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A closer look at the history
and genetics of Tourette syndrome

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SUMMARY

Tourette syndrome (TS) was named after Georges Albert Edouard Brutus Gilles de la Tourette, who made its first formal description at the end of the 19th century. Nevertheless, some evidence indicates the disorder may have been recognized at least two thousand years ago. Tic-like behaviours were recorded by Aretaeus of Cappadocia and several centuries later by Sprenger and Kraemer, followed by other descriptions. The English writer Samuel Johnson, author of the first English Language Dictionary, showed repetitive body twitches, facial grimaces, barks and grunts, among other tics. He was observed in situations such as going in or out at a door using a certain number of steps, from a certain point, which indicated he had also obsessive-compulsive behaviour. There was some evidence of features of TS as well as co-morbid conditions such as hyperactivity, obsessive-compulsive behaviour or rage attacks in other famous artists and world leaders. Some authors have even proposed that the creative, determined, competitive, and persistent nature of certain people may be related to the presence of TS.

Clinicians have observed that some patients are particularly sensitive to the feelings and experiences of others, and more prone to outside stimuli. In this way, empathy could be a common quality in these patients. In 1825, Jean Marc Gaspard Itard made the first known medical description of TS based on two cases, one of which was later followed by Jean-Martin Charcot. In 1885 Gilles de la Tourette put together information from previous fragmented reports and wrote a complete and formal description, thus establishing a novel clinical entity. Behavioural abnormalities such as obsessions, compulsions, inattentiveness and hyperactivity, commonly observed in TS patients, were considered mental tics at the time. Current diagnostic criteria are very similar to Gilles de la Tourette’s description. TS is characterized by the presence of multiple motor and one or more vocal tics. In this disorder, tics are not caused by the direct physiologic effects of a substance or a general medical condition. Tic symptomatology is persistent for over a year, and in this period, tics are not absent for more than three consecutive months.

There is no exact consensus between the DSM-IV and the Tourette Syndrome Classification Study Group on whether the age of onset should be prior to 18 or 21 years of age, how cases of onset after 21 years should be diagnosed, and if marked distress or significant impairment caused by tics is necessary to define the condition as definite TS. However, the text revision of the DSM-IV (TR) no longer specifies that TS symptoms have to cause distress or impair the functioning of the patients. With respect to the age of onset, the ICD-10 Classification of Mental and Behavioural Disorders describes the onset almost always in childhood or adolescence, and in this way it would no longer exclude cases with later onset. Numerous studies confirmed in the 20th century that genetics plays an important role in the etiology of TS. Family studies proved that the disease runs in families. First-degree relatives of TS patients are indeed in greater risk for TS than the general population. Twin and adoption studies demonstrated that genes have an important role in the etiology of TS, and as much as 90% of the vulnerability to this syndrome could be affected by genes. In addition, environmental, epigenetic and even stochastic factors may affect the susceptibility to TS.

At the molecular level, linkage in families and association in unrelated TS subjects have been the main methods used to search for vulnerability genes. Sequencing of almost the entire human genome made it possible to assess the gene expression of thousands of genes on a single chip; recent studies reported a preliminary specific profile in the blood of TS patients. If confirmed, this finding could be useful in the identification of genetic factors related with TS.

Given the multi-factorial nature of TS, a thorough clinical description in large samples should be considered; besides association, linkage and sequencing studies, possible gene-gene and gene-environment interactions would also need to be analysed, as well as epigenetic factors, and gene expression patterns.

Key words: Tourette syndrome, Gilles de la Tourette syndrome, Georges Gilles de la Tourette, genetics of Tourette syndrome, tic disorder.

