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The Genetics of Tourette Syndrome: A review

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Abstract

Objectives—This paper summarizes and evaluates recent advances in the genetics of Gilles de la Tourette Syndrome (GTS).

Methods—This is a review of recent literature focusing on: 1) the genetic etiology of GTS; 2) common genetic components of GTS, Attention Deficit Hyperactivity Disorder (ADHD), and Obsessive Compulsive Disorder (OCD); 3) recent linkage studies of GTS; 4) chromosomal translocations in GTS; and 5) candidate gene studies.

Results—Family, twin and segregation studies provide strong evidence for the genetic nature of GTS. GTS is a heterogeneous disorder with complex inheritance patterns and phenotypic manifestations. Family studies of GTS and OCD indicate that an early onset form of OCD is likely to share common genetic factors with GTS. While there apparently is an etiological relationship between GTS and ADHD, it appears that the common form of ADHD does not share genetic factors with GTS. The largest genome wide linkage study to date observed evidence for linkage on chromosome 2p23.2 ($P=3.8 \times 10^{-5}$). No causative candidate genes have been identified, and recent studies suggest that the newly identified candidate gene *SLITRK1* is not a major risk gene for the majority of individuals with GTS.

Conclusion—The genetics of GTS are complex and not well understood. The Genome Wide Association Study (GWAS) design can hopefully overcome the limitations of linkage and candidate gene studies. However, large-scale collaborations are needed to provide enough power to utilize the GWAS design for discovery of causative mutations. Knowledge of susceptibility mutations and biological pathways involved should eventually lead to new treatment paradigms for GTS.

Keywords

Tourette's Disorder; Genetics; Family study; Review

In the original description of the syndrome that bears his name, Georges Gilles de la Tourette observed that the disorder was familial [1]. Subsequently, there has been considerable research devoted to systematically examining whether that original observation could be replicated and whether the observed familiarity is due in part to genetic factors. These studies have included family studies, twin studies, genetic linkage studies and genetic association (candidate gene)

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studies. This review is based on the comprehensive literature search of Pubmed database with keywords such as Gilles de la Tourette, Tourette Syndrome, Tourette Disorder, GTS, ADHD, and OCD.

Family Studies

Family studies have repeatedly demonstrated that Gilles de la Tourette Syndrome (GTS) is highly familial. Establishing that there is familial aggregation does not “prove” that the disorder is influenced only by genetic factors, since family members also share common environmental factors. Nevertheless, results from these studies provide an important first step for determining whether genetic factors are important in the manifestation of the condition. Since first degree relatives share on average 50% of their genetic material, it is expected that the first degree relatives of an individual affected with a genetic disorder will have a greater chance of also being affected with that disorder compared to the general population [2]. Results from GTS family studies consistently show a 10 to 100 fold increase in the rates of GTS in first-degree relatives when compared to those rates in the general population [3–12] making it one of the most heritable childhood onset neuropsychiatric conditions [13]. Furthermore, chronic tics (CT) also occur significantly more frequently (reports range from 7 to 22%) among first degree relatives of GTS probands compared to relatives of control probands, suggesting that CT is a manifestation of the same underlying genetic susceptibility as GTS [3–12].

The vast majority of clinically referred GTS individuals have comorbid psychiatric conditions; in fact only about 10–15% of individuals with GTS have no comorbidities [14,15]. Obsessive Compulsive Disorder (OCD) and Attention Deficit Hyperactivity Disorder (ADHD) are the most common GTS-related comorbidities, each affecting over 50% of GTS individuals [11, 14,16,17]. These rates are significantly greater than those in the general population (e.g., 1.1 to 3.3% for OCD [18,19], and 5% for ADHD in school age children [20]), suggesting that these disorders may also have some shared underlying etiological mechanisms with GTS. Understanding the etiology of comorbid GTS conditions is especially critical, as children with comorbid diagnoses exhibit greater psychopathological burden [21], have more severe tic symptoms [15], and are at higher risk for aggressive behaviors and frequent anger outbursts [14,22,23].

