

WHY WE SEEK VERY UNUSUAL FAMILIES

We know that TS is genetic. What is the current state of the knowledge?

There is nearly two decades of work, much of it supported in one way or another by the TSA, that clearly shows genes are involved in TS and related conditions. Despite this, no one has yet been able to prove that they have found a specific gene that is responsible for these disorders, even in a small number of individuals.

Though no specific genes have been confirmed, there are some very promising leads. Several regions of the genome have been identified that show evidence of containing disease-related genes, and the Genetics Consortium and other labs are actively involved in trying to narrow these regions and test individual candidate genes to see if they are contributing to TS.

Why has it been so difficult to find a gene involved in TS?

First, let me clarify that when we say we are looking for a specific gene, what we are really looking for is a version of a specific gene (called a variant or allele) that is related to the condition. All of us basically share the same genomic material and set of genes, but with slight differences in their composition. Most of the times these minor variations do not cause problems and in fact help make us individuals. In this case, the search is for the slight variation in a gene or genes that contribute to a person having TS.

What has become increasingly clear is that there is not one single Tourette Syndrome gene in the genome that is waiting to be found. One of the most important things that has come out of studies of TS genetics has been the recognition that multiple genes as well as environmental factors are likely to be involved in one way or another in increasing the risk of having these symptoms. It may be that a number of gene variants that are relatively common in the population have come to

cause a "common" version of the disorder. In isolation, any one of a number of alleles may not be obviously harmful but in combination these could conspire to increase susceptibility to developing TS. The fact that any single one of these alleles or variants might likely contribute only a small amount to the overall risk makes them hard to identify.

In order to overcome this difficulty, studies need to have large numbers of subjects and use methods that are able to identify situations in which multiple genes are working at once. In fact, much of the effort of the TSA Genetics Consortium over the last decade has been aimed at addressing this issue, and as I have said, considerable progress has been made during that time.

What approach is your lab taking?

We are taking a slightly different tact. Instead of trying to study large numbers of people with TS at once, we are focusing on finding and studying small numbers of rare families or individuals who may have TS for unusual reasons and not have the "common form" of the disorder. The theory behind this strategy is that we may be able to develop clues from these unusual situations about the biological bases of TS, and this will help lead researchers to develop better hypothesis about what brain regions and genetic pathways may be contributing to the development of more common forms of the disorder.

This is an approach that has worked well in other branches of medicine to untangle complex disorders in which many genes and environmental influences interact. For example, some of the first genes identified as causing hypertension and Alzheimer's disease were identified in this way, focusing on rare families, and their discovery shed light on the physiology of these illnesses. These findings are now having a major impact on diagnosis

and treatment of these disorders in the entire population, even though the starting point was with very unusual individuals.

There are two principal ways in which our lab is trying to identify these unusual cases: the first is to find families or individuals who have chromosomal abnormalities, particularly chromosomal translocations or inversions. These are problems with the organization of a person's genetic material that can often be identified by simply looking in a microscope. While such individuals are not commonly found, when they are, they allow us to look at the areas of their genome that are different from typical individuals to see if there is a specific gene or small number of genes that might be causing the problem.

If someone has a chromosome translocation and TS is this the cause of their symptoms?

Not necessarily, about 1 in 500 people carry such abnormalities and most are likely to have no consequence. However, a rare individual may present to us a chromosomal translocation that is the cause of his or her symptoms. Until recently, the process of going from looking in a microscope to finding a related gene (at the molecular level) was painstaking and exceedingly time consuming. However, with the advent of the Human Genome Project it is now possible for our laboratory and others to very quickly go from identifying a possible lead in the form of a chromosomal rearrangement to knowing exactly what molecules are involved.

You mentioned that there were two ways that you were approaching the problem of complex genetics. What is the second?

