Published in final edited form as:
J Obsessive Compuls Relat Disord. 2014 October 1; 3(4): 380–385. doi:10.1016/j.jocrd.2014.06.003.

The Inheritance of Tourette Disorder: A review

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Abstract

Georges Gilles de la Tourette, in describing the syndrome that now bears his name, observed that the condition aggregated within families. Over the last three decades, numerous studies have confirmed this observation, and demonstrated that familial clustering is due in part to genetic factors. Recent studies are beginning to provide clues about the underlying genetic mechanisms important for the manifestation of some cases of Tourette Disorder (TD). Evidence has come from different study designs, such as nuclear families, twins, multigenerational families, and case-control samples, together examining the broad spectrum of genetic variation including cytogenetic abnormalities, copy number variants, genome-wide association of common variants, and sequencing studies targeting rare and/or *de novo* variation. Each of these classes of genetic variation holds promise for identifying the causative genes and biological pathways contributing to this paradigmatic neuropsychiatric disorder.

Keywords

Tourette Disorder; Genetics; Review; OCD; ADHD

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Financial Interest/Conflict of Interest: None of the authors have conflicts of interest related to this article.

INTRODUCTION

Georges Gilles de la Tourette, in describing the syndrome that now bears his name, observed that the condition was familial[1]. Over the last three decades, numerous studies have confirmed this observation, demonstrated that familiality is in part due to genetic factors, and are now beginning to provide clues about some of the underlying genetic mechanisms important for the manifestation of Tourette Disorder (TD). These studies include family, twin, linkage, candidate gene, cytogenetic, copy number variant, and genome-wide association studies.

The history of the genetics of TD has been similar, in many respects, to that described for other disorders with complex inheritance. However, in contrast to the efforts for other neuropsychiatric disorders of childhood (e.g., autism and attention-deficit/hyperactivity disorder (ADHD)), the scale of genetic research focused on TD has been relatively modest. The types of resources that have been efficacious in other areas of psychiatry and clinical neuroscience, including large patient cohorts and widely accessible biomaterials, are just now becoming available, and offer tremendous promise for upcoming discovery and confirmation of genetic mechanisms of TD.

METHODS

An extensive literature search of all studies dealing with the inheritance of Tourette Disorder.

RESULTS

Family Studies

Results from all family studies have revealed that TD is familial, i.e., that it aggregates in families. However, these results do not “prove” that TD is influenced by genetic factors, since members of the same family also share environmental factors. Nevertheless, results from family studies provide an important first step in determining whether genetic factors are important in increasing risk for a disorder. First degree relatives (parents, siblings, and children) share on average 50% of their genetic material; thus, first degree relatives of an individual with a genetic condition will have a greater chance of also being affected when compared to the risk in the general population[2]. The risk of TD in first degree relatives of affected individuals is 10 to 100 times higher than the prevalence of TD in the general population (see [3] for review). This degree of familial enrichment makes TD one of the most heritable childhood-onset neuropsychiatric conditions[4]. Furthermore, the rates of chronic tic disorders (CT) (chronic multiple motor or phonic tic disorder) are also significantly higher (from 7 to 22%) among first degree relatives of TD than controls, which supports the hypothesis that CT and TD are genetically related[3].

Most individuals with TD seen in a clinic also have additional neuropsychiatric conditions, with Obsessive Compulsive Disorder (OCD) and ADHD being the two most common TD-related comorbid conditions[5]. The prevalence of OCD and ADHD are significantly higher among individuals with TD than those in the general population (10 to 25 times higher),

suggesting that these disorders may share some etiological factors with TD. Since children with comorbid conditions exhibit a much higher psychopathological burden than those with an isolated disorder[6], it is critical to understand the etiology of these conditions and, in particular, to examine whether they share common genetic underpinnings. Results from a recent family study of TD, OCD, and ADHD support the hypothesis that these three conditions have some shared etiology[7].

