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Cross-Disorder Genome-Wide Analyses Suggest a Complex Genetic Relationship Between Tourette's Syndrome and OCD

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Cross-Disorder Genome-Wide Analyses Suggest a Complex Genetic Relationship Between Tourette Syndrome and Obsessive-Compulsive Disorder

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Abstract

Obsessive-compulsive disorder (OCD) and Tourette Syndrome (TS) are highly heritable neurodevelopmental disorders that are thought to share genetic risk factors. However, the identification of definitive susceptibility genes for these etiologically complex disorders remains elusive. Here, we report a combined genome-wide association study (GWAS) of TS and OCD in 2723 cases (1310 with OCD, 834 with TS, 579 with OCD plus TS/chronic tics (CT)), 5667 ancestry-matched controls, and 290 OCD parent-child trios. Although no individual single nucleotide polymorphisms (SNPs) achieved genome-wide significance, the GWAS signals were enriched for SNPs strongly associated with variations in brain gene expression levels, i.e. expression quantitative loci (eQTLs), suggesting the presence of true functional variants that contribute to risk of these disorders. Polygenic score analyses identified a significant polygenic component for OCD ($p=2\times10^{-4}$), predicting 3.2% of the phenotypic variance in an independent data set. In contrast, TS had a smaller, non-significant polygenic component, predicting only 0.6% of the phenotypic variance (p=0.06). No significant polygenic signal was detected across the two disorders, although the sample is likely underpowered to detect a modest shared signal. Furthermore, the OCD polygenic signal was significantly attenuated when cases with both OCD and TS/CT were included in the analysis (p=0.01). Previous work has shown that TS and OCD have some degree of shared genetic variation. However, the data from this study suggest that there are also distinct components to the genetic architectures of TS and OCD. Furthermore, OCD with co-occurring TS/CT may have different underlying genetic susceptibility compared to OCD alone.

INTRODUCTION

Obsessive-compulsive disorder (OCD) [MIM 164230] and Tourette Syndrome (TS) [MIM 137580] are highly familial neuropsychiatric disorders with complex overlapping genetic etiologies (1–3). 20–60% of TS-affected individuals have co-occurring OCD, and 10–20% of those initially diagnosed with OCD have TS or chronic tics (CT), well over what is expected based on their respective population prevalences (4–6). Both disorders are characterized by the presence of repetitive, ritualized or stereotyped behaviors (tics and compulsions), often preceded by cognitive or sensory phenomena (premonitory urges and obsessions), and clinical differentiation of compulsions versus complex tics can be challenging (7). Genetic epidemiological studies suggest up to 90% shared genetic variance between TS/CT and OCD (8–10), and abnormalities in cortico-striatal-thalamo-cortical (CSTC) circuitry have been identified in both conditions (1).

To date, most of the work aimed at elucidating the genetic causes of TS and OCD has

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focused on candidate gene studies and linkage analyses; a few studies examining chromosome abnormalities and copy number variants (CNVs) have also been reported (11–14). Recently, our group performed genome-wide association studies (GWAS) of TS and OCD, and for each disorder identified a number of genes and genomic regions of interest, most with modest significance levels. Here we report GWAS results for a combined sample of individuals with TS, OCD or TS+OCD, along with analyses aimed at elucidating the genetic architectures and genetic relationships between the two disorders. Combining these heterogeneous but related phenotypes in joint analyses could have one of two potential effects: 1) enhancement of the genetic signal as a consequence of increased power due to adding samples from genetically-related phenotypes; 2) reduction of the genetic signal as a consequence of increased genetic heterogeneity, outweighing potential benefits of increased sample size. Either way, given the prior evidence supporting shared genetic factors, and the lack of definitive susceptibility genes for either disorder, joint analyses of TS and OCD cases represent an important advance toward understanding the underlying causes of these common neuropsychiatric disorders.

MATERIALS AND METHODS

Cases

Individuals with TS or OCD were recruited as part of collaborative efforts to conduct the first GWAS for these disorders (details in Scharf et al, 2013; Stewart et al, 2013) (15, 16). Although data were collected independently for TS and OCD, all genotyping and data cleaning were done together, facilitating joint analyses. Participants ≥18 years of age provided written, voluntary informed consent. Individuals under 18 years of age provided assent; written parental consent for their participation was also obtained. The study was approved by the Ethics Committees of all participating sites and in accordance with the Declaration of Helsinki. For the cross-disorder analyses, any subject with either TS or OCD was considered affected. See Supplementary Methods for details of the inclusion and exclusion criteria and assessment protocols.

