Study on hnRNPA1 Pathobiology in ALS

https://neurodegenerationresearch.eu/survey/study-on-hnrnpa1-pathobiology-in-als/

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Country

USA

Title of project or programme

Study on hnRNPA1 Pathobiology in ALS

Source of funding information

NIH (NINDS)

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€ 1,439,332.11

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15/03/2016

Total duration of award in years

1

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Amyotrophic Lateral Sclerosis, protein TDP-43, Knock-in, Ribonucleoproteins, autosomal dominant trait

Research Abstract

? DESCRIPTION (provided by applicant): Mutations in hnRNPA1 are recently found in multiple families with amyotrophic lateral sclerosis (ALS). HnRNPA1 is known to regulate RNA processing and to interact with proteins related to varying cellular functions, but how hnRNPA1 mutation causes disease is not known. A critical step towards understanding hnRNPA1

pathogenesis is determining the effect of pathogenic mutation on hnRNPA1 function at both systematic and molecular levels. HnRNPA1, TDP-43 and FUS belong to ribonucleoprotein family and their mutations are all associated with ALS. The three ribonucleoproteins exhibit similarity in disease features: 1) the disease shows an autosomal dominant trait; 2) proteinopathy and mitochondrial impairment is prominent in the disease; and 3) both wildtype and mutant forms cause diseases when overexpressed in animal models. Even seven years after the discovery of TDP-43 mutation in ALS, how TDP-43 mutation causes the disease remains elusive. Our preliminary studies show that both deficiency and excess in hnRNPA1 expression causes neurotoxicity respectively in hnRNPA1 knockdown and transgenic rats, suggesting that hnRNPA1 must be tightly regulated to maintain its normal function. To unravel the effect of pathogenic mutation on hnRNPA1, we created hnRNPA1 knockin rats in which a single pathogenic mutation is introduced. The knockin rats differ from their wildtype littermates in a single nucleotide examined. Any phenotypes detected in the knockin rats must result from the pathogenic mutation. With unprecedented rat models, we will examine how pathogenic mutation impacts hnRNPA1 function at both the systematic and molecular levels, revealing the mechanism by which hnRNPA1 mutation causes neurodegeneration in ALS.

Lay Summary
PUBLIC HEALTH RELEVANCE Using novel rat models, this proposal will examine how pathogenic mutation impacts hnRNPA1 function at both systematic and molecular levels, improving our understanding of hnRNPA1 pathogenesis in amyotrophic lateral sclerosis.

Further information available at:

Types:
Investments > €500k

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United States of America

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