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Review

The genetic basis of Gilles de la Tourette Syndrome

Peristera Paschou*

Department of Molecular Biology and Genetics, Democritus University of Thrace, Greece

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ABSTRACT

Gilles de la Tourette Syndrome (TS) is a neuropsychiatric disorder that is caused by a likely complex genetic basis, interacting with environmental factors. Just as multiple large scale collaborative projects for TS are starting out and the first ever genomewide association study for TS has been published, this review provides a synthetic overview of more than two decades of active research. Studies of the dopaminergic and serotonergic pathways, have yielded inconsistent results, although, for instance, the involvement of DRD2, MAO-A, and DAT1 has been supported by independent findings. The study of chromosomal aberrations in TS etiology has implicated multiple genes, with SLITRK1 being the most prominent example. Common underlying themes with other neurodevelopmental disorders are emerging and attention on neurexins, neuroligins, and genes from the histaminergic and glutamatergic pathways is increased. Propelled by the gradual availability of large scale TS cohorts, and novel methodologies for the study of both common and rare genetic variants, the new era of TS genetics holds the promise to identify novel targets for improved therapies.

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Contents

1. Introduction	00
2. Candidate genes in the dopaminergic and serotonergic pathways	00
3. Scans for linkage and association with TS	00
3.1. Studies with genetic maps of Short Tandem Repeat markers	00
3.2. The L-histidine decarboxylase (HDC) gene	00
3.3. Genome scans for rare Copy Number Variants	00
3.4. The first genomewide association study for TS	00
4. Chromosomal aberrations pointing to candidate genes for TS	00
4.1. SLITRK1	00
4.2. Involvement of genes also implicated in autism	00
4.2.1. Neuroligin 4 (NLGN4)	00
4.2.2. Contactin-associated protein-like 2 (CNTNAP2)	00
4.2.3. The Inner mitochondrial membrane protein 2L region (IMMP2L)	00
5. Novel candidate genes	00
6. Conclusion	00
Acknowledgement	00
References	00

1. Introduction

Gilles de la Tourette Syndrome (TS) is a neurodevelopmental disorder, that presents early in childhood, and is marked by the

appearance of multiple involuntary movements and vocalizations (tics). Although it was once considered rare, a number of different studies now report a prevalence of TS between 0.4 and 1% (Robertson, 2008; Swain et al., 2007). It presents high comorbidity rates with other disorders such as attention deficit hyperactivity disorder (ADHD up to 60%) (Freeman, 2007; Ghanizadeh and Mosallaei, 2009; Roessner et al., 2007) and obsessive compulsive disorder (OCD in 45–60% of cases) (Ghanizadeh and Mosallaei, 2009). Autism spectrum disorders, learning disabilities, mood and anxiety disorders are also quite common among individuals with

* Correspondence address: Department of Molecular Biology and Genetics, Democritus University of Thrace, Panepistimioupoli, Dragana, Alexandroupoli 68100, Greece. Tel.: +30 2551030658; fax: +30 2551030613.

E-mail address: ppaschou@mbg.duth.gr

TS (Baron-Cohen et al., 1999; Coffey et al., 2000; Burd et al., 2005; Robertson and Orth, 2006; Kurlan et al., 2002). The observed high comorbidity rates lend support to the hypothesis of a shared neurobiological substrate and common genetic background among these conditions (Grados, 2010; State, 2010; Mathews and Grados, 2011). There is no cure for TS and treatment aims to diminish tic severity and frequency and treat comorbidities. In fact, comorbid conditions often dominate the clinical picture, and many individuals with tics alone do not seek medical attention. Unfortunately, TS is among those conditions that are underdiagnosed and, often, patients do not receive adequate information and care because of lack in education of medical professionals and educators. In Europe, it takes on average more than five years from first onset of symptoms to diagnosis (Mol Debes et al., 2008).

The mean age at onset of the disorder is seven years (range 2–15 years), and, in uncomplicated cases, the severity of tics peaks early in the second decade of life, with symptoms often showing a striking decline in frequency and severity by 19 years of age (Bloch and Leckman, 2009). This suggests the intriguing hypothesis that the etiology for TS is not neurodegeneration; rather, the disorder may be due to features of the developing brain that are present to a lesser degree in the mature nervous system. The cellular and molecular mechanisms implicated in the pathophysiology of TS remain poorly understood. It has been hypothesized that the same mechanisms that are involved in habit formation are also involved in tics (Leckman and Riddle, 2000). Neuropathological and neurosurgical data as well as in vivo imaging studies, strongly implicate the basal ganglia and related cortical and thalamic structures in the pathobiology of the disorder (Kalanithi et al., 2005; Kataoka et al., 2010; Peterson et al., 2003; Sowell et al., 2008). A popular model of basal ganglia functional anatomy suggests that involuntary movements are associated with decreased inhibitory output from the basal ganglia resulting in excessive activity in fronto-cortical areas (Albin and Mink, 2006). Imaging studies have shown that in children and adults with TS, the volume of caudate is smaller (Peterson et al., 2003) suggesting that there is a decrease in the number of the cells in the striatum. In accordance with these observations, recent studies of postmortem tissues from TS-affected individuals have shown a significant selective decrease in the number of the striatal cholinergic interneurons (Chat+) as well as of the striatal interneurons expressing parvalbumin (PV+) (Kalanithi et al., 2005; Kataoka et al., 2010). Furthermore, several studies have shown that neuroleptics and acetylcholinesterase inhibitors, which act by increasing the level and the duration of action of acetylcholine, are effective in treating motor and phonic tics in TS as well as stereotyped behavior in obsessive compulsive disorders (Aliane et al., 2010; Silver et al., 2001; Cubo et al., 2008).

Tics are common in childhood, with epidemiological studies showing that up to 20–30% of children exhibit brief, repetitive, involuntary movements or sounds in a classroom setting (Kurlan et al., 2001). However, several lines of evidence suggest that TS, is an inherited disorder, although, due to the complexity of the phenotype, it can be argued the exact heritable phenotype is unknown. In twin studies, monozygotic twins show approximately 53–56% concordance for TS and about 77% for chronic motor tics, whereas dizygotic twins display only 8% concordance for TS and 23% concordance for chronic motor tics (Price et al., 1985; Hyde et al., 1992). The recurrence risk of TS among relatives ranges between about 10% and 15%, and the rate of other tics ranges between 15% and 20% (Pauls et al., 1991; Walkup et al., 1996; Hebebrand et al., 1997a,b). First-degree relatives of individuals with TS have a 10- to 100-fold increased risk of developing the disorder, compared with individuals in the general population (Pauls et al., 1991). Same as in other neurodevelopmental disorders, TS occurs more frequently in males than in females, at a ratio of approximately 4:1 (Robertson, 2008). However, frequent male-to-male transmission within

families seems to rule out the possibility of an X-linked inheritance pattern. Early studies focused on large multigenerational pedigrees and reported either a pattern consistent with autosomal dominant inheritance (Kidd and Pauls, 1982; Pauls and Leckman, 1986; Eapen et al., 1993) or a model in which the penetrance of heterozygous individuals was intermediate between those of the homozygotes (Hasstedt et al., 1995). More recent studies, however, support a complex multifactorial and polygenic background (Walkup et al., 1996; Seuchter et al., 2000), with patterns being complicated by evidence of bilineal transmission (genetic contribution from both sides of the family) (Kurlan et al., 1994; McMahon et al., 1996).

