Approach #1) Identified variants will be filtered based on several criteria to generate a narrowed set of candidate variants. Candidate variants/genes observed in multiple families will be given highest priority. (Approach #2) The exomes of index PD cases will be subject to an unbiased genome-wide rare variant analysis by comparing to the raw data of over 20,000 control samples derived from several sources. The top 25 candidate genes from each approach will be validated and characterized in Aim #2. (2) Validation/Characterization of Novel Genes Associated with Familial PD. Top candidate genes from Aim #1 will be validated in an independent replication cohort of over 800 familial PD and ~5,000 control exomes. Variants that do not segregate properly or are present at a signification percentage in controls will be excluded and the candidate gene re-evaluated. The broader importance of our candidate genes will be tested in a cohort of over 3,000 sporadic PD exomes. Genes will be prioritized based on several criteria including the functional impact of the variants identified, variant allele frequencies and eQTL and splicing analysis. (3) Functional Analysis Novel Genes Associated with Familial PD. The functional consequences of identified mutations will be evaluated though the use of several model systems. The pathogenic effect of the mutations in induced pluripotent stem cells, Drosophila and yeast models will be studied using established assays. These studies may identify additional genes and pathways that have direct relevance to the development of PD. We are confident that the proposed project will lead to the discovery of one or more novel genes associated with PD. The identification of such genes will lead to an increased knowledge of the defects contributing to this devastating disease and open new avenues of research for the PD scientific community as well as the development of new therapeutic targets.

Lay Summary

PUBLIC HEALTH RELEVANCE Parkinson’s disease (PD) is the second most common cause of neurodegenerative disease characterized by resting tremor, bradykinesia, muscular rigidity and postural instability. The underlying genetic cause of familial forms of PD has been identified in only ~30-40% of cases. The purpose of this proposal is to identify and characterize novel genes associated with familial PD that will lead to an increased knowledge of the defects contributing to this devastating disease and open new avenues of research for the PD scientific community as well as the development of new therapeutic targets.

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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