TS—The TS sample consisted of 1286 individuals recruited from 20 sites in the US, Canada, UK, Netherlands, and Israel, and included subjects of general European (EU) ancestry as well as two EU-derived population isolates of Ashkenazi Jewish (AJ) and French Canadian (FC) descent. Co-occurring OCD symptoms were assessed in 77% of participants; 46% of those evaluated had co-occurring OCD (N=452). OCD status was unknown for 300 individuals with TS.

OCD—The OCD sample consisted of 1,437 OCD cases and 290 parent-child trios. While the original GWAS sample consisted of 1865 OCD probands recruited from 21 sites in North, Central and South America, Europe, the United Arab Emirates, and South Africa, only subjects of European ancestry (EU, AJ, and EU-derived Afrikaner (SA) descent) were included in the current study (16). Co-occurring TS or CT was assessed in 77% of OCD probands; of these, 12% had co-morbid TS or CT (N=159). TS/CT status was unknown for 405 OCD-affected individuals.

Controls

The EU control sample consisted of 4975 European Caucasian controls primarily derived from cohorts of previously genotyped, unselected population controls (Supplementary Methods). Ancestry-matched controls for the FC (N=196) and SA (N=158) samples were collected in parallel with their respective cases (15, 16). Ancestry-matched controls for individuals with AJ ancestry were identified from the EU control sample based on self-reported ancestry and principal component analysis (N=338).

Genotyping and Quality Control (QC)

Genotyping and quality control procedures have been described previously (15,16, and Supplementary Methods). Briefly, cases and trios with TS or OCD and controls were randomized across plates and genotyped on the Illumina HumanHap610 SNP array (Illumina, San Diego, CA) at the Broad Institute of Harvard-MIT (Cambridge, MA) or on the Illumina HumanHap370 at the Yale Center for Genome Analysis (New Haven, CT) (Supplementary Figure S1). Eighty-eight samples were genotyped on both platforms to allow for cross-platform concordance checks. QC analyses were performed using PLINK v1.07(17) and EIGENSTRAT(18). Multi-dimensional scaling (MDS) analysis was used to exclude case-control samples of non-European descent. Remaining EU and European-derived isolate samples were separated into four strata (EU, AJ, FC, and SA) based on observed genetic ancestry (15, 16). Imputation was performed using 1000 Genomes Project data (June 2011 Data Release)(19) as the reference panel using IMPUTE v2.1.2(20) (Supplementary Methods).

Genome-Wide Association Analyses

Individual ancestry-stratified case-control genome-wide association analyses (EU, AJ, FC, and SA) and one case/pseudo-control analysis using the OCD trios were performed in PLINK (17) using logistic regression under an additive model with significant subpopulation-specific MDS axes included as covariates to control for residual population stratification (Figure S2). These population-specific analyses were then combined in a fixed-effects model meta-analysis using case-weighting in METAL (21). SNPs with p-values $<10^{-5}$ were annotated with details including their genomic region and location, allele frequencies, nearby genes and p-values from individual TS and OCD GWAS studies. Heterogeneity tests were also conducted to assess subpopulation differences using Cochran's Q and I^2 statistics. As is standard in GWAS for complex traits, a genome-wide threshold of $p<5\times10^{-8}$ was considered statistically significant evidence of association (22, 23).

Enrichment analyses

GWAS results were examined for enrichment of functional SNPs previously associated with gene expression levels in several brain regions (i.e., expression quantitative trait locus SNPs, eQTLs) or with variation in gene methylation levels (methylation QTLs, mQTLs). eQTL data were generated from cerebellum, parietal, and frontal cortex (Supplementary Methods). mQTLs were derived from adult cerebellum (24). Only GWAS SNPs meeting high stringency criteria for eQTLs or mQTLs ($p<10^{-6}$) were considered. For each phenotype (TS,

OCD, combined), a quantile-quantile (Q-Q) plot of GWAS disease association p-values was generated for eQTL and mQTL SNPs and compared to a standard Q-Q plot of GWAS p-values expected under the null assuming no enrichment. A leftward shift in the eQTL/mQTL Q-Q plot relative to the diagonal line (representing the null distribution) indicates enrichment of eQTLs/mQTLs. The level of enrichment of eQTLs or mQTLs in each brain tissue associated with TS or OCD was then quantified using a false discovery rate (FDR) of <0.25, i.e., 75% of observed SNPs represent true disease associations (Supplementary Methods).

