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The Genetics of Tourette Disorder

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Abstract

Tourette disorder (TD) is a childhood onset neuropsychiatric syndrome defined by persistent motor and vocal tics. Despite a long-standing consensus for a strong genetic contribution, the pace of discovery compared to other disorders of similar prevalence has been slow, due in part to a paucity of studies and both clinical heterogeneity and a complex genetic architecture. However, the potential for rapid progress is high. Recent rare variant findings have pointed to the importance of copy number variation, the overlap of risks among distinct diagnostic entities, the contribution of novel molecular mechanisms, and the value of family based studies. Finally, analysis of a cohort of sufficient size to identify common polymorphisms of plausible effect is underway, promising key information regarding the contribution of common alleles to TD.

Introduction

Tourette disorder is defined by the combination of persistent motor and phonic tics. These are unwanted, rapid, repetitive and stereotyped movements or vocalizations. The natural history of the disorder includes onset in childhood, a waxing and waning course, and, for many individuals, symptom reduction in adulthood. Current diagnostic approaches dictate that only individuals with the combination of unwanted movements and vocalizations meet criteria for TD. However tics in only one of these domains often occur and, if persistent, are categorized as either chronic motor tics (CMT) or chronic vocal tics (CVT). These are thought to represent a TD spectrum of disorders that also includes the co-occurrence of tics ands obsessive-compulsive disorder (OCD).

TD was once thought to be rare; but estimates now converge on a world -wide prevalence of 0.3–1%, though study samples have tended to be small and many investigations have not met the highest standards for contemporary large scale epidemiological studies[1–3]. In addition, despite the observation that as many as 1 percent of the population meets diagnostic criteria for TD, a minority of affected individuals present to clinic with tics as a primary complaint. Moreover, it is typically the coincidence of chronic tics with other psychiatric syndromes, including OCD, depression, and attention deficit hyperactivity disorder that leads individuals and families to seek medical attention. Estimates of comorbidity among TD and these disorders are, accordingly, quite high.

The molecular, cellular and anatomical bases of tics and TD remain in question. However there has been a long-standing consensus regarding the contribution of genetic factors [4,5].

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From the earliest descriptions of the syndrome, a high degree of heritability has been noted. Indeed, TD was initially thought to represent a single gene, Mendelian disorder [6]. Presently there is a consensus that overall, TD has a far more complex allelic architecture, one that appears to be similar to other common neuropsychiatric syndromes, involving both a high degree of locus and allelic heterogeneity and polygenic inheritance.

The tentative quality of this description is a consequence of the fact that after a highly productive early era characterizing the heritability and familiality of TD, progress in genetics and genomics over the past decade has been halting. The field is just now beginning to analyze data from what would be considered sufficiently large samples to power reliable studies of common variation and there is, to date, only a single published report of genome wide detection of rare copy number variation (CNV), conducted in a sample of 111 probands and 73 controls [7]. Indeed when one queries Pubmed for Tourette genetics, fewer than 25 primary research papers are found annually for the last decade. When compared to other complex multi-genic neuropsychiatric syndromes such as autism or schizophrenia, both the differences in the volume of data currently available as well as the rate of growth of the field, based on this crude metric, is striking (Figure 1). Not surprisingly then, answers to key questions that have begun to be addressed in other areas of psychiatric genetics, regarding the overall contribution of common versus rare variation; the importance of *de novo* versus transmitted alleles, and the identity of definitive risk genes are all on the horizon.

Studies to date have comprehensively and rigorously explored and rejected the hypothesis of single gene inheritance and cumulatively point to limits on the effect sizes of contributing common alleles. Moreover over the last several years rare variant finding have pointed to novel hypotheses regarding pathogenic mechanisms and possibly new avenues for treatment, and recent data suggests the TD may follow a pattern emerging in the study of other neuropsychiatric disorders in which specific sequence or structural variations increase risk for range of outcomes that previously would have been considered distinct.

A brief history of TD genetics

Based on the largest twin study reported to date (N= 43 twin pairs) concordance rates are 50%–77% for monozygotic twins compared to 10%–23% for dizygotic twins [8], with the range dependent on whether TD alone or spectrum conditions, such as CMT or CVT are considered. Similar to other developmental neuropsychiatric syndromes, there is a strong male predominance (approximately 4:1) [2,9] However, family studies demonstrate that within TD pedigrees, if one includes OCD as affected status, the risk to male and female relatives of a TD proband approaches 1:1, with females relatives more likely to show obsessions and compulsions [10].

