Frontotemporal Dementia Induced Pluripotent Stem Cell Consortium

https://www.neurodegenerationresearch.eu/survey/frontotemporal-dementia-induced-pluripotent-stem-cell-consortium/

Principal Investigators

HUANG, YADONG

Institution

J. DAVID GLADSTONE INSTITUTES

Contact information of lead PI
Country

USA

Title of project or programme

Frontotemporal Dementia Induced Pluripotent Stem Cell Consortium

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,869,267.89

Start date of award

30/09/2013

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Frontotemporal Dementia, induced pluripotent stem cell, C9orf72, PGRN gene, zinc finger nuclease

Research Abstract
DESCRIPTION (provided by applicant): We propose to establish a comprehensive, validated

repository of adult human dermal fibroblasts and human induced pluripotent stem cell (hiPSC) lines from frontotemporal dementia (FTD) patients with genetically defined mutations and familial, non-mutation carrying controls. hiPSCs hold tremendous promise for the development of in vitro FTD models for studying disease pathogenesis in relevant human cell types that would otherwise be impossible to obtain, such as human neurons. Using an established, collaborative, multi- institutional approach, we will bank adult human dermal fibroblasts from FTD patients carrying common mutations in the genes currently known to cause FTD: tau (MAPT), C9ORF72, and progranulin (GRN). In Aim 1, we will recruit both FTD patients with defined genetic mutations and control subjects. Comprehensive and longitudinal clinical evaluations will be linked to each cell line, allowing us to correlate disease characteristics with molecular phenotypes. In Aim 2, we will reprogram fibroblasts into hiPSCs by non-DNA-integrating technologies with which we have had recent success. In addition, we will further create EGFP reporter lines for monitoring and standardizing differentiation protocols in FTD-relevant cell types such as forebrain neurons. We will also correct selective mutations to create isogenic control lines so that we can precisely differentiate mutation-specific phenotypes from the noise of inter-individual variability. In Aim 3, we will derive and validate human neurons to model and study FTD pathogenesis in culture and to deliver hiPSC lines with robust phenotypes for FTD research and drug development. Based on our previous research experience in RNA and Tau biology and pathophysiology, we will focus on human neurons with GGGGCC repeat expansions in C9ORF72 and MAPT mutations. All cell lines will be banked at the Coriell Institute and will be accessible to the worldwide FTD research and drug development community. These resources should significantly alter the FTD research landscape by accelerating discovery.

Lay Summary

PUBLIC HEALTH RELEVANCE: Our goal is to generate and characterize human induced pluripotent stem cell (hiPSC) lines from frontotemporal dementia (FTD) patients carrying defined genetic mutations. We will also establish cell-type specific reporter lines and generate isogenic control lines using zinc finger technologies. We will use these resources as in vitro disease models to directly study FTD pathogenesis and make them available to the worldwide FTD research community.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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N/A