The Genetics and Pathophysiology of Spinocerebellar Degeneration

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Title of project or programme

The Genetics and Pathophysiology of Spinocerebellar Degeneration

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

1793043.62

Start date of award

01-02-2010

Total duration of award in months

60

The project/programme is most relevant to

- Spinocerebellar ataxia (SCA)

Keywords

Research abstract in English

Aims

The purpose of this research is to build a genetic framework and establish the functional pathways

that lead to spinocerebellar degeneration. My initial work will identify both the common as well as the rare genetic risk factors and disease modifiers of spinocerebellar ataxia. The effects on expression of these variants will be examined in normal cerebellar, affected lymphoblastoid and brain mRNA. Pathogenic and modifying variants and their interacting proteins will be further investigated with tissue culture and neuropathological approaches. My current MRC fellowship has been very successful, achieving 4/5 goals with 15 months to go. This has allowed me to develop techniques and establish important collaborations, such as the ataxia DNA and brain bank collection, thus laying the groundwork for future projects.

Design and methodology This project incorporates a number of strategies.

1. Investigation of genetic variation in pure spinocerebellar ataxia (SCA) of unknown aetiology and the identification of genetic modifiers of the polyglutamine associated SCAs:

(a) Genome wide association study (GWAS) in pure spinocerebellar ataxia. In a total of 1680 samples, structural changes, copy-number variation and disease associated SNPs will be identified. This will be replicated in a European/USA cohort.

(b) GWAS to identify age-of-onset (AOO) modifiers of SCA1, 2, 3, 6 and 7 in 1255 SCA cases from the UK and EUROSCA. This data will be replicated in Huntington’s disease through the funded Euro-HD-study and we have further access to Japanese/USA/Chinese and Australian SCA cohorts.

(c) Deep sequencing for variants in the loci from 1(a) and (b) and for rare coding changes in candidate genes which include known ataxia genes, channel/inositol pathway genes, fly and yeast modifier screen genes.

2. Expression profiling: Many of the variants identified will be non coding and likely to act by altering gene expression. Analysing genome-wide cerebellar mRNA expression data will allow the identification of expression differences.

3. Functional investigation: Gene function and protein interactors will be investigated in affected lymphoblastoid/brain mRNA, transient or stable cell models and if a channel-gene is implicated we will collaborate with Hanna/ Schorge to perform channel electrophysiology.

4. Neuropathology: This resource has already proven vital to our research in the characterisation of neuropathological features and the investigation of interacting proteins.

Opportunities
A significant proportion of the genetic risk factors will be identified providing a framework of pathways to interrogate functionally. Defining these pathways will facilitate the identification of therapies and allow more effective trials by precise stratification of patient cohorts.

Lay Summary