Early gene discovery efforts focused on large multigenerational pedigrees that were hypothesized to reflect single gene autosomal dominant inheritance [6,11–13]. However, over time, as the techniques for mapping Mendelian disorders reached maturity and no TD locus was identified, this hypothesis was abandoned. Subsequent segregation analyses [14–16] led to the conceptualization of TD as a genetically complex multigenic disorder.

Importantly, it has become clear that TD pedigrees often demonstrate bilineal inheritance [15,17,18]. Depending on ascertainment approaches, between 25–40 percent of probands have a history of either TD or OCD on both the maternal and paternal lines. This finding provides some explanation for the thwarted early efforts at parametric linkage in what appeared to be highly promising dominant pedigrees and point to the continued importance of comprehensive phenotypic assessment in pedigrees showing putative Mendelian inheritance.

By the late 1990s, the lack of results from parametric linkage analyses resulted in a shift toward nonparametric approaches[19,20]. While these efforts are theoretically capable of identifying the contribution of either common or rare variation, they are not robust to the combination of small sample size and marked locus heterogeneity. As a limited number of TD sibling pairs have so far been studied, in practice these analyses have investigated the contribution of common variation of moderate to large effect. Based on cumulative recent experience in other complex disorders, it is not surprising that such loci have proven difficult to characterize, and, in general, these alleles would seem increasingly unlikely to constitute a significant proportion of the spectrum of variation contributing to TD.

Similar to other psychiatric syndromes, the lions' share of studies in TD genetics has focused on the contribution of common variants. Since 2000, 37 such studies are referenced in Pubmed, compared to 11 cytogenetic mapping and 10 parametric linkage papers. The majority has assessed association of one or a small number of candidate gene single nucleotide polymorphisms (SNPs) using either a case control or transmission disequilibrium test. Based on the results of genome wide association studies for a wide range of common, complex disorders, even the most recent TD studies have reported on sample sizes that would be considered unlikely to support the detection of common variant risks of plausible magnitude[21–27].

Rare variants and TD

While the search for common alleles has predominated, there has nonetheless been a steady parallel effort to evaluate the contribution of rare variants These have included cytogenetics, parametric linkage in individual pedigrees or isolated populations, targeted sequencing and analysis of copy number variation. As noted, the earliest of these studies were conducted in the context of a widely held belief that TD was a Mendelian disorder. However, since the late 1990s, these have largely shifted to an “outlier approach” to gene discovery, based on the notion that while mutations of large effect may represent only a fraction of the allelic spectrum underlying TD, they may nonetheless provide a valuable point of traction with regard to the molecular pathophysiology of the disorder (for review see [28])

Cytogenetics

Mapping of approximately a dozen TD probands or families with chromosomal abnormalities have been reported over the past decade. These include several cases of TD coincident with known genetic disorders including Smith Magenis [29] and 22q11 deletion syndrome [30]. One individual with 22q11 duplication was also ecently described [31], though the question remains whether this CNV carries any risk for neurodevelopmental phenotypes. Several mapping studies have pointed to novel candidate genes or regions[32–36]. As a follow-up to these findings, mutation screening or sequencing studies have been reported for *IMMP2L* [37] and several transcripts within a candidate region of chromosome 18q[34]. However, no pathogenic mutations have been identified among the small number of patients that have been screened.

To date, there has been only a single instance in which cytogenetic mapping has led to the identification of deleterious rare mutations in a nearby gene. In 2005, our laboratory [38] reported a *de novo* chromosome 13 inversion in a sporadic TD pedigree. Sequencing of *SLIT and TRK like family member 1 (SLITRK1)*, the gene mapping nearest to one of two breakpoints, revealed a single base frameshift deletion as well as two independent occurrences of a very rare mutation (var321) in a highly conserved base within the *SLITRK1* 3’UTR, corresponding to the binding site for the microRNA hsa-miR-189. This variant was found to be associated with TD based on a comparison with 4296 control chromosomes.