The complexity of TS etiology is increased by the contribution of environmental factors (such as perinatal hypoxic/ischemic events, prenatal maternal smoking, exposure to androgens, and heat and fatigue (Swain et al., 2007). Patients with TS usually suffer increased psychosocial stress, and the hypothalamic-pituitary-adrenal axis in TS patients seems to be more responsive to stress than in normal subjects, resulting in a significant elevation of cerebrospinal fluid corticotropin-releasing factor and a greater circadian change in saliva cortisol levels (Lin et al., 2006; Chappell et al., 1996; Corbett et al., 2008). Speculation about post-streptococcal onset has been a subject of intense debate (Mell et al., 2005; Leslie et al., 2008). A growing body of evidence suggests that children with TS are prone to develop autoimmune reactions, and an increased production of anti-neuronal antibodies, similar to those reported in children with other post-streptococcal neuropsychiatric illnesses, has been observed (Martino et al., 2009). In any case, the exact immunological mechanisms that may be involved in TS remain in doubt and the complex interaction of environmental adversities and genetic background in TS etiology is only now beginning to be investigated.

Although multiple genes and chromosomal regions have been implicated in TS etiology, to date, no gene or common variant of major effect has been discovered. In fact, as is the case with the early studies for many other complex disorders (like diabetes, schizophrenia, and depression), the study of the genetics of TS has so far been marked by difficulty to replicate original positive findings. This has been mostly due to the low power of individual studies, resulting from small sample sizes, analyzed in each study. Efforts to elucidate the etiology of TS were, until recently, fragmented, hampered by small sample sizes. Nonetheless, large-scale collaborative efforts are starting out and several recent studies seem to be providing converging and promising leads. Just as the first genomewide association study for TS, has been published, and large multidisciplinary consortia for TS are joining their forces, this review will provide a synthetic overview of current knowledge on the genetics of TS, describing emerging themes and setting the stage for the next generation of studies in the field of TS genetics.

2. Candidate genes in the dopaminergic and serotonergic pathways

Based on findings from pathophysiological studies, current hypotheses about the neuroanatomical localization of TS, and therapeutic response to neuroleptics, genes in the dopaminergic and serotonergic systems have been traditionally viewed as possible “suspects” for TS etiology (Anderson et al., 1992; Peterson et al., 2003). Therapeutic response to dopamine antagonists (Lavenstein, 2003) as well as postmortem and neuroimaging studies (Singer and Minzer, 2003; Peterson et al., 2003) support a dopaminergic abnormality in TS. On the other hand, evidence suggests the involvement of the serotonergic pathway. Serotonin (5-hydroxytryptamine; 5-HT) concentrations are decreased in subcortical brain regions in this disorder (Anderson et al., 1992). Similarly, levels of the 5-HT metabolite 5-HIAA are reduced in these brain regions (Anderson et al., 1992) and in cerebrospinal fluid of TS patients (Cohen et al.,

Table 1

Summary of findings from serotonergic and dopaminergic candidate gene studies for TS. It should be noted that, in most studies, only one or two classical markers (e.g. RFLPs or VNTR markers) have been studied. In cases where linkage or association was reported, the associated/linked variant is shown (NA: data not available).

Gene	Sample	Ancestry	Linkage or association	Reference
DRD1	1 multigenerational family	Mennonite	No	Gelernter et al. (1993)
	1 multigenerational family	British	No	Brett et al. (1995)
	50 TS/50 controls	European	No (mutation screen)	Thompson et al. (1998)
DRD2	148 TS/83 controls	Taiwanese	No	Chou et al. (2004)
	15 families	NA	No	Devor et al. (1990)
	2 multigenerational families	European	No	Gelernter et al. (1990)
	147 TS/314 controls	European	Taq I DRD2 A	Comings et al. (1991)
	4 multigenerational families	European	No	Gelernter et al. (1994)
	61 trios	German	No	Nöthen et al. (1994)
	1 multigenerational family	British	No	Brett et al. (1995)
	225 TS/67 controls	European	Taq I DRD2 A	Comings et al. (1996)
	274 TS/714 controls	European	Taq I DRD2 A	Comings et al. (1996)
	110 trios	French Canadian	No	Díaz-Anzaldúa et al. (2004a,b)
	151 TS/183 controls	Taiwanese	Taq I DRD2 A	Lee et al. (2005)
	69 trios	Antioquian	rs6279, rs1079597, rs4648318	Herzberg et al. (2010)
	DRD3	NA	European	Msc I, exon 1
1 multigenerational family		British	No	Brett et al. (1995)
16 nuclear families		NA	No	Devor et al. (1998)
DRD4	110 trios	French Canadian	No	Díaz-Anzaldúa et al. (2004a,b)
	1 multigenerational family	British	No	Brett et al. (1995)
	12 trios–3 large families	European	48 bp exon 3 VNTR	Grice et al. (1996)
	5 multigenerational families	European	No	Barr et al. (1996)
	61 OCD with and without tics	Mexican	48 bp exon 3 VNTR	Cruz et al. (1997)
	102 trios	German	No	Hebebrand et al. (1997a,b)
	223 TS/737 controls	European	No	Comings et al. (1999)
	110 trios	French Canadian	48 bp exon 3 VNTR	Díaz-Anzaldúa et al. (2004a,b)
	266 TS/236 controls	European	No	Yoon et al. (2007)
	225 TS/67 controls	European	40 bp VNTR	Comings et al. (1996)
DAT1	110 trios	French Canadian	40 bp VNTR	Díaz-Anzaldúa et al. (2004a,b)
	103 trios	Hungarian	40 bp VNTR	Tarnok et al. (2007)
	266 TS/236 controls	European	Ddel	Yoon et al. (2007)
HTR2C	87 TS/311 controls	European	rs3813929, rs518147	Dehning et al. (2010)
	110 TS/440 controls	Chinese	No	Guo et al. (2012)
5-HTTLPR	108 trios	Chinese	No	Liu et al. (2011)
DBH	352 TS/148 controls	European	Taq B	Comings et al. (1996)
	71 nuclear families	European, Turkish	No	Ozbay et al. (2006)
MAO-A	229 TS/90 relatives of TS/57 controls	European	exon 1 VNTR	Gade et al. (1998)
	110 trios	French Canadian	promoter VNTR	Díaz-Anzaldúa et al. (2004a,b)
TPH2	98 TS/178 controls	German	rs4565946	Mössner et al. (2007)

1978). As a result, several genes in both the dopaminergic and serotonergic pathways have been investigated for association with TS susceptibility, including various dopamine receptors (DRD1, DRD2, DRD4, and DRD5), monoamine oxidase-A (MAO-A), the dopamine transporter gene (DAT1), and the tryptophan hydroxylase-2 gene (TPH2), among others (Table 1). Results have often been inconsistent, which could be due to the small sample size of each individual study. It should also be noted, that the vast majority of TS studies of genes in these pathways, only investigated a very small number of polymorphisms each time; mostly one or two classical markers were studied for each gene, such as RFLPs (restriction fragment length polymorphisms) and VNTRs (variable number of tandem repeats).

