Candidate Genes and Pathways Associated with Gilles de la Tourette syndrome — Where are we?

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Introduction

Identification of major susceptibility genes contributing to the etiology of Gilles de la Tourette syndrome (GTS) has been challenging, presumably due to the complex interplay between several genetic factors and environmental influences, low penetrance of each individual factor, genetic diversity in populations and presence of comorbid disorders. Even though several strong candidate genes have hitherto been identified, none of these have yet turned out to be major susceptibility genes.

To create an overview of the studies that have aimed to identify GTS susceptibility genes, we generated a table listing 304 genes from 150 publications investigated in GTS etiology followed by a review of novel and promising candidate genes.

Supplementary Table S1 – Gilles de la Tourette Syndrome Candidate Genes and Regions

Supplementary Table S1A

Gene	Chromosome	Finding	Sample Size (Ancestry)	Analysis	Reference
SLITRK1 (Slit and Trk-like 1)	13q31.1	Chromosomal inversion near *SLITRK1*; varCDFs and two occurrences of var321 identified in GTS probands.	4 families (GTS probands +/- ADHD or OCD); 174 GTS probands; 253 controls; 3,600 control chromosomes (Mostly Caucasian)	Breakpoint mapping, Sequence analysis, association	[1]
		Association between GTS and rs9593835 plus haplotypes of three tagging SNPs.	154 GTS nuclear families (Canadian)	Sequence analysis, association	[2]
			222 GTS trios (European)	Association (TDT)	[3]
			92 GTS (Japanese); 361 controls (NA)	Sequence analysis, association	[4]
		Support for Abelson et. al (2005).	1,117 GTS (European); 758 GTS (Jewish); 7 var321 carriers and their relatives	Genotyping, MDS, haplotype mapping	[5]
		Finding of known variants rs150504822 and rs146746846 plus novel variants c.1158C>A and c.1061C>G.	382 GTS (European, Canadian)	Sequence analysis	[6]
		Finding of three rare missense variants in *SLITRK1*.	120 GTS; 788 controls (French)	Sequence analysis	[7]
		Only c.3225T>C suggested as a rare variant, no other variants identified.	160 GTS children (Taiwanese)	Sequence analysis	[8]

Neurotransmitter Pathways

The cortico-basal ganglia-thalamo-cortical (CBGTC) loops are associated with GTS pathogenesis and are home to several neurotransmitter pathways. In particular the dopaminergic, but also the serotonergic pathway has been studied in GTS. These studies have typically had low statistical power due to small cohorts, and there has been no indication that genes of either pathway plays a major role in GTS etiology. However, there may be several neurotransmitter systems involved either directly or indirectly and through modulation of each other, as dysfunction of one pathway may affect others due to interaction or self-regulation among them.

Novel GTS Candidate Genes

Exome sequencing of GTS individuals have recently suggested *ASH1L*, *CELSR3*, and *WWC1* as candidate GTS genes. One study reported 19 damaging variants in *ASH1L*. The authors also observed that *Ash1l*$^{+/-}$ mice manifested tic-like behaviours which could be rescued by a tic-relieving drug, and that the disruption of *Ash1l* affected dopaminergic modulation in the dorsal striatum in the basal ganglia.

CELSR3 and *WWC1* were reported as high confidence GTS risk genes as multiple *de novo* damaging variants were identified in 511 GTS trios.

An analysis of rare copy number variations (CNVs) in GTS found *NRXN1* deletions and *CNTN6* duplications to be present in 1% of the 2,434 GTS individuals evaluated, supporting a role for *NRXN1*, *CNTN6* and structual variation in general in GTS etiology.

Finally, *FLT3* was recently suggested as a GTS susceptibility gene, as is harbors the first SNP in a GTS GWAS that has reached the genome-wide threshold of significance. A variant of *FLT3* also drove the association between GTS and a lymphocytic gene set in a recent large pathway analysis. The association between lymphocytic genes, *FLT3*, and GTS suggests an involvement of *FLT3* in GTS.

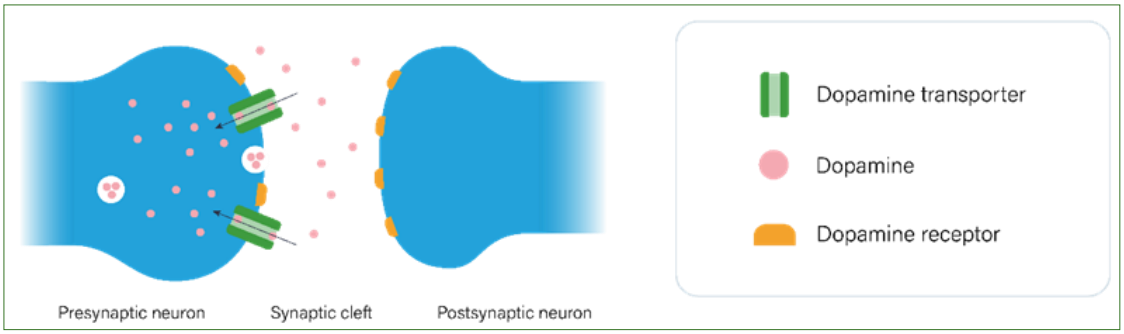
Outlook—Opportunities and Challenges

In order to better understand the genetic architecture of GTS, future studies should prioritize:

⇒ Large, clinically homogenous cohorts which also takes comobidities and ancestry into consideration.

⇒ Uniform methodology between studies.

Functional analyses and cross-disorder studies might offer novel insights into both the etiology and pathophysiology of GTS as well as overlapping neurodevelopmental, -psychiatric and movement disorders.



A better understanding of the complex etiology of GTS and new insights into the pathophysiology of GTS, which is far from being fully understood, are crucial in developing new treatment strategies of this disorder.

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