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Review Article

Tics and Swearing: a review of recent genetic data concerning Tourette Syndrome

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Abstract

Gilles de la Tourette Syndrome (TS) is a neurodevelopmental disorder characterized by a series of vocal and motor tics. It usually appears on childhood and affects 0.3-0.9% of the population, with the incidence ratio of boys: girls being 4:1. TS has a complex pathogenic basis, including genetic, epigenetic and environmental factors. It shows great heritability, but the underlying genetic etiology remains unclear. The purpose of this study was the review of the most important recent genetic discoveries concerning TS. The research was conducted mainly through studies and scientific articles dating 2010 and after. Over the last few years, genetic research over TS has linked the disease with SNPs (single nucleotide polymorphisms) and CNVs (copy number variants) of specific genes, mainly involved in the dopaminergic and serotoninergic path. Many genes have been associated with the disease, including DRD2 and D4 (dopamine receptors D2 and D4), DAT1 (dopamine transporter 1), TPH2 (tryptophan hydroxylase), MAO-A (monoamine oxidase -A), with more recent studies pointing towards NRXN1 (neurexin 1) and CNTN6 (contactin 6) genes. A mutation of a gene leading to insufficiency of histamine decarboxylase has been named as a risk factor for the syndrome. In other studies, CNVs in AADAC (arylacetamide deacetylase) gene have also showed possible involvement in the onset and course of TS. Moreover, a recent genome-wide study associated an SNP in gene COL27A1 (collagen type XXVII, alpha 1) with the disease. The recent genetic data in this field has led to the establishment of experimental genetically targeted therapies. Further scientific research over the genetics of TS is deemed necessary, as it can potentially lead to a personalized gene-targeted therapy to TS.

Keywords: Tics, Genetics, Dopamine, Serotonin

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Abbreviations:

TS: Tourette's Syndrome

ADHD: Attention deficit hyperactivity disorder

OCD: Obsessive compulsive disorder

CNVS: Copy number variants

SNPS: Single nucleotide polymorphisms

VNTRs: Variable number tandem repeats

5-HT: Serotonin

HDC: Histamine decarboxylase

AADAC: Arylacetamide deacetylase

Introduction

Gilles de la Tourette Syndrome or shortly Tourette Syndrome (TS) is a neurodevelopmental disorder that is characterized by a series of motor and vocal tics. It usually appears in childhood (mean age of onset is 6.4 years) and improves in severity further on during the patient's late adolescence or early adult life (Baldan et al, 2014; Hallett, 2015). 1/3 of TS patients seize having tics by early adulthood (Ünal and Akdemir, 2016). It affects 0.3-0.9% of the population (1 in every 4,000-6,000 school-aged children), with male to female ratio being 4.4 to 1 (Leckman, 2002; Hallett, 2015; Ünal and Akdemir, 2016; Paschou and Müller-Vahl, 2017). A family history is present in 51.7% of cases (Hallett, 2015). Tourette syndrome presents with great phenotypical heterogeneity, with only 10–13.5% of pure TS cases, and is highly associated with other comorbid psychiatric diseases, and especially with attention-deficit hyperactivity disorder (ADHD, seen in 55.6% of patients) and obsessive-compulsive disorder (OCD, reported in 45.9% of patients) (Hallett, 2015; Paschou and Müller-Vahl, 2017). These comorbid disorders are often associated with more distress and impairment than TS tics themselves (Fernandez, 2016).

Tourette Syndrome is a complex disorder with great heterogeneity at its clinical manifestations that points towards a pathogenic basis consisting of both genetical and environmental factors. From the environmental factors, psychosocial stress remains the most important one influencing tic severity (Hoekstra et al, 2013). Moreover, environmental exposures during the prenatal period, perinatal stages, and postnatal life, such as low birth weight and maternal smoking during pregnancy seem to affect the risk of both TS and comorbid ADHD /OCD. It has also been hypothesized that the onset of TS might arise as a result of autoimmune mechanisms following a group A β-hemolytic streptococcal infection, a condition known as pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS).