Twin Studies

While only two TD twin studies have been published, the findings in those studies provide strong evidence that genetic factors play a role in the manifestation of TD. Price et al.[8] reported that monozygotic (MZ) twin concordance rates ranged between 50%–77%, depending on the diagnosis used in the analysis, compared to 10%–23% for dizygotic (DZ) twins. In a later study of 16 pairs of MZ twins, Hyde et al.[9] reported that 56% of MZ twins were concordant for TD and 94% were concordant for tic disorders, suggesting that CT and TD are genetically related. More recent population-based twin studies of tics also support a genetic etiology, though the heritability estimates are slightly more modest[10].

Segregation Analyses

The goal of segregation analysis is to test the hypothesis that the transmission of phenotype within families is consistent with genetic transmission. Results from all segregation analyses of family studies demonstrate that the transmission of TD within families can be explained by a genetic model[4]. While the majority of these studies support the hypothesis of at least one genetic locus with major effect, a more parsimonious interpretation of the findings is that the transmission is complex, with the likelihood that many genetic loci contribute to an increased risk for TD and related conditions[4]. Several studies have reported substantial bilineal transmission, further complicating the search for genetic risk factors (see [3] for review).

Linkage Analyses

Early linkage studies focused on large multigenerational pedigrees, since the results of the initial segregation analyses were consistent with single gene autosomal-dominant inheritance[11–14] . None of these early studies identified a risk locus of major affect.

Given the lack of results in these early studies, a different strategy was employed that allowed for genetic heterogeneity both within and across families. In 1999, The Tourette Syndrome Association International Consortium for Genetics (TSAICG) reported a study of 92 affected sib pairs which resulted in multipoint maximum-likelihood scores of > 2 on chromosomes 4q and 8p. However, when the study was extended to 238 sib pairs and 18 large multigenerational families, the evidence for linkage in these regions on chromosomes 4 and 8 diminished. However, a locus on chromosome 2p was detected that achieved genome-wide significance ($p=9.8\times10^{-8}$)[15,16]. Several other linkage studies have resulted in logarithm of the odds (LOD) scores approaching genome-wide significance[17–20], but only one to date[21] has led to the identification of a mutation that alters the structure or function of a transcript mapping within or near a suggestive linkage region. In this study, parametric linkage analyses were used to examine whether a mutation was segregating with TD in a

single dense pedigree. These investigators studied a family in which a father and eight offspring met DSM-IV-TR criteria for TD. Linkage analyses of this family identified a single region (LOD = 2.1), which was the maximum theoretical LOD score possible for this pedigree. Sequencing of all 54 genes within the interval identified a single rare coding mutation, a premature termination codon (W317X) in the gene *L-histidine decarboxylase* (*HDC*), which is the rate-limiting enzyme in histamine (HA) biosynthesis. Given experimental evidence for incomplete or absent nonsense-mediated decay, and the knowledge that the wild-type (wt) HDC protein forms an active homodimer, the mutant protein was evaluated for possible dominant negative effects, and this was confirmed by *in vitro* studies.

Cytogenetic Abnormalities

Abnormal cytogenetic findings (translocations, duplications or deletions) can also be informative in individuals affected with TD. Within the last decade, several large chromosomal aberrations have been identified that appear to be associated with TD. In one of the earliest, a *de novo* duplication disrupting *IMMP2L* (*inner mitochondrial membrane protein 2L*) on chromosome 7q was reported in 2001[22]. In addition, four separate studies reported rearrangements in the chromosome 18q22 region in TD individuals; the breakpoints in these four studies mapped within approximately 1 Mb of each other[23]. However, to date, no missense or nonsense mutations in *IMMP2L* or in any transcripts within the 18q22 region have been described, though the number of individuals who have been screened for such mutations is small.

