The Genetics of Tourette Syndrome

Who it Affects and How it Occurs in Families

There are more than 4,000 inherited disorders known to geneticists, and among them is Tourette Syndrome (TS). As you read this booklet, please bear in mind that while it contains the most up-to-date information that we have about the inheritance of TS, it by no means represents the final answer.

Tourette Syndrome (TS) occurs throughout the world and affects people of all ethnic groups. Typically TS begins in childhood, is lifelong but is not a life-threatening condition. In the vast majority of cases, symptoms are mild to moderate, and often decrease by early adulthood.

Researchers have made major strides in understanding how TS occurs in families. Work now being carried out by NIH and TSA-funded genetic researchers holds real promise for providing us with a more complete picture of the mode of inheritance and causes of TS. Moreover, when the human genome is sequenced completely, that information will ultimately reveal the location and function of all of the genes that determine inherited human characteristics and disorders. When that happens, scientists will know much more precisely about the causes of these conditions and how to limit their effects.

What is Tourette Syndrome?

Tourette Syndrome is a disorder of the body's motor and speech systems that produces involuntary motor movements and vocalizations known as tics. Although the symptoms of TS can emerge at anytime (usually between the ages of 2 and 18 years), the typical age at onset is between 6 and 7 years. While the causes are still unknown, one theory is that TS is a disorder of the "boundary" that normally separates inner thoughts and functions from outward behavior.

TS typically persists throughout life, and its severity varies, ranging from mild symptoms that do not disrupt growth or development to very severe symptoms that can be quite impairing and cause considerable difficulty for some individuals. Currently, the best estimate of the prevalence among children and adolescents of this more impairing form is 1 per 1,500 individuals. Recent studies have suggested that the prevalence of the milder forms of TS may be much higher than previously thought.

Studies have shown that TS does not progressively worsen throughout life, but instead peaks during late childhood to late adolescence. In the vast majority of cases, symptoms begin to diminish by early adulthood.

There are no medical tests for diagnosing TS. A diagnosis is made by clinical observation based on medically agreed upon criteria. For a diagnosis, both motor and vocal tics must be present and persist for a year or more.

TS and Inheritance

In the overwhelming majority of cases TS is inherited. Thus, the vulnerability to having TS symptoms is passed down from parent to child. This inherited susceptibility to TS does *not* necessarily mean that the offspring will invariably develop symptoms. In other words, inheriting the genetic vulnerability to TS may not result in any symptoms at all. On the other hand, it is likely that a range of symptoms will be expressed to some degree.

Gender appears to play a part in the way the gene that causes susceptibility to TS expresses itself. Thus, tics are 2-3 times as likely to occur among the sons of a parent with TS. However, daughters are 2-3 times more likely than the sons to have obsessive-compulsive traits without tics. Similarly, other male relatives of someone with TS are more likely to have tics, while this same person's female relatives are more likely to have obsessive-compulsive behaviors.

Because a person may carry the gene for susceptibility to TS but not show any symptoms, other factors have been suggested as influencing whether TS symptoms appear. Such factors might include events during pregnancy or around the time of delivery. The fact that TS and its related conditions do not occur in some persons who are carrying the genetic susceptibility does not mean that the children of those asymptomatic individuals are necessarily at lower risk for developing TS and associated conditions. In this situation, the susceptibility genes can still be passed to some of their

children, and their offspring are at increased risk for developing TS and associated conditions. In order to determine what the risk to children is in these situations, very careful family histories need to be taken by a knowledgeable professional to determine the probability that the unaffected individual is truly carrying the susceptibility genes. Only when that is done, is it possible to provide estimates of risk to their children.