As far as the genetics are concerned, although family history is often positive, and a genetic etiology is assumed, no definitive TS-risk associated gene of major effect has yet been identified (Hallett, 2015; Paschou and Müller-Vahl, 2017). Lately many studies and worldwide collaborative projects have been trying to shed light on the genetics of TS and have managed to establish evidence for the first robust genetic associations concerning the disease. The aim of this study is to present a review of the literature regarding the genetic etiology of TS.

Methods

PubMed and Google Scholar were mainly used to obtain recent research papers and reviews (2010-2017). The keywords used were as follows: Tourette Syndrome, genetics, tic disorders, neurobiology, pathophysiology and treatment.

CLINICAL CHARACTERISTICS

The tics characterizing TS are multiple, recurrent, motor movements and at least one vocalization (motor and phonic tics respectively), with onset before age 18 and persistence for over

a year (Fernandez, 2016). Phonic tics usually follow the appearance of motor tics by several years (Leckman, 2002). Tics can be varying from simple to complex. Simple motor tics include eye blinking or other facial movements, head or shoulder jerks or sudden movements of the arms or legs, while extreme clinical manifestations include self-injuring complex motor-tics such as hitting or biting. Simple phonic tics include throat-clearing, flattening of the tongue, grunting, and sniffing. Coprolalia (swearing tics) is reported at 10% of cases, while repetition of others' phrases or words (echolalia) and repetition of one's own words or phrases (palilalia) are also usual complex vocal tics. It should be noted that most patients report also a premonitory phenomenon, sometimes cited as "sensory tic": a specific sensory feeling like "an urge" that usually precedes the tic; patients claim that they make the movement voluntarily to make the sensation go away (Hallett, 2015).

RECENT GENETIC DATA

Many twin and family studies have indicated TS as a non-mendelian heritable disorder with a population-based heritability estimated at 0.77, a concordance of 77% in monozygotic twins and 23% in dizygotic twins (Ünal and Akdemir, 2016; Paschou and Müller-Vahl, 2017). First degree relatives of patients with TS have a high risk of developing TS or other tick disorders.

This pattern of vertical transmission in family members suggests major gene effects (Leckman, 2002).

Recently numerous molecular genetic studies of TS, examining cytogenetic abnormalities, copy number variants and rare mutations have been conducted; however only a few findings were able to be replicated in larger patient cohorts (Fernandez, 2016; Hirschtritt et al, 2016). Genome-wide association studies of common variants haven't managed to generate statistically significant signals (Fernandez, 2016).

TS is closely interwoven with two types of DNA polymorphisms (individual differences in a patient's DNA): copy number variants (CNVs) and single nucleotide polymorphisms (SNPs) (Ünal and Akdemir, 2016). CNVs are genomic parts that consist of specific repeated large DNA sequences (200bp-2Mb) that vary in number among the population. In SNPs, usually 2 different nucleotides may appear in a single position of the human genome, thus creating different alleles per 1000 base pairs (Nussbaum, McInnes and Willard, 2017, p.230). There has also been association with specific variable number tandem repeats (VNTRs). VNTRs are polymorphisms that are characterized by the inlay of a varying number (ranging for hundreds to thousands) copies of a DNA sequence 10-100 bp wide.

It seems most likely that risk for TS is configurated by numerous genes harboring small effect common variants and large effect rare variants, that come into effect by environmental and epigenetic influences (Fernandez, 2016).

Neurophysiological and brain imaging data reveal disruption of the cortico-striato-thalamo-cortical (CSTC) circuits of the brain, as well as abnormalities in neurotransmitters such as dopamine, glutamate, serotonin,

histamine and acetylcholine to be involved in the pathogenesis of TS (Felling and Singer, 2011; Paschou et al, 2013; Paschou and Müller-Vahl, 2017).