Polygenic score analysis

Polygenic score analyses were conducted in PLINK using genotyped SNPs to test the hypothesis that multiple genes of small effect jointly contribute to TS and OCD susceptibility and to explore the genetic relationships between these disorders(25). Samples were divided into non-overlapping discovery and target samples (Supplementary Methods). For the primary OCD polygenic analysis, cases were restricted to subjects without known co-occurring TS/CT (OCD - TS/CT). SNPs with GWAS p-values passing pre-determined significance thresholds ($p<0.01$, 0.1, 0.2, 0.3, 0.4, and 0.5, respectively) in the discovery sample were extracted along with their risk alleles and odds ratios, and then LD pruned ($r^2<0.5$). For each significance threshold, a quantitative aggregate risk score was calculated for each individual in the target sample, defined as the sum of the number of risk alleles present at each locus weighted by the log of the odds ratio for that locus estimated from the discovery sample. The relationship between aggregate risk score and case-control status in the target sample was examined at each significance threshold using logistic regression. The percentage of phenotypic variance explained by the aggregate risk score (Nagelkerke's pseudo-R^2) was estimated.

Two separate statistical approaches were used to determine the significance of the observed differences in polygenic risk score prediction between discovery samples. First, permutation testing was conducted to derive an empirical significance of the magnitude of change in R^2 between polygenic risk scores derived from the OCD - TS/CT discovery sample compared to those derived from the "All OCD" sample (OCD +/− TS/CT). Second, risk alleles from each discovery sample were used to calculate the difference in polygenic risk scores between the transmitted (case) alleles and the untransmitted (pseudo-control) alleles in the OCD Trio target sample. The degree of risk score elevation ($\text{Risk Score}_{\text{transmitted}} - \text{Risk Score}_{\text{untransmitted}}$) was then standardized ($[RS_{trans}-RS_{untrans}]/RS_{untrans}$), and compared between different discovery samples using two-sided paired t-tests. See Supplementary Methods for further details of both approaches.

RESULTS

Combined TS/OCD GWAS

The final combined TS/OCD dataset consisted of 2723 cases (1310 with OCD, 834 with TS, 579 with OCD+TS/CT), 5667 controls, and 290 OCD trios. A total of 7,659,573 SNPs (439,840 genotyped and 7,219,733 imputed) were included in the meta-analysis. The

genomic control λ showed no evidence of residual population stratification or systematic technical artifacts (λ_{GC}=1.030; Figure S3).

Sixty-eight SNPs with $p<1\times10^{-5}$, representing 16 independent genomic regions, were identified, though none reached the genome-wide significance threshold of $p<5\times10^{-8}$ (Table 1,Figure 1; Table S1). The most significant association was found in rs4988462 on 3p11 ($p=3.72\times10^{-7}$, OR=1.18). This SNP lies within an intron of *POU1F1*, though the entire 279 kb region of association in linkage disequilibrium (LD) with rs4988462 contains 16 additional SNPs with $p<1\times10^{-5}$ and includes *CHMP2B* and *POU1F1*, as well as the microRNA *MIR4795*. Regional association and forest plots from the top five independent GWAS signals are provided in Figures S4–S8. Eleven of the 68 SNPs were also identified in the original OCD GWAS with $p<1\times10^{-5}$; none of these SNPs were identified in the TS GWAS at $p<1\times10^{-5}$ (15, 16) (Table S1).

Enrichment analyses

For TS, OCD, and the combined sample, we examined the subset of disease association p-values for SNPs meeting stringent criteria for eQTLs ($p_{eQTL}<10^{-6}$) derived from cerebellum, parietal cortex and frontal cortex, as well as cerebellar mQTLs ($p_{mQTL}<10^{-6}$) (Figure 2). Using the field standard FDR threshold of <0.25, we identified 38 cerebellar eQTLs from five LD-independent loci for TS, 161 cerebellar mQTLs (19 LD-independent loci) for OCD, and 53 parietal cortex eQTLs (four LD-independent loci) for the combined GWAS (Table 2).

Polygenic risk score analysis

Polygenic score analyses were conducted to test two related hypotheses: 1) that both TS and OCD individually harbor multiple, small effect, common risk alleles across the genome; 2) that TS and OCD may have shared common risk alleles (cross-disorder analyses). In the individual disorder analyses, risk scores derived from the "OCD - TS/CT" discovery sample strongly predicted case-control status in the OCD target sample ($p=2.1\times10^{-4}$), explaining 3.2% of the phenotypic variance (Figure 3, Table S3). In contrast, risk scores derived from the TS discovery sample demonstrated only weak prediction in the TS target sample (p=0.06; R^2=0.6% variance explained). Risk scores derived from the combined TS/OCD discovery sample also predicted case-control status in the OCD target sample (p=0.0075, R^2=1.7%), though less robustly than those derived from the OCD discovery sample alone (p=0.01, Figure 3, inset). Risk scores derived from the TS/OCD combined sample could not discriminate between cases and controls in the TS target sample (p=0.4, Figure 3, Table S3).

