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Genetic association signal near *NTN4* in Tourette Syndrome

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Abstract

Tourette Syndrome (TS) is a neurodevelopmental disorder with a complex genetic etiology. Through an international collaboration, we genotyped 42 single nucleotide polymorphisms (SNPs) ($p<10^{-3}$) from the recent TS genome-wide association study (GWAS) in 609 independent cases and 610 ancestry-matched controls. Only rs2060546 on chromosome 12q22 ($p=3.3\times10^{-4}$) remained significant after Bonferroni correction. Meta-analysis with the original GWAS yielded the strongest association to date ($p=5.8\times10^{-7}$). Although its functional significance is unclear, rs2060546 lies closest to *NTN4*, an axon guidance molecule expressed in developing striatum. Risk score analysis significantly predicted case/control status (p=0.042), suggesting that many of these variants are true TS risk alleles.

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Introduction

Tourette Syndrome (TS) is a highly heritable, childhood-onset neurodevelopmental disorder that is thought to arise from a complex genetic background interacting with additional environmental factors, underlining the need for large-scale genetic studies and replication of results in independent cohorts (Paschou, 2013). Here, following up on the first genome-wide association study (GWAS) for TS (Scharf et al. 2013), we analyzed an independent European-ancestry sample for 42 top variants of interest in the initial GWAS and provide evidence for enhanced association for one of these single nucleotide polymorphisms (SNPs) (rs2060546 on 12q22) with TS.

The GWAS performed by the Tourette Syndrome Association International Consortium for Genetics (TSAICG) (Scharf et al. 2013) is the first large-scale TS effort in a field that has been hampered by fragmented experiments from individual laboratories and small sample sizes. In this study of 1,285 TS-affected individuals and 4,964 European-ancestry controls, the top signals ($p<1\times10^{-3}$) were significantly enriched for functional variants associated with gene expression and/or methylation levels in cerebellum or frontal cortex (eQTLs/mQTLs, expression quantitative trait loci or methylation quantitative trait loci), although no single marker attained genome-wide significance ($p < 5\times10^{-8}$) (Pe'er et al. 2008, Dudbridge & Gusnanto 2008). Subsequent analyses of TS genetic architecture confirmed that the majority of TS heritability is captured by GWAS SNPs with allele frequencies >5% (Davis et al. 2013), although disproportionate heritability could be attributed to rarer variants. These discoveries underline the genetic complexity of the disorder, and highlight the value of follow-up studies in additional samples.

Patients and Methods

The Gilles de la Tourette Syndrome Genome-wide Association Study Replication Initiative (GGRI) is a collaboration of European and North American TS investigators. We recruited 609 TS cases and 610 ancestry-matched controls from Hungary (73 cases/93 controls), Germany (129 cases/185 controls), Austria (92 cases/103 controls), Italy (47 cases/44 controls), Greece (17 cases/49 controls), and Canada (French Canadian origin, 151 cases/136 controls). Participants aged 18 and older provided written, voluntary informed consent for participation. Individuals under 18 provided assent; written parental consent was also obtained. The study was approved by the Ethics Committees of all participating sites.

Forty-three SNPs, including the top 20 linkage disequilibrium (LD)-independent GWAS hits ($r^2<0.2$) and 23 additional SNPs with $p_{GWAS}<1\times10^{-3}$ that were either eQTL/mQTLs of interest (as described in Scharf et al., 2013) or located within 50kb of previously identified candidate genes for TS or related neuropsychiatric disorders, were selected for targeted genotyping (Table S1). Seventy-four additional ancestry-informative markers (AIMs) were also genotyped to control for population substructure (Table S2). Genotyping was performed using primer extension and mass spectrophotometry (Sequenom, San Diego, CA, USA) as previously described (Crane et al. 2011).

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Principal components analysis (PCA) was performed using EIGENSTRAT (Price et al. 2006) to exclude outliers based on observed genetic ancestry and to produce population structure covariates to correct for residual population stratification. One follow-up SNP failed genotyping, leaving 42 for analysis (Table S1). Genetic association analysis was conducted in PLINK (Purcell et al. 2007) using logistic regression under an additive model with the first two principal components, representing the major axes of variation in genetic ancestry of the sample (North-South and East-West European clines), included as covariates. Meta-analysis with the European-ancestry samples of the original TS GWAS (1,285 TS cases and 4,964 ancestry-matched controls) was performed in METAL (Willer et al. 2010).