A series of studies were conducted concerning candidate genes related to these neurotransmitters and many of them indicated that neurotransmitter SNPs and CNVs are highly linked to TS, especially gene polymorphisms in the dopaminergic and serotonergic pathways (Paschou et al, 2013; Hallett, 2015; Ünal and Akdemir, 2016).

Concerning the dopaminergic pathway (Table 1), *dopamine receptor D2* (*DRD2*) was initially associated with TS early in the 1990s (Paschou et al, 2013); a Taq1 A polymorphism (SNP rs1800497) in DRD2 and later three more SNPs in the same gene were reported (Ünal and Akdemir, 2016). In *DRD4*, a 48-bp VNTR has been associated with TS. Studies of the *DRD1* and *DRD3* genes have not shown any positive findings (Paschou et al, 2013). Furthermore, there have been indications of association between TS and the dopamine transporter DAT1 gene (SLC6A3); a 10-repeat allele of a common 40-bp VNTR in the 3′ untranslated region of the DAT1 gene has been reported to be more frequent in TS patients (Paschou et al, 2013; Ünal and Akdemir, 2016). It should be noted that the 10-repeat DAT1 allele has also been suggested as a genetic risk factor for ADHD (Paschou et al, 2013).

In the serotonergic pathway (Table 2), SNPs rs4565946 and rs4570625 of gene TPH2 have been associated with TS. TPH2 gene encodes the isozyme of tryptophan hydroxylase (rate-limiting enzyme in the synthesis of serotonin, or 5HT), found in the serotonergic neurons of the brain. As far as the 5HT receptor genes are concerned, very few genetic association studies have been conducted; only two polymorphisms in gene HTR2C (5HT receptor 2C) have been reported to have an association with the disorder. The SERT gene solute carrier family 6—neurotransmitter transporter, serotonin, member 4 (SLC6A4) is implicated in OCD etiology. Although so far the results concerning its effect on TS have been inconclusive, high expression variants of SLC6A4 as well as a rare SLC6A4 gain-of-function variant (I425V) were significantly associated to TS.

Monoamine oxidase-A gene (MAO-A), which is involved in the deactivation of both dopaminergic and serotonergic pathways, has yielded many positive results in genetic association studies (Paschou et al, 2013; Ünal and Akdemir, 2016). MAO-A has also been proposed as a susceptibility gene for ADHD (Paschou et al, 2013).

Recent genetic work concerning TS has pointed towards the HDC (histamine decarboxylase) gene, a rather neglected neurotransmitter (Table 3). (Paschou et al, 2013; Baldan, 2014; Hallett, 2015; Ünal and Akdemir, 2016). Specifically, it has been identified that a premature termination codon (W317X) forms at the gene due to a single rare coding mutation (Ünal and Akdemir, 2016). The HDC W317X mutation causes dysfunction in the HDC gene, which leads to overproduction of histamine, since the gene's product, L-histidine decarboxylase, regulates histamine biosynthesis (Paschou et al, 2013). Another study established association between TS and two SNPs (rs854150

Table 1: Genes associated with TS in the dopaminergic pathway

Genes	**polymorphisms assosiated with ts**
GENES CODING receptors:	
drd2	SNP rs1800497
drd4	48-bp VNTR
drd1, drd3	No positive findings
OTHER genes:	
GENE CODING dat1	10-repeat allele in a 40-bp VNTR

Table 2: Genes associated with TS in the serotoninergic pathway

genes	**polymorphisms assosiated with ts**
GENE CODING tph2	SNPs rs4565946, rs4570625
htr2c (CODING 5ht receptor)	Two polymorphisms, poor association (concerning all 5HT receptors)
slc6a4	I425V (rare gain-of-function variant) Mostly implicated in OCD etiology
GENE CODING MAO-A	Various findings Involved in both dopaminergic and serotoninergic pathways Also associated with ADHD

