Mechanisms of C9orf72-associated dipeptide toxicity

https://www.neurodegenerationresearch.eu/survey/mechanisms-of-c9orf72-associated-dipeptide-toxicity-3/

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Country

USA

Title of project or programme

Mechanisms of C9orf72-associated dipeptide toxicity

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

388532.1101

Start date of award

15/08/2015

Total duration of award in years

1

Keywords

C9orf72, Dipeptides, frontotemporal lobar dementia-amyotrophic lateral sclerosis, Toxic effect, Caenorhabditis elegans

Research Abstract

? DESCRIPTION (provided by applicant): Hexanucleotide expansions in the C9orf72 gene cause ~50% of all familial ALS cases. The mechanism(s) by which this expansion causes disease are not known. Current hypotheses to explain the disease mechanism include haploinsufficiency and gain-of-function RNA and/or protein toxicity. Despite its presence in an intron, the disease causing expansion is translated into protein in multiple reading frames from

both the sense and anti-sense strands to produce five distinct dipeptide proteins. Expression of each of these dipeptides has been specifically detected in ALS patient samples. Several recent studies, as well as our own data, show that the arginine dipeptides exhibit substantial neurotoxicity through unknown mechanisms. Here, we will use genetic screening in C. elegans, followed by validation in Drosophila and mammalian cells, to identify these mechanisms. Our studies will provide significant new insights into the pathways by which dipeptides engages and kill motor neurons and may identify novel risk factors and new therapeutic targets for treating this currently incurable disease

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A