A TS risk score was calculated based on the 42 SNPs in each GGRI case/control subject, representing a sum of the number of risk alleles present weighted by the effect size of each locus as estimated in the initial TS GWAS. The relationship between TS risk score and case-control status was then examined by logistic regression (risk score analysis) with number of genotypes included as a covariate to control for any potential bias related to SNP missingness. The percentage of phenotypic variance explained by the aggregate risk score (Nagelkerke's pseudo-R^2) was also estimated.

Results

One SNP, rs2060546, was significantly associated with TS in the GGRI sample ($p=3.3\times10^{-4}$, OR=2.41) after Bonferroni correction (corrected threshold for nominal significance set at p=0.05/42 SNPs = 0.0012) (Table 1, Table S3). Combined analysis of the original GWAS and GGRI samples for this SNP (1,894 cases and 5,574 controls) yielded an association p-value=5.8×10^{-7} and a combined OR=1.77, strengthening the evidence for association relative to the original GWAS ($p_{GWAS}<3.7\times10^{-4}$, OR=1.60). The association signal from the top SNP in the initial GWAS, rs7868992, located in an intronic region of *COL27A1* (collagen type XXVII, alpha 1 chain), was marginally weaker than the signal in the original study (GGRI OR=1.11, p=0.26; GWAS OR=1.29, $p=1.9\times10^{-6}$;combined meta-analysis $p=6.4\times10^{-6}$)(Table 1), with the same direction of effect. Although no other SNPs were nominally significant after experiment-wide correction in the GGRI sample, 26 of the 42 SNPs yielded the same direction of effect as in the original GWAS (one-sided binomial sign-test, p=0.08) (Table S3). Furthermore, the 42-SNP TS risk score significantly predicted TS case-control status in the GGRI sample (p=0.042), accounting for 0.52% of TS phenotypic variance.

Discussion

The top TS-associated SNP in our targeted genotyping study (rs2060546) lies in an intergenic region on chromosome 12q22, ~32kb distal (telomeric) to *NTN4*, and proximal to *SNRPF* (37kb) and *CCDC38* (45kb). SNRPF (small nuclear ribonucleoprotein polypeptide F) is a core component of the RNA spliceosome (Hermann et al. 1995), while the function of CCDC38 is unclear. NTN4 belongs to a family of extracellular proteins that direct axon outgrowth and guidance (Lai Wing Sun et al. 2011). In the developing nervous system, netrins interact with other axon guidance molecules, such as SLIT and WNT family members, to direct the trajectory of the growth cone at the tip of the migrating axon towards

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its final target (Killeen and Sybingco 2008). *SLITRK1*, whose protein bears great similarity to the SLIT family, represents one of the most debated genes in the TS literature, as it has been reported to be associated with TS in a number of studies (Abelson et al. 2005, Karagiannidis et al. 2012), but not in a large family-based investigation of the original association (Scharf et al., 2008). *SLITRK1* was not implicated in the TS GWAS; however, the intergenic region between *SLITRK1* and *SLITRK6* yielded one of the top signals (rs7336083; $p=9.5\times10^{-6}$, OR 0.80) (Scharf et al. 2013). Thus, *NTN4* is a strong candidate for a TS susceptibility gene; in fact, rs2060546 was selected for the current experiment based on having a $p<10^{-3}$ in the initial TS GWAS and being in linkage disequilibrium (D'=1) with the 5' end of *NTN4*.

However, it is not yet clear whether rs2060546 has any functional effect on either *NTN4* or other genes in this region. Although *NTN4* is the closest gene to rs2060546, recent work from the ENCODE and Roadmap Epigenomics consortia have demonstrated that ~40% of genome-wide significant GWAS SNPs lie in putative enhancer regions whose chromatin structure is most highly correlated with active promoters of genes >250kb from the putatively causal SNP (Maurano et al., Science 2012). While rs2060546 was not identified as a regulatory eQTL SNP in frontal lobe or cerebellum (Scharf et al., 2013), it appears to be a modest cis-eQTL in non-neural tissues for genes near *NTN4*, including two histidine catabolism genes, *HAL* (histidine ammonia-lyase, p=0.0012) and *AMDHD1* (amidohydrolase containing domain 1, p=0.002) in lymphoblast cell lines and *METAP2* (methionine aminopeptidase 2, p=0.0009) in adipose tissue (Stranger et al. 2012; Elbein et al., 2012). Impaired conversion of histidine to histamine via mutations in a third histidine catabolism gene *HDC* has been reported in one TS family, though whether this translates to TS risk in general or might involve other histidine-related pathways is uncertain (Erdan-Sencicek et al., 2010; Karagiannidis et al., 2013; Castellan-Baldan et al., 2013). Therefore, should further analyses confirm rs2060546 as a TS susceptibility variant, functional studies will be needed to determine the causative gene(s) at this locus and the biological mechanism through which this non-coding variant might contribute to this neurodevelopmental disorder.

