

Investigating mechanistic causes of C9ORF72-related amyotrophic lateral sclerosis (ALS).

<https://www.neurodegenerationresearch.eu/survey/investigating-mechanistic-causes-of-c9orf72-related-amyotrophic-lateral-sclerosis-als/>

Principal Investigators

Dr K Ning

Institution

University of Sheffield

Contact information of lead PI

Country

United Kingdom

Title of project or programme

Investigating mechanistic causes of C9ORF72-related amyotrophic lateral sclerosis (ALS).

Source of funding information

MRC

Total sum awarded (Euro)

€ 510,384

Start date of award

01/02/2015

Total duration of award in years

3.0

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Research Abstract

ALS is characterised by relentless motor neuron (MN) degeneration causing progressive paralysis and death usually within 3-5 years. Expansion of GGGGCC repeats in intron 1 of C9ORF72 is the commonest genetic cause of ALS, present in 10% of cases. Three potential pathophysiological mechanisms have been proposed: 1. Toxicity of the expanded c9orf72 pre-mRNA; 2. Aberrant synthesis of dipeptide repeat proteins (DPRs); 3. Haploinsufficiency due to

decreased levels of C9ORF72 mRNA/protein. However, recent work has shown that C9ORF72 mRNA/protein levels are not significantly altered in C9ORF72-ALS patients. In contrast, a large body of evidence favours a toxic gain-of-function(s) of the expanded pre-mRNA via formation of RNA foci, sequestration of RNA-binding proteins and/or by repeat-associated non-ATG (RAN) translation and cytoplasmic accumulation of DPRs. This proposal aims to identify the contribution and molecular mechanisms of the toxic gain-of-function that causes C9ORF72-related neurodegeneration. To achieve this, we have generated induced pluripotent stem cells derived from control and C9ORF72-ALS patient fibroblasts which are further differentiated into MNs, or astrocytes recently shown to play a toxic role in MN injury. In addition, we have engineered inducible motor neuron-like and lentiviral transduction based cell models of primary MNs/astrocytes that allow controlled expression of either hexanucleotide repeat expansions (RNA toxic gain-of-function) independently of RAN translation, or production of DPRs (protein toxic gain-of function) independently of GGGGCC RNA repeats. These will allow an extensive and in depth examination of altered stress responses, cell survival, metabolic pathways, disease-related gene expression signatures and aberrant nuclear export of mRNAs. This innovative research work is likely to define novel therapeutic strategies for neuroprotection and to characterise much-needed biomarkers of disease progression and therapeutic response.

Lay Summary

Further information available at:

Types:

Investments > €500k

Member States:

United Kingdom

Diseases:

Motor neurone diseases

Years:

2016

Database Categories:

N/A

Database Tags:

N/A