In addition to demonstrating that GTS is familial, the family study design can be utilized to examine the familial relationship between GTS and its comorbid disorders. That is, if the hypothesis of shared genes is correct, then first degree relatives of a proband with GTS will have an increased risk of the comorbid disorder when compared to the general population.

Examining the relationship between GTS and OCD

OCD is a common psychiatric disorder, with both childhood and adult onset forms, and is characterized by intrusive thoughts and images (i.e., obsessions) and ritualized repetitive behaviors (i.e., compulsions). Twin and family studies have demonstrated that there is a significant genetic component in the etiology of OCD, especially in the childhood onset form [24].

Increased rates of OCD have been reported in family studies of GTS-ascertained probands. Pauls and colleagues reported increased rates of OCD without tics among relatives of GTS probands even when the probands did not have OCD themselves [25]. In a larger follow-up study, Pauls and colleagues observed that the gender of the proband did not affect the rate of either OCD or tics in the relatives [6]. However, the gender of the relative was associated with the risk of GTS and OCD, such that female relatives were more likely to develop OCD without tics, while male relatives were more likely to develop tic disorders [6]. Subsequent family studies support this finding [7–9,26,27], providing evidence that OCD may be a sex-influenced

phenotype of GTS or CT. Thus it appears that GTS, CT, and some forms of OCD are likely to have a common underlying susceptibility.

Results from family studies of OCD-ascertained families have also supported this conclusion, though the relationship is more complex. It has been observed that childhood onset OCD in probands is associated with greater rates of GTS and tics in their relatives [28,29]. Furthermore, individuals with early onset of OCD appear more likely to have a tic disorder than individuals with adult-onset OCD [28,30], and relatives of female OCD probands have a greater risk of developing tic disorders [28]. These investigators have also observed a much higher rate of GTS and tics among relatives of OCD probands who had family histories of OCD (7.4% vs. 1.4%) compared to relatives of probands without a family history of OCD [28], suggesting that non-familial OCD is not associated with tic disorders. However, in contrast to the family studies of GTS summarized above in which all GTS families had higher rates of OCD regardless of whether the proband had GTS and OCD, some OCD family studies have demonstrated that OCD probands with tics have higher rates of tics in first degree relatives (10.6%), compared with only 3.2% of the relatives of OCD probands without tics [28], though this finding was not fully replicated in a subsequent sample [31]. Thus results from OCD family studies suggest that there may be different types of OCD (adult onset and childhood-onset), with only the childhood-onset form likely to share common genetic factors with GTS. However it is still unclear whether there is an additional subtype of early onset OCD that is unrelated to tics.

Examining the relationship between GTS and ADHD

ADHD is one of the most common childhood-onset developmental disorders [20], characterized by hyperactivity, impulsivity, and inattentiveness. ADHD has a significant genetic component, with 70–80% of risk believed to be due to genetic causes [32]. The familial relationship between GTS and ADHD is not fully understood, but it is becoming clear that, unlike the relationship between GTS and OCD, the most common form of ADHD does not appear to have a shared underlying susceptibility with GTS. Comings and Comings [33] proposed that ADHD represented a variant expression of the same genetic factors responsible for GTS [33,34]. However, several later studies did not find support for this hypothesis [2, 12,35]. While an increased rate of ADHD has been observed among the first degree relatives of GTS probands, even when the probands themselves did not have ADHD, that increase appears to be due to an increased rate of comorbid GTS+ADHD among those relatives who also had a diagnosis of GTS. In other words, rates of ADHD alone were not elevated in the relatives of GTS probands who did not themselves also have ADHD, suggesting that the “pure” form of ADHD is not present at an increased frequency in these families [2,12,35], but instead exists only when these disorders co-occur in the same individual. Recent work [36] demonstrated that a comorbid diagnosis of GTS and ADHD in a relative of a GTS or ADHD proband was strongly associated with an OCD diagnosis of that proband, and that comorbid GTS and ADHD diagnoses in a relative was associated with some degree of OC symptoms in the same individual [36]. These results suggest that there may be a GTS/OCD/ADHD familial subtype, which might be associated with an increased genetic burden and could represent a more severe form of GTS [37].

