Review Article: Special Edition

Current understanding of the genetics of tourette syndrome

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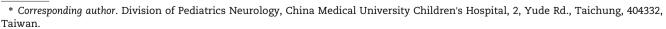[h] *Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan*

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ABSTRACT

Gilles de la Tourette syndrome (TS) is a common, childhood-onset psychiatric disorder characterized by persistent motor and vocal tics. It is a heterogeneous disorder in which the phenotypic expression may be affected by environmental factors, such as immune responses. Furthermore, several studies have shown that genetic factors play a vital role in the etiology of TS, as well as its comorbidity with other disorders, including attention deficit hyperactivity disorder, obsessive-compulsive disorder, and autism spectrum disorder. TS has a complex inheritance pattern and, according to various genetic studies, several genes and loci have been correlated with TS. Genome-wide linkage studies have identified Slit and Trk-like 1 (*SLITRK1*) and histidine decarboxylase (*HDC*) genes, and candidate gene association studies have extensively investigated the dopamine and serotonin system genes, but there have been no consistent results. Moreover, genome-wide association studies have implicated several genetic loci; however, larger study cohorts are needed to confirm this. Copy number variations, which are polymorphisms in the number of gene copies due to chromosomal deletions or duplications, are considered another significant source of mutations in TS. In the last decade, whole genome/exome sequencing has identified several novel genetic mutations in patients with TS. In conclusion, more studies are needed to reveal the exact mechanisms of underlying TS, which may help to provide more information on the prognosis and therapeutic plans for TS.

Gilles de la Tourette syndrome (or Tourette syndrome, TS) is a common, inherited, and childhood-onset neuropsychiatric disorder characterized by persistent motor and vocal tics. These tics are characterized by the appearance of short-lived, involuntary, or semi-voluntary attacks in the form of movement and/or voice. Tic disorders can be classified as transient (duration not exceeding one year), chronic (motor or vocal tics lasting more than one year), or TS (motor and vocal tics lasting more than one year). The incidence of tic disorders in school-aged children is 1–3% [1]. It is a heterogeneous disease involving genetic, environmental, and immune factors that interact to cause susceptibility.

In addition to tics, children with TS usually have a variety of mental illnesses, including obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), learning difficulties, sleep abnormalities, or other behavioral problems. However, the mechanism that links TS to other neurological disorders remains unclear. Commonly, affected children need treatment for their comorbid mental illness. In fact, most children with TS may not need drugs to control tics, but their comorbidities, which may be more likely than tics to cause harm. Specifically, it is estimated that 50–75% of children with TS also suffer from ADHD. Due to this high co-morbidity rate between ADHD and TS, it is assumed that they have a common pathophysiology, that is, in the basal ganglia circuit.

Anxiety, mood disorders, and other emotional symptoms have long been described in patients with TS or ADHD [2]. However, only in recent years have people become increasingly aware of the clinical and scientific significance of TS or ADHD combined with emotional and behavioral disorders. Overall, the incidence of mood and anxiety disorders is high among these patients. Using neuropsychological and psychological education testing, it will be beneficial to determine these specific defects, especially children with TS or ADHD who may be more susceptible to poor school performance, academic failure, and delayed socio-psychological development.

Heritability and risk factors

Decades of research have established that genetic factors have a significant impact on TS [1]. Several studies have shown that TS is familial [3,4]. However, a twin study found that the concordance rate was 53% and 8% for monozygotic and dizygotic twins, respectively. This clearly demonstrates that TS is not entirely determined by genes [3]. Therefore, it is thought to be a complex disease caused by multiple factors, including genetic predispositions and environmental triggers. OCD is a common comorbidity in patients with TS, and familial studies have shown that these two diseases seem to have some common genetic susceptibilities [5–8]. Studies using segregation analysis in affected families showed that TS manifested in an autosomal dominant pattern with variable phenotypes, including chronic tic disorders, and OCD [7,9]. However, more recent studies support polygenic or oligogentic inheritance models [3].