Conditions Associated with TS

Researchers believe that some **transient and chronic tic disorders** are conditions caused by the same genes that are responsible for causing TS, but these conditions are milder in expression. Emerging in childhood, a chronic tic can be either vocal or motor and persists for a year or more. A transient tic begins in childhood or adolescence, but typically goes away within a year. The frequency of chronic tic disorders among relatives of persons with TS provides strong evidence that both are manifestations of the same genetic underpinnings. Results from current studies suggest that most forms of chronic tic disorders and some forms of transient tic disorders are caused by the same genetic factors that are responsible for TS. Chronic tics and transient tics are believed to be milder forms of TS. However, it is possible that individuals with either condition can experience fairly disabling symptoms.

The chance or "risk" of chronic tic disorder occurring in a relative of someone who has either TS or chronic tics ranges from 10 to 17%. This is a far higher figure than the 2-3% frequency of chronic tics among non-TS families in the general population. Again, these percentages indicate that there is a common genetic basis for both TS and chronic tic disorder.

Perhaps the strongest evidence of a common genetic basis for TS and chronic tic disorder comes from studies of identical and fraternal twins. (Identical twins carry the same genetic endowment while fraternal twins are genetically no different from siblings born at different times.) When one identical twin has TS or chronic tic disorder, 77% of his/her siblings will have either TS or chronic motor tics. By comparison, only 23% of the fraternal twins of persons with TS or chronic tic disorder have either TS or chronic tics.

Obsessive-Compulsive Behaviors (OCB)

Symptoms of another disorder that appear to be genetically related to TS are obsessive-compulsive traits. These may be involuntary repetitive, intrusive and unwanted thoughts or ritual-like activities that may be mild or can cause distress and interfere with daily life. These behaviors may involve a compulsive need for symmetry such as aligning shoes in an exact manner or "evening up" rituals. Strong evidence of a common genetic basis for TS and OCB is the fact that at least 37% of persons with TS and 10% of their relatives have such traits, with only about 2-3% of the general population exhibiting OCB. Moreover, the full blown obsessive-compulsive disorder (OCD) occurs three times more often among the female relatives of persons with either TS or chronic tics than among their male relatives.

Attention-Deficit Hyperactivity Disorder

Another condition that occurs frequently among people with TS, chronic tics and OCB is attention-deficit hyperactivity disorder, or ADHD. It has been noted that attention deficits and hyperactivity occur in some children who later go on to develop tic disorders. However, unlike the confirmed genetic connection between TS and OCB, it is less certain that either ADHD or milder forms of hyperactivity/attention problems are genetically related to TS. Thus, some studies have found no evidence of a genetic relationship between TS and attention-deficit disorder, and others have found no greater frequency of ADHD among the relatives of persons with TS than among the relatives of persons without TS.

How TS is Inherited

In many families where there is a person with TS, the pattern of inheritance of TS, chronic tics and OCB is consistent with autosomal dominant transmission. In this case, either the mother or the father is affected and transmits the disorder to one or more of their children. The simplest genetic model to explain such a mode of transmission is the one that posits a single gene that has a major effect on the manifestation of TS and associated disorders. The assumption is that the affected parent passes on this gene to one or more of his/her children, and those children then have an increased risk for developing TS. It is important to remember that the gene will not necessarily be passed on to all of the children. In fact, in most instances, the gene will be passed to only 50% of the affected parent's children.

When transmission patterns were examined, results from the earliest TS family studies found that those patterns were consistent with autosomal dominant inheritance. However, more recent studies suggest that the underlying genetic mechanisms are more complex. In fact, it is likely that more than one gene increases

susceptibility for TS and related conditions. It is possible that one gene of major effect could cause TS in some families, and other genes of major effect could cause TS in different families. Yet another possibility is that two or more genes acting together are necessary for the expression of TS and related conditions in other families.

A decade of research indicates that the genetic mechanisms underlying TS are likely to be more complicated than was originally thought. This does not mean that TS is any "less genetic," it just means that it is highly likely that there will be several genes that may increase the risk for having TS and related conditions. In order to understand fully the underlying genetics of TS, scientists must find all of these genes to determine if and how they interact to cause increased risk in those who have inherited them.

