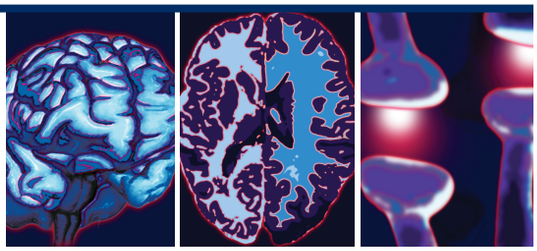
REVIEW



The complex genetics of Gilles de la Tourette syndrome: implications for clinical practice

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Practice points

- Gilles de la Tourette syndrome (GTS) is a neurodevelopmental condition characterized by the presence of multiple motor and phonic tics.
- The clinical picture of GTS is heterogeneous, ranging from simple tics to complex behaviors, frequently associated with psychiatric comorbidity.
- Once considered a rare condition, GTS is now estimated to affect 0.4–3.8% of school-age children.
- Since twin and family aggregation studies have suggested that there is a significant genetic basis to GTS, a wide range of genetic methods have been employed to elucidate the genetic architecture of GTS.
- Detailed consideration of clinical phenotypes and improved characterization of study populations may aid in delineating genetic loci in symptomatically homogeneous groups and developing tailored treatments.
- We anticipate that further investigation into the basis of genetic susceptibility in GTS will improve our understanding of its pathophysiology and guide the development of effective treatment strategies.

SUMMARY Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder of childhood onset, characterized by the presence of multiple motor and phonic tics. Early twin and family aggregation studies have suggested that genetic factors play a critical role in the development of GTS. However, identification of causative mutations and susceptibility regions has proved difficult. This may be attributed to various factors, including the clinical heterogeneity of GTS, the presence of comorbid psychopathology, gene–environment interactions and bilineal transmission. This review assesses the different methodologies of genetic studies with explanatory comment for the clinician, and summarizes key genetic findings in light of their potential implications for treatment strategies.

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Clinical complexity of Gilles de la Tourette syndrome

Gilles de la Tourette syndrome (GTS) is a neurodevelopmental condition characterized by the presence of a combination of multiple motor and phonic tics, complicated by the presence of psychiatric comorbidity [1]. Tics constitute rapid, recurrent and stereotyped motor behaviors or vocalizations. Motor tics comprise a range of both simple and complex phenomena, including eye blinking, head/neck jerking and shoulder shrugging, as well as movements involving the limbs and torso. Complex motor tics affect several muscular groups, and dystonic and tonic tics, characterized by sustained muscular contractions, can also occur as part of the tic repertoire. Case reports have yielded evidence of a range of bizarre and complex tics, which can pose considerable challenges to the clinical diagnosis [2,3]. Vocal tics range from simple phenomena manifesting as yelps and grunts to complex linguistic phenomena including phrases. The vast majority of patients with GTS report specific sensory symptoms ('premonitory urges') that are temporarily relieved by tic expression [4]. Complex related behaviors have also been reported in GTS populations [5]. One example is the publicly notorious manifestation of involuntary and inappropriate swearing (coprolalia). Coprophenomena include a motor equivalent in the form of involuntary obscene gesturing, copropraxia, and a written manifestation, coprographia, whereby coprolalic tendencies can also be demonstrated in writing. Similarly, other phenomena range from tendencies towards imitation (echolalia, echopraxia and echographia), repetition (palilalia, palipraxia and paligraphia), as well as the existence of wider nonobscene, socially inappropriate behaviors [3,6]. Nonobscene, socially inappropriate behaviors often take the form of involuntary insults, usually directed towards a familiar individual or family member, targeting personal aspects such as intelligence/general appearance [6]. Approximately 90% of patients with GTS have comorbid psychopathology; the most commonly reported conditions are ADHD, obsessive–compulsive disorder/behaviors and self-injurious behaviors, as well as affective disorders and impulse control disorders, including conduct disorders and rage attacks in children and adolescents **(Figure 1)** [5,7–9].

