

## DYSTONIA GENETICS: WHAT HAVE WE LEARNT?

In recent years, there has been considerable interest in the genetics of dystonias. The first gene causing childhood onset generalised dystonia was mapped to chromosome 9 in 1989, and then the gene itself was cloned (isolated) in 1997. This was called the DYT1 gene. Since then, numerous other genes causing various familial forms of dystonia have been mapped, and four have been cloned. Research has led to development of cell and animal models to try and answer questions of how these genes behave in normal life and, when they malfunction, how they cause dystonia. This has led to a large amount of research funding being targeted to address these questions.

The purpose of this talk is to address four important questions about genetic research. These are questions which have been put to me by various members of dystonia groups across Europe and indicate peoples' interest and concerns about genetic research.

### 1 Are genes important for dystonia?

Fifteen different dystonia genes have now been mapped in various familial forms of dystonia from childhood onset generalised dystonia through to families with adult onset focal dystonia such as torticollis (cervical dystonia). Genes have also been mapped for paroxysmal (episodic) forms of dystonia and also for dopa responsive dystonia and dystonia myoclonus syndrome. To date, only four of these genes have actually been cloned.

The commonest form of dystonia in the population, however, is primary focal dystonia. These are the individuals who as an adult developed cervical dystonia, blepharospasm, writer's cramp, oromandibular or laryngeal dystonia. The vast majority of cases are sporadic (in other words, there are no other family members with similar problems), but some can be familial. It is likely that the majority of these have a multifactorial cause. This means that there is an interaction between genetic factors as well as environmental factors, which lead to the development of dystonia. A recent study looking at large populations of patients with either cervical dystonia or blepharospasm suggests that a normal variation in the gene for a dopamine receptor (D5) may lead to susceptibility to developing these focal dystonias.

Whilst most of the genetic forms of dystonia which appear to be caused by a single gene are rare, the belief is that understanding how they are caused by analysing the molecular mechanisms will lead to greater understanding of how common forms of dystonia occur and, in the long run, lead to new treatment.

### 2 What have we learnt from genetic studies so far?

The gene that has been best studied is the DYT1 gene which causes familial childhood onset generalised dystonia. This is often the most disabling form of dystonia, and starts usually in early years, often in an arm or a leg. It progresses to affect most of the body, but rarely involves the head or the neck. It is inherited in a manner referred to as autosomal dominant, meaning that if an individual has this form of dystonia, they have a 50% chance of passing the gene to any of their children. However, we know that even people who carry the abnormal gene, can live their lives without developing dystonia, and this is a phenomenon known as reduced penetrance. Fortunately for DYT1 dystonia, the penetrance is around 30%, which means that only this proportion of people who carry the abnormal DYT1 gene ever develop dystonia.

The gene was mapped on to chromosome 9 and finally isolated. A single mutation has been identified which appears to cause almost all cases of DYT1 dystonia across the world. This leads to the loss of a

single amino acid (basic protein building block) in the protein product which has been called torsinA.

The function of torsinA in the nervous system is unknown, but it appears to be involved in interacting with other proteins as they are synthesised in a region of the cell called the endoplasmic reticulum. It is diffusely distributed in the nervous system especially, in parts of the basal ganglia involved with dopamine neurotransmission.

A number of groups have created cell models in which nerve cells grown in culture are transfected with either the normal or abnormal DYT1 gene which leads to the production of either the normal or abnormal torsinA. These studies have shown that the abnormal protein appears to form clumps or aggregates within the cells, and it is possible that these clumps lead to association with other important proteins which may disrupt the way in which nerve cells function. Analysis of these aggregates under the electron microscope shows that they appear to be made up of tightly curled pairs of membrane, which are probably derived from the endoplasmic reticulum. Thus torsinA appears to disrupt the way the endoplasmic reticulum functions, and this may well be the way in which it leads to the cells behaving in an abnormal way. Further studies have been to develop animal models both in organisms such as nematodes (worm), *Drosophila* (Fruit Fly) and in mice. The results of these studies suggest that normal torsinA plays a role in how specific proteins are handled or broken down and, when the mutation is present, this process is disrupted. This is an area of intense research, and will hopefully lead to further knowledge about what actually goes wrong leading to the development of dystonia.

### **3 How has the new genetic knowledge helped people with dystonia?**

At a fundamental level in terms of treatment, new genetic advances have not led to any new therapy. These will only come when the mechanisms by which abnormal genes lead to dystonia are clearer.

At a practical level the identification of a genes such as the DYT1 gene has led to improved genetic counselling and the ability to indicate risks of family members developing dystonia. In addition for DYT1, and the genes causing dopa responsive dystonia and dystonia myoclonus syndrome, genetic testing for family members is available.

Knowing the genetic type of dystonia does have some importance for treatment. In recent years, there has been an increasing interest in the use of deep brain stimulation for treating severe forms of dystonia which do not respond to any other medication. For childhood onset dystonia, it appears that DYT1 dystonia responds best to this form of treatment and so knowledge of the genetic abnormality may well help select the best individuals for surgery.

Other less tangible benefits include the fact that the identification of many genetic forms of dystonia have helped to confirm it as a 'real' condition rather than a psychological one. The other advantage of unravelling these genetic mechanisms is that it stimulates research in scientific disciplines such as biochemistry, cell biology and protein biology, and brings new scientists into the field of dystonia. This can only be a good thing for everyone involved with dystonia.

### **4 What does the future hold for dystonia genetics?**

It is clear that additional dystonia genes will be identified in the years to come. The important issue is what is done with this knowledge. The hope is that once a gene has been identified, we can identify the precise mechanism by which it leads to the development of dystonia and then devise specific treatments, either at a cellular level or a DNA level, to try and counter this. It may also be possible to try and prevent the development of dystonia by genetic testing and cancelling out the effect of abnormal gene before it leads to

the development of dystonia. The gold standard treatment in the future may well be forms of gene therapy to do this. Whilst this seems like a space age dream there has recently been a study in cell model where cells expressed the abnormal form of torsinA. By using a technique called allele specific silencing, researchers in the United States have been able to switch off the abnormal gene, and just allow the normal one to carry on producing torsinA. Whilst this is relatively easy to do in cells grown in a dish, the challenge in years to come will be to translate this sort of development into a potential treatment for patients with dystonia.