

The Genetics of Tourette Syndrome: How it Occurs in Families & Whom Might be Affected

The Tourette Syndrome Association appreciates greatly the professional guidance and expertise provided by David Pauls, Ph.D. and Jeremiah Scharf, M.D., Ph.D. in the development and revision of this brochure.

There are more than 3,000 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 everywhere 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, now that the human genome has been 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 neurobehavioral disorder that produces involuntary motor movements and vocalizations known as tics. Although the symptoms of TS can emerge at any time (usually between the ages of 2-18), the typical age at onset is between 6 and 9 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 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 1,000 individuals. Recent studies have suggested that the prevalence of the milder forms of TS may be much higher than previously thought, approaching 0.6% of the general population.

Studies have shown that TS does not progressively worsen throughout life, but usually 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 taking a medical history and clinical observation based on medically agreed upon criteria. For a diagnosis,

The Genetics of Tourette Syndrome

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 a 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 genes that cause susceptibility to TS express themselves. Thus, tics are 2-3 times as likely to occur among the sons of a parent with TS compared to daughters. 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 susceptibility genes for 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 a 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 compared to the risk in the general population. 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 TS 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 increased frequency of chronic tic disorders among relatives of persons with TS provides strong evidence that both are manifestations of the same genetic underpinnings. 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 of these conditions still 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 1-2% frequency of chronic tics among non-TS families in the general population. These percent-

The Genetics of Tourette Syndrome

ages 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, the chance of the other twin having either TS or chronic motor tics is 77%. 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 appears to be genetically related to TS include obsessive-compulsive behaviors. 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. Evidence of a common genetic basis for TS and OCB is the fact that at least 35% of persons with TS and 10% of their relatives have such traits, with only about 2-3% of the general population exhibiting OCB. Also, the full-blown Obsessive-Compulsive Disorder (OCD) occurs three times more often among the female relatives of persons with either TS or chronic motor tics than among their male relatives.

Attention-Deficit Hyperactivity Disorder (ADHD)

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 evidence of a genetic relationship between TS and ADHD, while others have found no greater frequency of ADHD among the relatives of persons with TS than among the relatives of persons without TS. Current thinking is that some forms of ADHD, but not all, may indeed share some of the same susceptibility genes as TS. A definitive answer to this question cannot be made until these genes are specifically identified.

How TS is Inherited

Early family studies of TS inheritance suggested that TS, chronic motor tics and OCB might be transmitted through families in an autosomal dominant pattern. That occurs when either the mother or the father was affected with TS or chronic tics or OCB then that parent transmitted one of these disorders to one or more of their children. The simplest genetic model to explain such a mode of transmission is one that posits a *single TS susceptibility gene* that has a major effect on the manifestation of TS and associated conditions. 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, even in this scenario, the “TS gene” will not necessarily be passed on to all children.

The Genetics of Tourette Syndrome

However, more recent studies of TS inheritance suggest that the underlying genetic mechanisms are much more complex than previously thought, and that there is not just one “TS gene.” In fact, for most individuals, it is likely that many genes, in concert with non-genetic, environmental factors, all join together to increase a person’s susceptibility for expressing TS and related conditions. Furthermore, in many cases, these susceptibility genes may be inherited from both sides of the family. 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 first must find all of these genes to determine whether and how they interact to cause increased risk in those who have inherited them.

Conclusion

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 lessen 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 symptoms of TS.

Identification of one or more of the 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 should lead to improved treatments and an eventual cure.

COMMON QUESTIONS ABOUT TS AND GENETICS

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 knowledgeable genetic professionals.

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?

If a father or mother has TS and comes from a family in which other members have TS or one of its related conditions, there is a significantly increased risk that his or her child will have either 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 5-10%. 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 10-20% for OCB without tics. The overall risk for a daughter is approximately 25-35%.

These risk factors increase further when both parents have TS and/or OCD. In this situation, the offspring risk for TS may be as high as 25-50%, with the risk for chronic motor tics an additional 15%. The overall risk of a TS/OC spectrum condition for a child of two parents with TS and/or OCD

may be 70-90%. It should be noted, however, that these recurrence rates in bilineal families are from a very small study in a single clinical sample, and thus may be overestimates of true risk. It is also important to note that, in general, most individuals who inherit a genetic susceptibility for TS have very mild conditions for which they do not seek medical attention.

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

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

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

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 distantly 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 great 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 antici-

The Genetics of Tourette Syndrome

pated child. If there is no family history of TS, tics or OCB, the risk to the child will be no greater than that of anyone else in the general population.

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

Unfortunately, at this time it is not 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?

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 supportive family are important ways to ease a person’s discomfort and concerns.