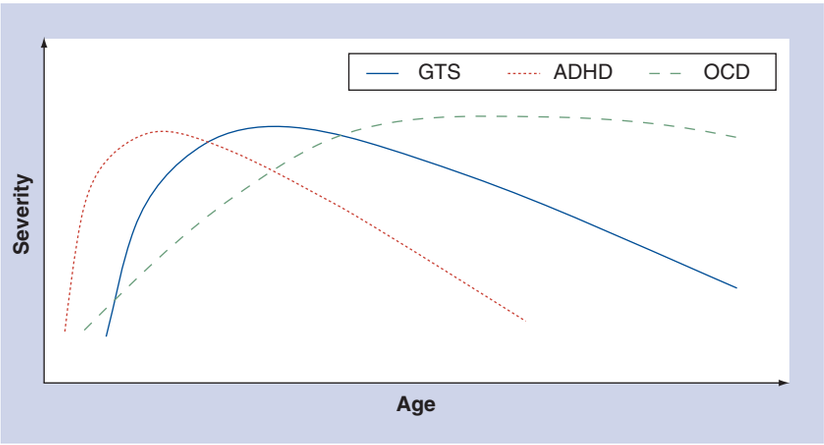

Figure 1. Neurodevelopmental trajectories of Gilles de la Tourette syndrome and associated behavioral problems: ADHD and obsessive–compulsive disorder.
GTS: Gilles de la Tourette syndrome; OCD: Obsessive–compulsive disorder.

■ No longer a rarity: epidemiology & etiology of GTS

The natural history of GTS is characterized by childhood onset, a waxing and waning course, and symptom improvement by adulthood in the majority [10]. Estimates quote a ballpark prevalence figure of 1% in school children aged between 5 and 17 years [11–15]. Global estimates range between 0.4 and 3.8% in 5–18 year olds [16,17]. Males are more commonly affected than females, with a ratio of 4:1 [18].

Although the pathogenesis of GTS has not been fully delineated, numerous aspects ranging from the role of the dopaminergic system [19], autoimmune responses and infection, and prenatal and perinatal factors have been implicated [20]. Historically, Gilles de la Tourette already perceived a familial aspect to his namesake syndrome [21–23]. Subsequently, empirical scrutiny has attempted to delineate the genetic basis of GTS. This has comprised twin studies, familial studies, genetic linkage work, genetic association studies and, recently, exome sequencing. This review provides a comprehensive summary of the key genetic findings on GTS.

Spectrum of genetic research in GTS

Research has contributed significantly to our understanding of GTS in a multitude of ways: in characterizing phenotypic diversity; prevalence; and in elucidating the role of nongenetic and genetic factors in its pathogenesis. Twin and familial studies have provided us with an understanding of the familial transmission element of GTS, while other studies have highlighted genomic regions potentially implicated in harboring susceptibility loci.

Twin studies

Twin studies aim to understand the genetic contribution to specific diseases. This involves determination of disease concordance in monozygotic twins compared with dizygotic twins.

There have been few reports of twins studies in GTS. Early reports have cited case studies with detailed phenotypic descriptions of monozygotic twins concordant for the disease [24–27]. More recent reports consider larger numbers of cases. A sample of 16 pairs of monozygotic twins demonstrated a concordance rate of 56% for GTS, with a concordance rate of 94% for tic disorders when the diagnostic criteria werebroadened [28]. In a subsequent study of 43 pairs of same-sex twins, comprising 30 monozygotic pairs and 13 dizygotic pairs, monozygotic twins demonstrated a concordance of 53% compared with only 8% concordance in dizygotic pairs. With the inclusion of any type of tic, concordance rose to 77 and 23% in monozygotic and dizygotic twins, respectively [29].

Therefore, the limited twin data published to date provide evidence for a significant genetic contribution in GTS.

Family data

The mere existence of family aggregation does not prove the role of purely genetic factors, as shared environmental factors are experienced by family members. However, as first-degree relatives share an average of 50% of genetic material, the recognition of familial aggregation of a disease is suggestive that genetic factors may be important in disease causation [30,31].