RESUMEN

El síndrome de Gilles de la Tourette (SdT) se nombró así en honor de Georges Albert Edouard Brutus Gilles de la Tourette, alumno de Charcot, quien realizó la primera descripción formal de esta entidad clínica a finales del siglo XIX. Sin embargo, hay evidencias que indican que probablemente el trastorno se había identificado de alguna manera desde hace por lo menos dos mil años. Areteo de Capadocia registró conductas similares a los tics, también descritas por Sprenger y Kraemer en el siglo XV y más adelante por otros. El escritor inglés Samuel Johnson, autor del primer Diccionario de la Lengua Inglesa, mostraba contorsiones en todo el cuerpo, muecas, ladrídos y gruñidos, entre otros tics. Se le observaba entrando o saliendo por una puerta...
During the 15th century, Sprenger and Kraemer of Cappadocia recorded cases of tic-like behaviours such years ago. In ancient Rome, the Greek physician Aretaeus Nevertheless, there is evidence that indicates the disorder outstand American author Samuel Johnson, author of the his mouth to avoid the production of noises. In the century, whose phonic tics forced him to stuff objects in the disease, which are motor and phonic tics. In addition, described a priest who also showed the main features of the disease, which are motor and phonic tics. In addition, other tics, which were described in detail by James Boswell. Johnson held his head towards his right shoulder and then shook it, moving his body backwards and forwards repetitively, in the same direction with his hand. Phonic tics included sounds similar to ruminating, whistling, clucking like a hen, protruding his tongue against the upper gums in front, as if pronouncing: «too, too, too», etc. He clucking like a hen, protruding his tongue against the upper gums in front, as if pronouncing: «too, too, too», etc. He clucking like a hen, protruding his tongue against the upper gums in front, as if pronouncing: «too, too, too», etc. He clucking like a hen, protruding his tongue against the upper gums in front, as if pronouncing: «too, too, too», etc. He clucking like a hen, protruding his tongue against the upper gums in front, as if pronouncing: «too, too, too», etc. He clucking like a hen, protruding his tongue against the upper gums in front, as if pronouncing: «too, too, too», etc. He clucking like a hen, protruding his tongue against the upper gums in front, as if pronouncing: «too, too, too», etc.

In 1825, Jean Marc Gaspard Itard realizó la primera descripción médica conocida del SGT, basándose en dos casos, uno de los cuales fue estudiado más adelante por Charcot. En 1885, Gilles de la Tourette reunió fragmentos de información de reportes previos y redactó una descripción formal y completa del trastorno, con lo que estableció una nueva entidad clínica. Las anormalidades del tipo de obsesiones, compulsiones, inatención e hiperactividad se consideraban tics mentales en esa época. Los criterios diagnósticos actuales del SGT son muy similares a los publicados por Gilles de la Tourette. El SGT se caracteriza sobre todo por la presencia de dos o más tics motores y uno o más tics fónicos. En este trastorno, los tics no son causados por el efecto fisiológico directo de una droga o por una afección médica general. La sintomatología de los tics persiste por más de un año y en este periodo los tics no se ausentan por más de tres meses consecutivos.

INTRODUCTION

La Maladie des tics, later called Gilles de la Tourette syndrome, and sometimes identified simply as Tourette syndrome (TS), was named after the author of its first formal description at the end of the 19th century. Nevertheless, there is evidence that indicates the disorder may have already been recognized at least two thousand years ago. In ancient Rome, the Greek physician Aretaeus of Cappadocia recorded cases of tic-like behaviours such as barking, twitching, and cursing, according to Oliver Sacks. During the 15th century, Sprenger and Kraemer described a priest who also showed the main features of the disease, which are motor and phonic tics. In addition, TS-like characteristics were present in the Prince de Condé, an important member of Louis XIV court in the 17th century, whose phonic tics forced him to stuff objects in his mouth to avoid the production of noises. In the following century, a well-known case refers to the outstanding English writer Samuel Johnson, author of the first English Language Dictionary and the most quoted English writer after Shakespeare. He showed repetitive body twitches, facial grimaces, barks and grunts, among other tics, which were described in detail by James Boswell. Johnson held his head towards his right shoulder and then shook it, moving his body backwards and forwards repetitively, in the same direction with his hand. Phonic tics included sounds similar to ruminating, whistling, clucking like a hen, protruding his tongue against the upper gums in front, as if pronouncing: «too, too, too», etc. He was observed in situations such as going in or out at a door using a certain number of steps, from a certain point, which indicated he also had an obsessive-compulsive behaviour.

Still controversial is the case of Wolfgang A. Mozart who, according to records such as letters, may have had tics, inclination to nonsense words, sudden impulses, and hyperactivity. There was some evidence of features of TS as well as co-morbid conditions such as hyperactivity, obsessive-compulsive behaviour or rage attacks in other famous artists and world leaders including Peter the Great...
and, more recently, the French writer André Malraux. Some authors have even proposed that the creative, determined, competitive, and persistent nature of certain people may be related to the presence of TS. The traits of TS may somehow be associated with elaboration, humorous mimicry, uninhibited inventiveness, and artistic creativity. There are reports of patients for whom the disorder was a source of inspiration in languages, arts, and athletics. Furthermore, clinicians have observed that some patients are particularly sensitive to the feelings and experiences of others, and more prone to outside stimuli. In this way empathy could be a common trait in these patients.