Several observations support this hypothesis. First, it has been reported that comorbid conditions are more frequent in GTS than in other less severe tic disorders. In a recent Swedish study of school-aged children, 66% of the GTS cases had comorbid ADHD compared to 33% of children with chronic vocal tics, 12% of children with chronic motor tics, and just 4% of children with transient motor tics [17]. A similar gradient was observed in the rates of OCD, as well as in the total number of comorbid disorders [17]. Another study found 44% of children with GTS had comorbid ADHD, compared with 23% of children with chronic tics, and 54% of children with GTS had comorbid OCD, compared with 8% of children with chronic tics

[11]. Second, an increased genetic burden appears to influence the risk of GTS and comorbid disorders. In a prospective study of children at risk for GTS, children of two GTS-affected parents had three times greater risk of developing ADHD compared to the children of one affected parent, and two times greater risk of developing either tics, ADHD, or OCD [38]. Third, there is some evidence that comorbid GTS/OCD/ADHD may be heritable. A recent latent class analysis of 952 individuals from 222 GTS families was performed to identify GTS subphenotypes based on diagnoses of GTS, OCD, OC symptoms and ADHD [39]. The investigators identified five classes of categorical GTS subphenotypes, of which only the comorbid GTS/OCD/ADHD class was highly heritable [39]. In addition, 34% of all GTS affected individuals had comorbid OCD and ADHD, while only 10% had comorbid ADHD without OCD [39]. Another study of almost 6,000 GTS affected individuals also found a significant increase in OCD and other psychiatric disorders in individuals with comorbid GTS and ADHD compared to individuals with GTS without ADHD [16]. Finally, individuals with comorbid conditions may exhibit a specific subset of symptoms. The evaluation of GTS symptoms in 410 GTS patients utilizing principal component analysis found that individuals who have GTS comorbid with ADHD or OCD are more likely to exhibit socially inappropriate behaviors and other complex vocal tics [40]. Further family studies of GTS-ascertained probands which would include GTS only, OCD only, ADHD only, comorbid GTS and ADHD, comorbid GTS and OCD, and comorbid GTS/OCD/ADHD probands and their relatives would help in understanding of the genetics of GTS and its comorbid disorders.

Segregation Analyses

Results from segregation analyses of family studies have been consistent with the hypothesis that GTS is genetically transmitted [7,8,26,41–49]. The majority of these studies support the hypothesis of at least one genetic locus with major effect, though in retrospect each indicate the likelihood of many additional genetic loci and/or the presence of genetic heterogeneity [7,8,26,42,44,46–49]. Several investigators have observed bilineal transmission [27,50–52] in a number of GTS and CT families, raising the possibility of nonrandom selection of partners for marriage (assortative mating). This fact further complicates the interpretation of segregation analyses, since the majority of these studies were performed under the assumption of random mating.

Twin Studies

Twin studies provide strong evidence for the genetic nature of GTS. The largest study included 30 monozygotic and 13 dizygotic pairs of twins [53]. These investigators utilized phone-based assessment and found that 77% of monozygotic twins were concordant for tic disorders (CT or GTS), but only 23% of dizygotic twins were concordant for these disorders [53]. Furthermore, the concordance rate of monozygotic twins reached 100% for GTS or CT when direct observational interviews were conducted [47]. In a second smaller study of 16 pairs of monozygotic twins, 56% of MZ twins were concordant for GTS and 94% were concordant for tic disorders [54]. High concordance rates for tic disorders in monozygotic twins suggest that GTS is a genetic disorder and that CMT and GTS are genetically related.