For instance, results of association with the DRD4 gene are equivocal (Table 1). A 48-bp VNTR (variable number of tandem repeats) has been associated with TS in French-Canadian trios (Díaz-Anzaldúa et al., 2004a,b), as well as multigenerational pedigrees (Grice et al., 1996), however, other studies failed to replicate this association (Table 1, e.g. Barr et al., 1996; Hebebrand et al., 1997a,b). These results underline the importance of large sample sizes for the study of complex phenotypes such as TS.

On the other hand, DRD2 was first reported to be associated with TS in the early 1990s (Comings et al., 1991). Multiple subsequent studies failed to replicate the original finding (Gelernter et al., 1994; Nöthen et al., 1994; Díaz-Anzaldúa et al., 2004a,b). However, an association between DRD2 and TS was later reported in Taiwanese children (Lee et al., 2005). Furthermore, recently, Herzberg et al. (2010), followed a tagging SNPs approach, and were also able to

show positive association with three SNPs and a five-SNP haplotype across the DRD2 gene, although they studied a limited sample of 69 trios.

Moving away from dopamine receptors, studies of the monoamine oxidase-A gene (MAO-A), the dopamine transporter gene (DAT1) and the tryptophan hydroxylase-2 gene (TPH2) have yielded promising findings (Table 1). MAO-A plays a vital role in the inactivation of dopamine and serotonin. Gade et al. (1998) and Díaz-Anzaldúa et al. (2004a,b) have both supported the association of polymorphisms in this gene with TS. Díaz-Anzaldúa et al. (2004a,b) studied a sample of 110 trios with TS (one child affected with the disorder and his/her parents) and found a promoter VNTR (variable number of tandem repeats polymorphism) as well as a haplotype of this VNTR with two adjacent SNPs to be significantly associated with the disorder. MAO-A has also been proposed as a susceptibility gene for attention deficit and hyperactivity disorder (ADHD) and investigated in several association studies with both positive and negative findings (Xu et al., 2007).

The DAT1 gene (SLC6A3) is a key element in dopamine neurotransmission, as it removes dopamine from the synaptic cleft thus influencing the magnitude and duration of the post-synaptic receptor-mediated signaling. A common 40 bp VNTR in the 3' untranslated region has been widely studied in relation to ADHD; the 10-repeat allele has been suggested as a genetic risk factor for this disorder (Faraone et al., 2005). The 10/10 genotype was also more frequent in a TS group (Comings et al., 1996); and tendency for preferential transmission of the 10-repeat allele has also been observed in family-based studies (Díaz-Anzaldúa et al., 2004a,b).

Table 2
Summary of scans for linkage and association with TS. Studies are presented alphabetically (NA: data not available).

Reference	Sample	Ancestry	Marker map
Barr et al. (1999)	7 multigenerational families	European	Genomewide STRPs
Breedveld et al. (2010)	1 multigenerational family	Italian	Genomewide STRPs
Curtis et al. (2004)	1 multigenerational family	British	Genomewide STRPs
Ercan-Sencicek et al. (2010)	1 multigenerational family	NA	Genomewide SNPs – fine mapping of linked region
Feng et al. (2004)	53 nuclear families	European	Genomewide STRPs
Knight et al. (2010)	1 multigenerational family	European	Genomewide STRPs
Laurin et al. (2009)	1 multigenerational family	European	Fine mapping of previously linked region
Leppert et al. (1996)	1 multigenerational family	European	Genomewide STRPs
Mérette et al. (2000)	1 multigenerational family	French Canadian	Fine mapping of previously associated region
Paschou et al. (2004)	4 multigenerational families–96 nuclear families	European	Fine mapping of previously linked region
Rivière et al. (2010)	95 nuclear families	French Canadian	Genomewide STRPs
Scharf et al. (in press)	1285 TS 4964 controls	European, French Canadian, Ashkenazi, Costa Rican, Colombian	Genomewide SNPs
Simoncic et al. (1998)	100 TS/96 controls	Afrikaner	Genomewide STRPs
Simoncic et al. (2001)	91 nuclear families	Afrikaner	Fine mapping of previously associated region
TSAICG (1999)	76 nuclear families	European	Genomewide STRPs
TSAICG (2007)	238 nuclear families	European	Genomewide STRPs
Verkerk et al. (2006)	1 multigenerational family	Dutch	Genomewide STRPs
Zhang et al. (2002)	51 nuclear families	European	Genomewide STRPs

The 10-repeat allele has been associated with internalizing disorders (Rowe et al., 1998), whereas externalizing behavior problems were linked to the 9-repeat allele (Young et al., 2002). Recently Yoon et al. (2007) found a polymorphism that involves the creation of a restriction site to be positively associated with TS in a sample of 266 individuals with TS and 236 controls. At the same time, Tarnok et al. (2007) using a dimensional approach and a family-based study, found the DAT1 40bp VNTR to be associated with increased tic severity (Table 1).

Finally, TPH2 is responsible for synthesis of serotonin in the brain (Walther et al., 2003). Until recently it was believed that TPH was a single enzyme, but it was demonstrated that a second brain-specific form of TPH exists, which was termed TPH2 (Walther et al., 2003). The classical TPH isoform (now termed (TPH1) is detected in the periphery and not in the brain, apart from the pineal gland (Walther et al., 2003). Mössner et al. (2006, 2007) studied one functional and one intronic SNP in the TPH2 gene in relation to obsessive compulsive disorder (OCD) and TS. Studying 71 trios with OCD they found the functional SNP to be significantly associated with the disorder (Mössner et al., 2006) and most recently (Mössner et al., 2007) they showed that the same SNP was also associated with TS (using a case–control study design). A haplotype of the two SNPs was also significant in the TS study. They argued that it may be serotonin synthesis in the brain that exerts its influence on TS risk.

3. Scans for linkage and association with TS

3.1. Studies with genetic maps of Short Tandem Repeat markers

In any case, genetic variation at any one gene is unlikely to be a major source of susceptibility to TS. Rather, multiple alleles acting in concert could have cumulative effects and contribute to phenotypic variability. Whole-genome scans with microsatellite markers have provided indications for linkage and association to TS with several genomic regions (Tables 2 and 3). However, once more, the results between studies are quite inconsistent. This is believed to be due to uncertainties in the definition of the phenotype, diagnostic assessment, and family ascertainment schemes, as well as a misspecified genetic model used for the data analysis, especially for early studies, which were based on parametric analysis. Such studies focused on large multigenerational pedigrees with multiple affected individuals that suggested Mendelian inheritance (Baron

et al., 1981; Kidd and Pauls, 1982; Curtis et al., 1992). However, no major TS susceptibility gene could be identified, and the single gene hypothesis was abandoned, after a decade of research mostly in this direction.

A partial genome scan in 1991 excluded 50% of the genome, under the assumption of an autosomal dominant gene in all of the families studied (Pakstis et al., 1991). Studying several multigenerational families with TS, Barr et al. (1999) reported genomewide significant linkage with eight markers, using the affected-pedigree method, a nonparametric approach (Table 3). Simoncic et al. (1998), in a genomewide search with a limited sample size and a case–control strategy, reported positive associations, with markers in seven regions. These regions were subsequently followed up in 91 Afrikaner families, using a transmission disequilibrium approach, and providing additional evidence for three of the previously implicated loci on chromosomes 2p11, 8q22 and 11q23–q24 (Table 3) (Simoncic et al., 2001). Interestingly, linkage to the 11q23–q24 marker (D11S1377) was also found in a large French Canadian pedigree that was analyzed by use of a multipoint approach (Mérette et al., 2000). A recent genomewide scan of 95 French Canadian trios with familial history of TS, showed association to markers on chromosomes 7, 13, 15, and 19, although none of the markers remained associated when 122 French Canadian trios with no history of TS were added to the analysis (Rivière et al., 2010). Of particular interest is the fact that, the chromosome 13 marker (D13S271) lies about 600 kb away from one of the top hits in the recent genomewide association study for TS (Scharf et al., in press), and the chromosome 15 marker (D15S1016) lies within the interval, the study of which led to the implication of the HDC gene in TS etiology (as described later on in this review) (Ercan-Sencicek et al., 2010).