Both historical and recent reports demonstrate that GTS aggregates strongly in families. First-degree relatives have a ten- to 100-fold increase in the rate of GTS compared with the general population [30,32–41]. Early genetic studies pointed towards simple genetic models [42–46] with a Mendelian inheritance pattern, consistent with a single causative gene defect. Over time, the inability to locate a specific causative gene has suggested that the single causative gene hypothesis is unlikely to be tenable [18]. Family segregation analyses aim to test hypotheses concerning the transmission of disease in families to determine whether the transmission pattern accords with Mendelian expectations. Such analyses employ data from related individuals (sibships, nuclear families and wider pedigrees). Segregation analyses of GTS have generated inconsistent findings. Initial studies have pointed to an autosomal pattern of inheritance with incomplete penetrance [47]. Subsequent segregation analyses in 30 nuclear families provided support for a highly penetrant, sex-influenced, autosomal-dominant trait [48]. An investigation of 40 families yielded results consistent with a highly penetrant autosomal dominant gene [36]. Ensuing work has yielded data supportive of a complex inheritance pattern, suggesting both recessive and/or polygenic patterns of inheritance [20]. A study of a large, single pedigree comprising 182 members, gave evidence for a major locus with an intermediate inheritance pattern, with varying penetrance in heterozygotes and homozygotes [49]. An analysis of 53 children and adolescents with GTS and 154 first-degree relatives pointed to a mixed model of inheritance, with a major locus accounting for over 50% of the phenotypic variance acting on a multifactorial background accounting for an additional 40% of the variance. All individuals homozygous for the susceptibility allele at the major locus were affected, compared with only 0.3 (females) and 2.2% (males) of heterozygotes [37].

Segregation analyses overall yield a mixture of causal genetic models but support the involvement of genes with major effect. These findings have provided an impetus to pursue the search for specific genetic influences in GTS through both genetic association and linkage studies.

Association studies

Genetic association studies aim to correlate genetic sequence information from unrelated individuals with the disease state. Population-based genetic association studies involve various approaches: whole/partial genome-wide association studies; 'fine mapping' approaches (narrowing the genetic region associated with the disease); polymorphism studies (analyzing regions of the genome by scrutinizing key polymorphisms); and candidate gene studies. Candidate gene studies examine particular genes, comparing a gene sequence in cases with and without a disease. This may involve sequencing of the entire coding region of specific genes or focusing on specific significant polymorphisms within the target gene. Other studies involve analysis of multiple single nucleotide polymorphisms (SNPs) within the gene, chosen because of their ability to tag other polymorphisms. While SNPs are used to provide information about variations within the gene in question, they may not represent true disease-causing variants [50].

Candidate gene studies constitute a large proportion of the recent genetic literature on GTS. The first report suggested an association between GTS, symptom severity and the A1 allele at the dopamine *DRD2* locus [51]. This genetic locus was targeted for study as it had previously been implicated in disorders associated with defective dopaminergic transmission, such as alcoholism. However, in a group of two extended kindreds and also a study of 15 smaller families, genetic linkage of GTS to this locus was not confirmed [52,53].

The adrenergic, noradrenergic and dopaminergic systems have traditionally been associated with the pathophysiology of GTS. Genes encoding proteins in the aforementioned systems have been examined, yielding either negative or equivocal results: *DRD1* [54], *DRD3* [55], *DRD4* [38,56], *DRD5* [57], dopamine transporter gene [58], serotonin receptor gene [58], serotonin transporter gene [59], catechol-*O*-methyl transferase gene [59], norepinephrine transporter gene [60] and α-1-subunit of the glycine receptor [61]. In a family-based association study of 110 patients with GTS from a French–Canadian population, no association was found between GTS and *DR2*, *DR3* or dopamine transporter gene 1. Both *DRD4* and monoamine oxidase A genes encode proteins implicated in dopamine transmission, and results obtained through two functional polymorphisms and haplotype analysis confirmed an increased risk for developing GTS [62].

Other genomic regions have been targeted for candidate gene screening based on identified chromosomal abnormalities in individual cases. An individual with GTS was reported to carry a translocation between chromosomes 7 and 18 [63]. Family members with the translocation were noted to display GTS features. Other reports detail an individual with GTS to have an 18q deletion [64] and another with a translocation breakpoint at 18q22.3 [65]. Subsequent genetic linkage studies in six extended families found no evidence of linkage and excluded the whole of chromosome 18 and the chromosome 7q21.3-qter region from harboring a GTS causative gene [66].

More recent studies have noted the possible role of the *LHX6* gene, which is involved in the development of striatal interneurons [67], the *DLGAP3* gene [68], which encodes a postsynaptic scaffolding protein expressed in striatal glutamergic synapses, *SLITRK1*, a susceptibility gene [69], and 17q25, a candidate susceptibility region [70]. Among regions demonstrating evidence for linkage to GTS, 17q25 has been noted to be of particular interest. Initial screening of chromosome 17 performed on two large pedigrees was followed by fine mapping of the candidate region with 17 additional markers. Genotyping for 25 SNPs yielded multiple haplotypes across three studied genes with significant associations. Three SNPs were found to be significantly associated with GTS [70].