Two additional reports of cytogenetic abnormalities associated with TD[2425] are notable in that the regions implicated have also been reported to be associated with other neuropsychiatric disorders (e.g., autism). Verkerk et al.[24] described an insertion of chromosome 2p21–p23 at 7q35–q36 that disrupted the *CNTNAP2* (*contactin associated protein-like 2)* gene in three affected individuals from one family, and Lawson-Yuen et al.[25] reported a family in which a deletion involving exons 4, 5, and 6 of the *NLGN4X* (*neuroligin 4, X-linked)* gene was transmitted along with TD. The siblings in the first family had social communication abnormalities as well as TD, and the index case in the latter family had autism as well as motor tics. In addition, a sibling who also carried the *NLGN4X* deletion had a diagnosis of TD and ADHD, and the carrier mother was described as having a learning disorder, anxiety, and depression. Of note, the region identified on chromosome 2p[24] that was inserted into 7q35-q36 lies under the genome-wide significant linkage peak reported by the TSAICG[1516].

Rearrangements of three additional chromosomal regions (8q21, 6q16 and 17p11) have also recently been described[32627]. Three separate reports identifying translocation breakpoints on 8q have been reported; two isolated cases and in a family where a father and six children had a t(1;8)(q21;q22) translocation, with four of those children having TD or CT. Two independent cases of a translocation and a deletion in 17p11 were reported in individuals with TD[2628]. Recently, a single case with a balanced translocation at t(6,22)(q16.2;p13) was identified in a patient with TD and OCD that was transmitted from the proband's mother[27]. In 2005, Abelson and colleagues[29] reported a *de novo* inversion on chromosome 13 in a

family with a single case of TD that mapped within 350 kb from the transcript *Slit and Trk-like, Family Member 1* (*SLITRK1*). Sequence analysis of 174 unrelated probands identified a single nucleotide deletion that occurred in both the individual with TD and another with a diagnosis of trichotillomania (TTM). In addition, two independent occurrences of a rare single base change (var321) were identified in a highly conserved region of the *SLITRK1* 3'UTR, that corresponded to the binding site for the microRNA hsa-miR-189. Screening for this variant in more than four thousand controls yielded a nominally significant association with TS (p=0.0056).

Subsequently, several studies have attempted to verify this association, yielding mixed results. First, sequencing of 334 individuals with TD did not reveal additional pathogenic coding mutations[30–32]. On the other hand, two studies reported an association with var321 and TD in small candidate gene studies of 154 nuclear families[33] and 376 parent-proband trios, respectively[34]. A third group[35] identified several rare missense mutations that occurred in individuals with TTM. These findings should be interpreted with caution, given the small sample size in the candidate gene study and the lack of a *bona fide* mutation burden analysis in the TTM study.

Finally, two separate groups specifically examined the variant var321 in relation to TD[36 37]. Given that this variant is extremely rare, neither study had sufficient power to statistically confirm or refute the association findings. However, both studies concluded that var321 was neither sufficient nor necessary for the expression of TD, as in some instances, an affected parent carried the variant but did not transmit it to their affected offspring.

Copy Number Variation Studies

Microarray technologies that can detect sub-microscopic structural variation have revealed extensive copy number variation (CNV) throughout the genome[38–41] and provide new opportunities for genome-wide studies of such variation in TD and other neurodevelopmental disorders. The first CNV study in 111 patients with TD[42] identified several rare variants and, given recurrent rare CNVs in the genes *NRXN1* (*neurexin 1*) and *CTNNA3* (*catenin, alpha 3*), hypothesized an overlap of risk with both autism spectrum disorders (ASD) and schizophrenia. A larger study of rare CNVs in 460 TD individuals and 1131 controls found that the genes mapping within these CNV regions overlap with those previously identified in ASD, but not schizophrenia or intellectual disability. In addition, pathway analyses using multiple algorithms revealed an enrichment of genes involved in histamine signaling[43]. Two recent CNV studies have also supported the idea that some TD risk loci overlap with ASD and other neurodevelopmental disorders[4445]. The first examined 210 TD cases and 285 controls from two Latin American populations and identified two additional CNVs spanning *NRXN1*[44]. This study also reported an excess of large (>500 kb) CNVs compared to controls, a finding that was not present in the other studies. The most recent study involved 1086 TS subjects, 1613 with OCD and 1789 controls[45]. While no global CNV burden was detected for either disorder, there was a 3.3-fold higher burden of large deletions within regions previously known to harbor recurrent, pathogenic CNVs in subjects with other neurodevelopmental disorders. Though no individual locus was

significant on its own, five subjects had large deletions within 16p13.11, including three with OCD, one with OCD and CT, and one with TS in the absence of OCD.

