

**Development of high throughput genetic testing for cerebellar ataxias.  
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**Scientific abstract**

Numerous genes have been identified in which mutations cause ataxia. However, genetic testing for most of these mutations is not available on the NHS, despite this being an essential part of clinical care that may benefit many additional patients. Since assessment of clinical features alone does not always distinguish one genetic cause from another, concurrent screening of several genes is necessary and requires high throughput technologies to put into practice.

We propose to develop a pilot genetic testing service for ataxias which employs high throughput sequencing for point mutations (or other small nucleotide changes) in genes causing autosomal recessive cerebellar ataxias (ARCA). We will focus on mutations causing ARCA because they are likely to have a high detection rate, are under-represented in testing services and are amenable to high throughput sequence analysis. To develop the service, we will assess the genes to be tested and commence the analysis using standard sequencing technology and assess the transfer to high throughput sequencers as part of the research project. Once the feasibility and clinical utility of the pilot service have been established, we will engage with policy makers and commissioners to promote transfer to a routine service within the Oxford Regional Genetics Laboratory.

**Lay Summary**

There are many different types of ataxia and many are caused by changes or “mutations” in the genetic material of an individual. These genetic changes lead to either missing proteins or changes in the function of a protein, which may be essential for the normal function of the nerve cells and brain. Genes are too small to see with the naked eye and to detect gene changes requires complex technology. Different gene changes need different types of technology to pick them up. The individual molecules making up genes are known as nucleotides and the change of even a single nucleotide can affect the gene and therefore the protein, leading to abnormal nerve function including ataxia. In the past years many changes in many different genes causing ataxia have been found in research laboratories. This means that a person with ataxia or their relative can be tested to find out if specific genetic change can be found. Finding the specific genetic cause of ataxia can be very beneficial to patients and their families. An accurate diagnosis can provide information about the outlook and course of the disease, can help to avoid patients having unnecessary, expensive, painful and time-consuming investigations, can



assist patients and their relatives to make informed reproductive decisions, can provide guidelines for management and follow-up of an affected person and can contribute to other research projects on ataxia. Any treatment trials for ataxia are also highly likely to require that a specific genetic diagnosis is made (for example the ongoing trial for Friedreich's ataxia using idebenone).

Unfortunately, the introduction of genetic tests into the NHS from a research environment is complex and considerable information is required about whether a genetic test will be beneficial for patients and whether it is technically possible to do the test. A significant problem has been that there are so many genes involved in ataxia which have been identified that there were not the resources or the technology to introduce such tests. However, advances in technology suggest that this is changing and "high throughput" equipment is available that may be able to process many more samples, allowing larger and more genes to be analysed. This makes it feasible to introduce into the NHS. The John Radcliffe Hospital in Oxford is very fortunate in having been awarded funds from the National Institutes of Health to develop an Oxford Biomedical Research Centre, which brings together the expertise of clinicians and scientists. One of the main projects is to develop a Unit which can transfer genetic tests from research into the NHS. This involves the collaboration of several individuals all with significant expertise in this field and is a partnership between Oxford Radcliffe Hospitals NHS Trust and the University of Oxford. This is an ambitious project which aims to evaluate genetic tests for ataxia, by collecting patients who are suitable for genetic testing, and by implementing testing, first using standard technology to develop the service whilst at the same time evaluating new and rapidly developing technologies which will be suitable for clinical diagnostics in a few years' time. The project will also have "side-arms" which will allow the development of additional projects, the results of which can be fed back into the clinical and research environments.

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