



Project Title: Supporting a genome-wide association study of genetic modifiers of age at onset in spinocerebellar ataxia 27B

Principal Investigator(s): A collaborative group, including Professor Stephan Züchner, David Pellerin, Henry Houlden and Bernard Brais; with the lead site being at University of Miami Miller School of Medicine (US).

Scientific Summary:

Spinocerebellar ataxia 27B (SCA27B) is a recently described autosomal dominant cerebellar ataxia caused by an intronic GAA·TTC repeat expansion in the fibroblast growth factor 14 (FGF14) gene. The size of the FGF14 expansion only weakly correlates with the age at onset and appears to account for only 10 – 30% of the observed variance, suggesting that additional genetic factors influence the age at onset. Such modifiers may involve variations in DNA repair pathways, which have been shown to modify the age at onset in some repeat expansion disorders.

In this study, the researchers plan to conduct a genome-wide association study (GWAS) involving approximately 1,000 patients with molecularly-confirmed SCA27B to look for genetic modifiers modulating the age of onset (primary aim) and disease progression (secondary aim), as measured by the SARA score and need for walking aid. They will perform a transcriptome-wide association study to identify gene expression changes associated with genetic modifiers, which will allow them to guide network analysis and identify potential druggable targets. To unravel shared genetic risk factors with other spinocerebellar ataxias, the researchers aim to compare candidate genetic modifiers from this study to those identified in the ongoing age-at-onset GWAS in SCA1, SCA2 and SCA3.

Lay Summary:

Spinocerebellar ataxia 27B (SCA27B) is a genetic condition caused by repeated sequences in the DNA code for a gene called fibroblast growth factor 14 (FGF14). Unlike in other SCAs, the size of this repeated sequence only slightly influences when symptoms start and how quickly they progress. Research has shown that other genetic factors may play a role in determining the age at which symptoms appear and how the disease progresses. These factors might involve changes to DNA repair mechanisms, which have an effect in similar genetic disorders. Diagnostic testing and clinical evaluation for UK patients is offered in NHS clinics in London (Dr. Henry Houlden), in Canada (Dr. Bernard Brais) and in the USA (Dr. Zuchner and colleagues).

This study will explore these genetic factors by analysing the DNA of 1,000 people with SCA27B around the world to look at genetic variations that might influence the onset and progression of SCA27B, which may potentially identify new targets for treatments.

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