Conclusions

TS, chronic tics and OCB affect millions of persons throughout the world. None of these conditions is life threatening, and in the vast majority of cases, they are mild and often diminish considerably by adulthood. Major strides have been made in revealing the patterns in which susceptibility to these disorders is inherited. Additionally, medications and other treatments have proven effective in reducing many of the effects of having TS.

Identification of the one or more genes responsible for causing TS and its associated disorders is likely to occur in the near future. Once we have those genes in hand, further research will clarify just how they cause these disorders, and knowing this will lead to improved treatments and an eventual cure.

COMMON QUESTIONS ABOUT TS AND GENETICS*

Q. ***What is the likelihood of a child's having TS or one of its related disorders if the child's mother/father has TS?***

A. If a father or mother have TS and come from a family in which other members have TS or one of its related conditions, there is a significantly increased risk that their child will have TS or one of its related conditions. The risk is different for boys and girls. Specifically, the chance that a son will develop TS is approximately 10-15%. Furthermore, the chance that he will manifest chronic tics is about 15-20%, and the chance that he will have OCB without tics is approximately 5-7%. Thus, the overall risk that a son will express something in the TS spectrum is approximately 40-45%. The risks for a daughter are approximately 3-5% for TS, 10-15% for chronic tics and 12-15% for OCB without tics. The overall risk for a daughter is approximately 30-35%. Given current knowledge, it is likely that an affected child will have both tics and OCB at some point in his/her life.

Q. ***What is the likelihood of a child having TS when the parents already have a child with TS or a related disorder?***

A. If the second child is not an identical twin, the risks are the same as those described above. However, if the child is an identical twin, there is a 75%-90% chance that the second identical twin will also have one of these disorders.

Q. ***If neither parent of a child appears to have TS, OCB or chronic tics, what is the chance that this couple will have a child with TS?***

A. In this case, determining the risk to the child requires that a careful family history be taken to determine if and how many relatives have TS and/or related conditions. If there are affected relatives, the risks for TS, chronic tics and/or OCB will decrease depending on how closely related the affected relative is to the expected child. In general, the risk to second degree relatives (grandchildren, nieces and nephews) will be about half as high as those described above for children of TS affected parents. The risk to third degree relatives (first cousins, great grandchildren, great nieces and nephews) will be reduced even more. These risks will vary depending on the sex of the affected relatives and the sex of the anticipated child. If there is no family history of TS, tics or OCB, the risk to the child will be no greater than that of the general population.

* *The risk factors cited here are derived from very careful and complicated analyses of family histories taken from hundreds of families not unlike those of the reader. This way of determining probabilities is called "empirical risk figures." Because there is no TS diagnostic test, this is the method that must be used by knowedgeable genetic professionals.*

Q. ***Can the severity of TS in an offspring be predicted based on the severity of the TS affected parent?***

A. Unfortunately, it is not yet possible to predict the severity of TS or its associated disorders either prenatally or in young children. However, in the vast majority of cases, TS, chronic tics, and OCB are mild, and most long-term studies of persons with these disorders suggest that symptoms decrease with age, and are often essentially unnoticeable by adulthood.

Q. ***Putting genetics aside, are there risk factors in the shared family environment that can be managed so as to reduce the likelihood that symptoms will develop?***

A. Because studies have not identified any clear risk factors for TS or its related conditions in the shared familial environment, there are no measures that can be taken to prevent the occurrence of symptoms. However, it is important to remember that TS symptoms are *involuntary,* and children and adults do not "choose" to manifest these symptoms. Patience, understanding, and a supporting family are important ways to ease a person's discomfort and concerns.

Q. ***Can TS be diagnosed with a genetic test?***

A. Until the chromosome that carries a TS gene is located, a diagnostic test cannot be developed. However, the current accelerated pace of TS genetics research holds great promise for the development of a diagnostic test.

