The Role of C9ORF72 Protein Function in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

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The Role of C9ORF72 Protein Function in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

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NIH (NIA)

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Motor neurone diseases|Alzheimer's disease & other dementias

Keywords

C9orf72, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis, protein function, Guanine

Research Abstract

Project Summary/Abstract The C9ORF72 repeat expansion mutation is the most common cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), accounting for over 50% of ALS cases in northern Europe and 10% of cases worldwide, making it a critical target for therapeutic intervention. The pathogenic mechanism of the C9ORF72 repeat expansion is unclear and is the focus of this proposal because its elucidation is crucial for therapeutic development. Studies showing that the repeat expansion generates neurotoxic species including dipeptide repeat proteins and nuclear RNA foci have oriented the field towards a therapeutic focus on blocking the toxicity of these products. However, our preliminary studies using patient-specific induced motor neurons (iMNs) generated by cellular reprogramming, and primary patient tissue analysis, suggest that C9ORF72 has guanine exchange factor activity for RAB GTPases that mediate early endosomal trafficking and lysosomal biogenesis. Moreover, they indicate that haploinsufficiency for this activity leads to neurodegeneration. The goal of this study is to definitively show that haploinsufficiency for guanine exchange factor activity leads to neurodegeneration in C9ORF72 ALS/FTD through the following specific aims: (1) Identify neurodegenerative processes caused by low C9ORF72 protein levels, (2) Determine the function of C9ORF72, (3) Determine if PIKFYVE inhibition promotes iMN survival by rescuing endosomal trafficking. This application seeks to shift current research by demonstrating that haploinsufficiency for guanine exchange factor activity induces neurodegeneration in C9ORF72 ALS/FTD. The proposed study will establish C9ORF72 protein activity as a critical therapeutic target. More broadly, our work will highlight a mechanistic convergence on endosomal trafficking in ALS and FTD, identifying a pathway with therapeutic potential for a large percentage of ALS/FTD patients.

Lay Summary

Project Narrative The C9ORF72 repeat expansion mutation is the most common cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), but the mechanisms by which it causes neurodegeneration are unclear. We will apply modern disease modeling approaches including cellular reprogramming and genome editing to determine how reduced levels of the C9ORF72 protein due to the repeat expansion leads to neurodegeneration. This study will establish C9ORF72 activity as a critical therapeutic target and identify pathways that may compensate for its loss within the nervous system.

Further information available at:

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