Some studies have suggested that environmental factors that lead to immune activation can influence a subgroup of patients with TS and OCD. Part of this association may be due to the similarity between TS and Sydenham's Chorea, which is caused by group A β-hemolytic streptococcus (GABHS) infection [10,11]. Specifically, some immune studies have shown that infections, such as pediatric autoimmune neuropsychiatric diseases associated with streptococcal infections (PANDAS), may induce or increase the susceptibility of individual to tics and related characteristics via abnormal humoral immune responses directed against self-tissue antigens. Cross-sectional [11–13] and longitudinal research [14] support an association between GABHS infection and the onset or exacerbation of pediatric OCD, TS, and tic disorders. However, other prospective longitudinal study results suggest no obvious relationship between new GABHS infections and symptom exacerbations in groups of patients with TS and/or OCD [15]. Since its first definition in 1998, PANDAS has been considered controversial. Another PANDAS-related disorder, pediatric acute-onset neuropsychiatric syndrome (PANS), has been proposed. PANS is characterized by sudden onset of OCD and/or severe dietary restrictions, and at least one other accompanying cognitive, motor, behavioral, or emotional symptoms, but no streptococcal infection. Better definition of clinical manifestations, precise biological markers, neuro-imaging tests, and systematic data collection are needed to determine which of the available diagnostic tests are most discriminating for a PANDAS/PANS diagnosis; this will also help to establish more precise diagnostic guidelines and indications [16,17]. A nationwide population-based case–control study investigated the association between allergic diseases (such as allergic rhinitis, asthma, atopic dermatitis, and allergic conjunctivitis) and TS and determined that allergic diseases increase the risk of TS. This risk also rises with an increase in the number of allergic comorbidities [18].

In addition to antibody-mediated mechanisms, symptoms observed in patients with TS, such as tics, obsessive-compulsive (OC) symptoms, and anxiety/depression, may be directly or indirectly induced by cytokines. Animal studies have shown that cytokines injection can have many effects on the brain, especially on the neuroendocrine system and behavior [19]. Cytokine administration also alters neuro-transmission, which might be responsible for these effects. Of these activation of the hypothalamic-pituitary-adrenal (HPA) axis by interleukin-1 (IL-1) is the most studied [20,21]. Clinical studies on TS and early-onset OCD have shown that these diseases are quite sensitive to psychosocial stress [22–25]. In fact, several reports have suggested that patients with TS have an abnormal stress response [26–29]. Lin et al. [29] monitored the psychosocial stress levels of 45 children with tic disorders and/or OCD and 41 healthy control participants for 2 years. A continuous monthly assessment of the severity of tic and OC and depressive symptoms was recorded. The modern structural equation model of unbalanced repeated measures was used to evaluate the time series of psychosocial stress, which measures the changes that accompany the severity of tics and OC and depressive symptoms. This study found that psychosocial stress was a powerful predictor of the severity of future tics and OC and depressive symptoms [29].

Genetic linkage studies of TS

Genome-wide linkage studies (GWLSs) have identified several potential candidate loci in chromosomal regions related to TS [30,31]. The use of the GWLS method helps uncover genes that may be related to TS, and has identified special chromosomal regions from several families with TS. However, no genes or mutations that affect pathogenicity have been observed, except for the Slit and Trk-like 1 (SLITRK1) gene on chromosome 13 [32] and the histidine decarboxylase (HDC) gene on chromosome 15 [33]. These early studies to identify disease-causing genes using GWLSs had their own constraints. They include phenotypic complexity, such as the clinical and genetic heterogeneity of TS and its related comorbidities, limited number of samples, and limitations of genetic technology and statistical methods at that time, such as low coverage and resolution of the microsatellite marker sets used. Linkage analysis is based on calculating the frequency of recombination events in a limited number of generations, and therefore it is sensitive to mislabeled genetic information, such as whether the individual is affected, allele frequency patterns, and genetic parameters. Nevertheless, the limited but significant statistical results obtained from TS GWLSs strongly indicate that the genetic factors of TS and related comorbidities are far more complicated than simple Mendelian inheritance.