Linkage Analyses

Five genome wide linkage analyses have been performed to date [55–59]. The Tourette Syndrome Association International Consortium for Genetics (TSAICG) has conducted the largest of these genetic linkage studies. Their sample represents a joint analysis of most of the individuals contained in the four previous studies and consists of 238 nuclear families and 18 large multigenerational families totaling 2,040 individuals [59]. Both parametric and non-parametric analyses were performed using two diagnostic classifications: 1) GTS alone; 2) combination of either GTS or CT. Strong evidence for linkage was observed in the

multigenerational families for markers on chromosome 2p23.2 using the combined phenotype of GTS or CT, with suggestive evidence for linkage on chromosomes 5p, and 6p. A combined analysis including both affected sib pair and multigenerational families showed a slightly increased linkage signal on 2p, and the fine mapping of the 15 centiMorgan (cM) critical region yielded a signal with an empirical $p=3.8 \times 10^{-5}$.

Subsequent linkage analyses of the large families provide additional evidence that GTS may be genetically heterogeneous. A heat map, shown in Figure 1, indicates the individual family Z scores on chromosome 2 for each of fifteen multigenerational families. Most of the families have positive linkage signals on chromosome 2p; however comparison across families indicates the absence of linkage in some families (Family 5, and likely Families 1 and 6). Furthermore, some families appear to have strong (Z score >3.719) linkage signals further along chromosome 2: Family 11 at D2S2216, Family 14 at D2S352 and D2S2368, and Family 15 at D2S2259. Thus, heterogeneity could partially explain the inconsistent results from previous linkage studies, as recently reviewed by Scharf and Pauls [60].

Chromosomal Translocations

Another valuable approach for identifying disease genes is the identification of chromosomal aberrations in patients. Translocations, duplications or deletions of large chromosome segments can be visualized by karyotyping or fluorescence in situ hybridization (FISH). Newer methods for detection of duplications or deletions ranging from ~1kb to several Mb in size, referred to as copy number variations (CNVs), have identified *de novo* and inherited CNVs associated with risk of many neuropsychiatric disorders [61–65].

The only study that systematically examined structural variation of chromosomes in GTS has karyotyped 68 consecutive patients and has identified one individual with XYY chromosome, and two individuals with normal heterochromatin variations on chromosomes 1 and 9 [66]. Since karyotyping can only detect duplications and deletions larger than 5 megabases, the rate of structural abnormalities could be significantly greater if newer techniques such as chromosomal microarrays (CMA) are utilized. In fact, a recent study of children with Autism Spectrum Disorders has detected abnormal karyotype in 2.2% of patients, and CMA identified deletions or duplications in 18.2% of patients [67]. Although, less than a half of the detected CMA deletions or duplications could be considered as abnormal CNV (variants associated with known genetic disorders), possibly reflecting normal structural variations in the genome [68].

Three chromosomal regions (7q22-q31, 8q13-q22, and 18q22) have been reported in the literature in at least two independent translocations and have been observed to co-segregate with GTS, CT, or OCD in several family members. In addition, two independent cases of translocation and deletion of 17p11 in GTS affected individuals were recently reported [69, 70].

7q22-q31: Three groups have reported rearrangements on 7q22-q31: one large family consisted of nine individuals with a balanced translocation $t(7;18)(q22-31;q22)$, in which six individuals were affected with GTS or CT [71]; a single GTS patient had a duplication of 7q22-q31 [72]. Lastly, a third GTS patient was reported with a *de novo* duplication of the long arm of chromosome 7 [46, XY, $dup(7)(q22.1-q31.1)$] [73]. Mapping of the breakpoints implicated disruption of the inner mitochondrial membrane peptidase 2-like (IMMP2L); however recent screening of 39 GTS individuals did not find any coding mutations [74].

8q13-8q22: Three separate instances of a translocation breakpoint on 8q have been described in GTS: two isolated cases with breakpoints on 8q13 [75] and a the third which included a father and six children with a $t(1;8)(q21;q22)$ translocation [76], with four children reported to have GTS or tics.

