Variability in human axon survival

https://neurodegenerationresearch.eu/survey/variability-in-human-axon-survival/

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Country

United Kingdom

Title of project or programme

Variability in human axon survival

Source of funding information

MRC

Total sum awarded (Euro)

€ 932,244

Start date of award

01/02/2016

Total duration of award in years

3.0

The project/programme is most relevant to:

Motor neurone diseases|Neurodegenerative disease in general

Keywords
Research Abstract

We study the pathway of axon degeneration after injury: Wallerian degeneration. Data from animal models suggest related mechanisms influence axon survival in some diseases and in ageing, including multiple sclerosis (MS), peripheral neuropathies (PN), glaucoma and some motor neuron diseases. Early axon loss is also prominent in Alzheimer's disease, Parkinson's disease and ALS. There are no disease-modifying therapies. Here, we address the role of this pathway in human axon survival. Mutations of five genes are now known to robustly delay Wallerian degeneration in mice and other model organisms but whether a similar phenotype

exists in humans has remained an intriguing but unanswered question. Recent GWAS and exome linkage between Wallerian pathway genes and ALS and a painful neuropathy, and animal studies, suggest that such a phenotype could function as a disease modifier. SNP databases indicate polymorphisms likely to delay Wallerian degeneration and others likely to confer an opposite phenotype of axon vulnerability. Our mouse and preliminary human studies support this notion. We will test which human variants alter axon survival by testing their function in mouse neurons that lack the homologous mouse gene. Using established assays, we will ask whether human variants in a pro-survival protein, NMNAT2, support axon survival and if so how strongly, and whether variants in human SARM1, a pro-degenerative protein, restore rapid Wallerian degeneration when mouse SARM1 is missing. We will then estimate the prevalence of these phenotypes. We will test whether NMNAT2 deficiency is a risk factor for neuropathic pain, and having shown that SARM1 deletion completely rescues nerve growth and early lethality in NMNAT2 null mice, we will test whether it also rescues a premature age-related decline that we find in mice expressing low levels of NMNAT2. These data will complement ongoing GWAS and exome studies to understand the roles of this pathway in human disease.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Motor neurone diseases, Neurodegenerative disease in general

Years:
2016

Database Categories:
N/A

Database Tags:
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