ALS/FTD mutant C9orf72-induced genetic and nuclear pathology in iPS cell models

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Principal Investigators

ROTHSTEIN, JEFFREY D

Institution

JOHNS HOPKINS UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

ALS/FTD mutant C9orf72-induced genetic and nuclear pathology in iPS cell models

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,659,477.06

Start date of award

01/09/2013

Total duration of award in years

2

The project/programme is most relevant to:

Motor neurone diseases

Keywords

frontotemporal lobar dementia-amyotrophic lateral sclerosis, C9orf72, induced pluripotent stem cell, Cell model, RNA-Binding Proteins

Research Abstract
DESCRIPTION (provided by applicant): The overall aim of this proposal is to study the

pathology of the expanded hexanucleotide repeats in the C9orf72 gene using human iPS differentiated neurons and glia cells. The expanded GGGGCC hexanucleotide repeat in the non-coding region of the C9orf72 gene on chromosome 9p21 has been discovered as the cause of approximately 30-50% of familial and up to 10% of sporadic ALS cases as well as 12% of familial FTD cases, making this the most common known genetic cause of ALS/FTD to date. Expanded repeats are highly unstable and potentially yield toxic RNAs that accumulate in the nucleus and are hypothesized to cause cellular dysfunction via aberrant DNA and protein binding. Preliminary data from our laboratory confirm (GGGGCC)n nuclear RNA foci, aberrant gene expression and nuclear retention of RNA binding proteins (RBPs) in C9orf72 patient derived fibroblasts and iPS differentiated neurons. We therefore propose to elaborate on these early findings by generating an extensive genetic profile of ALS/FTD human iPS neurons and glia cells through the use of microarray and validate whether the iPS changes are relevant by comparing to human autopsy C9orf72 brain tissues. Furthermore, we will use C9orf72 iPS cell lines to investigate the RNA toxicity/pathology thru the identification of aberrant accumulation and binding of RNA binding proteins. Finally we will determine if we can abrogate C9orf72 genomic toxicity and pathology with antisense oligonucleotides already designed and validated in our laboratory. The likelihood of success will be greatly enhanced through a collaborative working relationship, the availability and experience of using iPS cells and human tissues. The extensive use of iPS cells to model disease, to cross correlate with human tissues and their use to validate ameliorative antisense therapy provides an important and possibly new direction for understanding disease pathophysiology and therapeutics development. !

Lay Summary
PUBLIC HEALTH RELEVANCE: Understanding the pathophysiology and development of new therapeutics for ALS, ALS/FTD and FTD has been an enormous challenge. Recently the development of human disease induced pluripotent cell lines, representing the natural disease in the most relevant cell types, motor neurons and glia, provides unprecedented tools to 1) study the underlying disease process, 2) allow for identification of disease biomarkers of pathology and of drug actions and 3) provide critical tools for drug discovery and drug action validation. Eventually these ALS/FTD cell lines will also be useful to compare common and uncommon pathways between ALS and other neurodegenerative iPS models.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
N/A