Association studies of candidate genes

Research suggests that TS may be caused by defects in the dopamine system. This hypothesis is supported by the fact that an effective reduction of tics is observed in many patients who use neuroleptics (dopaminergic blockers). It has also been reported that the use of a drug that blocks dopamine accumulation in presynaptic storage vesicles (tetrabenazine) and a drug that blocks dopamine synthesis (α-methylparatyrosine) can effectively inhibit tics. Contrastingly, drugs that increase the concentration of dopamine, such as central nervous system stimulants, often worsen tics. Comings et al. reported a highly significant association between TS and a restriction fragment length polymorphism of the dopamine receptor D2 (DRD2) locus [34]. However, Nothen et al. reported that there was no significant difference in the DRD2 A1 allele frequency between patients with TS and subgroups of patients classified according to the severity of tics or parental control alleles [35]. In addition, Diaz-Anzaldua et al. reported that DRD2, DRD3, and dopamine transporter 1 are not significantly associated with TS, but DRD4 and monoamine oxidase-A genes may increase the risk of TS development in the French-Canadian population [36]. Linkage studies on some genes, including dopamine D3-5 receptors [37−39], glycine alpha-1 subunit; gamma-aminobutyric acid A (GABAA) receptor alpha-1, beta-1, and alpha-2, alpha-6, and gamma-2 subunits (GABRA1, GABRB1, GABARA2, GABRA6, and GABRG2); alpha-adrenergic receptor ADRA1; beta-adrenergic receptor ADRB1; glutamate receptor GLUR1; glucocorticoid receptor GRL [40]; the norepinephrine transporter gene [41]; and catechol-O-methyltransferase [42], did not show a positive association with TS occurrence. Researchers have also attempted to find an association between TS and other movement disorders [43].

In one study, a total of 151 children with TS and 183 healthy controls were included. Polymerase chain reaction was used to identify the TaqI DRD2 and DRD2 (H313H, rs6275) polymorphisms of the DRD2 gene. There was a significant difference in the genotype proportions of TaqI DRD2 and DRD2 (H313H) polymorphisms between the two groups ($p < 0.01$). The odds ratio for developing TS was 2.253 (95% confidence interval, 1.124−4.517) in homozygous individuals with the TaqI DRD2 A1 allele compared to those homozygous for the TaqI DRD2 A2 allele. Likewise, compared to homozygous individuals with DRD2 (H313H) T, those homozygous for DRD2 (H313H) C had an odds ratio of 2.96 (95% confidence interval, 1.398−6.269) for developing TS. These data indicate that the DRD2 gene or adjacent genes might be susceptibility factors for TS [44]. In contrast, polymorphisms in the DRD1 gene showed no association [45,46], as well as the norepinephrine genes (ADRA2A and ADRA2C), have not been associated with TS [47]. Furthermore, a genetic screening in the SLITRK1 gene, which was recently identified mutations with TS, was performed, but it did not appear to be of utility in TS diagnosis [48]. Contrastingly, while further evaluating the association between immunity and TS, it was found that the interleukin 1 receptor antagonist gene, encoding the IL-1 Ra protein, might be a candidate genetic marker for TS [49].

Neurophysiological and neuroimaging studies suggest that TS is also associated with the serotonin (5-hydroxytryptamine, 5-HT) system. A link between serotonin neurotransmission and TS has been suggested to a lesser extent. One study reported that the serotonin/platelet ratio was reduced in a large number of individuals with TS and their family members [50]. In addition, drugs with a high affinity for serotonin receptors, mainly atypical antipsychotics, have been used to relieve tics [51]. Serotonin receptors have been shown to promote and inhibit dopamine activity [52,53]. The serotonin transporter (5-HTT, SERT) transports serotonin from the synaptic cleft to presynaptic neurons to regulate serotonin and nerve signal transmission. It also uptakes dopamine at the same time, which means it can also act as a dopamine transporter [54]. The serotonin system may therefore directly or indirectly participate in TS pathology by regulating other neurotransmitter systems, particularly the dopaminergic system.

Candidate gene studies suggest that the serotonergic receptor (HTR1A) and transporter (SLC6A4) genes are involved in TS pathogenesis [55,56]. SERT is encoded by SLC6A4. Studies have shown that SLC6A4 is related to the etiology of TS: higher expression of SLC6A4 mRNA in the blood is correlated with the severity of TS tics [57]. SLC6A4 expression was elevated in the striatum of a rat model of TS [58]. A rare SLC6A4 gain-of-function variant, Ile425Val, regulates SERT activity. Studies have found that patients with TS have a higher carrier rate of this variant than controls [56,59]. The SERT-linked polymorphic region (5-HTTLPR), upstream of the promoter region of SLC6A4, is related to the etiology of OCD [60,61] and TS [56].

