

GGGGCC hexanucleotide repeat expansions in neurodegenerative disease

<https://www.neurodegenerationresearch.eu/survey/ggggcc-hexanucleotide-repeat-expansions-in-neurodegenerative-disease-2/>

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Contact information of lead PI Country

USA

Title of project or programme

GGGGCC hexanucleotide repeat expansions in neurodegenerative disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,456,576.15

Start date of award

30/09/2012

Total duration of award in years

1

The project/programme is most relevant to:

Motor neurone diseases|Alzheimer's disease & other dementias

Keywords

C9orf72, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis, Neurodegenerative Disorders, mutation carrier

Research Abstract

DESCRIPTION (provided by applicant): The last few years have been extremely exciting for

genetic research into the understanding of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), two closely related devastating neurodegenerative disorders with overlapping clinical, genetic and neuropathologic features. In 2011, we identified a GGGGCC hexanucleotide repeat expansion in the non-coding region of C9ORF72 as the long-sought cause of FTD and ALS linked to chromosome 9p, further demonstrating the clinical and molecular overlap between these diseases. Genetic studies now suggest that this repeat expansion is the most common cause of familial FTD and ALS, explaining 10-20% of FTD and 25-40% of ALS families worldwide. This mutation also explains the disease in 1-5% of sporadic patients. What determines whether mutation carriers develop FTD and/or ALS and whether symptoms occur as early as 30 years of age or after the age of 70 has not yet been studied. Interestingly, in line with studies in other non-coding repeat expansion disorders, we showed that the repeat expansion leads to the formation of nuclear RNA foci, suggesting a possible toxic RNA gain-of-function disease mechanism. Our working hypothesis is that GGGGCC repeat expansions cause FTD and/or ALS, at least in part, through aberrant gene expression and alternative splicing changes that may result from the formation of these toxic RNA foci. The Specific Aims of this grant proposal are focused on 1) characterization of the variability in GGGGCC repeat size in blood, brain tissue and human cells in C9ORF72 mutation carriers and a detailed study of the effect of repeat size on clinical and pathological phenotypes; 2) identification of genetic modifiers of disease onset and/or presentation in patients carrying GGGGCC repeat expansions in C9ORF72; 3) study of the contribution of other GGGGCC repeats in the human genome to the development of FTD and ALS and 4) identification of gene expression and alternative splicing changes resulting from GGGGCC repeat expansions using high-throughput RNA sequencing in human brain tissue. The proposed studies are relevant to obtain a better understanding of the factors that contribute to the clinical and pathological variability associated with GGGGCC repeat expansions and have the ability to lead to the identification of mRNA targets implicated in FTD and ALS pathogenesis.

Lay Summary

This proposal is focused on the study of GGGGCC repeat expansions in C9ORF72, a novel common genetic cause of FTD and ALS. The proposed studies aim to provide a better understanding of the factors that contribute to the variable clinical and pathological phenotypes seen in GGGGCC repeat carriers and have the ability to lead to the identification of mRNA targets implicated in FTD and ALS disease.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Alzheimer's disease & other dementias, Motor neurone diseases

Years:

2016

Database Categories:

N/A

Database Tags:

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