Role of C9orf72 in Neurodegeneration

https://neurodegenerationresearch.eu/survey/role-of-c9orf72-in-neurodegeneration/

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Country

USA

Title of project or programme

Role of C9orf72 in Neurodegeneration

Source of funding information

NIH (NIA)

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias|Motor neurone diseases

Keywords

C9orf72, Nerve Degeneration, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis, Dipeptides

Research Abstract

Project Summary Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are disorders with overlapping clinical presentation, genetics, and pathology. Large expansions of a GGGGCC hexanucleotide repeat in the first intron/promoter of the C9orf72 gene are the most commonly identified genetic cause of familial and sporadic ALS and FTD (C9-ALS/FTD), and

recently C9orf72 repeat expansions were reported in other neurodegenerative diseases including Alzheimer’s disease.It remains uncertain whether the repeat expansion in C9orf72 causes neurodegeneration primarily through a toxic gain of function, loss of function, or both. In our preliminary data we found that contrary to current dogma, C9orf72 expression is higher in microglia than in neurons, and that the primary defects in C9orf72 deficient mice are due to altered myeloid cell function in both the spleen and the brain. Our goal in this project is to test the hypothesis that decreased levels of C9orf72 caused by the repeat expansion lead to altered microglial function, which acts in concert with gain of function manifestations in neurons (RNA foci, RAN dipeptides) to drive neurodegeneration in C9-ALS/FTD. We propose to i) define the molecular defects in C9orf72 deficiency macrophages and microglia, ii) determine whether peripheral blood macrophages from C9orf72 patients show similar alterations, and iii) cross the C9orf72 deficient mice to a novel BAC transgenic C9orf72 model to test the idea that C9orf72 deficiency contributes to the pathogenesis of C9-ALS/FTD.

Lay Summary
Project Narrative Amyotrophic lateral sclerosis (ALS) is a progressive and incurable disease that leads to death within 3-5 years of onset. C9orf72 is the most common genetic cause of ALS, and this application tests novel ideas about the role of loss of C9orf72 in innate immune cells in the brain and how this contributes to the neurodegeneration.

Further information available at:

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Investments > €500k

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United States of America

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