The biology of SLITRK1 has subsequently been pursued on several fronts. Following previous evidence that the protein is involved in the regulation of neurite outgrowth [39] our initial study demonstrated that over-expression of *SLITRK*1 in cortical neurons promotes dendritic growth, while the deletion/frameshift mutation does not. *SLITRK1* expression was confirmed in cortical striatal circuits, regions long implicated in TD pathology [40]. The regulation of neurite outgrowth was later determined to be mediated by binding to 14-3-3 molecules [41]; and the mouse knockout was found to have an anxiety phenotype and evidence for increased noradrenergic neurotransmission[42], recapitulating results from early human CSF studies in TD [43]. A particularly intriguing result has been the very recent finding of a striking obsessive-compulsive phenotype and impaired striatal dendritic morphology resulting from the mouse knockout of the closely related molecule, *SLITRK5* [44].

However, on balance, the contribution of *SLITRK1* to TD remains in question. Resequencing efforts, though of modest scale, have not revealed additional pathogenic coding mutations [45–47] and subsequent association studies have been inconclusive. Two publications specifically evaluated var321 [48,49] using tests of transmission within families. Given the low allele frequency (<.001 in the Caucasian population) neither cohort approached the sample size necessary to conduct a meaningful statistical analysis. However both suggested that stratification, particularly among the Ashkenazi population, may have accounted for the initial finding.

Our laboratory recently tested this hypothesis [50] using a combination of genome-wide genotyping, a multi-dimensional scaling analysis and dense haplotype mapping and found no evidence to support this contention. Instead the data further confirmed the initial observation that the initial var321 mutations were not present on a common haplotype, indicating they were either independent events or reflected an ancient allele shared by unrelated affected individuals, with either alternative providing support for the association with TD.

Finally, two cytogenetic findings have been notable for their overlap with the other psychiatric and developmental syndromes: An insertion of chromosome 2p21-p23 at 7q35-q36 was found to disrupt the gene coding for Contactin Associated Protein 2 (CNTNAP2) in three affected individuals from a single family [51] and a transmitted deletion in the gene *Neuroligin 4X* [52] was found in a proband with autism and motor tics; both his sibling with TD and ADHD and his mother, suffering from a learning disorder, anxiety, and depression, also carried the deletion. These two genes have been strongly implicated in intellectual disability and autism spectrum disorders [53–60] and emerging data points to a possible association with schizophrenia[61–63] (Table 1). Large-scale sequencing of TD probands has not yet been reported for either transcript.

Copy Number Variation

The theme of overlapping risks among diagnostically distinct syndromes has been further supported by a recent genome wide CNV study [7]. The authors addressed potential confounds that have often been overlooked in studies of structural variation, including population stratification and batch effects. While they did not find an overall increase in any category of CNV among cases versus controls, they did find an interesting overlap with CNVs previously implicated in autism spectrum disorders and schizophrenia, including involving *NRNX1* and 1q21 (Table 1). As the authors note, these findings are preliminary and, given the small sample size (111 cases and 73 controls), they were not able to firmly establish the overall contribution of rare structural variation, determine the role of de novo CNVs, or demonstrate a clear association of particular variants with TD.

Parametric linkage

After the initial failure to map a single gene mutation in very large pedigrees, parametric linkage efforts turned to studying smaller families based on the notion that the identification of any gene carrying a variation of major effect might help illuminate the biology of TD. Several of these studies have reached or approached genome wide significance [64–69]. To date they have not led to the identification of a likely deleterious sequence variation within the linkage interval(s), with one exception: In this case, parametric linkage of a family consisting of a father and 8 offspring and no evidence of bilineal inheritance was reported by our group. Traditional mapping efforts revealed a single region of the genome reaching the maximum theoretical LOD score (Lod =2.1). Sequencing of all known genes in the interval led to the finding of one nonsense mutation, in the gene *L-histidine Decarboxylase (HDC)*, the rate-limiting enzyme in histamine biosynthesis [70].