In cross-disorder analyses, risk scores derived from the TS discovery sample did not predict case-control status in the OCD target sample (p=0.66), nor did OCD-associated risk scores predict into the TS target sample (p=0.37) (Figure 3, Table S3).

To explore the influence of phenotype co-morbidity on polygenic risk score prediction, an additional "All OCD" discovery sample was created which included the primary OCD discovery sample plus 345 additional cases with OCD + TS/CT. As expected, the polygenic score using risk alleles derived from this discovery sample predicted case-control status in

the OCD target sample ($p=2.3\times10^{-3}$) (Figure 3). However, the proportion of variance explained by the "All OCD" risk score was significantly attenuated compared to the risk score derived from the primary "OCD - TS/CT" discovery sample, despite the 30% increase in sample size ("OCD - TS/CT", n=1154, R^2=3.2%; "All OCD", n=1499, R^2=2.1%; permutation p=0.01, Figures 3 and S9).

In addition, the magnitude of elevation in the polygenic risk scores (risk score elevation) between transmitted risk alleles and untransmitted non-risk alleles in the OCD trios was calculated using risk alleles from the different OCD discovery samples and compared (Figure 3, inset). The risk score elevation in the OCD trios was highest when the primary "OCD - TS/CT" discovery sample was used to derive the risk score compared either to the "All OCD" sample or the combined TS/OCD sample (paired t-test; p=0.022 and p=0.010, respectively), consistent with a dilution of risk when either OCD cases with TS/CT or TS cases without OCD were incorporated in the discovery sample.

DISCUSSION

The goal of this study was to leverage phenotypic and genotypic data of two phenotypically-related and frequently co-occurring neurodevelopmental disorders, TS and OCD, to explore the hypothesis that these disorders share common genetic susceptibility variants by: 1) combining the samples in a joint GWAS, 2) examining their patterns of eQTL/mQTL enrichment, and 3) exploring cross-disorder polygenic signals. Although limited by small sample sizes, the results of these diverse analytic approaches suggest a complex genetic relationship between TS and OCD.

While our previous work in this sample provides evidence of genetic sharing between TS and OCD, with a genetic correlation of 0.41 between the two disorders (10), we did not identify any genome-wide significant variants for the combined TS/OCD phenotype in this GWAS analysis, despite the increase in sample size. However, the combined GWAS signals were significantly enriched for functional alleles (parietal eQTLs), suggesting that these subthreshold variants contain some proportion of TS/OCD risk loci that are not simply due to stochastic variation. In the presence of genetic heterogeneity (see below), the current sample is underpowered to determine whether these loci contribute to both TS and OCD susceptibility, or to one or the other individually. As with any genetic association result, replication in an independent sample is required to know whether any of the individual eQTLs identified here are truly shared TS/OCD susceptibility variants (9, 26, 27).

However, the results of the polygenic analyses do provide strong evidence that OCD and TS have at least some distinct genetic risk factors. First, the individual disorder analyses confirm that OCD has a significant polygenic component. The proportion of OCD variance explained by directly interrogated SNPs (3.2%) is similar to the findings in schizophrenia (3–6%) and bipolar disorder (2.8%)(25), indicating that OCD likely arises from the joint influence of a large number of susceptibility genes spread across the genome, either as common variants or as rare variants in tight linkage disequilibrium with GWAS SNPs. This result is consistent with a parallel heritability study of the same datasets using mixed linear

modeling which found that OCD heritability is concentrated in common variants with minor allele frequencies (MAF)>30% (10).

In contrast, the proportion of TS variance explained was substantially lower (0.6%). Although some of the difference in polygenic risk prediction between OCD and TS may be due to the smaller discovery sample size for TS, a sensitivity analysis in which the OCD discovery sample size was reduced to match that of the TS sample ("Downsized OCD"), still detected a larger, and statistically significant, OCD polygenic signal than the comparable TS signal (p=0.01) (Figure 3, Table S3). The TS discovery sample was also too small to examine polygenic signals in TS subgroups (TS+OCD vs. TS-OCD); thus, it is possible that the TS polygenic signal could increase if "TS only" discovery and target samples were available. The TS polygenic signal may also have been attenuated by restricting polygenic risk score SNPs to those with MAF>5% (done to reduce bias due to undercalling of rare variants, see Supplementary Methods), as this class of SNPs has been shown to account for ~20% of the variance in liability to TS, with 80% attributable to common variants (10). Both the investigation of TS subgroups and the analysis of polygenic signal including SNPs with MAF ≤5% may be possible in the future as the number of subjects with available GWAS data increases.

