

Genetic epidemiology of dominant ataxia in Scotland
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Final Report

Background

Following the Ataxia UK funded study on the genetic epidemiology of ataxia in the north east of England, we embarked on a follow-up study in Scotland with the following aims:

1. To confirm that SCA6 is the most prevalent cause of inherited ataxia in the UK by determining the number of individuals with SCA6 who either have the disorder or are at risk of developing the disorder.
2. To demonstrate the high prevalence of SCA17 relative to other forms of dominant ataxia in the UK.
3. To confirm that SCA 10, 12 and 14 are exceptionally rare, and should not form the focus diagnostic service development in the UK
4. To determine the prevalence of mitochondrial disorders as a cause for inherited ataxia.

Progress

The project began in October 2004 and ran for 2 years, the first year involving the clinical component and collection of samples and the second year involving the laboratory work carried out by Dr Kate Craig. Dr Craig travelled to Edinburgh and identified **10** SCA6 families and a cohort of **192** patients with undiagnosed ataxia.

The cases of undiagnosed ataxia had already been screened for SCA1,2,3,6,7,8, DRPLA and Friedreich's ataxia. DNA samples were assembled into a panel and brought back to Newcastle for further analysis. The samples were tested for known genetic causes of ataxia using fluorescent labelled PCR amplification of triplet repeat expansions in the following genes: SCA10, SCA12, SCA17. Remarkably, we did not detect a single positive case in the Scottish cohort. This contrasts with our findings in England, where we detected a number of SCA17 cases.

Recent evidence has implicated expansions in the Huntington's disease gene (*HD*) in patients with ataxia. We therefore developed an assay to test for this gene, and screened both English and Scottish cases for mutations. None had pathological expansions in the gene.

During the project, the mutations in *SPECTRIN* underlying SCA5 were identified by a North American group¹. SCA5 is of historical interest because it was identified in relatives of President Lincoln. We therefore developed an assay to search for these

mutations in both English and Scottish patients with ataxia. One patient was found to have a SCA5 mutation, making this the first UK family with the disorder. We are characterising this family in more detail at present.

Also during this project, work in our laboratory showed that mutations in *POLG* coding for the mitochondrial DNA polymerase, are another possible cause of ataxia². Two mutations in *POLG* appear to be a common cause of ataxia in Scandinavia, being more common than Friedreich's ataxia³. We therefore screened both English and Scottish cohorts for mutations in *POLG*. This work identified a single case of ataxia due to compound heterozygous mutations in *POLG*.⁴ The sibling of this case had a post-mortem. We are currently carrying out mechanistic studies of the ataxia in this family using this unique tissue resource.

Conclusion

Our observations show both similarities and differences between the Scottish and English subjects. SCA6 is the most common form of inherited ataxia in both regions, and rare forms of SCA are uncommon in both countries – but SCA17 was only present in England, and SCA5 only in Scotland. These differences could simply reflect statistical sampling for very rare disorders. Although the funded period is over, follow-up work is ongoing. In addition to the paper already published, two further manuscripts are in preparation.

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References

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