C9ORF72 in Motor System Biology and ALS

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Country

USA

Title of project or programme

C9ORF72 in Motor System Biology and ALS

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

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Start date of award

15/09/2014

Total duration of award in years

3

The project/programme is most relevant to:

Motor neurone diseases

Keywords

C9orf72, Amyotrophic Lateral Sclerosis, Systems Biology, motor neuron degeneration, gene product

Research Abstract

DESCRIPTION (provided by applicant): A hexanucleotide repeat expansion at C9ORF72 has recently been found in a significant fraction of patients suffering from Amyotrophic Lateral Sclerosis (ALS). However, it remains to be determined whether this mutation acts through a gain of function or loss of function mechanism. Resolving this issue is essential for long term

efforts to design and implement therapies that counteract the effects of this mutation in ALS. As preliminary data, we provide evidence that heterozygous and homozygous mice harboring a loss of function mutation in the ortholog of C9ORF72 are viable, survive to adulthood and initially display motor system functionality similar to their wild type littermates. However, as heterozygous animals aged, we found they displayed a significantly increased rate of mortality. Death in heterozygous animals was associated with declining motor function and paralysis that were accompanied by muscle atrophy, denervation and motor nerve degeneration. Homozygous mutant animals displayed a similar but accelerated and quantitatively more severe phenotype. Our preliminary studies suggest that C9ORF72 serves an important dose dependent function in the long-term maintenance of the mammalian motor system. These findings support the hypothesis that reduced C9ORF72 function and haploinsufficiency resulting from the repeat expansion that many patients harbor contributes directly to the development of ALS. Here we propose three aims to increase understanding of the role that C9ORF72 plays in the biology of motor neuron degeneration. First, we will determine the extent to which features of motor neuron degeneration in mice harboring a loss of function mutation in the C9ORF72 ortholog are consistent with those observed in ALS. These studies will allow us to determine to what extent the mice we have generated might have utility as a mouse model for both mechanistic and drug discovery studies. Second, we will determine whether motor neuron degeneration in C9ORF72 ortholog mutant animals occurs through cell autonomous mechanisms in motor neurons, or is due to the non-autonomous influence of mutant immune cells. Third, we will determine the extent to which transcriptional changes found in patient derived motor neurons by the C9ORF72 repeat expansion can be explained by loss of function of the C9ORF72 gene product. If funded, our studies will provide important insight into the extent to which loss of the C9ORF72 gene product contributes to motor neuron degeneration.

Lay Summary
PUBLIC HEALTH RELEVANCE: A significant fraction of patients suffering from Amyotrophic Lateral Sclerosis (ALS), a fatal neurodegenerative disease, have a mutation in the C9ORF72 gene. The aims of this proposal include the extensive characterization of a rodent model harboring a mutation in the C9ORF72 ortholog, the generation of additional models using alternative technologies and the greater understanding of how this mutation contributes to the development of ALS. Our findings will have important implications for planned therapeutic intervention in ALS patients harboring this mutation.

Further information available at:

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Investments > €500k

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United States of America

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Motor neurone diseases

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