A genome screen of 110 affected sib pairs (76 families) performed by the Tourette Syndrome Association International Consortium for Genetics (TSAICG, 1999) provided suggestive positive-linkage results with markers on chromosomes 4q and 8p (Table 3). When affected individuals in this study were stratified according to obsessive compulsive symptoms, significant allele sharing was noted for hoarding phenotypes for markers at 4q34–35, 5q35, and 17q25.3 (Zhang et al., 2002; Feng et al., 2004) (Table 3). We followed up on the 17q25 region (marker D17S784) and were able to provide further support for linkage and association of the TS phenotype to this region, both in large multigenerational

Table 3

Chromosomal regions implicated in TS etiology by genomewide scans for linkage and association. Regions are ordered by chromosome and physical position (NA: data not available).

Chromosomal region	Physical position start (bp) (build NCBI36/hg18)	Top hits of linkage or association	Reference
1p31.1	82,315,937	D1S207	Knight et al. (2010)
2p11.2	84,928,791	D2S1790	Simonic et al. (1998)
2p12	79,617,035	D2S139	Simonic et al. (2001)
2p23.3	25,354,275	D2S144	TSAICG (2007)
3p14.3	54,454,497	D3S1289	Knight et al. (2010)
3q13.13	110,707,002	rs13063502	Scharf et al. (in press)
3q29	198,502,373	D3S1311	Verkerk et al. (2006)
4q31.21	143,720,350	D4S1625	TSAICG (1999)
4q34.3	180,405,470	D4S2417	Zhang et al. (2002)
4q35.1	185,388,050	D4S408	Feng et al. (2004)
5p13.3	33,863,314	D5S1506	Laurin et al. (2009)
5p15.32	5,047,043	D5S406	Barr et al. (1999)
5p15.33	1,207,414	D5S1981	Curtis et al. (2004)
5q35.3	179,920,771	D5S408	Feng et al. (2004)
5q34	166,446,326	D5S2050	Curtis et al. (2004)
6p25.1	6,085,381	D6S477	Simonic et al. (1998)
7q21.11	83,997,436	D7S2485	Rivière et al. (2010)
7p21.3	12,026,331	rs769111	Scharf et al. (in press)
7q36.1	151,829,051	D7S483	Barr et al. (1999)
8p22	12,880,230	D8S1106	TSAICG (1999)
9p13.3	33,849,593	D9S1817	Verkerk et al. (2006)
9q32	116,030,892	rs7868992 (COL27A1)	Scharf et al. (in press)
10p14	6,761,880	D10S189	Curtis et al. (2004)
10p15.1	4,399,166	D10S591	Curtis et al. (2004)
11p13	34,624,002	D11S907	Barr et al. (1999)
11q24.1	121,956,926	D11S1377	Mérette et al. (2000)
11q24.1	121,956,926	D11S1377	Simonic et al. (2001)
11q24.2	124,177,190	D11S933	Simonic et al. (1998)
12q23.3	105,309,684	rs6539267 (POL3RB)	Scharf et al. (in press)
13q12.3	28,269,791	D13S217	Curtis et al. (2004)
13q31.1	80,007,095	D13S170	Verkerk et al. (2006)
13q31.1	84,278,764	D13S271	Rivière et al. (2010)
13q31.1	84,901,388	rs7336083	Scharf et al. (in press)
13q34	113,332,433	D13S293	Barr et al. (1999)
14q11.2	21,186,185	D14S1003	Simonic et al. (1998)
14q13.1	33,528,945	D14S70	Barr et al. (1999)
14q21.2	43,171,519	D14S288	Curtis et al. (2004)
14q31.1	NA	D14S100	Breedveld et al. (2010)
15q21.1–q21.3	47,089,559– 55,221,723	D15S126–GATA153F11 (HDC)	Ercan-Sencicek et al. (2010)
15q21.3	51,320,121	D15S1016	Rivière et al. (2010)
16p12.1	24,143,583	D16S420	Barr et al. (1999)
17q21.32	42,211,428	D17S791	Paschou et al. (2004)
17q25.3	NA	D17S782	Leppert et al. (1996)
17q25.3	75,416,716	D17S784	Zhang et al. (2002)
17q25.3	75,416,716	D17S784	Feng et al. (2004)
17q25.3	77,846,128	D17S928	Paschou et al. (2004)
19p13.2	7,184,616	INSRE3	Barr et al. (1999)
19p13.2	7,777,647	D19S912	Barr et al. (1999)
19q13.42	60,443,625	D19S605	Rivière et al. (2010)
20q13.2	52,114,887	D20S1085	Simonic et al. (1998)
21q22.13	36,748,729	D21S1252	Simonic et al. (1998)

pedigrees, and an independent sample of 96 small nuclear families from Toronto (Paschou et al., 2004). The TSAICG reported results on an additional genome scan for linkage in 2007, including 238 nuclear families and 18 separate multigenerational families (total of 2040 individuals), genotyped with 390 microsatellite markers (TSAICG, 2007). This study yielded significant evidence of linkage to marker D2S144 on chromosome 2p32.2. Analysis of other chromosomal regions, including 3p and 3q gave non-parametric lod (NPL) scores suggestive of linkage (above 2.5).

3.2. The L-histidine decarboxylase (HDC) gene

The recent implication of the L-histidine decarboxylase (HDC) gene in TS etiology, ignited an intriguing hypothesis about the possible involvement of histaminergic pathways in the genesis or mediation of tics and suggested new lines of research on the role of histamine in striatal dopamine regulation. Linkage mapping on a single family with one father and eight of his children affected with

TS led Ercan-Sencicek et al. (2010) to investigate a region of chromosome 13 with a LOD score of 2.1. Interestingly, as mentioned earlier here, this same region produced one of the top hits for association in a recent genomewide scan of 95 French Canadian trios (Rivière et al., 2010) (Table 3). In the study of Ercan-Sencicek et al. (2010), sequencing of all genes within the interval led to the discovery of a single rare coding mutation, a premature termination codon (W317X) in the HDC gene, the rate-limiting enzyme in histamine biosynthesis. The mutation could not be found in any of the 3000 control individuals of Western European origin who were screened. At the same time, resequencing of the coding region of HDC in 720 patients with TS and 360 controls revealed no additional nonsense variants, demonstrating the fact that the nonsense mutation identified in the index family is extremely rare. Lei et al. (2012) screened the HDC gene for exonic mutations in 100 Chinese Han patients with TS, and could only find three variants that were not predicted to induce amino acid changes. However, a recent genomewide scan for de novo or transmitted rare CNVs in TS found enrichment of

genes within histamine receptor signaling pathways (Fernandez et al., 2012), as described in more detail below.

