An iPSC based platform for functionally assessing genetic and environmental risk

https://neurodegenerationresearch.eu/survey/an-ipsc-based-platform-for-functionally-assessing-genetic-and-environmental-risk/

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Contact information of lead PI
Country

USA

Title of project or programme

An iPSC based platform for functionally assessing genetic and environmental risk

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 4,586,556.88

Start date of award

23/09/2014

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Genetic Risk, induced pluripotent stem cell, risk variant, Parkinson Disease, Environmental Risk Factor

Research Abstract

DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is the second most common

chronic progressive neurodegenerative disease worldwide, with a prevalence of more than 1% in the population over the age of 60, thus constituting a major global health problem of the aging population. The disease is primarily characterized by a major loss of nigrostriatal dopaminergic neurons but the genetic etiology leading to the neuronal cell loss has largely remained unknown. Numerous genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) that point to more than 50 genomic loci containing “”risk variants”” for sporadic PD. However the identified risk variants predominantly map to poorly understood non-coding regions of the genome, which has impeded functional and molecular understanding of how these genetic variants contribute to the increased risk for PD. Importantly, it has been established that PD GWAS associated loci are typically non-coding and mediate allele-specific effects on distal gene expression, consistent with a central role for disruption on enhancer element function in PD pathogenesis Human induced pluripotent stem cell (hiPSC) technology offers for the first time the unique opportunity to study sporadic diseases whose genetic components are poorly understood, by allowing for the generation of human patient-derived somatic cells such as midbrain dopaminergic neurons which carry all the genetic alterations that contributed to the development of the disease. The overall goal of this project is to establish a transformational paradigm, which overcomes the substantial technical limitations of the iPS system and creates a genetically defined experimental in vitro system for studying the molecular and biological mechanisms of sporadic PD in the dish. To achieve this, we will establish a novel experimental framework to link “”descriptive”” GWAS PD hits to genomic regulatory enhancer elements and establish functional assays for connecting PD risk alleles to the expression of disease relevant effector genes. Our aim is to gain molecular understanding of the complex interactions between multiple genetic risk alleles and to identify key genes of which the expression level affects the PD specific cellular phenotype. To identify functional relevant candidate risk variants (PD-eQLTs) we will link PD associated risk alleles to genomic regulatory (enhancer) elements that are relevant for gene activity in neurons by establishing an enhancer map in cultured homogenous dopaminergic neurons as well as in sorted neuronal nuclei from human brain. Insights into these interactions will facilitate devising rational therapeutic strategies. This experimental in vitro platform will be used to define the interactions of environmental risk factors with the genetic determinants that have been predicted from GWA studies to predispose to PD (GxE).

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson’s disease (PD) is the second most common chronic progressive neurodegenerative disease worldwide, with a prevalence of more than 1% in the population over the age of 60, thus constituting a major global health problem of the aging population. While genome-wide association studies (GWAS) have pointed to more than 50 genomic loci that contribute to the risk of PD, little functional and molecular understanding has been gained into which and how these genetic variants contribute to the increased risk for PD, and this lack of insight has impeded the development of rational therapeutic strategies. The overall goal of this project is to establish a genetically defined experimental in vitro system for studying the molecular and biological mechanisms of sporadic PD in the dish and to identify novel genes that are causally involved in the pathogenesis of Parkinson’s.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

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