Given the conspicuous and fascinating features of Tourette syndrome, there were some non-medical descriptions of the disorder in the literature since the 19th century, as Larner pointed out. Charles Dickens described, for example, a Mr. Pancks in *Little Dorrit*, a character who had motor and phonic tics, as well as obsessive-compulsive behaviour and trichotillomania. In turn, Leo Tolstoy described in *Anna Karenina* the TS features of a character known as Nikolai Levin.

**Clinical descriptions of TS**

In 1825, Jean Marc Gaspard Itard made the first known medical description of TS based on two cases, one of which was later followed by the French neurologist Jean-Martin Charcot. When Charcot began studying tics, the now considered relatively common neuropsychiatric disorder became recognised, but still as a rare condition. At last, the most detailed and accepted description of TS was written by a Charcot’s student, Georges Albert Edouard Brutus Gilles de la Tourette in 1885, based primarily on a patient described by Itard. Gilles de la Tourette put together information from previous fragmented reports and wrote a complete and formal description, thus establishing a novel clinical entity.

Behavioural abnormalities such as obsessions, compulsions, inattentiveness and hyperactivity, commonly observed in TS patients, were considered mental tics at the time.

Two years later, during the Tuesday lessons at the Salpêtrière, Charcot meticulously described an adolescent whose tics included eye blinking, stamping with the foot, coprolalia, and growls; the patient’s maternal grandmother had been insane, which helped hypothesize that he had an inherited disorder. Charcot mentioned the relevance of Gilles de la Tourette’s work and the fact that this medical condition was characterised by physical and psychologica symptoms, which sometimes included obsessions and compulsion. Coprolalia could be present either in boys or in girls, and patients were exposed to aggression, given that other people did not understand their symptoms.

**Current classification of TS**

Current diagnostic criteria are very similar to Gilles de la Tourette’s description, and six out of the nine patients he reported would still fulfill the criteria for TS. The diagnosis of the remaining three would be chronic motor tics, given that in these cases there was no report of phonic tics. TS is characterized by the presence of multiple motor and one or more vocal tics. In this disorder, tics are not caused by the direct physiologic effects of a substance or a general medical condition. Tic symptoms are present many times a day, usually in bouts, nearly every day, or intermittently for over a year, and in this period, tics are not absent for more than three consecutive months. There is no precise consensus between the DSM-IV and the Tourette Syndrome Classification Study Group of whether the age of onset should be prior to 18 or 21 years of age, how cases of onset after 21 years should be diagnosed, and if marked distress or significant impairment caused by tics is necessary to define the condition as definite TS. However, the text revision of the DSM-IV (TR) no longer specifies that TS symptoms have to cause distress or impair the functioning of the patients. The Tourette Syndrome Classification Study Group differentiates definite Tourette syndrome (motor and/or phonic tics are witnessed by a reliable examiner) from Tourette syndrome by history (in this case tics were not witnessed by a reliable examiner, but by a relative or a close friend, whose description is accepted by the examiner). With respect to age of onset, if the current ICD-10 Classification of Mental and Behavioural Disorders describes the onset almost always in childhood or adolescence, it would not necessarily exclude cases with later onset.

The anatomic location, number, frequency, complexity, type, and severity of tics change over time. The onset is observed during the first or second decade of life, and the mean age of onset is six to seven years of age. In some cases, there is a pre-pubertal exacerbation, post-pubertal attenuation, and adult stabilization of the symptoms.

**Genetic transmission of TS**

In a time when Gregor Mendel’s laws of hereditary transmission were still largely unrecognized, Gilles de la Tourette described the familial aggregation of TS, which he considered an inherited disease of childhood onset. Numerous studies confirmed in the 20th century that genetics plays an important role in the etiology of TS. Family studies proved that the disease runs in families. First-degree relatives of TS patients were shown to have a risk for the disorder that ranges from 9.8% to 15%. If any tic disorder was considered, even if not definite TS, first-degree relatives

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had a risk of 15% to 20%. Although a control group of healthy subjects and their relatives was not always included, it seems clear that first-degree relatives of TS patients are indeed in greater risk for TS than the general population.