Histaminergic signaling is mediated by four known G protein-coupled receptors – H1 through H4 – that are known to modulate circadian rhythms, appetite, memory, and behavior (Haas et al., 2008). H2 and H3 receptors are highly enriched in the human and rodent striatum (Haas et al., 2008) and H3R regulates a variety of neurotransmitters, including dopamine and serotonin. Hdc-deficient mice have several traits relevant to features of TS and have shown decreased brain histamine and increased sensitivity to stereotypic behaviors upon administration of dopamine agonists (Kubota et al., 2002). Such stimulant-induced movements, including rearing, sniffing, and biting have previously been proposed as a model of human tics (Saka and Graybiel, 2003). Interestingly, the pharmaceutical industry has recently shown widespread interest in the development of H3R compounds for a variety of neuropsychiatric indications (Esbenshade et al., 2006).

3.3. Genome scans for rare Copy Number Variants

In the last couple of years, two genomewide scans of single nucleotide polymorphism genotyping microarray data have been performed aiming to uncover the possible role of rare exonic Copy Number Variants (CNVs) in TS. Sundaram et al. (2010) identified five exon-affecting rare CNVs that are either de novo or recurrent in 10 out of 111 patients they studied and were not found in 73 ethnically matched controls or in the entries of the Database of Genomic Variants (NRXN1, CTTNBP2, and CTNNA3, AADAC, and the KCHE1, KCHE2, RCAN1 region). Three of the implicated genes encode cell adhesion molecules (NRXN1, CTTNBP2, and CTNNA3). More specifically, NRXN1 belongs to the neurexin family of proteins. Neurexins and neuroligins have recently been implicated in TS, autism, schizophrenia, and other neurodevelopmental diseases, linking synaptic cell adhesion to cognition and its disorders (Knight et al., 2011). This overlap, led authors to speculate that the identified CNVs produce a continuum of neuropsychiatric disturbances that manifest in different ways depending on other genetic, environmental, or stochastic factors.

Fernandez et al. (2012) studied 460 unrelated affected individuals (including 148 trios) and 1131 control individuals (including 436 trios) aiming to identify a possible increase in the number of de novo or transmitted rare CNVs in cases versus controls. No such increase could be found, however, pathway analysis using multiple algorithms showed enrichment of genes within several pathways, with the top signals of significance obtained from those involving ubiquitin, GABA receptor signaling, sphingolipid metabolism, histamine receptor signaling, and alpha-2 adrenergic receptor function. Same as Sundaram et al. (2010), when Fernandez et al. looked closely at the genes that mapped within rare CNVs in TS individuals, they observed significant overlap with those previously identified in autism spectrum disorders.

3.4. The first genomewide association study for TS

The first ever genomewide association study (GWAS) for TS was just published in 2012 (Scharf et al., in press). The TSAICG studied 1285 cases and 4964 ancestry-matched controls of European ancestry, including two European-derived population isolates, Ashkenazi Jews from North America and Israel and French Canadians from Quebec, Canada. Following several quality control steps, the final analysis was performed on a joint dataset of 484,295 SNPs. In a primary meta-analysis of GWAS data from these European ancestry samples, no markers achieved a genome-wide threshold of significance (set by the authors at $P \leq 5 \times 10^{-8}$). Nevertheless, the SNP with the strongest signal, rs7868992, lies on chromosome 9q32

within an intron of COL27A1. COL27A1 is the most recently discovered collagen gene, and codes for type XXVII collagen. It is strongly expressed in developing cartilage and weakly expressed in many other tissue types. A SNP within the POLR3B gene on chromosome 12q23 (the second largest subunit of RNA Polymerase III), as well as a SNP that lies in a 1.7-Mb intergenic region on chromosome 3q13, and an intergenic SNP on chromosome 7p21 between THSD7A and TMEM106B are also among the top signals. Interestingly, one of the top five hits is SNP rs7336083, located on chromosome 13q31 within a 1.9-Mb intergenic region between SLITRK6 and SLITRK1. In the secondary meta-analysis combining all 1496 TS cases and 5249 controls (European ancestry samples plus 211 cases and 285 controls from the Costa Rica and Colombian isolates), the strongest association was again found in rs7868992 within COL27A1 on 9q32. Scharf et al. (in press) proceeded to seek functional evidence to support the observed associations by evaluating the effect of the top associated SNPs on transcriptional expression and DNA methylation levels. They found the top SNPs from the primary analysis to be nominally enriched for eQTLs in frontal cortex with a trend toward enrichment in cerebellum. The highest association signals were also nominally enriched for cerebellar mQTLs.

4. Chromosomal aberrations pointing to candidate genes for TS

Based on an alternative approach of tracking chromosomal aberrations in patients with TS, additional candidate regions have been suggested to harbor susceptibility genes for the disorder with the SLITRK1 gene being the most prominent example (Table 4). Again, for most of these regions, results have been contradictory, and no single region has so far been shown to harbor a major TS susceptibility locus.

4.1. SLITRK1

The implication of a member of the SLIT and TRK family of proteins (SLITRK1) in TS etiology (Abelson et al., 2005) has spurred intense debate in TS literature. SLITRK1 is a type-I transmembrane protein with an extracellular leucine-rich repeat (LRR) domain homologous to SLIT and a short intracellular domain lacking the tyrosine phosphorylation motifs that are found among the other members of SLITRK family (Aruga and Mikoshiba, 2003). It has been shown to control neurite outgrowth and it is expressed in the embryonic and postnatal brain, including the cortex, thalamus, and basal ganglia, reflecting the neuroanatomical regions most commonly implicated in TS (Proenca et al., 2011). Studying a TS patient with a de novo inversion of chromosome 13, Abelson et al. (2005) mapped the 13q31.1 breakpoint approximately 350 kb from SLITRK1. By resequencing this gene in a cohort of 174 individuals with TS, two additional mutations were discovered: a single nucleotide deletion that led to a frameshift and a prematurely truncated protein (varCDf) and a missense mutation in the 3' untranslated region (3' UTR), (variant 321 – var321), predicted as a binding site for microRNA hsa-miR-189. These mutations were absent in over 3600 control samples (Abelson et al., 2005). Subsequent mutation screens of SLITRK1 were unable to find these two reported variants in individual with TS of European, and Japanese origin, while three additional extremely rare exonic variants were reported in these studies (Deng et al., 2006; Chou et al., 2007; Zimprich et al., 2008). Direct testing for var321 in almost 2000 individuals with TS of mixed European, Ashkenazi and Costa Rican origin (Keen-Kim et al., 2006; Scharf et al., 2008), and 322 patients with OCD (Wendland et al., 2006), only found the variant in a total of seven patients with TS, as well as one Ashkenazi and one European control. It was reported that var321 was over-represented in

Table 4
Chromosomal regions implicated in TS etiology due to identified chromosomal abnormalities in individuals with TS (NA: data not available).