Methylation studies of the SLC6A4 promoter region from the peripheral blood of patients with major depression [62], children with childhood physical aggression [63], ADHD [64],

and the saliva of children with OCD [65] found that, compared with the control group, increased methylation was observed in affected individuals. Hypermethylation at two CpG sites was also associated with increased expression of *SLC6A4* mRNA in affected individuals [62]. However, the degree of DNA methylation at the promoter region of *SLC6A4* was not significantly correlated with the occurrence of TS (with or without OCD), mRNA expression level, or individual genotype, indicating that the expression of *SLC6A4* is not affected by methylation of the studied CpG site in the promoter region [66].

Genome-wide significant common variant associations with TS

In the past ten years, genome-wide association studies (GWASs) have become a widespread method for identifying the genetic factors of common diseases. The first GWAS results for TS were published in 2013 [67]. The TSA International Consortium for Genetics (TSAICG) studied 1285 TS cases and 4964 ancestry-matched European controls, including two isolated populations derived from Europe, Ashkenazi Jews from North America and Israel, and French Canadians from Québec, Canada. After several quality control steps, a final analysis was performed on the joint dataset of 484,295 single nucleotide polymorphisms (SNPs). In the primary meta-analysis of GWAS data from these European ancestry samples, no significant marker reached the genome-wide threshold (set by the authors at $p \leq 5 \times 10^{-8}$). Nevertheless, SNP rs7868992 was the strongest associated signal, which is located in the intron of the *COL27A1* gene on chromosome 9q32. *COL27A1* is a recently discovered collagen gene that translates into type XXVII collagen. It is abundantly expressed in developing cartilage, but is lower in many other tissues. In addition to *COL27A1*, several top-level signal SNPs were identified, which were located in various chromosomal regions, including within the *POLR3B* gene (the second largest subunit of RNA polymerase III) on chromosome 12q23, in the 1.7-Mb intergenic region on chromosome 3q13, and in the intergenic region between *THSD7A* and *TMEM106B* on chromosome 7p21. Furthermore, one of the top five SNPs with significance, rs7336083, was in the 1.9 Mb intergenic region between the *SLITRK6* and *SLITRK1* on chromosome 13q31. Combining the previously mentioned European ancestry samples and isolated ethnic samples from Costa Rica and Colombia, a total of 1496 TS cases and 5249 controls were included in a secondary meta-analysis. Rs7868992, located in *COL27A1* on 9q32, was found to be the strongest association. The effects of these highly associated SNPs on transcriptional expression and DNA methylation were further explored to find functional evidence supporting the association observed by GWAS. From the primary analysis, top SNPs were nominally enriched for expression quantitative trait loci in the frontal cortex, with a trend towards abundance in the cerebellum. The highest association signals were also nominally enriched for the cerebellar methylation quantitative trait loci. Yu et al. performed another TS GWAS on 4819 cases and 9488

controls and discovered a statistically significant TS-related gene (*FLT3*). In addition, they confirmed that most TS heritability can be attributed to the aggregation of common genetic risk variants distributed throughout the genome [68]. Their study also demonstrated that, in subjects with a family history of tic disorders (TS or chronic tics), the aggregated genome-wide TS polygenic risk score (PRS) was significantly correlated with the lifetime worst-ever tic severity score. In addition, Yu et al. and Abdulkadir et al. used the TS GWAS PRS to explore two independent population-based GWAS samples, and found that individuals with non-TS tic disorders also had a higher TS PRS compared to unaffected controls, although the degree was lower than that of individuals with TS [68,69]. Therefore, these two findings confirm, at the genetic level, that TS and other tic disorders may exist as a continuous spectrum, rather than their current classification as different diagnostic entities. In addition, in the Enhancing Neuro Imaging Genetics Through Meta-Analysis consortium, the same TS GWAS PRS was used to detect imaging data of subcortical brain volume, linking the genetics of TS with brain volume [70]. Finally, a large-scale study on GWAS data for more than one million people with various neurological and mental diseases showed that TS has a genetic variation common with OCD, major depression, and unexpectedly with migraine, especially migraine with aura [71].