Other genes have been investigated in view of their involvement in pathways targeted in GTS treatments. Given the positive therapeutic effect of marijuana consumption and δ(9)-tetrahydrocannabinol treatment in patients with GTS, the *CNR1* gene, involved in the central cannabinoid system, has been investigated [71]. Screening of *CNR1* identified three single-base substitutions. One was a synonymus mutation, with no predicted amino acid change, and the second showed a significant association but was not reproduced in subsequent cohorts (56 patients with GTS and 55 controls; 64 patients with GTS and 66 controls). The third variant does not play a causal role in GTS [71]. Likewise, in view of the therapeutic effects of adrenergic receptor agonists, such as clonidine, genes involved in the adrenergic system have also been investigated in GTS. Genes encoding ADRA1C, positioned on chromosome 8p, and ADRA2A, on chromosome 10q, have been studied in 113 families with GTS, but both have been rejected as major factors contributing to genetic susceptibility in GTS [72].

Linkage studies

Linkage analysis is based on the principle that two or more genes or loci located close to one another on the same chromosome are likely to be transmitted together, or 'cosegregate', in subsequent generations [73]. Linkage analysis considers the likelihood of obtaining specific pedigree data if the disease under scrutiny is due to causative gene mutations residing in various locations throughout the genome.

Collaborative linkage studies conducted in the 1990s, involving 31 multigenerational families [74,75,76] and screening over 800 marker loci, failed to demonstrate convincing evidence for genetic linkage with GTS [77]. Among more recent genome-wide linkage analyses, the largest comprised 18 large multigenerational families and 238 nuclear families [78–82]. These recent studies have provided evidence suggestive of linkage to loci on chromosomes 5p and 6p, and

demonstrated evidence for linkage to a locus on chromosome 2p23.2.

Work involving a single, large, Dutch pedigree and a panel of 382 markers has generated significant linkage peaks on chromosomes 3q, 9p and 13q [83], while genome-wide linkage analysis on a large Utah pedigree with 108 affected individuals demonstrated significant peaks on chromosome 1p and 3p [84]. Linkage to chromosome 14q31.1 was suggested in a genome-wide linkage scan involving four generations of an Italian family [85]. These heterogenous causative locations may reflect different genes being responsible for GTS in different large pedigrees. Alternatively, the individual studies may not be sufficiently powered to capture the true GTS location, requiring larger genetic linkage studies.

Genetic linkage studies have also been used to exclude several potential candidate genes from further consideration in GTS, including genes encoding dopamine β-hydroxylase, tyrosinase and tyrosine hydroxylase [86].

■ Cytogenetic abnormalities

Various chromosomal abnormalities, including inversions, deletions, translocations and aneuploidy [87,88], have been reported in the presence of a GTS phenotype. Some have been used to drive candidate gene studies (see the 'Association studies' section).

In a male patient with GTS, an inverted duplication of the long arm of chromosome 7 was identified. *IMMPL2*, a gene coding for the IMMPL2 protein, was disrupted by the breakpoint in the duplicated fragment and the insertion site in 7q31. The 7q31 breakpoint has been associated with other clinically overlapping neuropsychiatric disorders, including autism [89]. Chromosome 8q22.1 has also been associated with GTS, based on a report detailing the balanced translocation t(1;8)(q21.1;q22.1) in family members with GTS [90].

The involvement of SLITRK1, a transmembrane protein involved in the control of neurite growth, is controversial [91]. It is expressed in regions of the embryonic and postnatal brain consistent with locations implicated in GTS [92]. A *de novo* inversion on chromosome 13 was noted in a patient with GTS [93]. Sequencing of *SLITRK1* revealed two mutations. First, a single-nucleotide deletion generating a frame-shift leading to the expression of a truncated protein [93]. Second, a missense mutation, altering a binding site and negatively modulating *SLITRK1* mRNA expression. A number of studies, however, suggest that the gene may be implicated in only a proportion of cases [69], with *SLITRK1* mutations seldom causing GTS [94,95]. A more recent analysis involving a family sample and a meta-analysis of a total of 376 nuclear families with GTS has, however, confirmed an association between GTS and *SLITRK1* [96]. Overall, the data suggest that, in at least a proportion of GTS cases, genetic factors mediated via *SLITRK1* are involved.