18q22: Four independent translocations or deletions involving 18q22 have been reported: an 18q22 deletion [77], an 18q21-q22 inversion [78], a t(2;18)(p12;q22) translocation [79]; and the t(7;18)(q22-31;q22) translocation [71].

Two children with GTS, OCD, and mental retardation had an insertion of 2p21-23 within 7q35-36, resulting in trisomy of 2p21-23 and disruption of 7q35-36 [80]. The trisomy of 2p21-23 is especially notable, since this region overlaps with the 2p23.2 linkage signal in the TSAICG linkage study as discussed above [59]. Another recent study described the translocation t(7;15)(q35;q26.1) in phenotypically normal individuals [81].

Finally, two earlier reports have indicated possible involvement of 9p locus: 9p terminal deletion in a 16 year old male with GTS, developmental delays, and dysmorphic features [82]; and triple X and 9p mosaicism in a woman with mild mental retardation, seizures and aggressive outbursts [83].

Candidate Gene Studies

Candidate gene studies have focused mainly on genes involved in the dopaminergic pathway due to the fact that dopamine antagonists are the most effective medications for tic suppression. As shown in Table 1, similar to findings in other complex disorders [84], candidate gene association studies in GTS have not yielded any clearly replicated results that unequivocally identify a causative GTS susceptibility gene. It is likely that most of these candidate genes tested are not involved in the etiology of GTS, since candidate gene selection is a subjective process, complicated by the lack of clear understanding of the biological pathways involved in GTS. In addition small study sizes are significantly underpowered to detect genes with small-to-medium effect sizes.

Recently, Abelson and colleagues identified a patient affected with GTS and ADHD with a *de novo* chromosome 13 inversion, inv(13)(q31.1;q33.1) [85,86]. Out of three genes that mapped within 500 kilobases of the chromosomal breakpoints, the Slit and Trk-like family member 1 (*SLITRK1*) was selected for further study based on its homology to the axon guidance molecule SLIT. *SLITRK1* was screened in 174 GTS affected individuals, and three subjects were found to carry functional variations in this gene: One frameshift mutation and two unrelated occurrences of a sequence variation in the 3' untranslated region of the gene (var321) that disrupted the binding site for a microRNA miR-189. These variants were absent from 3,600 and 4,296 control chromosomes respectively [85]. While another study [87] detected two independent, novel, non-synonymous sequence changes in *SLITRK1* in a set of 44 families with trichotillomania, an OCD-spectrum disorder that has been previously hypothesized to be genetically related to GTS, additional studies in GTS and OCD samples have failed to replicate association with these variants (Table 2) [86,88–93]. The largest study to date screened over 1,000 patients with GTS and found only two var321-positive individuals, one in a GTS patient and the other in a mother of a GTS patient who herself had OCD, but no tics. Both patients failed to transmit this mutation to their GTS affected offspring. While this study does not support a role for var321 in GTS, it should also be noted that due to the low frequency of *SLITRK1* var321 in the general population (0.1%), even this sample size of 1000 cases is markedly underpowered to detect an association of such a rare allele [88]. Another large study evaluated 307 Costa Rican and 515 Ashkenazi patients for association between GTS and *SLITRK1* [86]. No var321 alleles were identified in the Costa Rican sample, but five instances of var321 were found in Ashkenazi GTS patients, two of whom transmitted var321 to affected children. This high number of *SLITRK1* var321 polymorphisms in the Ashkenazi sample prompted analysis of this variant in 256 Ashkenazi control individuals. One unaffected Ashkenazi individual was identified with *SLITRK1* var321, suggesting overrepresentation of the var321 polymorphism in Ashkenazi Jews and raising the possibility that population

stratification of Ashkenazis in GTS cases compared to controls might account for the association between GTS and *SLITRK1* var321 in the original study [86]. Finally, a recent study by Miranda et al. [94] screened 208 GTS affected children from 154 nuclear families for association between common single nucleotide polymorphisms (SNPs) in *SLITRK1* and GTS. This study detected a significant association of a common single polymorphism and of a haplotype of three tagging SNPs located in *SLITRK1*, albeit at an experiment-wide threshold of $p < 0.05$ following permutation. Future studies of larger samples will be needed to attempt to replicate this finding.