The cross-disorder polygenic analyses also provide evidence for genetic heterogeneity between OCD and TS. First, the polygenic risk scores generated from the individual OCD and TS discovery samples did not predict case-control status of the other disorder. Second, the combined TS/OCD sample was a worse predictor of OCD or TS status than either disorder alone, suggesting that the degree of genetic heterogeneity generated by combining the two phenotypes outweighs any improvement in statistical power due to increased sample size. As noted above, however, we are likely underpowered to detect a modest shared signal, which we have previously identified in this sample using a mixed-model approach (10).

Although we were not able to examine TS subgroups, we were able to examine the polygenic composition within OCD subgroups (i.e., OCD +/− TS/CT). These results clearly suggest that OCD with and without chronic tics have different genetic architectures. When OCD cases with co-occurring TS/CT were added to the OCD discovery sample, the polygenic signal in the independent OCD target sample was attenuated by 35% (permutation p=0.01), despite the 30% increase in sample size. Similarly, the risk score elevation between transmitted and untransmitted alleles dropped substantially with the addition of these 345 OCD cases with TS/CT (p=0.022).

The hypothesis that OCD may be genetically heterogeneous, with some individuals and families segregating OCD without tics and others a subtype of OCD with tics that may share genetic risk with TS, was originally proposed by Pauls and colleagues in 1986 (27), and more recent epidemiologic studies have provided additional support for this concept (9, 26, 28). Although not yet studied, these genetic differences may also correlate with well-documented differences in treatment outcomes of patients with OCD alone compared to OCD with tics, in which the latter are more refractory to treatment and may require neuroleptic augmentation (29–31).

Limitations

The primary limitation of this study relates to sample size. While our study represents the largest genetic sample of either disorder studied to date, the total sample of 3013 cases and 5957 controls has 67% power to detect a disease variant with an odds ratio of 1.25 (assuming risk allele frequency is 20% in the general population), and only 25% power to detect a variant with an odds ratio of 1.20. Recent studies of other psychiatric disorders with evidence of genetic overlap have required substantially larger sample sizes in order to detect individual variants that contribute to both disorders (32, 33). Therefore, caution is necessary when drawing conclusions about the genetic architecture of TS and OCD based exclusively on the results of the combined GWAS. However, we have more confidence in our interpretation of the polygenic analyses, where demonstrated significant differences between the aggregate polygenic risk for the TS/OCD phenotypes despite comparatively small sample sizes. Of note, aggregate polygenic signals have been successfully detected with a comparable number of subjects in other cross-disorder studies as well (32, 33).

In addition, although we propose that the differences in polygenic risk prediction between TS and OCD and between OCD with and without tics are due to divergent genetic architectures, alternative explanations should be considered, such as diagnostic misclassification or differences in case ascertainment between study sites or over time. It is also important to note that we focused on common variation, and that rare inherited variation, unique mutations within individual families, *de novo* mutations, structural variation and/or epigenetic and non-genetic factors are all likely contributors to the overall etiology of these related disorders. While our initial studies suggested that common variants account for most of the heritability of TS and OCD (10), it is still extremely important to explore all of these potential contributors to disease in order to acquire a full understanding of their relative contributions to TS and OCD.

Finally, interpretation of the eQTL/mQTL analyses are limited by the fact that the tissues analyzed represent a convenience sample based on currently available data, and thus, conclusions about tissue-specificity should be reserved until larger eQTL datasets across the full range of brain regions and developmental time periods are available.

Summary

Overall, our results argue that, in addition to some shared genetic variants contributing to susceptibility of either TS or OCD, genetic variants likely exist which provide phenotypic specificity for each disorder. This observation contrasts with the hypothesis that genes contributing to neuropsychiatric disorders provide a “generalist” framework of neuronal connections from which non-genetic factors determine specific phenotypes, as has been proposed to explain the wide range of phenotypes observed in patients with similar large recurrent CNVs across various regions of the genome (34, 35). Furthermore, the apparent difference between OCD with and without tics supports the importance of detailed phenotypic characterization to identify future subtype-specific risk alleles. Collection of additional samples through ongoing collaboration will be crucial to further elucidate the specific underlying susceptibility genes for TS and OCD, both shared and unique.

