

## **Report from National Ataxia Foundation Scientific Conference**

The National Ataxia Foundation (NAF) Annual Investigators' Meeting took place on 9-11 March in Chicago. It was attended by over 100 researchers as well as representatives from the ataxia charities FARA, FARA-Australasia and FASI. Sue Millman and Alison Stevenson attended on behalf of Ataxia UK.

### **Measuring ataxia – searching for biomarkers**

MRS is a non-invasive imaging technique that can be used to measure metabolites in the brain and thereby assess its function. Researchers have been using MRS to look for biomarkers for ataxia. Biomarkers are chemicals whose levels change in line with changes in ataxia which could therefore be used to measure the progression of ataxia.

Several types of ataxia were investigated; spinocerebellar ataxia types 1, 2 and 6 (SCAs1, 2 and 6), ataxia with oculomotor apraxia type 2 (AOA2) and Friedreich's ataxia (FA). Interestingly, different patterns of metabolite changes were found in the different ataxias, suggesting that it may be possible to recognise different ataxia subtypes based on MRS data.

One potential biomarker was identified for SCA1; a brain-specific metabolite called N-acetylaspartate (NAA). Levels of NAA were altered in people with SCA1 and a mouse model of the condition, and correlated with the severity of ataxia. This suggests that MRS biomarkers could be used to detect early signs of SCA1, and maybe monitor its progression. If this is the case, MRS could be used to measure the efficacy of potential treatments in clinical trials.

Researchers also showed that magnetic resonance imaging (MRI), which measures the volumes of different brain regions, could be useful for diagnosing and monitoring SCAs 1, 2, 3 and 6.

### **Understanding episodic ataxia**

Episodic ataxia type 2 (EA2) is the most common of the seven types of episodic ataxia, where 'attacks' of ataxia last for hours to days. Work on mouse model of EA2 has shown that release of calcium ions from stores inside Purkinje cells in the cerebellum is necessary to induce ataxia attacks. Therefore, manipulating calcium ion regulation in Purkinje cells could be a novel therapeutic strategy for EA2.

Other studies in the EA2 mice reveal a pacemaker function for Purkinje cells, which regulates the information sent from them. This function is upset in the mice, but can be improved with some drugs that act on potassium channels. These treatments also improved motor control in the mice.

### **Developing cell models for Friedreich's ataxia research**

Researchers have been working on ways to develop better cell models of FA. Nerve cells and cardiac cells are most affected by the condition and would therefore be the best cells to use in research. However, it is not possible to obtain these cells from living people so researchers have been developing ways to create them in the lab.

Induced pluripotent stem (iPS) cells are generated by reprogramming other types of cell, eg blood cells, so they lose their tissue specificity and acquire stem cell-like properties. They are able to replicate and develop into other types of cell and can therefore be cultivated into specific cell types in the lab. Three research groups have been developing this cutting edge technique and creating iPS cells from blood cells from people with FA. They found that iPS cells retain the genetic defects associated with FA, making them good models of the condition. These iPS cells have been successfully developed into nerve cells and work is also underway to create cardiac cells.

Another research group is developing FA nerve cells a different way; by obtaining neural precursor cells from the nasal cavity and cultivating them into nerve cells in the lab. Additionally, Ataxia UK-funded researcher Dr Lufino has developed a neuronal cell line that can be used to monitor expression of the frataxin gene.

These cell models will be useful tools for investigating how FA progresses and for testing new therapies.

### **Cerebellar ataxia research update**

Vascular endothelial growth factor (VEGF) has been identified by one research group as a potential biomarker and/or treatment for **SCA1**. Expression of the VEGF gene was found to be significantly decreased in the Purkinje cells of a SCA1 mouse model and increasing VEGF levels slowed progression of the ataxia.

A drug that alters calcium signalling in cells is being investigated as a new approach for treating **SCA2**. Research has shown that mutant ataxin-2, which causes SCA2, triggers the death of Purkinje cells grown in culture by increasing the release of calcium ions from stores in the cell. Recent studies showed that stabilising calcium signalling using a drug called dantrolene promoted survival of the cultured cells and prevented the deterioration of motor coordination in a mouse model of SCA2. However, the side effects and dosing regime need to be addressed if this treatment is to be considered for human testing. Dantrolene may cause sedation and muscle weakness and in these experiments the mice were given the drug prior to the onset of symptoms which would not be practical clinically.

Mutations in ataxin-3 cause **SCA3** and the mutated protein aggregates in the nucleus of affected cells. Researchers have found a way of preventing the movement of mutant ataxin-3 to the nucleus and shown that this inhibits its aggregation and can



improve lifespan in a fruit fly model of the condition. Other research into the causes of SCA3 has revealed changes in ion channels and a reduced response to oxidative stress which may be playing a part. Work from another group has involved using a cell based assay system to screen for possible therapeutic compounds.

**SCA6** mutations affect voltage-gated calcium channels, which are involved in signalling from Purkinje cells. The mutations are concentrated in a particular area of the protein and recent research suggests that the normal function of this region is to activate genes that promote the health of Purkinje cells. However, when mutated this region loses its normal function and acquires an additional, toxic property that results in increased DNA damage in cells.

Mutations in ataxin-7 cause **SCA7**, which is associated with retinal degeneration. Ataxin-7 forms part of a large protein complex that is involved in the expression of a number of genes in the retina. Expression of these genes is reduced when ataxin-7 is mutated which may be due to disruption of the protein complex. Ataxin-7 RNA processing is also disrupted when ataxin-7 is mutated and this may additionally contribute towards SCA7.

Ataxia UK-funded researcher Dr Scholefield is developing a potential new therapy for SCA7; short stretches of RNA (short hairpin RNA; shRNA) to silence the mutant ataxin-7 gene. She will use cells from people with SCA7 to generate iPS cells and develop a neuronal cell model in which to test the shRNAs.

**SCA17** pathology is being investigated in mouse models by Dr Li and colleagues. Their recent work suggests that SCA17 mutations result in decreased levels of heat shock protein 27 (Hsp27), a potent neuroprotective factor.

#### **New ataxias**

**SCA32** is the latest SCA to be described. It is inherited in a dominant fashion, is progressive in nature and causes infertility in affected males. The causative gene has been linked to a region on chromosome 7.

A new **recessively inherited ataxia** has been found in a large Algerian family. It has a young age at onset (less than seven years old) and is caused by a mutation in the rundataxin gene. The rundataxin protein is involved with vesicle trafficking within the cell. It is the first time that this process has been linked to ataxia.

**For more support or information please contact: Ataxia UK, Lincoln House, Kennington Park, 1 – 3 Brixton Road. London SW9 6DE**

**Website:** [www.ataxia.org.uk](http://www.ataxia.org.uk).

**Helpline:** 0845 644 0606 **Tel:** +44 (0)20 7582 1444 **Fax:** +44 (0)20 7582 9444

**Email:** [helpline@ataxia.org.uk](mailto:helpline@ataxia.org.uk).