Chromosomal Abnormalities and Copy Numbers Variants (CNVs)

Several rare large-segment structural aberrations associated with TS and related phenotypes have been identified by studying chromosomal aberrations. For example, a *de novo* chromosome inversion was found in a TS patient near the *SLITRK1* gene on 13q31.1 [32]; exons 1–3 of the inner mitochondrial membrane protein 2 L (*IMMP2L*) gene were deleted and its function was destroyed in a male patient with TS-like tics [72]; all three patients from a TS family had an inversion on chromosome 7q35-q36 that destroyed the Contactin-associated protein-like 2 (*CNTNAP2*) gene [73]; and, in a family with both autism spectrum disorders (ASDs) and TS symptoms, exons 4–6 of the neuroligin 4 (*NLGN4*) gene on Xp22.3 was deleted [74]. Several large-scale CNV studies have also been conducted on TS using DNA microarrays [75–80]. Results from these studies show that approximately 1% of patients with TS carry one known or potentially pathogenic CNV. Overall, these studies show that chromosomal structural variations and extensive CNV increases, which are very important in many common and rare clinical diseases, also have a significant impact on the genetic structure of TS. In these studies, CNVs detected in patients and families with TS were related to previous findings in patients with schizophrenia, autism, and ADHD. Therefore, these CNVs will produce a continuum of neuropsychiatric disorders, which manifest in different ways due to differences in genetic, environmental or other factors. Large CNV fragments could cause more abnormal gene expression during neurodevelopment, leading to more serious lesions [81].

Next-generation sequencing Era - rare genetic coding variants with TS

Whole exome sequencing (WES) is an efficient method that allows sequencing of the entire coding region of the human genome to discover rare variants that may affect function in these protein-coding regions. In contrast, whole genome sequencing (WGS) involves the sequencing of the entire genome, including introns, exons, flanking sequences, and intergenic regions. GWAS research usually uses common variants (frequency $\geq$5%), while WES/WGS can identify rare (frequency $\leq$1%) and *de novo* mutations in the genome. WES has achieved remarkable results in the study of Mendelian genetic diseases [82] and is also an effective method for gene identification for complex traits or diseases [83]. It is important to note that although these protein-coding regions account for less than 2% of the entire genome, approximately 85% of disease-causing mutations fall in these regions [84—86].

After studying 120 TS patients using WES and comparing them with a rigorous control group, Depienne et al. identify pathogenic variants in *OPRK1* (encoding the opioid kappa receptor). This result echoes an idea that has existed since the 1980s, which is that the opioid system plays a role in the pathophysiology of TS; it also suggests a new potential treatment approach [87]. WES of 100 trios (patients with TS and their parents), identified point mutations in ASH1 Like Histone Lysine methyltransferase (*ASH1L*), which cause defects in its enzyme activity, thereby making *ASH1L* a susceptibility gene for TS. Previous studies on this gene have shown that it is related to intellectual disability and autism [88]. Furthermore, the transgenic mouse strain (*Ash1l* heterozygous mouse) exhibits tic-like movements and compulsive behaviors, and dopaminergic hyperinnervation in the dorsal striatum, indicating that it is a good model to study TS. In another WES study of a cohort of 222 parent and child trio with OCD, two disease-related genes were found, chromodomain helicase DNA binding protein 8 (*CHD8*) and signal peptide, CUB domain and EGF-like domain containing 1 (*SCUBE1*). Interestingly, these two genes also appear in the list of previously discovered TS-associated genes [89]. Moreover, animal studies have shown that mice heterozygous for the *Chd8* mutation show behavioral characteristics similar to ASD, including repetitive behavior, increased anxiety, and changes in social behavior [90]. The other study reported WES data from 802 TS trios (2406 samples); the results identified a high-confidence TS risk gene, *CELSR3*, and two probable risk genes (*OPA1* and *FBN2*). They also suggested that the number of *de novo* sequence damaging variants was increased in simplex (parents without tics) but not multiplex (one parent has tics) families. This study also observed a significant overlap in *de novo* sequence variants between TS and OCD, and *de novo* CNVs between TS and ASD, which represent common genetic risk factors [91].