Investigations in families represent one of the first steps to determine if genes significantly contribute to the vulnerability to a disorder, but more precisely, if the disease is especially clustered in families. They are usually followed by twin studies, which are an adequate approach to determine if familial aggregation of the disease could be due mainly to the effect of genes or shared environment. In this way, it was shown that while 50% to 70% of monozygotic (identical) twin pairs were concordant for the presence of TS, only 8% to 10% of dizygotic (fraternal) twin pairs were concordant. According to these results, as much as 90% of the vulnerability to TS could be affected by genes (heritability of TS). In the same studies, the concordance shown for any tic disorder was of 75% to 90% in monozygotics and 23% in dizygotic twins. These results demonstrated that genes play an important role in the etiology of TS, given that an identical twin of a TS subject has a 5-fold risk to develop the disorder when compared to a fraternal twin. It was also concluded that there must be critical non-genetic factors involved, since being a monozygotic twin of a TS subject does not always determine full concordance for the disorder. This means that environmental, epigenetic, and even stochastic factors may affect the susceptibility to TS; environmental and epigenetic factors could interact with TS-susceptibility genes.

Among the proposed environmental factors that could affect the appearance of TS in some cases are autoimmune processes caused by streptococcal infections, perinatal complications, and sex-specific factors, but these have not been totally confirmed. On the other hand, epigenetic factors such as methylation of the cytosine residue at the DNA can affect the function of genes. Concordances of less than 100% for monozygotic twins have been reported in other psychiatric disorders as well. For this reason, it has been suggested that a new generation of twin studies could help identify and/or confirm environmental factors and genetic or epigenetic differences between monozygotic discordant twins. In fact, monozygotic twins can slightly differ in their genetic information due to de novo mutations and chromosomal anomalies, but they can also differ in their epigenome.

In a third step to investigate the importance of genes in TS, adopted TS subjects and available relatives were analyzed. The objective was to determine if the genetic variants transmitted by the biological relatives and/or the environmental factors, mainly shared with the adoptive relatives, could account for the vulnerability to TS in the patients. By means of the family history method, a complete negative history of tics was found in the adoptive families of 22 TS patients. Unfortunately, only two of the biological families were available for analysis, but in both instances a first or second-degree relative was found to have a tic disorder. In addition, these authors examined the family history of tics in 641 independent TS cases that, in contrast to the first group of patients, were raised by their biological relatives. They found that 35% of them had a first-degree relative with tics, which differed with the negative history of tics in the adoptive families of the first group. In conclusion, tic disorders were more common in biological relatives, who shared genes but almost no environmental factors with the TS offspring.

**Complex inheritance in TS**

Segregation analyses were performed in order to obtain information about the mode of transmission of this disease. The initial analyses suggested that there was a major genomic locus for TS, which was transmitted in an autosomal dominant way, with variable penetrance, i.e. the probability of developing TS varied in carriers of the TS-susceptibility gene. However, other studies failed to confirm this model. Consequently, an intermediate model of inheritance was proposed, with one or few major loci and a multifactorial background. In addition, a study on 108 German TS probands proposed that TS inheritance could not be explained by a single model of Mendelian transmission, which could be due to an oligogenic or multigenic inheritance combined with non-genetic factors in presence of genetic heterogeneity (complex traits). In other words, the difficulties encountered by these studies may be due at least in part to the complex etiology of TS. It is possible that two or more susceptibility or modifier genes (possibly each conferring a different degree of vulnerability) interact in the same affected person. Most importantly, it is highly probable that not all TS-patients carry the same susceptibility genetic variants and have the same genetic risk to TS, in which case there could be genetic heterogeneity (different loci in the genome increasing susceptibility to TS in different people) and/or allelic heterogeneity (different genetic variants within the same locus involved in susceptibility).

In this way, different interactions between genetic, epigenetic and environmental factors may be required for the TS phenotype to appear in different people, which may affect the penetrance and mode of inheritance estimations, when pooling all sorts of TS families together. Furthermore, it is also probable that some of the genetic variants affect the expression not only of TS, but also of co-morbid conditions such as a subtype of obsessive compulsive disorder. This complexity has hindered the establishment of a unique phenotype in TS.

