

# Investigating Shared Genetic Basis Across Tourette Syndrome and Comorbid Neurodevelopmental Disorders Along the Impulsivity-Compulsivity Spectrum

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## ABSTRACT

**BACKGROUND:** Tourette syndrome (TS) is often found comorbid with other neurodevelopmental disorders across the impulsivity-compulsivity spectrum, with attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) as most prevalent. This points to the possibility of a common etiological thread along an impulsivity-compulsivity continuum.

**METHODS:** Investigating the shared genetic basis across TS, ADHD, ASD, and OCD, we undertook an evaluation of cross-disorder genetic architecture and systematic meta-analysis, integrating summary statistics from the latest genome-wide association studies (93,294 individuals, 6,788,510 markers).

**RESULTS:** As previously identified, a common unifying factor connects TS, ADHD, and ASD, while TS and OCD show the highest genetic correlation in pairwise testing among these disorders. Thanks to a more homogeneous set of disorders and a targeted approach that is guided by genetic correlations, we were able to identify multiple novel hits and regions that seem to play a pleiotropic role for the specific disorders analyzed here and could not be identified through previous studies. In the TS-ADHD-ASD genome-wide association study single nucleotide polymorphism-based and gene-based meta-analysis, we uncovered 13 genome-wide significant regions that host single nucleotide polymorphisms with a high posterior probability for association with all three studied disorders ( $m$ -value  $> 0.9$ ), 11 of which were not identified in previous cross-disorder analysis. In contrast, we also identified two additional pleiotropic regions in the TS-OCD meta-analysis. Through conditional analysis, we highlighted genes and genetic regions that play a specific role in a TS-ADHD-ASD genetic factor versus TS-OCD. Cross-disorder tissue specificity analysis implicated the hypothalamus-pituitary-adrenal gland axis in TS-ADHD-ASD.

**CONCLUSIONS:** Our work underlines the value of redefining the framework for research across traditional diagnostic categories.

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Tourette syndrome (TS) is a common childhood-onset neuropsychiatric disorder that is often comorbid with other neurodevelopmental disorders along the impulsivity-compulsivity spectrum. In fact, only 10% of cases of TS appear as pure TS, while up to 54.3% of patients are also diagnosed with attention-deficit/hyperactivity disorder (ADHD), 50% with obsessive-compulsive disorder (OCD), and up to 20% with comorbid autism spectrum disorder (ASD) (1–3). The high comorbidity rates among these disorders have led to the hypothesis that TS, OCD, ADHD, and ASD might actually lie on an impulsivity-compulsivity continuum, sharing overlapping etiologies that converge in dysfunctional brain circuitries (4).

Here, pursuing a transdiagnostic approach, we seek to identify the common genetic factors and neural underpinnings across this spectrum of phenotypes.

TS, ADHD, ASD, and OCD all have a complex and highly heterogeneous genetic architecture, with both common and rare genetic variants contributing to their etiology (5–9). Over the past few years, 12 genome-wide significant loci have been identified for ADHD (10), and five genome-wide significant loci were described for ASD (11,12). For OCD, no genome-wide significant loci have been detected to date (13), while one genome-wide significant locus was recently reported for TS (14).

Several cross-disorder analyses have previously evaluated the genetic overlap across these disorders, revealing broad genetic correlations (15–20). Most recently, as part of the Psychiatric Genomics Consortium (PGC), we presented a data-driven meta-analysis of genome-wide association studies (GWASs) across eight common psychiatric disorders for which large GWAS data were available. The disorders analyzed included TS, ADHD, ASD, OCD, anorexia nervosa, bipolar disorder, major depressive disorder, and schizophrenia (15). Exploratory factor analysis revealed that early-onset disorders, including ADHD, ASD, and TS, fell into one of the three identified factors (together with major depressive disorder, which is not typically early onset). TS was also found to be weakly correlated in another factor together with compulsive disorders, including OCD and anorexia nervosa. However, anorexia nervosa was not found to be significantly correlated with TS in pairwise analysis and is not observed frequently in patients with TS. This previous eight-disorder GWAS meta-analysis included multiple psychiatric disorders that are not clinically or genetically correlated to TS, thus possibly diluting relevant signals. Although power is high because of the overall sample size, the trade-off is increased heterogeneity and thus difficulty to interpret results for one specific set of phenotypes that could be regarded as a group. Factor analysis, tests of pleiotropy, and cross-disorder GWAS meta-analysis are all influenced by the input datasets and subject to change based on what disorders are analyzed. Therefore, to investigate a specific subset of traits that present with high comorbidity and high genetic correlation, more focused cross-disorder studies are warranted.