The result points to an interesting mechanistic link to prior hypotheses regarding the involvement of dopaminergic pathways in TD: histaminergic (HA) neurotransmission is mediated by three of four known G-protein coupled histamine receptors (H1-H4). Both histamine 2 (H2R) and histamine 3 (H3R) receptors are significantly enriched in the human and rodent striatum [71]. H3R is of particular interest as it acts: 1) as a presynaptic auto-receptor on HA projection neurons; 2) as a pre-synaptic receptor on non-HA containing neurons regulating a variety of neurotransmitters, including dopamine and serotonin; and 3) as a post-synaptic receptor that co-localizes with and modulates dopamine signaling through both D1 and D2 receptors in the striatum. Finally, HDC null mice show decreased brain HA and increased sensitivity to stereotypic behaviors upon administration of DA agonists [72], These repetitive behaviors have previously been proposed as a model of human tics [73].

The convergence of the human genetic and model systems data and the potential availability of clinically-useful H3R compounds being studied in related psychiatric conditions [74] suggests several promising avenues to further evaluate the generalizability of the biology implicated by gene discovery in this single outlier pedigree.

Conclusions

Tourette disorder is a tremendously interesting and surprisingly common syndrome for which there is long standing evidence of a genetic contribution. The limited number of published reports and, in retrospect, the small scale of study cohorts likely accounts for the relatively slow rate of progress compared to other neuropsychiatric disorders. However, despite these obstacles, recent investigations have pointed in promising and unexpected directions, including suggesting the contribution of impaired dendritic growth in the striatum, an overlap of genetic risks with a range of other developmental disorders, and a possible role for histamine in the genesis, exacerbation and, potentially, treatment of some cases of TD.

In fact, TD may be particularly amenable to a broad range of gene discovery efforts. The developmental time course, which typically improves by early adulthood, would at least suggest that selection against TD alleles might be moderated and, consequently, that common alleles of modest effect may account for a proportion of genetic risk. Given the maturity of genome wide common variant methods, this question will soon be answered by the ongoing a large cohort GWAS currently underway by the Tourette Syndrome International Consortium on Genetics. Alternatively, despite the general skepticism regarding parametric linkage among psychiatric geneticists through much of the late 90s and early 2000s, it is striking that multiple promising multigenerational pedigrees have been identified with TD and mapped during this time. The ability to identify multiplex families

and the increasing availability of next generation sequencing technologies promises to further invigorate these family based gene discovery efforts. Finally, the results from copy number variation studies in other areas of medicine and the earliest data from the TD field suggest that this is likely to be productive avenue of inquiry and may reveal surprising biological links between TD and what are now conceptualized as distinct neuropsychiatric conditions.

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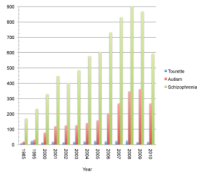

Figure 1. Annual publication number in the genetics of Tourette syndrome, autism and schizophrenia

A Pubmed search was conducted using the terms “Tourette genetics”; “autism genetics” or “schizophrenia genetics.” The searches were performed for the dates January 1-Dec 30th of the year noted in the graph. Articles annotated as reviews in pubmed were subtracted before tallying the total number of publications per year.

Table 1

Overlap of variants/genes identified in Tourette syndrome, autism, schizophrenia and attention deficit hyperactivity disorder (ADHD)

	Tourette syndrome	**Autism***	**Schizophrenia***	**ADHD**
Neuroligin 4	Exonic deletion in a single affected family [52]	Molecular Cytogenetics; sequencing, parametric linkage [53–54]		
Contactin Associated Protein 2	Complex chromosomal rearrangement in a single pedigree [51]	Molecular cytogenetics (*de novo* inversion), sequencing, homozygosity mapping, common variant association [55–59]	CNV, common variant association [60–63]	Copy number variation (one occurrence, intronic) [86]
Neurexin 1	CNV (2 occurrences) [7]	CNV study, molecular cytogenetics, homozygosity mapping [79–83]	CNV, sequencing [75–78]	
1q21 deletion	CNV (1 occurrence) [7]	CNV [87]	CNV[88–91]	
IMMPL2	Molecular Cytogenetic mapping of a *de novo* duplication [32]	Common variant analysis [84] and CNV [85]		CNV (1 occurrence) [86]

* references with regard to autism and schizophrenia provide illustrative data and are not intended to be comprehensive; Not all observation reported in the various disorders reflect confirmed associations