Genome-wide Association Studies

In contrast to linkage analyses and studies of chromosomal rearrangements or submicroscopic CNVs that aim to identify rare, moderate-to-highly penetrant genetic variation, a parallel approach to disease gene discovery in disorders with complex inheritance is to evaluate the contribution of more common variants that are present in >5% of the general population[46]. This method, known as genome-wide association (GWA), detects disease variants (single nucleotide polymorphisms, SNPs) with smaller individual effects but which in aggregate can explain a large proportion of disease susceptibility[47]. In addition, while most genome-wide association study (GWAS) SNPs lie outside protein-coding regions of the genome, many are located within gene enhancer regions that regulate specific genes and in combination can identify candidate disease pathways[48].

The TSAICG, in collaboration with additional investigators, recently published the first TS GWAS in 1,285 TS European ancestry cases and 4.964 ancestry-matched controls[45]. While the sample was too small to identify an individual locus at the stringent threshold for genome-wide significance ($p<5\times10^{-8}$), the top signals in aggregate were enriched for functional gene variants associated with brain gene expression levels. Further studies analyzing TS GWAS data and a parallel GWAS of OCD demonstrated that the vast majority of TS heritability (h^2) could be captured by GWAS (h^2 captured by SNPs=0.58; overall h^2 of TD from prior twin/family studies=0.6–0.8), and that TS and OCD had an estimated genetic correlation of 0.41, confirming the presence of shared genetic variation between the two disorders.[49–51] These data suggest that additional, large scale sample collection is likely to lead to discovery of a large number of definitive TS susceptibility genes, as seen in other neuropsychiatric disorders[46].

Studies of Rare Variation

The paucity of specific genetic findings precludes gene discovery efforts to define molecular models of TD. Furthermore, a comprehensive review of neuroanatomical studies of TD is provided in other papers in this special issue. Briefly, most studies have primarily examined the cortical striatal-thalamo-cortical (CTSC) circuitry that is important for the integration of movement, sensation, emotion, and attention. It is important to note that two recent neuropathological findings suggest that there are abnormalities in striatal cholinergic and GABAergic interneurons[5253]. In addition, there has also been considerable work examining dopaminergic (DA) neurotransmission in individuals with TD. Interest in this line of work has been driven by the fact that DA antagonists have been the most effective pharmacological treatment for the reduction of tics[54]. In addition, it has been reported that DA agonists may bring about tics and stereotypies in individuals who do not have TD. Unfortunately, neither genetic nor neuroimaging studies have yielded definitive results and it is still not well understood what the underlying molecular mechanisms that are important in the expression of TD may be[5556].

To date, there have been no consistently replicated molecular genetic findings that identify genes increasing risk in most individuals with TD. However, there have been reports of potentially important findings in isolated cases of TD. The *SLITRK*1 gene discussed above has been examined in a number of different ways. A recent study[29] noted the conserved and developmentally regulated pattern of expression of *SLITRK1* in CTSC circuits in which both mRNA and protein expression in cholinergic interneurons and the striosomal compartment were observed[57]. In addition, Kajiwara and colleagues[58] reported that the regulation of neurite outgrowth, as described by Aruga and Mikoshiba[59], is mediated by binding to 14-3-3 molecules. Finally, Katayama et al.[60] reported increased noradrenergic neurotransmission in a *SLITRK1* mouse knockout that showed manifested an anxiety phenotype. A particularly interesting result reported recently by Shmelkov and colleagues[61] was the observation of excessive grooming, responsive to agents that treat obsessive compulsive disorder in a mouse knockout of the closely related molecule, SLITRK5.