CNTNAP2 encodes a membrane protein located at the nodes of Ranvier of myelinated axons. The disruption of the expression of *CNTNAP2* alters the distribution of potassium channels in the nervous system, affecting action potential repolarization and conduction generating GTS symptoms [97]. A family comprising an affected father and two affected children with a chromosomal insertion/translocation involving chromosomes 2 and 7 exemplify the involvement of *CNTNAP2*. They shared a chromosome 2p21–p23 insertion on chromosome 7q35–q36 causing disruption of *CNTNAP2* [93]. However, the report of a balanced reciprocal translocation t(7;15)(q35;q26.1) in phenotypically normal individuals, despite disruption of *CNTNAP2* via the 7q35 breakpoint, suggests that truncation of the gene does not always lead to GTS symptoms [98].

■ Critical appraisal

Although the cause of GTS is poorly understood, genetic factors are thought to be the primary contributors to its pathogenesis, with environmental factors being proposed to have a smaller role. Converging lines of evidence suggest that GTS results from the combined effects of monogenic, multigenic and environmental causes.

However, identification of the causative gene mutations or risk alleles has proved to be challenging, as early studies focused on multigenerational lineages and suggested Mendelian inheritance, whereas subsequent segregation analyses suggested a more complex inheritance pattern. The identification of rare genetic mutations associated with the GTS phenotype highlighted the possibility that some cases of this disorder might be due to a single gene effect. Although mutations in an important domain of a gene may cause a monogenic form of disease, nucleotide variants in a noncritical region may enhance susceptibility to, or protect against, the disorder. Therefore, the identification of rare

copy number variants, including genomic deletions and duplications, has provided important information to develop more accurate etiological models for GTS, as well as related neurodevelopmental disorders. Finally, genome-wide association studies and exome sequencing have recently started providing useful insights into how susceptibility variants increase the heritability patterns of GTS.

Clinical implications

Genetic findings have improved our understanding of the possible pathogenic mechanisms of GTS, suggesting the involvement of multiple neurochemical systems (especially dopaminergic, noradrenergic and serotonergic). An improved understanding of the affected pathways can, in turn, lead to the development of new treatment strategies. The genetic heterogeneity of GTS is reflected in the varying phenotypic presentations. Classification systems consider GTS to be a unitary condition, yet investigations have demonstrated it to be a multidimensional disorder [99]. Clinicians have become increasingly familiar with the notion of a syndrome comprising three phenotypic clusters: 'simple GTS' (motor and phonic tics only); 'full blown GTS' (tic symptoms associated with paliphenomena, echophenomena and/or coprophenomena); and 'GTS plus' (including comorbid behavioral problems) [100]. Of these, the presence of specific obsessive–compulsive symptoms (e.g., checking, concerns for symmetry, counting/arithmomania, 'just right' perceptions and obsessional thoughts with vivid content) and possibly ADHD symptoms (predominantly hyperactivity/impulsivity in children and residual concentration problems in adults) might be related to the same neurotransmitter alterations that characterize GTS (Figure 2). Thus, a better understanding of the pathophysiological mechanisms of these common comorbidities is likely to play a major role in elucidating the genetics of GTS.

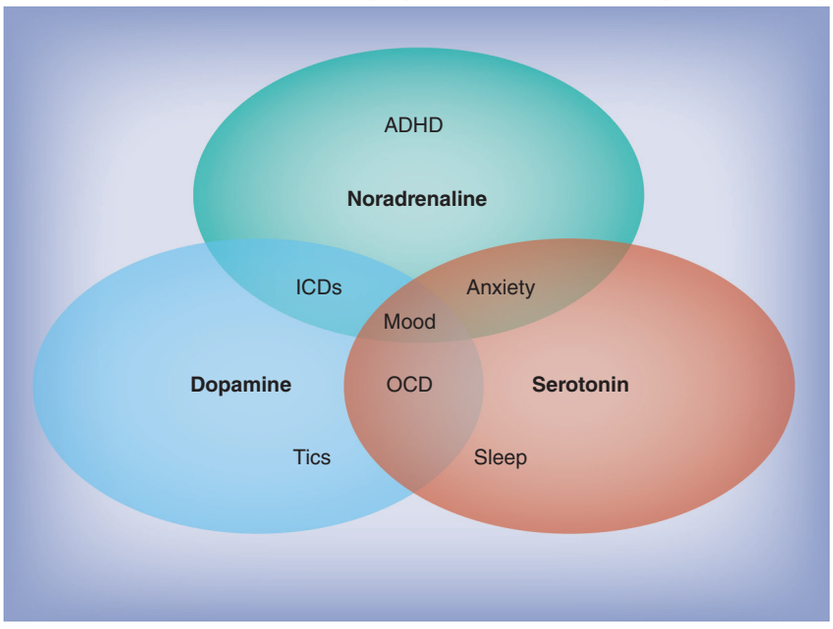

Figure 2. Involvement of different neurotransmitter systems in the phenotypic presentations of Gilles de la Tourette syndrome.
ICD: Impluse control disorder; OCD: Obsessive–compulsive disorder.