Q. Are there any genes that have been proven definitively to cause TS?

While there are some encouraging leads, at this writing, no genes have been consistently proven to increase the risk of developing

TS. The TSA International Consortium for Genetics, an NIH- and TSA-funded collaboration of TS geneticists worldwide, have identified a region of the human genome on chromosome 2 that appears to harbor a TS susceptibility gene, but the specific gene has yet to be identified. Another NIH and TSA-funded investigator has identified a few TS individuals with rare mutations in a gene called *SLITRK1*. Currently these changes seem to be present in only 1 in 1000 cases of TS (0.1%) and analysis of this gene has not yet been demonstrated to be useful outside of the research setting. Nonetheless, ongoing research projects from these and other groups offer great promise in identifying more definitive TS susceptibility genes in the coming years.

Q. Can TS be diagnosed with a genetic test?

Until specific TS susceptibility genes are verified, a diagnostic test cannot be developed. However, the current accelerated pace of TS genetics research holds 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?

Once again, it is necessary to obtain a detailed family history to obtain 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 Genetics of Tourette Syndrome

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 unaffected sibling of someone with TS will have TS?

The risk factors are the same as described above.

Q. Can other factors cause TS?

Although genetic factors clearly contribute to the development of TS, genetics are not the entire story. Non-genetic factors are also important, both as causes and modifiers of TS. Developmental and environmental factors are likely responsible for the wide range of symptoms observed among different individuals, including the course, severity, and type of symptoms, as well as the development of associated disorders such as OCD and ADHD. Studies of non-genetic factors have primarily focused on stressful and other events during

the prenatal, perinatal, or early life periods, particularly those which could cause damage to the developing brain. Although there are little data as yet in this area and much of these data are retrospective, studies have indicated that children with tics or TS have somewhat higher rates of maternal/obstetric complications such as traumatic birth, forceps delivery, or hypoxia when compared with the general population. In particular, prenatal exposure to nicotine and/or alcohol appears to increase both the severity of tics and the risk of developing OCD. The results of two studies examining identical twins, in which one twin had TS and the other did not, showed decreased birth weight in the twin with TS compared to the unaffected twin. In the general population, decreased birth weight is often associated with a compromised fetal environment. Although not yet conclusive, these studies do point to the potential importance of environmental factors that affect early brain development in the appearance and expression of TS symptoms.

GLOSSARY

Autosomal dominant: A pattern of genetic inheritance in which a disease is caused by an alteration of one copy of a gene on one of the 22 non-sex related human chromosomes. With diseases and disorders caused by this inheritance pattern, there is a 50/50 chance of the condition being passed on from one parent to a child. Note: TS is no longer thought to be inherited by this pattern, except possibly in very rare instances.

Bilineal inheritance: Inheritance of genetic risk factors 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 a chemical substance known as deoxyribonucleic acid, or DNA. In any particular gene, the DNA occurs in a specific, sequential order that determines the effects of the gene.

Gene of major effect: A 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 cells in the body. The human genome consists of 30,000-40,000 genes.

Twin study: A study in which the occurrence of a disorder or trait is studied in identical and 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.

MEDICAL ADVISORY BOARD

John T. Walkup, M.D., Chairman

Johns Hopkins Hospital, Division of Child & Adolescent Psychiatry
(*Child & Adolescent Psychiatry*)

Cheston M. Berlin, Jr., M.D.
The Milton S. Hershey Medical Center
(*Pediatrics*)

James T. McCracken, M.D.
UCLA Neuropsychiatric Institute
(*Adult/Adolescent/Child Psychiatry*)

Cathy L. Budman, M.D.
North Shore University
Long Island Jewish Health System
NYU School of Medicine
(*Psychiatry & Neurology*)

Tanya Murphy, M.D., M.S.
University of South Florida
All Children's Hospital
(*Psychiatry*)

Leon S. Dure, M.D.
Children's Hospital
(*Pediatrics & Neurology*)

Paul Sandor, M.D.
University of Toronto
(*Neuropsychiatry*)

Donald L. Gilbert, M.D., M.S.
Cincinnati Children's Hospital Medical Center
(*Pediatric Neurology*)

Lawrence Scahill, M.S.N., Ph.D.
Yale University School of Nursing
Child Study Center
(*Child Psychiatry*)

Jorge L. Juncos, M.D.
Emory University School of Medicine
(*Neurology*)

Douglas W. Woods, Ph.D.
University of Wisconsin-Milwaukee
(*Psychologist*)

Katie Kompoliti, M.D.
Rush University Medical Center
(*Neurology*)

Samuel H. Zinner, M.D.
University of Washington School of Medicine
(*Developmental/Behavioral Pediatrics*)

Carol Mathews, M.D.
University of California – San Francisco
(*Psychiatry*)

Revised 2008

Permission to reprint this publication in any form must be obtained from the national
TOURETTE SYNDROME ASSOCIATION, INC.



Tourette Syndrome Association, Inc.
42-40 Bell Boulevard • Suite 205
Bayside, New York 11361-2820
Tel 718-224-2999 • Fax 718-279-9596
ts@tsa-usa.org • www.tsa-usa.org