Analysis of three large multigenerational GTS families also has not detected any *SLITRK1* mutations [91,95–97]. However, in large families only founder individuals are informative and thus it would be extremely unlikely to detect this rare mutation in large families.

Future directions

Recent advances in cataloging human genetic polymorphisms, in addition to the decreasing cost of high throughput SNP genotyping and the development of statistical methodology to analyze large sample sets in a rigorous manner have made genome-wide association studies (GWAS) a feasible method for genetic studies of complex disorders [84]. Based on the hypothesis that a proportion of the genetic susceptibility for common diseases may be caused by common genetic variants that arose early in human history and thus are shared across members of a population derived from a common set of ancestors (the common-disease, common variant or CDCV hypothesis), this approach has been remarkably successful, with over 150 common variants identified within the past 2 years [84,98].

Genome-Wide Association Studies provide several advantages over linkage and candidate gene studies. With a sufficiently large sample, it is possible to overcome the lack of power in linkage analyses to detect common alleles with low penetrance. GWAS can also detect much smaller associated DNA regions compared to linkage studies, since linkage analyses are based on rare recombination events in only a few generations, thus resulting in large linked regions. Unlike linkage analyses, GWAS rely on historical recombination events in populations over the course of human history, thus resulting in much smaller regions of association. Furthermore, a great advantage of GWAS over candidate genes studies is the fact that GWAS assume no prior biological knowledge of the disease process, but instead test for association across the whole genome in an agnostic approach. Newer GWAS genotyping platforms now also have the additional benefit of containing copy-number probes to allow examination of both SNPs and CNVs in a single experiment [99,100].

For conducting GWAS it is critical that the sample is sufficiently large to provide enough statistical power to reduce Type I error and detect an association. The power of GWAS to detect an association is dependent both on the allele frequency of the disease variant as well as its effect size, expressed as a genotype relative risk (GRR). GRR is defined as the probability of a person with a specific disease variant to have a disease compared to the probability of a person without that gene variant. Larger sample sizes are required to detect alleles of low frequency or of small effect.

As can be seen in Figure 2, for $GRR=1.2$ the number of cases and controls needed to detect a causative allele reduces from about 23,000 at minor allele frequency (MAF) =5% to ~ 8,000 at MAF=20% and to ~6,000 at MAF=40%. The effect of GRR on the study size is even greater: at MAF=10% and GRR 1.1, about 47,000 cases and controls are needed, but as GRR increases to 1.2, 1.3, 1.5, 1.7, and 2.0 the required number of individuals decreases to ~12,500, ~6,000, 2,300, 1,300, and 700 respectively. For instance, a GWAS for age-related macular degeneration (AMD) of only 96 cases and 50 controls was able to detect an association with a common variant in the complement factor H gene (CFH) at a nominal P value $< 10^{-7}$ [101]. The power

to detect this association was due to the high GRR caused by CFH variant: the presence of two risk alleles in an individual increased risk of developing AMD by a factor of 7.4 [101]. On the other hand, in order to detect alleles with modest effect sizes, tens of thousands of cases and controls could be needed, as demonstrated by studies on human height variation with a combined sample size of ~63,000 individuals [102–104]. These studies found 54 variants, each with an average size effect of 0.4 cm per allele, indicating that an even larger sample size maybe needed to detect common, small-effect alleles responsible for the residual population variance [105].