Chromosomal region	Ancestry	Associated gene	Reference
7q22–q31	NA	IMMP2L	Boghosian-Sell et al. (1996)
	NA		Kroisel et al. (2001)
	NA		Petek et al. (2001a,b)
7q35–q36	Austrian and English	CNTNAP2	Petek et al. (2007)
	European-British		Patel et al. (2011)
	NA		Verkerk et al. (2003)
8q13–q22.1	Danish	CBFA2T1	Belloso et al. (2007)
	NA		Poot et al. (2010)
	NA		Devor and Magee (1999)
13q31.1	NA	SLITRK1	Matsumoto et al. (2000)
	NA		Crawford et al. (2003)
	NA		Abelson et al. (2005)
9p	European	SLITRK1	Singh et al. (1982)
	African American		Taylor et al. (1991)
15q13–q22.3	South American	SLITRK1	Jankovic and Deng (2007)
	European		Kerbeshian et al. (2000)
16q22–q23	European	SLITRK1	Shelley et al. (2007)
	NA		Dehning et al. (2008)
17p11	NA	SLITRK1	Donnai (1987)
	NA		Cuker et al. (2004)
	NA		State et al. (2003)
18q21.1–q22.3	Korean	SLITRK1	Robertson and Orth (2006)
	NA		Clarke et al. (2009)
	NA		Lawson-Yuen et al. (2008)
22q11	NA	SLITRK1	
Xp22.3	Irish-English	NLGN4	

the Ashkenazi population, suggesting that population stratification had led the original study to a false-positive result (Keen-Kim et al., 2006). However, additional population genetics studies of an independent set of seven TS patients carrying var321 argued against population stratification, confounding the original data (O'Roak et al., 2010). Furthermore, novel mutations in the SLITRK1 gene have been found that co-segregate with OCD spectrum disorders (Zuchner et al., 2006).

Undertaking a different approach, a recent study tested for association of the TS phenotype with three common tagging SNPs (tSNPs) spanning SLITRK1 (Miranda et al., 2009). The study included 154 nuclear families from Canada, with one or more affected children, with a total of 208 affected children for the association analyses. None of the patients carried any of the variants reported by Abelson et al. (2005). However, significant associations with SNP rs9593835 as well as two three-marker haplotypes were identified, suggesting, for the first time, that there is a common TS risk factor of low penetrance in linkage disequilibrium (LD) with the associated marker and/or haplotypes (Miranda et al., 2009). Following up on the results of Miranda et al. (2009), we studied a large sample of European trios with TS (one individual affected with the disorder and their parents) for the three tSNPs selected by Miranda et al. (2009), using the HapMap CEPH European population as reference (rs9593835, rs9531520, and rs9546538) (Karagiannidis et al., 2012). 222 trios were collected as part of an international effort, the Tourette Syndrome Genetics–Southern and Eastern Europe Initiative (TSGeneSEE, <http://tsgeneseeb.mbg.duth.gr>). We found significant transmission disequilibrium of two of the studied SNPs (rs9593835 and rs9546538) as well as three-marker haplotypes both in our own sample as well as in joint analysis with the original Canadian sample (total of 375 nuclear families with TS) (Karagiannidis et al., 2012). In fact, the alleles that we found to be most significantly associated with TS, lie on the haplotype that is most commonly observed around the world (ranging in frequency from 38.9% to 86% (Speed et al., 2008). On the other hand, a protective haplotype is found in Africa at a frequency of 20% and is quite rare in Europe (5%). Our study clearly suggests that the role of SLITRK1 in TS etiology may have been previously under-appreciated, and the LD structure of the region indicates a possible involvement of SLITRK1 regulatory variants in TS etiology (Karagiannidis et al., 2012).

4.2. Involvement of genes also implicated in autism

TS is often considered as a model for understanding neurodevelopmental disorders and the hypothesis of a common genetic background between TS and disorders such as ADHD, OCD, and autism spectrum disorders is quite intriguing. Such speculation is supported by studies that provide evidence of a common genetic thread. For instance, the fact that multiple genes that have been found disrupted in TS patients have also been found to play a role in autism is quite striking. It should be noted, that in a large epidemiological study of children with autism, 6.5% of participating children were diagnosed with TS (Baron-Cohen et al., 1999). The convergence of results among autism and TS genetic studies, as exemplified in the cases of the CNTNAP2, IMMP2L, and NLGN4 genes, may point to a common etiological background in the spectrum of neurodevelopmental disorders.

4.2.1. Neuroligin 4 (NLGN4)

The involvement of cell adhesion molecules, and notably, the neuroligins and neuroligins in the development and modulation of synaptic connectivity is gaining increasing attention in recent literature. In fact, neuroligins and neuroligins are emerging as central organizing molecules for excitatory glutamatergic and inhibitory GABAergic synapses in the mammalian brain (Craig and Kang, 2007) and the identification of mutations in disorders such as autism, TS, and schizophrenia is becoming a recurrent theme. Neuroligins are expressed in postsynaptic neurons and interact with neuroligins expressed in presynaptic neurons (Knight et al., 2011). NLGN3 and NLGN4 (neuroligin 3 and 4) are X-linked genes that have been implicated in intellectual disability and autism spectrum disorders (Laumonier et al., 2004; Jamain et al., 2003). Recently, a deletion involving coding segments of the gene NLGN4 was also associated to TS, and identified in a family with affected individuals represented by an autistic boy with a motor tic, his brother with TS and ADHD, and their carrier mother with learning disorder, anxiety, and depression (Lawson-Yuen et al., 2008). Mutations in both NLGN3 and NLGN4 have been reported in several families that include members with mental retardation and/or pervasive developmental disorders ranging across the spectrum from Asperger syndrome to autism (Jamain et al., 2003; Laumonier et al., 2004; Yan et al., 2005 among others). For instance, Jamain et al. (2003)

identified a truncating frame-shift mutation in NGLN4 arising de novo in an unaffected mother and transmitted to two brothers, one with Asperger syndrome and the second with “typical” autism (Jamain et al., 2003). Furthermore, linkage mapping of a multi-generational pedigree affected with both mental retardation and autism led to the identification of a segregating non-sense mutation, nearly identical to the one initially reported by Laumonnier et al. (2004).

4.2.2. Contactin-associated protein-like 2 (CNTNAP2)

The CNTNAP2 gene (contactin-associated protein-like 2 – Caspr2) is another gene in the cell adhesion molecules pathway and member of the neurexin superfamily that has been reproducibly implicated in neurodevelopmental phenotypes and has also been found disrupted in patients with TS. Caspr2 regulates neuron-glia contact in vertebrates and has been shown to colocalize with Shaker-like K⁺ channels in the juxtaparanodal areas of Ranvier nodes in myelinated axons of both the central and peripheral nervous system (Arroyo et al., 2001; Poliak et al., 2003). CNTNAP2 messenger RNA (mRNA) is significantly enriched in the developing human brain in the frontal and temporal lobes, as well as in striatal circuits and in the frontal cortex of adult brain (Abrahams et al., 2007). Recently, a possible common role in the morphological organization of synapses has been suggested for its fly ortholog (Nrx-IV) and the single *Drosophila* neurexin (Nrx-1) (Zweier et al., 2009). Verkerk et al. (2003) reported on a TS family where the affected father and two affected children shared a chromosome 2p21–p23 insertion on chromosome 7q35–q36, thereby interrupting the CNTNAP2 gene. The children had TS, OCD, and mild mental retardation. Interestingly, upon examination of previously reported candidate TS genes in the recent GWAS dataset, only one SNP had a nominally interesting trend for association, and this lied within the CNTNAP2 gene, although this locus did not survive a Bonferroni correction for gene size (Scharf et al., in press). Disruption of introns 8–13 of the CNTNAP2 gene was reported in a boy with mild facial dysmorphisms, speech delay and autism spectrum disorder, along with features of TS such as violent outbursts and obsessive and self-directed behavior (Poot et al., 2010). However, Belloso et al. (2007) also described three-generational pedigree with a balanced t(7;15) translocation, and no clinical features. Poot et al. (2010) hypothesized, that this could be due to the fact that this was a smaller and more distal disruption than those reported by their own group and Verkerk et al. as phenotypically relevant.

