

## Back to Basics

This article, based on a talk given at the 1999 AGM by Dr. Jeremy Stern (Chairman of the Tourette Syndrome (UK) Association) is published in response to the continuing demand for a clear, concise explanation of the known facts insofar as Tourette's syndrome is concerned.

### Introduction

Genetic issues invariably arise when questions are put to our panel of experts during the "Q&A" sessions held at the end of each year's AGM.

Two queries which have cropped up every year for (at least) the last decade are:

**1. Why do I, or why does my child, have GTS ?**

**2. What are the chances that future children in the family will have GTS ?**

To date, the combined efforts of international medical researchers have not been able to answer these crucial points - here, I try and explain why that is.

### Is GTS in the Genes?

Firstly, we have to know if GTS really is "genetic" or not. Some diseases occur exclusively due to faulty genes e.g. cystic fibrosis, muscular dystrophy. Others are a result of a complex (i.e. not well-understood) interaction between genes and the environment e.g. multiple sclerosis, heart attacks. Important factors in the environment could include events during pregnancy, the way we are brought up, infections in childhood, smoking etc. Some may be obvious, others may be very difficult to reveal. Other medical conditions are probably due entirely to environmental factors e.g. drug poisoning.

Where does GTS fall on this spectrum? From studies, including Professor Robertson's (which were supported by the TSA), we know that GTS does run in families - often a severely affected child has relatives with very mild forms of the disease, so mild that they might not even have noticed! In addition to family histories we also know that identical twins (who have identical genes) are more likely to share GTS than non-identical twins although it is not 100% either way - indicating that in GTS both genes and the environment have an important part to play.

The next step is to determine what pattern of inheritance causes GTS. Genes can be dominant or recessive, meaning strong or weak. We all have two copies of each gene, one from each parent. For a dominant trait or disease one copy of the disease gene from either parent can cause the disease (e.g. Huntington's disease). For a

recessive condition both copies would be required to transmit the disease (e.g. cystic fibrosis).

In general, a disease like GTS that often runs through the generations on one side of a family must be dominant.

This means that the child of an affected parent has a 50% chance of inheriting the gene. There are more complexities though - in the case of GTS some people may have the gene without having the disease, probably about 50% in fact. This is called reduced penetrance. Therefore the child of an affected person has about a 25% chance of having GTS... BUT there is currently no way of predicting the severity- it could be a 25% chance of a very mild form.

### **Finding the gene(s) for GTS**

So how do we find the gene, and why has it remained elusive ? The first step is actually to be able to diagnose who has GTS and who does not. This is surprisingly difficult because of the associated behaviours like hyperactivity and obsessiveness - some clinical definitions can include more people than others.

Three main methods of probing the genes have been used:

- 1) Find families with GTS, diagnose the cases and compare their DNA with non-affected family members using linkage analysis. The DNA is examined using enzymes called restriction endonucleases. The enzymes in your "biological" washing powder are supposed to cut up greasy stains. The restriction endonucleases cut up the genetic material into smaller segments of DNA. They make breaks in the DNA at certain points and these points can be different in two people if they have different versions of a particular gene. The cut-up DNA is run through an electrified gel, called a "Southern blot", to separate pieces of different length, and when these pieces appear at different points on the gel it can indicate a genetic difference.
- 2) The second method is for researchers to examine specific genes that may be expected to be involved- candidate genes. As treatments for TS like haloperidol and sulpiride affect the neurotransmitter dopamine, several related candidate genes have been examined, to look for variations and abnormalities. The results are controversial. One group in the USA believes that certain dopamine-related gene types are associated with GTS and a variety of other neuropsychiatric conditions that other groups, including Professor Robertson's, think may not be linked to GTS.

In general, these first two methods have so far succeeded only in excluding the vast majority of the genetic material.

- 3) Sib-Pair analysis. Affected siblings from different families are tested in order to look for genes that are shared by both siblings. This has the advantage of not requiring prior assumptions about how GTS is inherited. A recent international collaboration

has produced a result using this method in 76 families - showing that two regions on chromosomes numbers 4 and 8 may be involved. The significance of this will need to be investigated further.

### **Complications**

The notion that a single gene is responsible for GTS is probably too simplistic - indeed if this basic model of a single dominant gene with reduced penetrance is wrong then it is not surprising that the gene probes have not produced a definitive answer. The problems of defining which family members have GTS has been mentioned above. It may also be that more complicated mechanisms could explain the distribution of the condition in families. Some other theories that have been put forward are that more than one gene may be involved (polygenic), that there may be different genetic varieties of GTS (phenocopies), that some cases may be inherited from both parents (bilineal), that the effects of inheriting the genes from the father may be different from the mother (imprinting). Finally there is growing evidence of the importance of environmental factors in GTS, in particular the importance of certain kinds of childhood infections, in some cases.

### **The future: Why do we want to find the genes?**

Knowledge about the genes involved can lead to advances in understanding and treatment of a disease. Genes contain the sequence for proteins, which are the building block of our bodies and help to regulate the operation of every organ including our brains.

### **What about the two questions I posed at the beginning?**

If researchers can identify faulty genes in GTS then they will be able to track down the faulty proteins. This could teach us more about what causes GTS, hopefully leading to better treatments or preventative strategies. It may also allow ante-natal testing for GTS, but even if the disease could be predicted it may not be straightforward to predict the severity. The use of that kind of information would of course be a matter for individual families.