Supplementary Material

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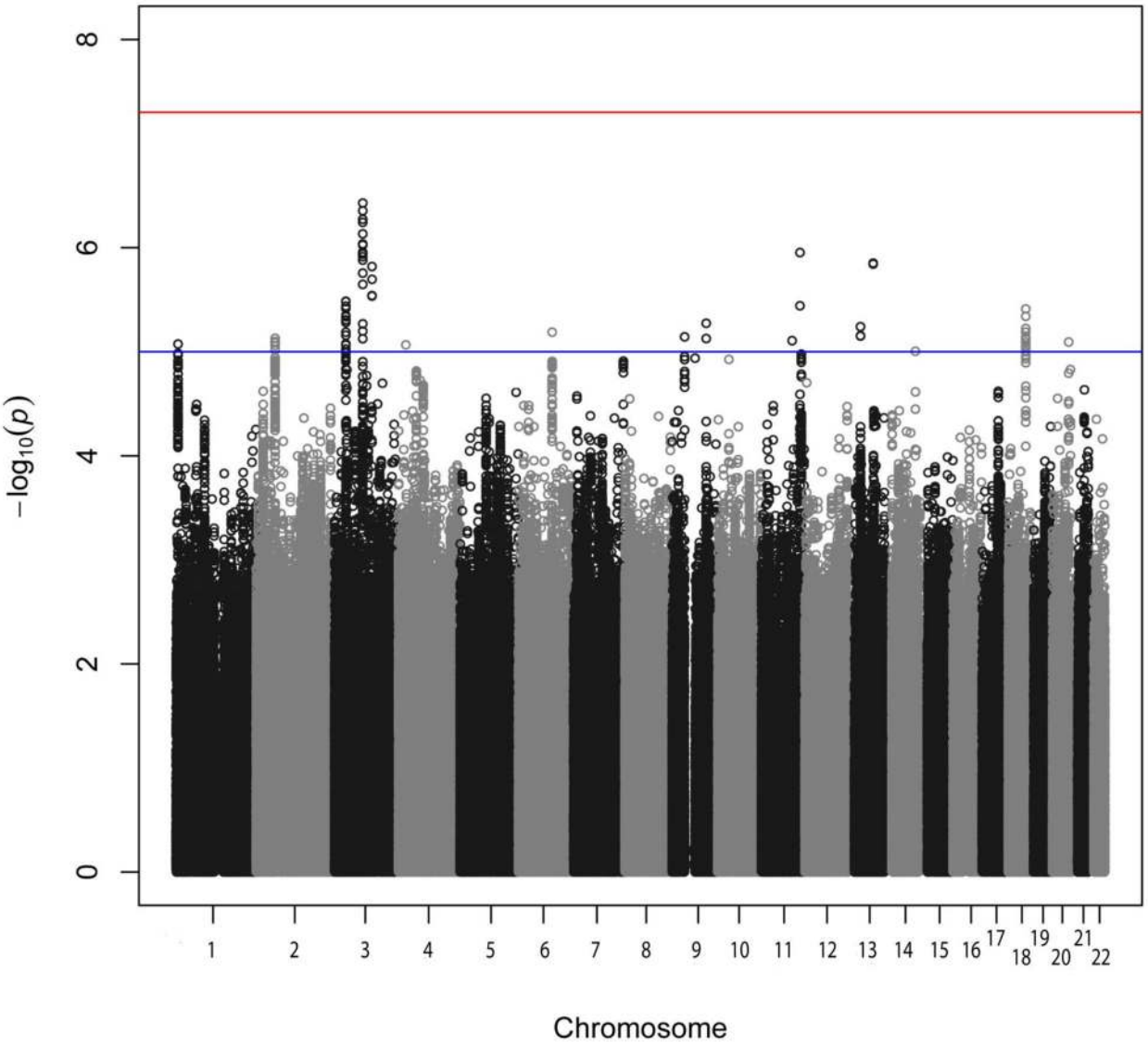

FIGURE 1. Manhattan Plot of All Genotyped and Imputed Single-Nucleotide Polymorphisms for 3,013 Tourette's Syndrome-Obsessive-Compulsive Disorder European Ancestry Cases and 5,957 Controls[a]

[a] Red and blue lines indicate significance thresholds of 5×10^{-8} and 1×10^{-5}, respectively.

