Using RNA signatures for therapy development in neurodegeneration due to C9orf72 expansions

https://neurodegenerationresearch.eu/survey/using-rna-signatures-for-therapy-development-in-neurodegeneration-due-to-c9orf72-expansions/

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Country

USA

Title of project or programme

Using RNA signatures for therapy development in neurodegeneration due to C9orf72 expansions

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,352,155.96

Start date of award

05/09/2015

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1

The project/programme is most relevant to:

Motor neurone diseases|Alzheimer's disease & other dementias

Keywords

C9orf72, Nerve Degeneration, therapy development, RNA, Frontotemporal Dementia

Research Abstract

DESCRIPTION (provided by applicant): RNA processing alterations are increasingly recognized to play a crucial role in the pathogenesis of a wide range of diseases including two devastating neurodegenerative conditions, amyotrophic lateral sclerosis (ALS) and frontal temporal dementia (FTD). The seminal discovery in 2011 of a hexanucleotide expansion in the C9orf72 gene as the most common cause of familial ALS and FTD significantly changed our perspective of these neurodegenerative diseases. The pathogenic mechanisms of this expansion are not yet understood. However recent lines of evidence, including from my own work, strongly support a gain of toxic property by accumulation of repeat-containing RNAs that are bidirectionally transcribed from the C9orf72 locus. Independent reports of RNA changes in fibroblasts, neurons derived from iPS cells and motor cortex from C9orf72 patients have offered evidence that RNA processing misregulation accompanies C9orf72 disease. However, it is still unresolved whether these RNA alterations are induced by the functional disruption of one or more RNA binding proteins sequestered into RNA foci or induced by another cytotoxic mechanism such as the striking accumulation of dipeptide repeat proteins translated from expanded RNAs that was recently reported in C9orf72 patients. In this project, I propose to define a set of alterations in mRNA processing that delineate a disease-dependent signature and that will serve as functional readouts to distinguish among current hypotheses for disease mechanism underlying C9orf72 ALS/FTD. By using genomic approaches optimized for precise identification of splicing and expression changes and human neurons specifically engineered to individually explore toxic mechanisms currently proposed, my group will determine which factor(s) drive the emergence of RNA processing alterations in C9orf72 disease. In particular, we will test the hypothesis that RNA alterations are induced either by sense or antisense repeat- containing RNAs. We will also use a functional screen to determine whether C9orf72-related RNA alterations are driven by reduced activity of one or more RNA binding proteins, including the proteins recently found to interact with the C9orf72 expanded repeats. Finally, my team will use the C9orf72 molecular signature to screen therapeutic compounds. Indeed, we and others have already established that antisense oligonucleotides (ASOs) targeting C9orf72 transcripts efficiently reduce pathological RNA foci in patient cells. I now propose to determine whether degradation of expanded RNAs transcribed from either the sense or antisense directions (or both), is necessary to restore RNA processing alterations linked to C9orf72 disease, an approach that may provide crucial information for the design of a clinical trial using ASOs in C9orf72 ALS/FTD patients. Disease-related RNA signatures will also serve as readouts to screen new therapeutic compounds in neurons directly derived from patient fibroblasts. Indeed, instead of using a single target RNA to determine drug efficacy, we will use quantitative analysis of a large panel of genes perturbed by C9orf72 expansions to identify small molecules that can intervene with disease-linked pathways to restore levels of the most affected RNAs.

Lay Summary

PUBLIC HEALTH RELEVANCE: The most frequent cause of two devastating neurodegenerative diseases amyotrophic lateral sclerosis (ALS) (also called Lou Gehrig’s disease) and frontotemporal dementia (FTD) has recently been identified in the uncharacterized C9orf72 gene. We will use state of the art sequencing approaches to identify disease mechanisms and screen therapeutic compounds.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias, Motor neurone diseases

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2016

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