Numerous investigations highlight the variable responses of patients with GTS to behavioral, pharmacological and surgical interventions; arguably, treatment efficacy relates, at least in part, to phenotypic variation and may be traced to the underlying genetic heterogeneity of GTS.

Although far from being fully elucidated, the complex genetics of GTS is relevant to clinical practice. For example, many of the implicated genes point to a key problem with excitatory synapse formation during brain development. Medical treatments for GTS cross a range of pharmacological classes. Antidopaminergic agents encompassing both neuroleptics and atypical antipsychotics, as well as α-adrenergic agonists, are principle agents. The therapeutic repertoire also includes other agents with less established use. The efficacy of haloperidol, arguably the most effective agent for tic control, is variable, with an estimated 78–91% reduction in tics [101]. Atypical antipsychotics, such as risperidone and aripiprazole, also display variation in efficacy. Most studies demonstrated a positive response with risperidone [102,103], as success rates of 30–62% have been reported [104,105]. In a study assessing the efficacy of risperidone in 14 children, doses were titrated from 0.5 to 3.5 mg/day and tic severity ratings were recorded from baseline and over 8 weeks of treatment. In the final week efficacy was 85.7% [106]. Aripiprazole poses as a newer well-tolerated agent, efficacious for tic reduction and improvement in behavioral symptoms, for both adults and young patients [102]. Both efficacy and development of adverse effects may be related to genotype/phenotype variability. Comprehensive investigations have studied aripiprazole's adverse effect profile [107,108]. Variable metabolic responses induced by agents such as aripiprazole

and pimozide, relating to glycemic control and hypercholesterolemia, present as one example of a variable response that may be traced to genetic heterogeneity [109]. α2-agonists are indicated in patients with comorbid ADHD [110,111], suggesting a variation in response according to phenotype. Variable responses in accordance with phenotype were reflected in a European-wide survey considering the prescribing habits for five key symptomatic domains of GTS (tics, ADHD symptoms, obsessive–compulsive symptoms, anxiety and depression). This study demonstrated considerable variation in a choice of agents prescribed and dosage used, which is driven by phenotypic heterogeneity and medication responses, in addition to variations in licensing laws across different countries [112].

Further clarification of underlying genetics will allow for an improved understanding of phenotypic manifestations, in turn aiding the development of target-specific treatments. Deep-brain stimulation has been advocated for selected cases of GTS. Despite variations in selection criteria, pre-/post-operative assessments and stimulation targets, patients with significant tic-related functional impairment and who are unresponsive to conventional therapies make the best candidates [113,114]. Better delineation of clinical phenotypes may provide a clearer method of patient selection for surgery and aid in locating optimal neuroanatomical targets. Likewise, optimal clinical phenotyping may aid in the selection of behavioral therapies designed to target particular or most prominent symptomatic features [115,116]. Habit reversal training, for instance, has been reported to be particularly efficacious in treating motor tics, leading to improvements of 89–96% in four children [117], and improvement of vocal tics by 38–96% [118].

Conclusion & future perspective

Unraveling the genetic underpinnings of GTS is complicated by the intrinsic symptomatic heterogeneity of the disease and the presence of comorbidities. GTS is a genetically heterogeneous condition, encompassing a complex combination of monogenic, multigenic and environmental factors [20].

There has been limited success in identifying specific genes, with conflicting findings and inconsistent results. Over the last 20 years, the single major gene approach has been characterized by major/critical limitations. New approaches in genetics may allow for further discoveries, such as whole-genome sequencing and epigenomics, and, in particular, the study of gene sets or gene networks. Well-characterized populations with better demarcated, homogeneous phenotypic groupings will be crucial in providing the genetic resource for future studies [119]. Large collaborative studies are likely to be key to future success in determining important genetic influences in the disease.

It is anticipated that increased knowledge of the genetic factors in GTS will enhance our understanding of the therapeutic response in the disorder, including refractoriness, and aid in the development of new therapies.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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