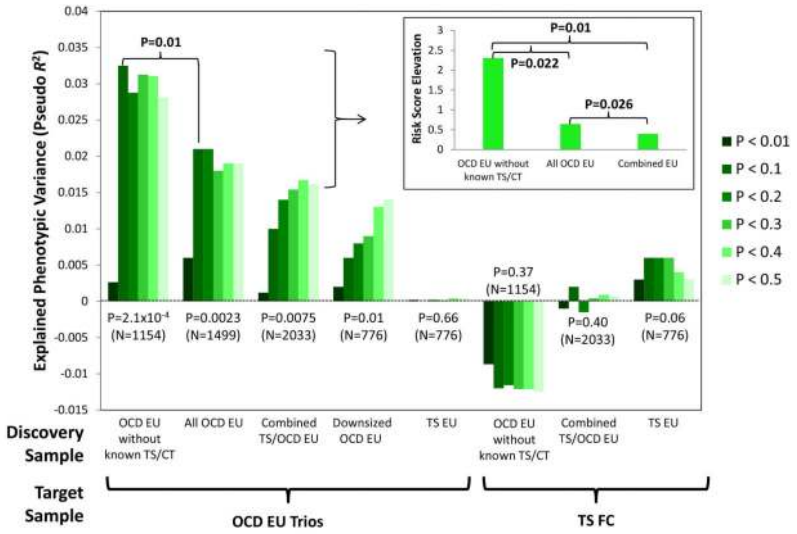

FIGURE 2. Q-Q Plot of Nominal Disease Association p Values Versus Expected p Values Among the Cis eQTLs and mQTLs in Different Brain Tissues in the Tourette's Syndrome, Obsessive-Compulsive Disorder (OCD), and Combined Genome-Wide Association Study (GWAS)[a]

[a] eQTL=expression quantitative loci. A horizontal shift to the left from the diagonal line (of complete concordance between the observed p values and expected p values) in the Q-Q plot indicates enrichment.

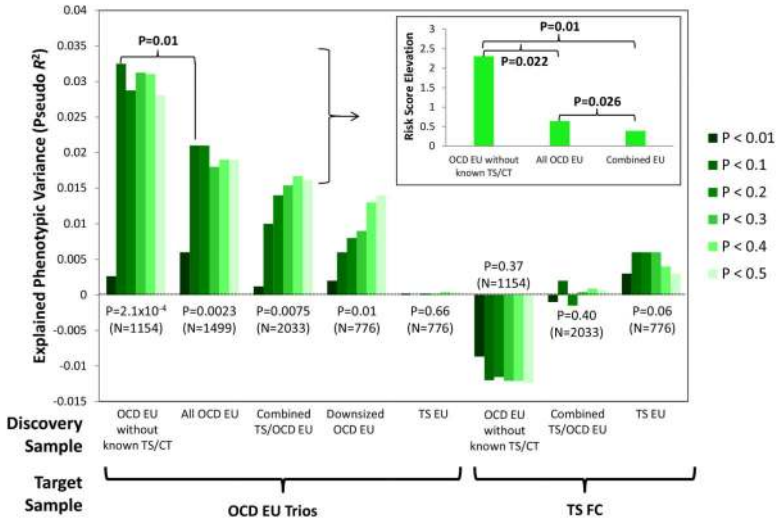

FIGURE 3. Individual Disorder and Cross-Disorder Polygenic Score Analysis in Tourette's Syndrome and Obsessive-Compulsive Disorder (OCD)[a]

[a] The variance explained in two target samples (OCD European ancestry [EU] parent-child trios and Tourette's French Canadian [FC] cases) is based on risk scores derived from an aggregated sum of weighted single-nucleotide polymorphism risk allele effect sizes estimated from discovery samples at six significance thresholds. The y axis indicates Nagelkerke's pseudo R^2. The p value under each discovery sample indicates how well the risk scores derived from the discovery sample can predict the illness phenotype in the target sample. N is the number of cases in each discovery sample. Negative R^2 values indicate a negative correlation between risk scores and illness status in the target sample. OCD EU without known Tourette's/chronic tics=European-ancestry OCD genome-wide association study (GWAS) samples after removing samples with known co-occurring Tourette's/chronic tics; all OCD EU=European-ancestry OCD GWAS samples plus additional EU GWAS samples with co-occurring OCD and Tourette's/chronic tics; combined Tourette's/OCD EU=all European-ancestry Tourette's GWAS samples and OCD GWAS samples; downsized OCD EU=randomly selected subset of OCD EU samples to match the number of cases in the Tourette's EU discovery sample; Tourette's EU=European-ancestry Tourette's GWAS samples; OCD EU trios=the OCD EU parent-child trio probands and matched pseudo-control data derived from nontransmitted alleles; Tourette's FC=Tourette's French Canadian cases and matching controls. A permutation test was carried out to determine the significance of the difference in R^2 between risk scores derived from OCD EU without known Tourette's/chronic tics and all OCD EU, resulting in a two-sided empirical p value of 0.01. The inset box at upper right demonstrates the risk score elevations (difference in risk scores of transmitted alleles and untransmitted alleles in the OCD EU trios, standardized by the risk score of the untransmitted alleles) derived from three discovery samples: OCD EU without known Tourette's/chronic tics, all OCD EU, and combined Tourette's/OCD EU. Two-sided paired t tests were conducted for the pairwise comparisons of risk score elevations derived from three discovery samples.

