

Researchers working on ataxia



An occasional feature focusing on researchers who specialise in the ataxias. Here, Dr Kevin Talbot reports.

Research into inherited ataxia at Oxford University: Genes and the brain

Most people will be aware that the human genome has now been decoded. It appears that we have between 25,000 and 30,000 genes, though there is still some debate about the exact number. We have two copies of each gene, one inherited from each parent. Genes serve as the template or code for a specific protein. Proteins are key elements in keeping our cells healthy, either by providing the structural elements of cells (the 'bricks and mortar' that make up cell walls, for example) or by maintaining cell metabolism (including energy production and communication between cells).

As you can imagine, nerve cells have very special requirements. They are exceptionally long, very demanding of energy and communicate with many thousands of other cells. Special genes, are required to maintain nerve cells throughout life. Unfortunately, unlike blood cells, nerve cells do not appear to be able to regenerate and must last a whole lifetime. All of this means that the cells in your brain are vulnerable from the outset. If one of the genes required to maintain nerve cells throughout life contains an error (a 'genetic mutation'), this vulnerability is compounded and nerve cells degenerate with age.

Inherited ataxias

There are many genes which, when mutated, can give rise to ataxia. This can happen in two ways. In recessive diseases (eg Friedreich's ataxia and Ataxia Telangiectasia) the genetic mutation must be present in both copies of the relevant gene. Affected individuals inherit one abnormal copy from each parent and have a very low likelihood of passing the disease on to their offspring (which could only happen if they had children with a carrier). In dominant inheritance, only one copy of the abnormal gene can cause the disease,

so affected individuals have a 50% chance of passing on the condition to their children. Autosomal dominant cerebellar ataxia (ADCA) is the commonest form of adult inherited ataxia. Individually the different forms of ADCA are called spinocerebellar ataxias (SCAs) and given a number (at the last count we are now up to SCA25).

Testing

Patients attending neurology or genetics clinics in the UK can readily be tested for SCA1,2,3,6 and 7 with a simple blood test, and a result is generally available within a few weeks. In these diseases the genetic mutation consists of an expanded repeat in the DNA sequence of the gene that produces a protein with too many copies of a building block (amino acid) called glutamine. In these polyglutamine diseases, for reasons that are still not clear, this abnormal protein is toxic to nerve cells. Testing for SCA12 and SCA17 may be available in certain research laboratories but is not routinely carried out in NHS genetic departments. Your neurologist may be able to arrange this in selected cases. For the other forms of SCA, either a gene has not been identified yet or routine testing is not available and can only be done by research laboratories.

In the UK it appears that SCA2 and SCA6 are the commonest forms of ADCA. A few families have tested positive for some of the other conditions, but individually each SCA appears to be rare. If the clinical features fit, there are other tests for the recessive ataxias (Friedreich's ataxia, Ataxia Telangiectasia and vitamin E deficiency) which are also routinely available. Similarly, there are a number of rarer recessive ataxias for which testing is only available in research laboratories.

SCA14

We have recently identified the first UK family with SCA14. This is a very slowly progressive form of ataxia

that first appears in the twenties or thirties and is associated with a normal lifespan. Patients generally retain the ability to walk into old age, but suffer from unsteadiness and incoordination. SCA14 is due to mutations in a gene called Protein Kinase C gamma. It is not due to an expanded polyglutamine repeat. PKC gamma is part of a large family of molecules which have a variety of functions within cells, including localising important proteins to the cell membrane. Therefore we hope that understanding its function may give us some insight into the function of nerve cells in the cerebellum as well as why these cells are especially vulnerable. We are currently analysing the effect of these mutations in cells grown in the laboratory.

We would be very happy to receive DNA from any patient with ataxia who would like to be tested for SCA14, though this should be done through a referring neurologist or geneticist. If you have adult-onset ataxia (especially if there is a family history) and have tested negative for SCA 1,2,3,6 and 7 your doctor can arrange for DNA to be sent to my laboratory.

There are a number of research groups in Oxford focusing on ataxia and we are happy to see any patients with the condition (referred by their GP or neurologist) who would like to contribute to research or simply to discuss their condition in more detail. I collaborate with colleagues working on recessive ataxia (Dr Andrea Nemeth), neuropathology of ataxia (Dr Olaf Ansorge) and mouse models (Professor Kay Davies).

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