RNA metabolism in pathology of AOA2/ALS4 neurodegenerative disorders

https://neurodegenerationresearch.eu/survey/rna-metabolism-in-pathology-of-aoa2als4-neurodegenerative-disorders/

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Country

United Kingdom

Title of project or programme

RNA metabolism in pathology of AOA2/ALS4 neurodegenerative disorders

Source of funding information

MRC

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€ 592,522

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Total duration of award in years

4.0

The project/programme is most relevant to:

Motor neurone diseases

Keywords
Research Abstract

Ataxia oculomotor apraxia type 2 (AOA2) and amyotrophic lateral sclerosis type 4 (ALS4), are highly disabling disorders, characterised by neurodegeneration in the brain and spinal cord, causing progressive muscle weakness and finally atrophy, arising due to mutations in human senataxin protein. Senataxin shares homology with the yeast RNA/DNA helicase Sen1p and it has been suggested that senataxin may be involved in the regulation of gene expression. This

research project will uncover molecular function of human senataxin protein using a combination of our expertise in RNA field and the cutting edge high throughput technology. In the first part of this project we will study transcriptional and RNA processing defects associated with AOA2/ALS4 mutations genome-wide. We propose that the function of senataxin in human cells is related to its RNA/DNA helicase function and its ability to unwind RNA/DNA hybrids (or R-loops) formed between nascent RNA transcripts and single stranded DNA template behind the elongating Pol II. We will investigate the effect of senataxin on genome-wide distribution of R-loops and study their contribution to the neurodegenerative phenotype, employing Solexa sequencing following DNA-immuno-precipitation (DIP-seq). Secondly, we will define the molecular functions of R-loops and senataxin in splicing regulation. Finally,we will identify novel RNA and protein senataxin-interacting partners, using mass-spectrometry and iCLIP approach, followed by the study of their function in gene expression and AOA2/ALS4 pathology. The long term goal of our work is to create a foundation for the collaboration between basic and clinical science beneficial to therapeutic advancement of AOA2/ALS4 diseases and development of novel molecular therapies, improving the health and quality of patients' life.

Lay Summary
Further information available at:

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Investments > €500k

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Motor neurone diseases

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2016

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