



The Genetic and Functional Characterisation of Spinocerebellar Ataxia type 11
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Scientific abstract

This research will characterise and determine the processes that lead to spinocerebellar ataxia type 11 (SCA11) using established genetic, neuropathological and cell biology techniques.

Recently we identified a novel ADCAI11 gene as the cause of SCA11 (manuscript in preparation). We have screened 40 families and identified four mutations in large ADCAI11 families, suggesting a preliminary mutation frequency of approximately 10%.

To determine the prevalence of SCA11 defects we will screen our entire cohort of ADCAI11 families that have an unknown genetic defect and subsequently analyse further families referred with a pure ataxia phenotype.

The function of the SCA11 gene is unknown but it has been implicated as a putative microtubule associated protein tau (MAPT) kinase. Antibodies to the SCA11 gene will be developed and the functional effects of SCA11 defects will be analysed in transient and stable neuronal cell lines. We will then carry out kinase assays on the wild type and mutant SCA11 gene protein to determine the role of the SCA11 gene in MAPT phosphorylation.

The *in-vitro* SCA11 work in tandem with the characterisation of SCA11 affected brain tissue will define the function of this gene and its relationship to the MAPT gene as well as identifying potential therapeutic targets to block neuronal degeneration.

Papers:

Johnson J, Wood N, Giunti P, Houlden H. Clinical and genetic analysis of spinocerebellar ataxia type 11. *Cerebellum* 2007; Jul 16:1-6

Houlden H, *et al.* Mutations in *TTBK2*, encoding a kinase implicated in tau phosphorylation, segregate with spinocerebellar ataxia type 11. *Nature Genetics* advance online publication Published online: 25 November 2007

Lay summary

This research is an exciting opportunity to characterise and determine the processes that lead to a type of pure cerebellar ataxia known as SCA11. Pure inherited autosomal dominant ataxia is the commonest type of pure inherited ataxia but the majority of cases remain unknown. Prior to our research only two genes had been identified in pure ataxia, SCA5 and 6.

Recently we identified a novel gene as the cause of SCA11 (Manuscript in preparation). We have screened 40 families and identified four mutations in large families with pure cerebellar ataxia containing over 40 affected members. This suggests a preliminary mutation frequency of approximately 10%.

To determine the prevalence of SCA11 gene defects we will screen our large cohort of pure ataxia families and subsequently analyse further families sent to us and seen in the ataxia and neurogenetics clinic.

The function of the SCA11 gene is unknown but through this research we aim to characterise and determine the mechanism by which this gene causes ataxia. We will develop cell models with the SCA11 gene defect and analyse the functional properties of the gene, which is thought to be a protein kinase. We will also analyse the SCA11 gene defect in donated brain tissue from patients suffering from a number of different types of ataxia.

The SCA11 gene is thought to interact with a protein that is very common in all neurodegenerative disorders called microtubule associated protein tau (MAPT). Characterising this interaction with MAPT will help us to understand the SCA11 gene function and the overlap with other neurodegenerative disorders. There are a number of therapies currently being investigated in neurodegenerative disorders that are characterised by MAPT deposition. Inhibiting MAPT deposition by certain therapies leads to longer lifespan and reduced disease effect in mouse models. If the association with MAPT is proven then these therapies may be beneficial to patients with pure ataxia.

What does this mean for patients?

This research aims to find out more about the gene which causes spinocerebellar ataxia type 11 (SCA11) and how many people carry this gene. It will also explore a possible link between the SCA11 gene and a particular protein called MAPT which has been found in other neurodegenerative disorders such as Parkinson's disease and Alzheimers. A number of therapies are currently being developed which target MAPT, and finding out whether MAPT is important in SCA11 will allow us to discover whether these therapies may also be useful for patients with ataxia.



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