C9orf72 hexanucleotide repeat expansion caused neurodegeneration in ALS and FTD

https://www.neurodegenerationresearch.eu/survey/c9orf72-hexanucleotide-repeat-expansion-caused-neurodegeneration-in-als-and-ftd-2/

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USA

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C9orf72 hexanucleotide repeat expansion caused neurodegeneration in ALS and FTD

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3

The project/programme is most relevant to:

Motor neurone diseases

Keywords
Research Abstract

? DESCRIPTION (provided by applicant): Hexanucleotide repeat expansion in a non-coding region of C9orf72 was recently identified to be the most common genetic cause of both amyotrophic lateral sclerosis (ALS) and frontal temporal dementia (FTD). The leading hypothesis for the disease mechanism is gain of toxicity from the expanded repeats, with two non- mutually exclusive mechanisms: 1) RNA foci formed by hexanucleotide repeats that could

sequester RNA binding proteins and disrupt RNA processing; and 2) accumulation of dipeptide repeat proteins (DPRs) produced by repeat-associated non-ATG translation (RAN translation). Furthermore, the repeats are transcribed in both sense and antisense directions. How exactly or to what extent these different products contribute to disease is not established. In this project, propose to combine new genomic, biochemistry and cellular and mouse modeling tools to determine the molecular mechanism of disease pathogenesis and identify candidate targets for therapeutic development. I will define a C9orf72 repeat expansion-dependent RNA signature in human neurons derived from a large number of patient fibroblasts, including alterations in both RNA expression and alternative splicing using genome-wide sequencing approaches. I will determine whether decreasing sense and/or antisense repeat- containing transcripts by antisense oligonucleotide (ASO) treatment reverses the RNA signature in C9orf72 patient neurons. I will also decipher the functional contribution from repeat-containing RNAs and RAN translation-encoded poly-dipeptides by genome engineering control cells with individual potentially toxic product. I will identify specific RNA-binding protein(s) associated with either sense or antisense hexanucleotide repeats in intact cells using an in vivo RNA tagging system, and determine whether “”loss of function”” of any of these contributes to the RNA signature in C9orf72 neurons. I will then decipher the damaging pathways in neurons by manipulating the candidate gene changes, perturbed pathways and RNA-binding proteins. Finally, I will determine whether the repeat expansion in glial cells have toxic effects on neurons through a non-cell autonomous mechanism by combining mouse modeling for identification of cell type-specific, age- and repeat length-dependent RNA changes caused by C9orf72 repeat expansion in vivo, and co-culturing of iPSC- differentiated neurons with astrocytes or oligodendrocytes. Overall, I believe that my proposal has the potential to test several key hypotheses regarding C9orf72-mediated pathogenesis of ALS/FTD and identify a disease- dependent molecular signature that enables the development of therapeutic strategies.

Lay Summary

PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig’s disease, is a devastating disease in which progressive degeneration of motor neurons leads to muscle weakness and fatal paralysis. It is increasingly recognized to have clinical and pathological overlaps with frontotemporal dementia (FTD). Mutation in the C9orf72 gene has recently been identified to be the most frequent genetic cause of the two diseases. The proposed work will use multiple modern molecular approaches to determine disease mechanisms and identify targets for therapeutic interventions.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Motor neurone diseases

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