As described above, GWAS are designed specifically to detect association of common disease variants (typically with allele frequencies $\geq 5\%$ in a population) [106]; GWAS have essentially no power to detect multiple rare variants in either the same gene or in different genes (the multiple rare variants hypothesis) [107]. However the ability to detect CNVs is a promising parallel approach, since these polymorphisms appear to exist both in common and rare forms and have been demonstrated to contribute to the manifestation of other psychiatric disorders such as autism [62] and schizophrenia [65]. In addition, rare, highly penetrant CNVs can be detected in a relatively small sample size, as demonstrated by studies of schizophrenia which consisted of about 150 individuals [63,108].

What has become evident in GWAS of other diseases is that large-scale, multi-center collaborations are needed to obtain a sample sufficiently large enough to provide adequate power for a GWAS. A recent genome-wide association analysis of bipolar disorder, which combined three datasets [109–111] totaling over 4300 cases and 6200 controls [109], detected two markers with genome wide significant association. Combining the datasets was instrumental in providing enough power to reach a genome-wide level of statistical significance, since none of these associations were detected in the individual samples.

In collaboration with other investigators, the TSAICG has undertaken a GWAS for GTS. The GTS GWAS should help identify short genomic segments (either SNPs or CNVs) harboring susceptibility genes for GTS. Once these genes are identified, research can be initiated to elucidate the biological pathways and processes influencing the development of the GTS phenotype. These pathways will hopefully reveal cellular and molecular mechanisms previously unsuspected in GTS pathogenesis, and thus could help to develop new treatment paradigms to significantly reduce the suffering experienced by individuals with GTS and related disorders.

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X	Z	Colors
>4	>3.719	
3~4	3.09~3.719	
2~3	2.326~3.09	
1~2	1.282~2.326	
0~1	0~1.282	
<0	<0	

Figure 1.

Heat map of chromosome 2 linkage analysis from 15 large multigenerational pedigrees [59].

$X = -\log(P)$ if $Z > 0$ and $X = \log(1-P)$ if $Z < 0$

Positive Z scores indicate an increased likelihood of linkage, while negative Z scores indicate a decreased likelihood of linkage.

No single locus shows moderate or significant linkage across all pedigrees, suggesting that there is genetic heterogeneity of GTS, although low positive Z scores can also indicate the lack of power in a particular family to reach a significant threshold for linkage. The most significant overall linkage at D2S319 (Z score >3.719) resulted from one pedigree with a high Z score (3.09~3.719), and 8 pedigrees with moderate Z scores (2.326~3.09). The adjacent marker

D2S2211 has only a moderately significant overall Z score because fewer pedigrees with moderate Z scores (2.326~3.09) contribute.

Furthermore the map shows three different pedigrees with strong evidence for linkage (Z score >3.719) at adjacent loci on chromosome 2: Family 11 at D2S2216, Family 14 at D2S352 and D2S2368, and Family 15 at D2S2259. However, the summed Z scores for these markers across all 15 pedigrees are only moderately positive, indicating that in the majority of tested pedigrees these loci either do not have enough power to detect linkage or do not contribute to the susceptibility to GTS.

Figure 2.

The number of cases and controls required in an association study to achieve 80% power across a range of minor allele frequencies (MAF) and genotype relative risks (GRR) for a multiplicative model. GTS prevalence was set at 2% (1% GTS genes + 1% OCD genes) and linkage disequilibrium between marker and causative allele was set to 1. Power calculations were performed for Type I error rate (alpha) of $p < 5 \times 10^{-8}$ as required to reach a Bonferroni corrected $p < 0.05$ significance level for ~ 1million independent tests performed in a GWAS [162]. Calculations were performed with the Genetic Power Calculator [163].

Table 1

Summary of the candidate gene studies, adopted from Scharf and Pauls [60].