Table 3: Other TS risk genes

GENES	**POLYMORPHISMS ASSOSIATED WITH ts**
GENE CODING HDC	W317X premature termination codon SNPs rs854150 and rs1894236 in indronic regions may be implicated in several neuropsychiatric disorders
COL27A1 (9Q32 CHROMOSOME)	SNP rs7868992
polr3b	SNP rs6539267
gene coding aadac	Deletion CNV Other CNVs probably implicated
genes coding nrxn1 and cntn6	20-fold and 10-fold (respectively) rare CNVs

and rs1894236) within intronic regions of the HDC gene (Karagiannidis et al, 2013). These findings established dysregulation of histaminergic neurotransmission as a rare cause of TS. The importance of histamine as a neurotransmitter and its role in several neuropsychiatric disorders are only recently starting to be appreciated.

Lately, a recent large genome-wide association study identified an SNP (rs7868992) on chromosome 9q32 within the gene COL27A1 (Hallett, 2015). COL27A1 is a fibrillar collagen, but the function of COL27A1 in the developing nervous system is unknown (Scharf et al, 2013). The same study identified a second SNP in its analysis, rs6539267, within an intron of POLR3B. This gene encodes

a major part of RNA polymerase III, which transcribes eukaryotic non-coding RNAs (tRNAs, small rRNAs, microRNAs).

Moreover, a study conducted by Thomas V. Fernandez (2016) revealed a statistically significant association of TS with a deletion CNV in AADAC (arylacetamide deacetylase) gene. The function of this gene in the brain remains obscure, but it seems that AADAC expression peaks in the striatum between birth and adolescence, which is accordant with the typical age of TS onset. This study followed an earlier study that had associated AADAC CNVs with TS but within a smaller group of subjects.

More recently, an important collaborative study by Tourette Syndrome Association International Consortium for Genetics (TSAICG) has shown that rare CNVs increase the risk for TS (Huang et al, 2017). Specifically, NRXN1 (neurexin 1 gene) and CNTN6 (contactin 6 gene) each conferred a substantially increased risk of TS: 20-fold and 10-fold, respectively (Black, 2017). These are the first definitive TS risk genes that have been identified (Paschou and Müller-Vahl, 2017). Only 1% of TS cases carry one of these risk alleles in these two genes, which confirms the vast dispersion of the genetic risk for TS among numerous genes. NRXN1 had been associated with TS again in the past, when 2 CNV studies indicated this gene's involvement in the pathogenesis of TS, along with COL8A1(collagen, type VIII, alpha 1) and CTNNA3 (catenin, alpha 3) genes ((Paschou et al, 2013; Ünal and Akdemir, 2016; Fernandez, 2016).

Of course, these results point towards the need for further investigation on the cellular effects of these genes and perhaps related treatments.

A wealth of studies has associated TS with variations spanning many other genes, but the meaning of this remains unclear. Such genes are, among others (Table 4):

DBH gene, encoding dopamine beta-hydroxylase, the enzyme which catalyzes the conversion of dopamine to norepinephrine (Paschou et al, 2013), NLGN4 (neuroligin 4) gene and CNTNAP2 gene (contactin-associated protein-like 2—Caspr2), a member of the neurexin superfamily (Paschou et al, 2013; Ünal and Akdemir, 2016). Neurexins and neuroligins have a vital role in the development of synaptic connectivity and are main organizing molecules in excitatory glutamatergic and inhibitory GABAergic synapses (Paschou et al, 2013). The effect of these molecules in the pathogenesis of TS is also implied by the recent findings concerning NRXN1 gene and its association with TS that were mentioned earlier.

gene of SAP90/PSD95-associated protein 3 (SAPAP3/DLGAP3), postsynaptic scaffolding protein highly expressed in striatal glutamatergic synapses, serotonin receptor (5-HTR2A) and Androgen Receptor (AR) genes (O'Rourke et al, 2009), IMMP2L (inner mitochondrial membrane protein) gene, SLITRK1 (SLIT family membrane protein, 1) gene, containing functional defects that were pointed out by cytogenetic studies (Ünal and Akdemir, 2016), DLGAP3 gene, encoding a postsynaptic scaffolding protein highly expressed in striatal glutamatergic synapses (Felling and Singer, 2011), FSCB (fibrous sheath cabyr-binding protein) gene (Fernandez, 2016).