Here, we build on the PGC cross-disorder GWAS results as well as the high comorbidity and existing hypotheses for shared etiology across TS and related disorders across the impulsivity-compulsivity spectrum. Our work highlights variants and genes that may contribute to neurobiology across this spectrum of neurodevelopmental phenotypes, many of which could not be previously identified.

## METHODS AND MATERIALS

### Data Sources

Analyses were conducted using summary statistics from GWASs for TS, ADHD, ASD, and OCD as made available by the PGC. These are the same data analyzed as in the PGC eight-disorder GWAS meta-analysis (15) with a change in the TS dataset, for which our summary statistics did not include 413 patients from the Tourette International Collaborative Genetics Consortium. For all data obtained from the PGC, the Ricopili pipeline (<https://github.com/Ripkelab/ricopili/wiki>) or comparable quality controls were carried out.

### Cross-Disorder Genetic Architecture and GWAS Meta-analysis

Linkage disequilibrium score regression analysis was carried out using the LDSC package (21). To test for the presence of a common genetic factor across all traits of interest, we tested the common factor model using genomic structural equation modeling (22) for summary statistics of all disorders showing significant genetic correlation with TS.

To estimate the causative association across traits, we carried out bidirectional generalized summary data-based Mendelian randomization (23).

Cross-disorder GWAS meta-analysis was carried out for TS, ADHD, and ASD jointly, as well as for TS and OCD. Single nucleotide polymorphism (SNP)-based GWAS meta-analyses were performed using ASSET (24). We also carried out partitioned heritability and cell-type specificity analysis using the LDSC package (25). To further highlight SNPs that contribute to risk across multiple phenotypes, we estimated the posterior probability of association (*m*-value) with each disorder using a Bayesian statistical framework as implemented by MetaSoft (26). The *m*-value can be interpreted as confirmation of the joint effect of an SNP from different contributing datasets. If an SNP shows high *m*-values for all studies participating in the meta-analysis, the interpretation is that the effect is contributed by all input studies rather than a subset. To further dissect the contribution of genetics on different groups of traits, we carried out multitrait-based conditional and joint analysis (23). This analysis provides SNP effects on a trait (or in this case group of traits) conditioned on another trait (or group of traits) and points to SNPs with trait-specific (or in this case group-specific) effect. Here, using multitrait-based conditional and joint analysis, we adjust the summary statistics of TS-ADHD-ASD conditioning on TS-OCD and vice versa. A group-specific effect for an SNP can be identified if we observe an increased effect (in *z* score) after conditioning compared with the original result. Finally, gene-based cross-disorder GWAS analysis was carried out using the MAGMA plug-in on the FUMA GWAS annotation platform (27,28). See Supplement 1 for full details on all analyses.

## RESULTS

### Architecture of Genetic Correlations Across TS, ADHD, ASD, and OCD

Here, we focus on analyses on TS and highly comorbid neurodevelopmental disorders along the impulsivity-compulsivity spectrum. First, to set a foundation for our analysis, we repeated the measurement of genetic overlap across TS, ADHD, ASD, and OCD using linkage disequilibrium score regression (Table 1). Our analysis replicated the results from (15). High genetic correlations were observed between all pairs of disorders, except ASD and OCD. The highest genetic correlation was found between TS and OCD ( $r_g = .38, p = 2.00 \times 10^{-4}$ ). A negative genetic correlation was observed between ADHD and OCD ( $r_g = -.17, p = 2.00 \times 10^{-2}$ ), although it was not significant under Bonferroni correction.

