Investigating disease Mechanisms in C9orf72-linked ALS/FTD

https://neurodegenerationresearch.eu/survey/investigating-disease-mechanisms-in-c9orf72-linked-als-ftd-2/

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Country

USA

Title of project or programme

Investigating disease Mechanisms in C9orf72-linked ALS/FTD

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,593,061.47

Start date of award

15/05/2015

Total duration of award in years

4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

C9orf72, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis, G-Quartets, Link

Research Abstract

? DESCRIPTION (provided by applicant): Nucleotide repeat elements, including microsatellites or short tandem repeats, are common in eukaryotic genomes. Expansions of short nucleotide repeats have been linked to nearly 40 different types of genetic disorders, primarily neurological

and neuromuscular disorders. Our understanding of how these repeat elements in the human genome cause diseases is still at its infancy. Recently, a hexanucleotide repeat expansion in a noncoding region of C9orf72 was linked to the neurodegenerative disease amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). ALS is characterized by loss of motor neurons, and the C9orf72 repeat expansion represents the most common genetic cause of both familial and sporadic ALS. FTD is characterized by degeneration of the frontal and temporal lobes of the brain and is the second most common type of dementia for people older than 65; the C9orf72 repeat expansion is also one of the most common genetic causes for FTD. The C9orf72 repeat expansion is also found to contribute to Alzheimer's disease and Huntington's disease. To help relieve the public health burden associated with these diseases, it is important to understand the mechanisms underlying the pathogenesis. We have recently discovered that the C9orf72 nucleotide repeat structures initiate molecular cascades of disease. The goal of the proposed project is to elucidate the mechanisms through which nucleotide repeat expansions, such as that in C9orf72, lead to molecular defects and neuronal toxicity. The specific aims are to identify and characterize key biochemical features of the repeat expansion, to delineate the pathways through which the pathogenesis is generated, and to identify potential intervention strategies. The proposed studies, which combine biochemical, molecular, and genetic approaches, are expected to provide insight into fundamental mechanisms of neurodegeneration associated with nucleotide repeats that may ultimately leads to novel approaches for treating relevant neurodegenerative diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: The work in this proposal is aimed at elucidating the basic molecular mechanisms of pathogenesis underlying neurodegenerative diseases that are associated with a genetic anomaly in C9orf72, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Although these diseases are becoming an increasingly relevant public health challenge in our aging society, the mechanisms underlying most of these neurodegenerative conditions remain poorly understood. The biochemical, molecular, and genetic studies outlined in this proposal could lead to novel therapeutic interventions for those neurodegenerative diseases, for which effective treatments are still lacking.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:
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