Table 4: Other genes potentially implicated in TS

COL8A1	AR
CTNNA3	TPH2
CNTNAP2	IMMP2L
NLGN4	SLITRK1
DBH	DLGAP3
SAP90/PSD95	FSCB
5-HTR2A	

Although so far the research of TS mainly focuses on the genetic etiology of the disease, there are a few studies that have investigated the role of epigenetic factors and non-coding RNAs in the development of TS. One of these studies identified a nucleotide variant(var321) in the3′ UTR of the SLITRK1 gene (mentioned above), which leads to its stronger repression by miRNA-189 (Pagliaroli et al, 2016). Another study, the first Epigenome-Wide Association Study (EWAS) with an aim of investigating DNA methylation differences between controls and patients, showed only small methylation differences between the two groups. Finally, IDH2 (isocitrate dehydrogenase 2) and malic enzyme 1 genes, both of which seem to play a role in epigenetic modifications, have been associated with TS, thus potentially linking the disease with altered neural epigenetic patterns. Generally, it seems that environmental factors act via epigenetic modifications including modifications of the chromatin and regulatory non-coding RNAs, but further research in this area is required.

Discussion

It is apparent that further investigation of the role of variants in TS etiology will require the study of large sample sizes and collaborative efforts. Already, many large-scale collaborative projects have recently been established, aiming to elucidate the obscure genetic etiology of TS (Paschou and Müller-Vahl, 2017). Such projects are the Tourette Syndrome Association International Consortium for Genetics (TSAICG), the Tourette International Collaborative Genetics (TIC Genetics), the European Multicenter Tics in Children Study (EMTICS), TS-EUROTRAIN (a Marie Curie Initial Training Network), the European Society for the Study of Tourette Syndrome (ESSTS) and the newly established ENIGMA-TS working group (Dietrich et al, 2015; Paschou and Müller-Vahl, 2017). These international collaborations use different approaches and work complementary, raising hopes for robust genetic discoveries concerning TS and related disorders over the next few years.

TREATMENT

Until now, the usual first-line treatment for tics is behavioral/ psychological intervention (Black, 2017; Paschou and Müller-Vahl, 2017). The most common therapy of this kind is habit reversal therapy, which is based on the idea that tics are habits; patients are taught to recognize the "urge" and to try avoiding it by doing something more socially acceptable than the tic itself (Hallett, 2015). Pharmacological interventions are second-line options whereas some experimental approaches include deep brain stimulation (DBS) in the ventromedial thalamus; the latter is recommended only for severe and treatment refractory cases (Paschou and Müller-Vahl, 2017). The most common pharmacologic approaches for TS are a2 agonists and atypical and typical neuroleptics (Leckman, 2002; Fernandez, 2016). A2 antagonists include clonidine and guanfacine (Hallett, 2015). Moreover, atypical antipsychotics are recommended as a second line treatment, especially risperidone and aripiprazole. Is seems that aripiprazole, a partial agonist at dopamine receptors, improves not only tics but also OCD and possibly other comorbid disorders such as depression, anxiety, and ADHD, but has no effect on premonitory urges. The development of new research strategies concerning the genetics of TS may hold the promise to identify definitive TS susceptibility genes and be the first step towards personalized gene-targeted therapy in TS.

Conclusion

Tourette Syndrome is a disorder with a complex genetic background and an equally complex set of environmental and epigenetic risk factors. The efforts to unravel the genetic architecture of the disease started only a few decades ago but are moving vigorously towards new discoveries that will hopefully give ground for the development of genetically personalized therapies for patients with TS to ameliorate their quality of life.

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