Our second approach is based on the same basic idea of leveraging unusual families. However, instead of chromosomal abnormalities, we are searching for families in which second or third or fourth



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Ask The Expert (continued)

cousins have married and have children affected with the disorder. These are called "consanguineous pedigrees." Such families, which are quite common in some regions of the world, provide the opportunity to look within a "closed" genetic system. As a result they are remarkably useful in tracking down segments of DNA that might be involved in a genetic illness. We are actively seeking such families to try and capitalize on their unique genetic attributes. In this case, even a single child from one such family has the potential to help narrow in on a chromosomal region contributing to TS, CT (chromosomal translocation) and OCD.

Since TS runs in families, what are the chances if I have TS that my child will have it as well?

Multiple studies have looked at the risk for first degree relatives of a person with TS. Most agree that there is about a 10 percent chance of the relative being affected with TS and about a 15 percent chance of the person having tics. Studies in Japan have shown a much lower level of risk on the order of 2 percent for full blown TS. At this point, there has not been enough research to say for certain whether there is in fact less of a risk based on ethnicity. Additional studies will need to be completed.

Is there a genetic test available to see whether my child will develop TS? Is it likely that one will exist sometime in the near future?

There is no genetic test currently available to determine if someone carries a risk for having TS. Until a specific gene is identified, this will not be possible. I remain very optimistic that one of my genetic colleagues will find a specific gene relevant for TS in the relatively near future. Once this happens, whether it will make for a commonly available test for TS will depend upon the nature of the gene that is discovered, in particular it will depend on how common the particular gene variant is in people with TS and how much it increases the risks of having the disorder.

How would someone know if they had a chromosomal abnormality?

The most common circumstance is that during pregnancy an amniocentesis is done for some reason unrelated to concerns about TS and an abnormality is found. In most cases, unless there is clearly a loss of genetic material, these are considered to be benign and the person having the test will be informed but no additional action will be taken. In some cases if a child is developmentally delayed or has some other medical condition like seizures, a chromosome study might be done.

Unlike other types of studies, we do not exclude people with other medical or developmental issues. We believe these individuals may be exceedingly helpful in identifying genes of importance.

How do you find subjects to participate in your studies?

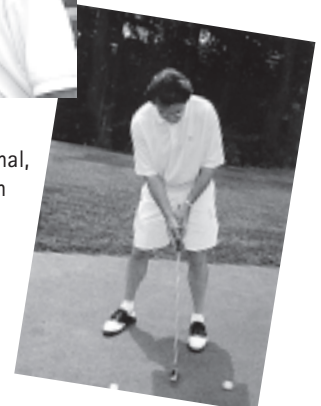
With a lot of help. The search for study participants is very much like looking for the proverbial needle in a haystack. The TSA has been enormously helpful in finding subjects for our lab to study. We face the challenge that the few people who have TS and also have known chromosomal abnormalities or come from consanguineous families, often have no way of knowing that their situation could be extremely valuable from a genetics standpoint. We have been exceedingly fortunate to have Sue Levi-Pearl and David Pauls, Ph.D., head of the Genetics Consortium, keeping an eye out for promising cases and families and making a match with our laboratory when they come to their attention.

GOLF OUTING SCORES AN EAGLE FOR TSA

The 2004 TSA Rosenthal/Wein Golf Outing, held at the magnificent Glen Arbor Golf Club in Bedford Hills, New York, was a real winner. It raised a record \$300,000 for TSA programs.



Pictured above (from l.) are event co-chairs Michael Rosenthal, Tom Rosenthal and Evan Wein (l.) Evan Wein congratulates David Simon, winner of the Shoot-Out (r.) Keep your eye on the ball (top) On the green



THE CFC, THE UNITED WAY AND TSA

If your company participates in the United Way, the Combined Federal Campaign (CFC) or other payroll deduction plan, then Fall is an important season in which to show your support for the Tourette Syndrome Association. These campaigns can raise a great deal of money for TSA if you indicate the Association as a choice on the form provided by your company. If we're not listed, write in "TSA," speak to your Human Resources Department about including us as an option, or call TSA's Development Office for information.