Table 1

Genomic regions in the combined TS/OCD GWAS with $p<1\times10^{-5}$.

CHR	SNP	A1/A2	A1 FRQ	OR	Combined GWAS p-value	Position (hg19)	#SNPs in LD	Genes	TS GWAS p-value	OCD GWAS p-value
3	rs4988462	T/C	0.42	1.18	3.7×10^{-7}	87,127,019–87,406,369	343	MIR4795, CHMP2B, POU1F1	1.1×10^{-3}	4.9×10^{-5}
11	rs4271390	T/C	0.25	1.2	1.1×10^{-6}	119,514,810–119,537,683	18	PVRL1	1.1×10^{-3}	4.4×10^{-5}
13	rs11149058	C/T	0.22	0.82	1.4×10^{-6}	77,515,486–77,992,185	135	IRG1, CLN5, Mir_633, FBXL3, MYCBP2	1.6×10^{-5}	3.1×10^{-3}
3	rs149183310	T/A	0.044	1.52	1.5×10^{-6}	115,864,394–116,185,436	77	LSAMP	3.1×10^{-3}	3.4×10^{-5}
3	rs73070160	T/C	0.14	1.24	3.3×10^{-6}	34,819,681–35,152,858	152	FECHP	1.3×10^{-3}	3.8×10^{-4}
18	rs12959570	G/A	0.23	1.2	3.9×10^{-6}	54,247,051–54,522,865	174	TXNL1, WDR7	3.9×10^{-2}	8.7×10^{-7}
9	rs7848024	A/G	0.27	1.19	5.3×10^{-6}	105,520,114–105,753,694	248	CYLC2	1.2×10^{-3}	1.2×10^{-4}
13	rs6563569	C/T	0.44	1.16	5.7×10^{-6}	38,087,567–38,290,276	238	POSTN, TRPC4	3.0×10^{-4}	3.3×10^{-3}
6	rs859980	T/C	0.47	0.87	6.5×10^{-6}	104,462,081–104,517,073	93	LOC100129694	8.6×10^{-3}	5.0×10^{-5}
9	rs10973956	A/C	0.16	1.23	7.2×10^{-6}	38,643,129–38,677,136	29	FAM201A	5.6×10^{-4}	1.0×10^{-3}
2	rs35881094	G/T	0.43	1.16	7.4×10^{-6}	58,847,436–59,058,234	122	FLJ30838	5.9×10^{-4}	7.6×10^{-4}
11	rs11021169	T/G	0.08	0.77	7.8×10^{-6}	95,194,927–95,253,183	16	5S_rRNA	1.7×10^{-4}	4.5×10^{-3}
20	rs55797066	C/T	0.06	1.33	8.1×10^{-6}	50,165,634–50,442,187	25	NFATC2, ATP9A, SALL4	7.2×10^{-4}	5.4×10^{-5}
1	rs7524258	T/C	0.4	1.16	8.4×10^{-6}	7,250,522–7,352,143	87	CAMTA1	1.4×10^{-2}	2.4×10^{-5}
4	rs61792199	G/A	0.15	1.23	8.6×10^{-6}	22,833,517–22,935,712	53	GBA3	5.4×10^{-4}	1.1×10^{-3}
14	rs1040832	A/G	0.2	1.21	9.9×10^{-6}	93,247,868–93,374,784	33	GOLGA5, CHGA	5.1×10^{-3}	2.6×10^{-4}

CHR, Chromosome; SNP, Single Nucleotide Polymorphism; A1, reference allele; A2, alternative allele; A1 FRQ. Frequency of A1 allele in the European-ancestry control samples; OR, odds ratio; # SNPs in LD, number of additional SNPs in linkage disequilibrium (LD) with association p-values $<1\times10^{-3}$ (LD defined as $r^2>0.5$). Complete annotation of these SNPs as well as all SNPs with association p-values $<1\times10^{-3}$ are provided in Supplementary Tables 1 and 2.

Table 2

Number of associated eQTLs/mQTLs with False Discovery Rate (FDR) <0.25 in the TS, OCD, and Combined GWAS eQTL, expression quantitative trait locus; mQTL, methylation quantitative trait locus;

		# of QTLs (# of loci*)		
Tissue	**Functional Subset**	**TS GWAS**	**OCD GWAS**	**Combined GWAS**
Frontal Cortex	eQTLs	0 (0)	0 (0)	0 (0)
Parietal Cortex	eQTLs	0 (0)	0 (0)	**53 (4)**
Cerebellum	eQTLs	**38 (5)**	0 (0)	0 (0)
Cerebellum	mQTLs	0 (0)	**161 (18)**	0 (0)

*Number of LD-independent loci among the identified eQTLs.