Mutations in CNTNAP2 were first identified in Old Order Amish children with the CDFE syndrome (presenting with cortical dysplasia, epilepsy, microcephaly, as well as autism spectrum disorder) (Strauss et al., 2006). Since then, the CNTNAP2 gene has been implicated in a range of developmental neuropsychiatric disorders, including autism and language disorders (Falivelli et al., 2012; Anney et al., 2012; Peñagarikano et al., 2011; Stein et al., 2011; Friedman et al., 2008; Newbury and Monaco, 2010). In a recent large-scale study with 2705 families analyzed (autism genome project) the SNP that achieved the smallest *P*-value fell within CNTNAP2 (rs1718101) (Anney et al., 2012). In a molecular pathway analysis comparing the ratio of nominally significant (*P* < 0.05) to non-significant SNPs in a given pathway to identify the enrichment for association signals, the CNTNAP2 and NRXN1 genes were significantly associated in large-scale genome wide association datasets of both schizophrenia and bipolar disorder (O'Dushlaine et al., 2011). Interestingly, in a study of rare inherited CNVs in ADHD patients and their parents (335 patients, 2026 healthy individuals), CNTNAP2 was among the genes that showed a high frequency of such structural variation (Elia et al., 2010). The IMMP2L gene was also found in this inherited rare CNV-associated gene set in ADHD patients (Elia et al., 2010) and is reviewed in relation to TS below.

4.2.3. The Inner mitochondrial membrane protein 2L region (IMMP2L)

In 1996, Boghosian-Sell et al. (1996) reported on a family where TS was segregating with an apparently balanced 7;18 translocation in several affected patients. The breakpoint on chromosome 7 was described to be within genomic markers D7S515 and D7S522, which are mapped to chromosomal bands 7q22 and 7q31, respectively. In 2001, a 13-year-old boy with TS, moderate mental retardation, minor physical anomalies and no autistic signs was identified, who carried a de novo inverted duplication of the long arm of chromosome 7 [46,XY,dup(7)(q22.1–q31.1)] (Petek et al., 2001a,b). The distal chromosomal breakpoint occurred between the same genetic markers (D7S515 and D7S522) as described by Boghosian-Sell et al. (1996). IMMP2L, a gene coding for the human homologue of the yeast mitochondrial inner membrane peptidase subunit 2, was found to be disrupted. IMMP2L is thought to have a role in targeting proteins to the inner membrane of the mitochondrion. Díaz-Anzaldúa et al. (2004b) studied the transmission-disequilibrium pattern of the region in 86 French-Canadian trios with TS and found nominal association with markers D7S522, D7S523, and D7S1516. In fact, D7S1516, lies within the IMMP2L gene. Recently, Patel et al. (2011) identified a male patient with no autistic signs, TS-like tics and an apparently balanced de novo translocation [46,XY,t(2;7)(p24.2;q31)] and a cryptic deletion at 7q31.1–7q31.2, which, again, disrupted the IMMP2L gene (deletion of exons 1–3). In this patient, mutation of the IMMP2L gene prevented transcription of an integrated mRNA, which led to the translation of a defective protein (Patel et al., 2011; Lu et al., 2008). The dysfunctional IMMP2L protein could not fully process mitochondrial protein cytochrome c1, causing an increase in production of superoxide and promoting the formation of a mitochondrial permeability transition pore that permitted release of mitochondrial proteins, thereby activating cell death pathways (Deng et al., 2012; Ma et al., 2011). The deleted region (7q31.1–7q31.2) of 7.2Mb of genomic DNA also encompasses numerous genes, including FOXP2, associated with verbal dyspraxia (Feuk et al., 2006). Nevertheless, screening 39 TS patients as well as 95 multiplex families with autistic disorder, Petek et al. (2007) could not identify any coding mutations.

Notably, the 7q22–q31 region and the IMMP2L gene in particular have been reproducibly implicated in numerous studies carried out in cohorts of patients with autism spectrum disorder (International Molecular Genetic Study of Autism Consortium, 1998; Maestrini et al., 2010; Huthcheson et al., 2003) as well as a ADHD (Elia et al., 2010) and speech-language disorders (Lai et al., 2001; Warburton et al., 2000). In fact, the 7q22–q31 region was among the very early linkage signals for autism (International Molecular Genetic Study of Autism Consortium, 1998). Pagnamenta et al. (2010) also reported a 594 kb IMMP2L-DOCK4 deletion resulting in a fusion transcript and an intragenic DOCK4 deletion segregating with autism and dyslexia. Recent high-density association studies provide further support that the IMMP2L gene as well as the neighboring DOCK4 gene are involved in autism as well as dyslexia etiology (Maestrini et al., 2010; Casey et al., 2012; Girirajan et al., 2011). The DOCK4 gene has been shown to regulate dendritic growth in neuronal cell lines in rats (Ueda et al., 2008).

5. Novel candidate genes

Recent studies have suggested a number of genes as interesting candidate genes for TS, although their implication in TS etiology requires further investigation. Motivated by recent studies of post-mortem basal ganglia from TS-affected individuals, which raised the possibility that genes involved in the development and function of striatal GABAergic PV⁺ interneurons as well as cholinergic

striatal interneurons are involved in TS etiology (Kalanithi et al., 2005; Kataoka et al., 2010), we studied the LHX6, LHX8 genes as candidate genes in TS (Paschou et al., 2012). Lhx6 and Lhx8 play a critical role in the specification of forebrain interneurons: Lhx6 is required for the specification of the PV+ and somatostatin expressing interneurons of the cerebral cortex and the striatum (Lioidis et al., 2007), while Lhx8 for the specification of two other subpopulations, namely the cholinergic interneurons of the striatum and the cholinergic projection neurons of the basal forebrain (Fragkouli et al., 2009; Zhao et al., 2003). We studied two independently collected family samples, and found positive association with LHX6 variants in our TSGeneSEE sample (127 trios originating from Italy, Hungary and Poland), but no association in our German sample (95 trios) (Paschou et al., 2012). Although further analysis in larger sample sizes is required, the genetic heterogeneity we observed, suggests, for the first time, the hypothesis that different etiological factors may be implicated in TS etiology in different populations, even within Europe.