Data from the Swedish National Registry on maternal polycystic ovary syndrome (PCOS) was used to observe the risk of prenatal androgen exposure to diseases such as TS, ADHD, and ASD [92]. These results strengthen the evidence that prenatal androgen exposure has a potential causal effect on the development of male-dominated neuropsychiatric disorders in the offspring of women with PCOS. Another population level study in Sweden investigated whether tic-related OCD has a stronger family tendency than non-tic-related OCD. They found that relatives of patients with tic-related OCD have a significantly higher risk of developing OCD compared to relatives of patients with non-tic-related OCD. Therefore, it was concluded that tic-related OCD is a familial subtype of OCD [93]. These results have important implications for genetic exploration.

Challenges of TS genetic study

Although much genetic information is available, gene discovery for TS is still in its early stages. The available results suggest that numerous common variants with small effects and a few rare variants with moderate or large effects exist. No single gene, locus or common or rare variant can fully explain the cause of TS. One study examined a large family affected by TS that spanned six generations and included 122 members (28 with TS, 20 with chronic multiple tics, and five with obsessive-compulsive behavior). SNP array and WES analyses were performed. No notable CNVs, single nucleotide variants, insertion/deletions, or repeat expansions of near-Mendelian effect were found. All affected members of this family had a higher carrier frequency of common TS variant risk loci, as observed in separate unrelated TS cases. The results of this study strongly support that the most important contribution to TS risk is duo to a variety of common risk variants, rather than one or several variants that exert a strong effect [94].

Similar to other early-onset neurodevelopmental disorders, identifying recurrent *de novo* variants is a powerful strategy for managing long-term side effects including chronic movement disorders [95]. Due to lack of understanding of pathophysiology, the development of more extensive and effective treatments is currently restricted. However, given that genetic factors play an important role in TS [80,96], a large number of TS risk-related genes, loci, and physiological information can be integrated and used to shed light on the potential and promising path forward that combines genomic, neurological, and clinical data [97]. In the past decade, advances in genomics technology, including microarray genotyping and WES/WGS, have contributed to the substantial growth of genetic data for neurodevelopmental disorders, including OCD, ADHD, ASD, intellectual disability, epileptic encephalopathy, mental disorders, and schizophrenia. Especially for early onset diseases, such as TS, it is obvious that when too many associated genes are found, identifying current *de novo* variants are a highly reliable and productive way to discover disease-causing genes. As mentioned in "*Chromosomal Abnormalities and Copy Numbers Variants (CNVs)*", some studies have also shown that rare CNVs are associated with the risk of TS. However, *de novo* CNVs have not yet been identified as risk factors.

Conclusions and future directions

TS is a complex, genetic disease with a highly variable phenomenology, pathophysiology, and etiology. An expertise in different clinical disciplines, including neurology and psychiatry, as well as research fields, such as neurophysiology, neuroanatomy, cognitive psychology, and neurogenetics, is required to properly understand TS. Soon, GWAS using SNP arrays is likely to be replaced by WGS, which has higher excavation capabilities, thus allowing more rare variants to be discovered. For many years, genotyping technology has been the limiting step in the discovery of disease-causing genes, gradually, this bottleneck has turned into a phenotypic description. The phenotypic description can be linked with genetic data to assist in disease stratification, which can be helpful for treatment. Therefore, a more in-depth phenotypic analysis combined with genetic research will promote the understanding of disease risks and mechanisms.

Although the current knowledge is limited, epigenetic research shows promise in linking genomic variation to environmental exposure and disease outcomes, especially for psychiatric diseases and behavioral phenotypes. Specially, further studies on TS using larger sample sizes are required to understand the impact of dynamic epigenomes on developmental gene regulation and behavior. Other large-scale studies can also help differentiate TS from other psychiatric and behavioral phenotypes, according to disease-specific genomic and epigenomic variants. Lastly, since TS is a male-biased disease, understanding the mechanisms underlying gender differences may also help to further understand how gene expression is regulated in the brain and its significance in the pathogenesis of TS.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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