In some studies, subjects with TS, any other tic disorder, and OCD were considered to have the same phenotype (broad definition). Others used an intermediate
definition with the inclusion of TS, chronic motor or vocal tics, and OCD in the same category. Finally, there were some researchers who made a distinction between probable and definite TS cases, with or without co-morbid OCD.

Molecular Genetic Studies in TS

Taking into consideration the difficulties to establish a TS phenotype, some researchers have proposed to consider a thorough clinical evaluation in a large sample and the analysis of specific clinical characteristics of the patients (presence of tics only in pure TS, comorbid OCD, etc.) or to search for possible endophenotypes, which may represent more homogenous heritable traits within the disease. Endophenotypes can be searched with different approaches, including electrophysiology, neuroimaging, and neuropsychology. It is possible that specific subgroups selected through clinical characteristics or through endophenotypes could be more directly associated with the action of specific genes than the complete symptomatology of a broad definition of TS. According to a recent study, prepulse inhibition of the acoustic startle response, a measure of sensorimotor gating that could be affected in TS, could be an endophenotype for TS. In addition, neuropsychological deficits related with fine motor coordination and visual-motor integration have been reported in TS patients and are currently being investigated as possible endophenotypes.

At the molecular level, linkage in families and association studies in unrelated TS subjects have been the main methods used to search for vulnerability genes. In spite of the genetic complexity of TS, results obtained with both methods have suggested several TS-candidate regions in the genome, but more research is needed in order to establish definite susceptibility variants. Regarding linkage, markers with known chromosomal location can help find susceptibility variants if they are close enough to TS-related mutations. Likewise, because of this proximity, these markers tend to be transmitted along with the disorder within the studied families. The traditional model-based method of linkage has been very helpful to localize mutations of single-gene disorders that have a clear mode of Mendelian transmission, but has tended to produce negative results for TS as well as for other complex traits. The common lack of success when using this method may be caused by several factors, including the uncertainty of assigning the correct mode of inheritance and penetrance, which are unknown (or possibly variable) in TS. Moreover, these studies tend to ignore the possibility of genetic and/or allelic heterogeneity in TS, if there are phenocopies (apparently the same phenotype caused by nongenetic factors), assortative mating, or bilineality (if different branches of the family were contributing with different susceptibility variants). In addition, linkage studies have been performed in one or very few large multigenerational families, and the results, even if true, cannot be extrapolated to other families. Some years ago, however, the 11q23-24 region gave positive linkage results for TS in one large French Canadian family, but we were not able to confirm this result with a family-based association analysis in 199 TS cases. This may indicate that the linkage, if true, may be diluted by the presence of other possibly more common susceptibility variants in the French Canadian population or at least that the region needs to be analysed with a much larger set of polymorphic markers in French Canadians and even in other ethnic groups before establishing it as a true TS locus. A recent analysis of two candidate genes within the 11q24 region including 155 nuclear families did not support an association with TS. Also, a genome scan analysis with parametric and non-parametric linkage was performed on a single large pedigree with multiple affected members. Suggestive results were found at 5q34, 10p15, and 13q12.

The second molecular method used for the study of TS has been non-parametric linkage analysis that does not require specifications about the mode of transmission; most commonly, pairs of TS-affected siblings are compared to determine if they share more genetic variants (alleles) than expected if there were no linkage with TS at the studied loci. A few suggestive results have been obtained for regions on chromosomes 8 and 4. In a genome scan study of 76 families with 110 total sibling-pairs, maximum likelihood scores >2.0 were obtained in the long arm of chromosome 4 (4q) and the short arm of chromosome 8 (8p) regions. Excess of allele sharing in 77 sibling pairs concordant for TS, and partially concordant for hoarding, was observed for dichotomous and quantitative hoarding phenotypes at 4q, 5q and 17q. Non-parametric linkage and association results supported again the implication of 17q in TS. Recently, the Tourette Syndrome Association International Genetics Consortium for Genetics analyzed 238 nuclear families and 18 multigenerational families, for a total of 2040 individuals. Results showed a strong linkage at the short arm of chromosome 2.