Gene	Findings	References
Dopamine Receptor D ₁ (DRD1)	No linkage/association to GTS/CMT	[112-115]
	Positive association with tic severity	[116]
Dopamine Receptor D ₂ (DRD2) *	No linkage/association to GTS/CMT	[117-121]
Dopamine Receptor D ₃ (DRD3)	Positive association with GTS	[122-125]
	No linkage/association to GTS/CMT	[112,120,126-128]
	Positive association with GTS	[129]
Dopamine Receptor D ₄ (DRD4) *	No linkage/association to GTS/CMT	[112,116,130-132]
	Positive association with GTS/CMT; positive association with comorbid OCD and tics	[120,133,134]
Dopamine Receptor D ₅ (DRD5)	No linkage/association to GTS/CMT	[112,135]
Tyrosine hydroxylase (TH)	No linkage to GTS/CMT	[112,130]
Dopamine β-hydroxylase (DBH)	No linkage to GTS/CMT	[112,136]
	Positive association with GTS	[123,136]
Dopamine-associated transporter (DAT1, SLC6A3)	No linkage/association to GTS/CMT	[116,120,137,138]
	Positive association with GTS	[123,139,140]
Monoamine oxidase A (MAOA) *	Positive association with GTS	[120,141]
Catechol-O-methyltransferase (COMT)	No linkage/association to GTS/CMT	[116,142,143]
α _{1c} - and α _{2c} - and α _{2a} - Adrenergic receptors	No linkage/association to GTS/CMT	[144,145]
Norepinephrine transporter (NET, SLC6A2)	No association with GTS	[146,147]
Serotonin transporter (5HTTLPR)	No association with GTS	[143]
β ₂ -Adrenergic receptor	No linkage to GTS/CMT	[148]
Serotonin receptor (5-HT1A) *	No linkage, association to GTS/CMT	[149,150]
Serotonin receptor (5-HT2A)	Positive association with GTS and OCD	[151,152]
Serotonin receptor 5-HT3A and 5-HT3B	No association with GTS	[153]
Serotonin receptor 5-HT7	No linkage to GTS/CMT	[154]
Tryptophan oxidase	No linkage to GTS/CMT	[149]
	Positive association with GTS	[155]
γ-Aminobutyric acid-A receptor α1, α2, α6, β1, γ2 subunits	No linkage to GTS/CMT	[148]
Androgen Receptor (AR)	Positive association with comorbid GTS and ADHD	[156]
Huntingtin	No association with GTS	[157]
HLA-DR	No association with GTS	[158]
Myelin oligodendrocyte glycoprotein (MOG)	Positive weak association with GTS	[159]
SLITRK1 pathway genes (ROBO3 and ROBO4)	No association with GTS	[160]
TPH2	Positive association with GTS	[161]

*

Indicates positive associations that have been reproduced in more than one study

Table 2Summary of the findings for *SLITRK1* gene.

Analysis	Results	Reference
Sequencing, SNP genotyping	Identified one frameshift mutation and two var321 alleles in 174 unrelated probands, these variants were absent from 3600 and 4296 control chromosomes respectively.	[85]
SNP genotyping	Out of 1048 GTS or CT affected individuals, only one had var321 present, but did not transmit it to the affected offspring.	[88]
Sequencing	Sequenced 82 Caucasian patients with TS from North America. No var321 alleles found. Novel Ile236Ile variant found in one GTS patient.	[89]
Sequencing	No var321 alleles found in 160 Taiwanese children with GTS.	[90]
SNP Genotyping	No var321 alleles found in 307 Costa Rican patients. Five var321 alleles found in 515 Ashkenazi patients, two of whom transmitted var321 to affected children. One in 256 Ashkenazi control individuals also had var321, suggesting overrepresentation of this variant in this population.	[86]
SNP Genotyping	No var321 or frameshift mutation found in 208 affected children. Haplotype analysis found significant association with GTS, making this the first study to support the original study that found <i>SLITRK1</i> association with GTS.	[94]
Sequencing	No var321 alleles or frameshift mutations found in 92 Austrian patients with GTS. One female patient and two affected patients were found to carry a variant within 3' untranslated region, which was absent from 192 controls.	[93]