The State Laboratory has reported two studies of rare variation which implicate HA signaling in TD: (1) the dense TD pedigree mentioned earlier segregating a loss-of-function (W317X) mutation in the gene *L-histidine Decarboxylase* (*HDC*), the rate-limiting enzyme in HA biosynthesis[21], and (2) an over-representation of rare CNVs involving histamine signaling pathways in TD. Since these reports, behavioral and neurochemical studies in patients carrying the W317X mutation and *Hdc* knockout and heterozygous mice provide strong evidence for a causal association between disruption of *HDC* and TD[62]. In addition, a study interrogating 12 tagging SNPs across the HDC region in 520 nuclear European families found evidence for strong over-transmission of alleles at two SNPs and significantly associated haplotypes[63]. These observations, and the availability of histamine modulating medications in late state clinical development for other neuropsychiatric indications[6465], suggest there could be opportunities to translate these genetic findings into treatment trials in the not-too-distant future.

SUMMARY, CONCLUSIONS AND FUTURE PROSPECTS

In sum, there have been significant advances over the last several decades that have documented the familial transmission of TD. However, there have been a considerable number of gene discovery efforts to date that have yet to account for a significant proportion of individuals who suffer with TD. Nonetheless, there is reason for optimism; remarkable advances over the last decade in both laboratory technology and computational resources have transformed the search for susceptibility genes in common disorders with complex etiologies and are now being applied to TD. These efforts have led to new and important insights: the effects associated with common alleles have generally been smaller than initially anticipated, but have nonetheless provided critical insights into disease mechanisms. Similarly, over the past decade the value of rare genetic findings in offering new avenues for treatment has been repeatedly demonstrated[23].

What is clear is that, whether the field focuses the identification of rare mutations or common polymorphisms or both, large patient cohorts (likely in the tens of thousands) will be essential to identify relevant genes and to minimize the risk for false positive findings. Over the last decade, the TSAICG, which consists of 14 different collaborative sites, has

been working to collect such a sample. Using this collection and additional samples from by other investigators, the TSAICG in collaboration with these other groups completed the first genome-wide association study of TD as described above, and have recently undertaken a second TD GWAS in 3000 cases and 5000 ancestry-matched controls (http://www.findtsgenes.org). The analyses of these data are nearing completion and should help identify DNA variants that contain either common or rare variants of genes that increase the risk for TD. The hope is that once these genes are characterized, subsequent research can be done to identify the biological processes that are important for the development of TD.

In 2011, a second consortium, the Tourette Collaborative Genetics (TIC Genetics; http://tic-genetics.org) study, was established, with the aims of collecting clinical data and biomaterials (DNA, transformed cell lines, RNA) from TD patients and their family members. Recruitment is from more than twenty sites from the USA, Europe, and South Korea, and these materials are part of a sharing repository of the National Institute for Mental Health (NIMH) Center for Collaborative Genetic Studies on Mental Disorders. Data and biomaterials will be made available to the widest possible research community to hasten the identification of causal genetic factors and facilitate better understanding and treatment of TD[66]. Both consortia, TSAICG and TIC Genetics, are currently working closely to plan complementary analyses and to combine existing data for analyses of larger TD data sets. Lastly, a large consortium of TD investigators in the European Union are conducting a parallel, longitudinal study of 1000 TD subjects, with a plan to complete a third GWAS in the next 3 years (http://www.emtics.eu).

There is great hope that the efforts of these groups and their research will elucidate novel cellular and molecular mechanisms that may not have been previously hypothesized to be important for the development of TD. Recent findings with regard to rare mutations in the histamine system serve as an example of how such a process might proceed from gene discovery to the development of new intervention strategies. In the final analysis, the continued generosity of patients and their families participating in research, the sharing of biomaterials across the scientific community and the effective collaboration among scientists, patients, families, the federal government and private foundations will all be critical to success in the field, ensuring that genetic studies play a central role in reducing the suffering of individuals with TD and related disorders.

Acknowledgments

Funding sources: NIH Grants R01 NS016648 (DLP), U01 NS040024 (DLP/JMS), K23 MH085057 (JMS), K02 NS085048 (JMS), R01 MH096767 (CAM), K08 MH099424 (TVF) and R01 MH092289 (MWS)

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