Association analysis has been considered a good alternative for complex traits such as TS. The purpose of this type of studies is to test whether some alleles, genetic variants within a known genetic region, are more common in the affected-subject group with respect to the healthy-subject group. Proposed associations with TS involve candidate genes, including dopaminergic ones. Dopaminergic dysfunction is suspected given that neuroleptics tend to be an effective treatment for TS and changes in brain structures functionally related with dopamine have been found in TS patients. In case-control studies it is essential to match patients and healthy subjects at least by gender, age, and ethnic origin to decrease the possibility of false positive results. Given that human
populations tend to mix, it is sometimes especially difficult
to achieve a good ethnic matching. Allele frequencies can
vary among human races, but even among subgroups of
the same race. It has been shown, for example, that allele
frequencies at some loci vary considerably among sub-
groups of the white population of the United States, so
case-control studies should compare individuals from a
very well-defined, ethnically homogenous population. It
has been suggested that patients of this kind of population
might share longer stretches of DNA around at least some
of the genetic variants associated with TS, which would
also facilitate the identification of relevant genes or
regulatory regions. Environmental exposure on this kind
of population could be slightly more homogenous. This
may be important, given that non-genetic factors are known
to be involved in the etiology of the disorder.

Another possibility is to use the genotypic control
method, proposed by Devlin and Roeder, which requires
genotyping at multiple markers unlikely to be related with
the disease. The genotypic control method is expected to be
as robust as family-based designs, but it uses population-

Family-based association methods compare the alleles
that the parents transmitted to their TS-offspring (case
alleles) to the alleles that these parents did not transmit to
their TS-offspring (control alleles). This allows to test
whether there is an excess of transmission of certain alleles
to the affected offspring (transmission disequilibrium test),
which gives information of linkage and/or association with
TS. Family-based association studies have a potentially
higher power to map complex disease genes, such as TS,
and are more robust in the presence of population
stratification because the non-transmitted alleles of the
parents belong to the same ethnic pool than the alleles of
their TS offspring.

By means of family-based association, we were able
to confirm two previously suggested associations with
dopaminergic genes, i.e. the genes that encode for the
dopamine D4 receptor and the monoamine oxidase-A. Finally,
besides linkage and association studies, cytogenetic
findings have been described for TS patients, including
chromosomal translocations or inversions at 18q, 7q, and
8q regions.

DISCUSSION

It has been suggested that the ideal situation in the study
of complex traits is to try to replicate results in independent
families, but also to perform new studies with different
methodologies that might complement previous findings.

TS is an etiologically complex disorder, influenced by both
genetic and environmental factors. While variants that cause
several Mendelian traits have been successfully pinpointed
using the traditional model-based linkage approach, this
technique has generally failed in the study of TS and other
neuropsychiatric disorders. In contrast with Mendelian
disorders, the mode of transmission of TS is still unclear,
and above all, it is very probable that there is locus
heterogeneity, along with the possibility of bilineal
transmission of TS-related variants to an affected offspring.
This may explain the almost general failed attempts to find
linkage with parametric (model-based) methods in large
pedigrees, with the premise that one single mutation relates
to TS with a clear Mendelian mode of transmission.

Another approach when trying to optimize genetic
studies in TS is to analyze polymorphisms that are potentially
functional. It has been suggested that among
polymorphisms, those that appear to have a functional effect
on the gene product should be preferentially analyzed in
the study of complex traits. Genetic variants with significant
functional effect are most likely related to an amino acid
substitution in the gene product, a deletion or insertion that
results in a frameshift in the coding region, the complete or
partial deletion/duplication of a gene, the polymorphism
directly affecting gene transcription, RNA splicing, mRNA
stability or mRNA translation. In a particular way,
polymorphisms occurring in promoter regions upstream of
genes may in some cases affect the process of transcription
and as such, the levels of expression of the gene product. A
variation in the DNA sequence at the promoter region may
alter the affinities of existing protein-DNA interactions or
even create new binding sites for proteins. Thus, the
specificity and kinetics of transcription may be altered.

Sequencing of almost the entire human genome made
it possible to assess gene expression of thousands of genes
on a single chip; recent studies reported a preliminary
specific profile in the blood of TS patients. If confirmed,
this finding could be useful in the identification of genetic
factors related with TS. Given the multi-factorial nature of
TS, a thorough clinical description in large samples should
be considered. In addition to association, linkage and
sequencing studies, possible gene-gene and gene-
environment interactions could also need to be analysed,
as well as epigenetic factors.

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