Q. ***The adult child of a parent with TS appears to be unaffected. What is the risk to that adult child's offspring?***

A. Once again, it is necessary to obtain a detailed family history to provide more accurate estimates of risk. In this case, what would have to be determined first is the probability that an adult offspring inherited the genes from the affected parent. This probability is dependent upon factors such as the sex and age of the adult offspring and the sex of the affected parent. Once that probability has been estimated, it is included in the estimate of risk to children of this unaffected adult. Individuals wanting this type of information should seek the guidance of a qualified genetic counselor who is knowledgeable about the familial risks for TS and related conditions.

Q. ***What are the chances that the child of an <u>unaffected</u> sibling of someone with TS will have TS?***

A. The risk factors are the same as described above.

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GLOSSARY

Autosomal dominant: Refers to a disorder that is caused by a gene on one of the 44 non-sex-related human chromosomes.

Bilineal inheritance: A type of inheritance in which a genetically determined disorder or other trait is caused by genes acquired from both parents.

Family study: When a genetically caused disorder is investigated in members of a family to determine how the disorder is inherited.

Gene: A unit of hereditary material that determines a particular trait or characteristics such as a medical condition or hair or eye color. All genes consist of the chemical substances known as deoxyribonucleic acids, or DNAs. In any particular gene, these DNAs occur in a specific, sequential order that determines the effects of the gene.

Gene of major effect: The gene that chiefly determines a trait or characteristic, such as hair color or an inherited disorder.

Genome: The complete array of all human genes which is found in nearly all body cells. The human genome consists of more than 100,000 genes.

Penetrance: The percentage of people that actually show or express the disorder caused by a particular gene they are carrying.

Sib-pair study: A method whereby the genetic material of two or more affected siblings is compared with that of their parents in order to identify the location of one or more genes that are causing a disorder.

Twin study: A study in which the occurrence of a disorder or trait is studied in identical and/or fraternal twins in order to determine whether the trait is genetically determined.

Should readers have additional questions, they should consult directly with a professional knowledgeable in TS genetics. The information contained herein is provided solely to clarify current thinking about the genetics of TS. Indeed, the genetic research presently being carried out may well provide new data that could change our perceptions of the inheritance of this disorder. Should that occur, TSA will endeavor to provide that new information to its members in a timely manner.

ADDITIONAL TSA RESOURCES

Videos & Vignettes

AV-9 After the Diagnosis . . . The Next Steps

Produced expressly for individuals and families who have received a new diagnosis of TS. This video was developed to help clarify what TS is, to offer encouragement, and to dispel misperceptions about having TS. Features several families in excerpts from the Family Life With TS A Six-Part Series who recount their own experiences as well as comments from medical experts. Narrated by Academy Award Winner Richard Dreyfuss. 35 min.

AV-10 The Complexities of TS Treatment: A Physicians' Roundtable

Three internationally recognized TS experts, Drs. Cathy Budman, Joseph Jankovic and John Walkup provide colleagues with valuable information about the complexities of treating and advising families with TS. Emphasis is on different clinical approaches to patients with a broad range of symptom severity. Co-morbid and associated conditions are covered. 15 min.

AV-10a Clinical Counseling: Towards an Understanding of Tourette Syndrome

Targeted to counselors, social workers, educators, psychologists and families, this video features expert physicians, allied professionals and several families summarizing key issues that can arise when counseling families with TS. Includes valuable insights from the vantage point of those who have TS and those who seek to help them. 15 min.

AV-11 Family Life With Tourette Syndrome . . . Personal Stories . . . A Six-Part Series

Adults, teenagers, children, and their families . . . all affected by Tourette Syndrome describe lives filled with triumphs and setbacks . . . struggle and growth. Informative and inspirational, these stories present universal issues and resonate with a sense of hope, possibility, and love. 58 min.

An up-to-date Catalog of Publications and Videos can be obtained by contacting:

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