A few limitations should be considered. While we took specific steps to control for bias from population stratification, including the use of ancestry-matched cases and controls and a carefully selected AIMS panel to detect outliers, in the absence of genome-wide data, it is possible that residual population stratification could have introduced bias. However, the rs2060546 risk allele frequency is consistently increased in cases compared to controls from each of the 6 GGRI countries, suggesting that the association is unlikely to be caused solely by residual population stratification (data not shown). In addition, the current sample is still underpowered to detect the majority of GWAS variants with effect sizes similar to those found in other neuropsychiatric disorders (Sullivan et al., 2012). However, the finding that a TS risk score combining all 42 SNPs in this study predicted TS case-control status suggests that, although not reaching genome-wide significance in this sample, a significant number of these variants are likely to be true TS susceptibility alleles. These results underline the need for future collaborative efforts in larger TS samples to clarify the potential significance of all variants in the current analysis and to identify definitive TS susceptibility genes.

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Supplementary Material

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Table 1

Top 10 association signals in the GGRI TS GWAS follow-up study (609 cases and 610 ancestry-matched controls)

Results of the original TS GWAS for these top linkage disequilibrium (LD)-independent SNPs as well as results of a meta-analysis of the replication and prior GWAS sample (total of 1894 cases and 5574 controls) are also shown. The closest genes around each SNP of interest and association with gene expression and/or methylation levels in cerebellar or frontal cortex tissue are also indicated.

					TS GWAS		GGRI sample		Meta-analysis			
CHR	**SNP**	**BP (hg19)**	**A1/A2**	**MAF**	**OR**	**P**	**OR**	**P**	**OR**	**P**	**Gene**	**eQTL/mQTL**
12	rs2060546	96,215,456	A/G	0.027	1.60	3.7×10^{-4}	2.41	3.3×10^{-4}	1.77	5.8×10^{-7}	SNRPF|NTN4|CCDC38	
2	rs1922786	58,863,573	G/A	0.35	0.83	2.1×10^{-4}	0.76	2.4×10^{-3}	0.81	1.9×10^{-6}		SEL1L2, LMAN1L, INSL3
9	rs7868992	116,991,071	G/A	0.28	1.29	1.9×10^{-6}	1.11	0.26	1.24	6.4×10^{-6}	COL27A1	SYTL4, AMBP, HSPC152, OAS2, PWP1, RALBP1
11	rs11603305	10,997,949	G/A	0.28	1.27	1.3×10^{-5}	1.16	0.10	1.24	7.2×10^{-6}		
7	rs1882078	37,436,975	C/T	0.28	1.27	1.9×10^{-5}	1.15	0.11	1.23	1.1×10^{-5}	ELMO1	
12	rs6539267	106,785,554	C/T	0.31	0.79	7.4×10^{-6}	0.90	0.22	0.82	1.1×10^{-5}	TCP11L2|POLR3B	TMEM119
7	rs769111	12,059,806	G/T	0.38	0.81	1.2×10^{-5}	0.90	0.19	0.83	1.6×10^{-5}		MEOX2, PLSCR1, PCDHB16
11	rs7123010	86,341,186	A/G	0.30	0.79	4.2×10^{-5}	0.89	0.20	0.82	4.9×10^{-5}	ME3	NFKBIZ, FLJ23514, KLF8, PICALM
11	rs621942	85,783,738	A/C	0.24	1.23	1.3×10^{-4}	1.15	0.14	1.21	6.8×10^{-5}	PICALM	TMEM126B, TMEM126A, PICALM, CREB3L3, LRRC2
3	rs2282755	50,442,800	T/G	0.28	0.80	5.6×10^{-5}	0.90	0.24	0.82	7×10^{-5}	TMEM115|CACNA2D2	ZMYND10, PTH1R, HYAL3, SEMA3G

CHR, Chromosome; **BP (hg19)**, Physical position according to NCBI Build 37/hg19 genome assembly; **A1/A2**, Allele 1/Allele 2 (Allele 1 is the minor allele); **MAF**, Minor Allele Frequency; **OR**, odds ratio; **P**, p-value of genetic association test; **eQTL/mQTL**, SNP associated with gene expression levels (cerebellum or frontal cortex) and/or methylation levels in cerebellum (as described in Scharf et al. 2013). Complete results of all 42 targeted SNPs are provided in Table S3.

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