The role of glutamate in corticalstriatal–thalamocortical circuitry (Harris and Singer, 2006), as well as growing evidence that disrupted neurotransmission of glutamate plays a role in OCD pathogenesis, is currently renewing interest in the investigation of the role of the glutamatergic pathway genes in TS etiology. The role of glutamate in OCD etiology has unfolded rapidly in recent years, with this hypothesis gaining support, both from animal models, as well as genetic association studies. In TS, both pathophysiological as well as recent genetic studies are also starting to point in the same direction. In 1992, Anderson et al. (1992) found reduced levels of glutamate in globus pallidus interna, globus pallidus externa, and substantia nigra pars reticulata in a small number of postmortem brains from individuals with TS. A study of the glutamate transporter Solute Carrier, Family 1, Member 3 (SLC1A3) gene, identified a functional missense variant involving a highly conserved residue (E219D) (in 11 out of 256 individuals with TS and four out of 224 controls). Although, the allele frequency for this variant was 2.4 times higher in the TS group, the comparison was not statistically significant (Adamczyk et al., 2011). It should be noted that another member of the same family, the SLC1A1 gene represents, one of the most well-supported candidate genes for OCD, as supported by linkage studies (Hanna et al., 2002; Willour et al., 2004), as well as independent association studies (Arnold et al., 2006; Shugart et al., 2009; Samuels et al., 2011; Wendland et al., 2009). Toward the same direction, of investigating the glutamate hypothesis in TS etiology, the SAP90/PSD95-associated protein 3 (SAPAP3/DLGAP3), has recently been investigated in association to TS (Crane et al., 2011). In a family-based sample of 289 TS trios, nominally significant associations were identified, suggesting the fact that further investigation of the involvement of the DPGAP3 gene in TS etiology is warranted (Crane et al., 2011). DLGAP3 is a postsynaptic scaffolding protein which is highly expressed in striatal glutamatergic synapses (Crane et al., 2011). PSD95 family proteins are known to regulate the trafficking of both AMPA and NMDA types of glutamate receptors (Welch et al., 2007), and DLGAP3 knockout mice display OCD-like behavior, consisting of compulsive grooming behavior leading to facial hair loss and skin lesions, as well as anxiety-like phenotypes (Welch et al., 2007). In 2009, a large family based association study (383 families) reported nominal association of DLGAP3 variants with grooming disorder (Bienvenu et al., 2009). Of note is the fact that, in a recent genome-wide association study for OCD, the most significant hits of association were observed with SNPs at the DLGAP1 gene, another member of this family (Stewart et al., in press).

Next generation sequencing technologies are only now beginning to be implemented in the world of TS research. Applying whole-exome sequencing on a three-generation pedigree, with seven of the family members showing a TS phenotype, Sundaram

et al. (2011) identified three novel nonsynonymous variants in the mitochondrial ribosomal protein L3 (MRPL3) gene, the DnaJ (Hsp40) homolog subfamily C member 13 (DNAJC13) gene, and the orofacial cleft 1 candidate 1 (OFCC1) gene. These variants were not present in 100 control subjects or in dbSNP/1000 Genomes databases. The interpretation of results from whole-exome sequencing studies is difficult, and further studies of the implicated genes in relation to TS is required.

Prompted by recent findings of genomewide association studies for the phenotypes of restless legs syndrome (RLS – characterized by a recurrent urge to move the legs, with or without an uncomfortable sensation) (Allen et al., 2005) and periodic limb movements during sleep (repetitive and stereotyped movements of the legs) (Hornyak et al., 2006), Rivière et al. (2009), identified overtransmission of alleles in the BTBD9 gene in a sample of 298 TS trios. A high prevalence of RLS has been reported in TS and, like TS, RLS has also been linked to dysfunction in frontostriatal circuits, and is responsive to modification of dopamine neurotransmission (Turjanski et al., 1999). Recently, Guo et al. (2012) investigated the BTBD9 gene in the Chinese Han population (110 individuals with TS and 440 controls) and found positive association of one of the same SNPs (rs9296249) as Rivière et al. (2009). Interestingly, the recent genomewide association study for OCD produced findings indicative of association, with a gene of this same family, the BTBD3 gene (Stewart et al., in press).

On the other hand, based on the hypothesis of TS as an immune-mediated disease, Chou et al. (2010) recently identified positive association with the interleukin 1 receptor antagonist gene (IL1RN), although, the studied sample was very small (159 Taiwanese children with TS and 175 controls). In any case, given the evidence on the existence of a neuroimmunological component in TS, further exploration of inflammatory mediators, such as cytokines in relation to TS etiology, is an exciting area of research, that may help shed some light into the challenging question of how environmental triggers may interact with genetic background in order to lead to the onset of the disorder.

6. Conclusion

After more than two decades of active research aiming to identify the genetic background of TS etiology, we are on the verge of a new era, promising exciting and rapid discoveries in the field of TS genetics. Finally, multiple resources are being consolidated and coming together for the study of TS; large well-characterized patient cohorts, specialized epidemiological databases, novel genomewide genotyping and sequencing technologies, and sophisticated methodology for the analysis of large-scale datasets are powerful new tools in our quiver. Investigators from around the world, representing multiple disciplines and scientific approaches, are joining their efforts in large-scale initiatives supported both by European Union and US National funding agencies (such as the European-based EMTICS, TACTICS, and TSGeneSEE consortia as well as the COST Action “European Network for the Study of TS”, the Marie Curie Initial Training Network TS-EUROTRAIN and the European Society for the Study of TS joining forces with the US-based consortia TSAICG, GGRI, and Tic Genetics) (<http://tourette-eu.org>).

TS genetics research has not moved as quickly as was the case for the study of the genetic basis of other complex phenotypes (State, 2010). Nevertheless, at this point, we are in a unique position to benefit from lessons taught from the study of other complex disorders, including psychiatric and neurodevelopmental disorders such as autism. During the past decade, the field of psychiatric genetics was fuelled by the so called Common Disease-Common Variant hypothesis, postulating that common variants underlie the

susceptibility to common complex disorders (Risch and Merikangas, 1996; Reich and Lander, 2001). This hypothesis, coupled with rapid advances in technology and our increased understanding of the structure of the human genome, led to the GWAS explosion. Indeed, GWAS proved successful in identifying common variants contributing to the inherited component of common diseases. However, GWAS demanded extremely large sample sizes, and the identified variants only accounted for modest effect sizes, leaving a large proportion of missing heritability for the studied disorders (McCarthy et al., 2008). Propelled by the advent of next generation sequencing technologies, interest in the study of rare variants is rekindled and it is expected that at least part of the “missing heritability” of complex disorders such as TS, will be attributable to low-frequency variants with intermediate penetrance effects (Manolio et al., 2009). Furthermore, although, for quite some time, studies were hypothesis-free, focusing on statistical association with single genes, novel analytical methods, allow the combination of statistical evidence with biological hypothesis. Through pathway analyses, it is now possible to examine, for instance, the involvement of variants mapping to genes that interact with, or lie within the same pathways as previously implicated genes (Fernandez et al., 2012). Finally, the breakthrough of the ENCODE project, is paving novel paths for genetic research, allowing us to interrogate regions of the genome that were previously thought to be non-functional (The ENCODE Project Consortium, 2012). These advances can be expected to shape the future studies of TS research.

Disentangling the complex etiology of TS will lead to the identification of novel targets for drug treatment and psychotherapy, ultimately improving treatment and increasing the quality of life for patients and their families. It should be expected that, within this decade, genomewide meta-analysis studies of several thousands of individuals with TS will become realized. Importantly, we may be witnessing a paradigm shift in the study of neuropsychiatric disorders, which, given the complex and multidimensional nature of TS, may act to accelerate the emergence of new knowledge; a shift from a strict categorical DSM-dominated disease classification system to an integrated approach recognizing overlapping risks and comorbid disorders as points on a continuum rather than distinct entities. Such an approach will target the whole spectrum of neurodevelopmental phenotypes in concert with an aim to detect underlying common pathways rather than divergences in neurobiology and may offer novel insights in our understanding of the development of the nervous system, as well as the biological substrates of behavior and cognition.

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