We proceeded with novel analysis that is focused on the specific set of TS-related disorders across the impulsivity-compulsivity spectrum. All of the tests carried out were influenced by the input datasets; thus, when compared with the PGC eight-disorder GWAS meta-analysis (15), the results presented here have a direct interpretation for the neurobiology of the specific four disorders of interest. Because ADHD, ASD, and OCD showed a high genetic correlation with TS, we tested for the existence of a common genetic factor across these four disorders using genomic structural equation modeling. It should be noted that analysis with four

**Table 1. Pairwise Genetic Correlation**

	Disorder Pairs					
	ADHD/ASD	ADHD/OCD	ADHD/TS	ASD/OCD	ASD/TS	OCD/TS
#SNPs	1,042,563	1,030,018	1,062,415	1,012,959	1,044,625	1,100,873
$r_g$	.35	-.17	.26	.12	.18	.38
SE	.05	.07	.06	.08	.06	.10
$p$ Value	$1.33 \times 10^{-11}$	$2.00 \times 10^{-2}$	$2.05 \times 10^{-5}$	$1.50 \times 10^{-1}$	$5.50 \times 10^{-3}$	$2.00 \times 10^{-4}$

LD score regression analysis showing pairwise genetic correlation across ADHD, ASD, OCD, and TS. #SNPs indicates the number of overlapping SNPs used in the analysis.  $r_g$  is the genetic correlation; SE and  $p$  are the standard error and  $p$  value for  $r_g$ , respectively.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; LD, linkage disequilibrium; OCD, obsessive-compulsive disorder; SNP, single nucleotide polymorphism; TS, Tourette syndrome.

phenotypes only allows the identification of a single factor. Results showed positive loads from ADHD, ASD, and TS to the common factor, but not OCD (Figure 1A; Table S1 in Supplement 2). The highest load was contributed by ADHD. This was in broad concordance with our previous work with eight disorders (15). Based on these results and the identified high genetic correlation between TS and OCD in pairwise analyses, we proceeded to pursue further analysis focusing on TS-ADHD-ASD and TS-OCD. In doing so, we aimed to

increase homogeneity, hoping to identify the most relevant genetic signals.

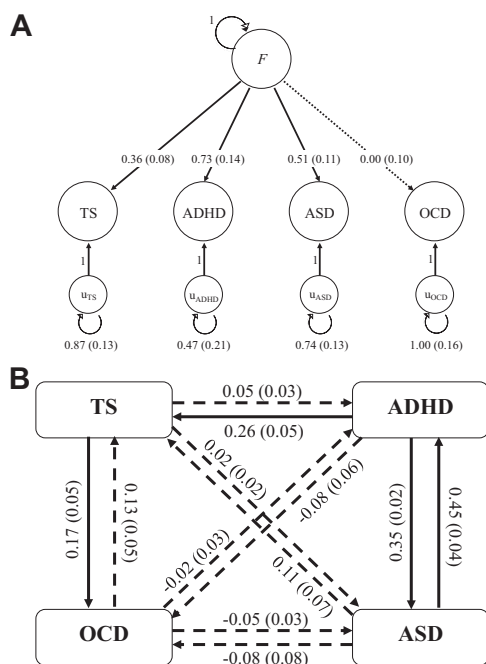
### Inferring Causal Relationships Across TS, ADHD, ASD, and OCD

To infer the potential causal relationship across the studied traits, we carried out bidirectional generalized summary data-based Mendelian randomization for all pairwise combinations across TS, ADHD, ASD, and OCD. Results from this analysis point to broad causality networks across the studied disorders, indicating causal impact of the exposure disorder inducing the outcome disorder while using near-independent SNPs as instruments. After multiple testing correction, the significant threshold was  $p < 4.17 \times 10^{-3}$ . Under this threshold, our results indicated that being diagnosed with ASD is a causative risk factor for ADHD and vice versa. TS also showed a significant risk effect over OCD, and ADHD turned out to be a risk factor for TS. Results can be found in Table S2 in Supplement 2 and Figure 1B.

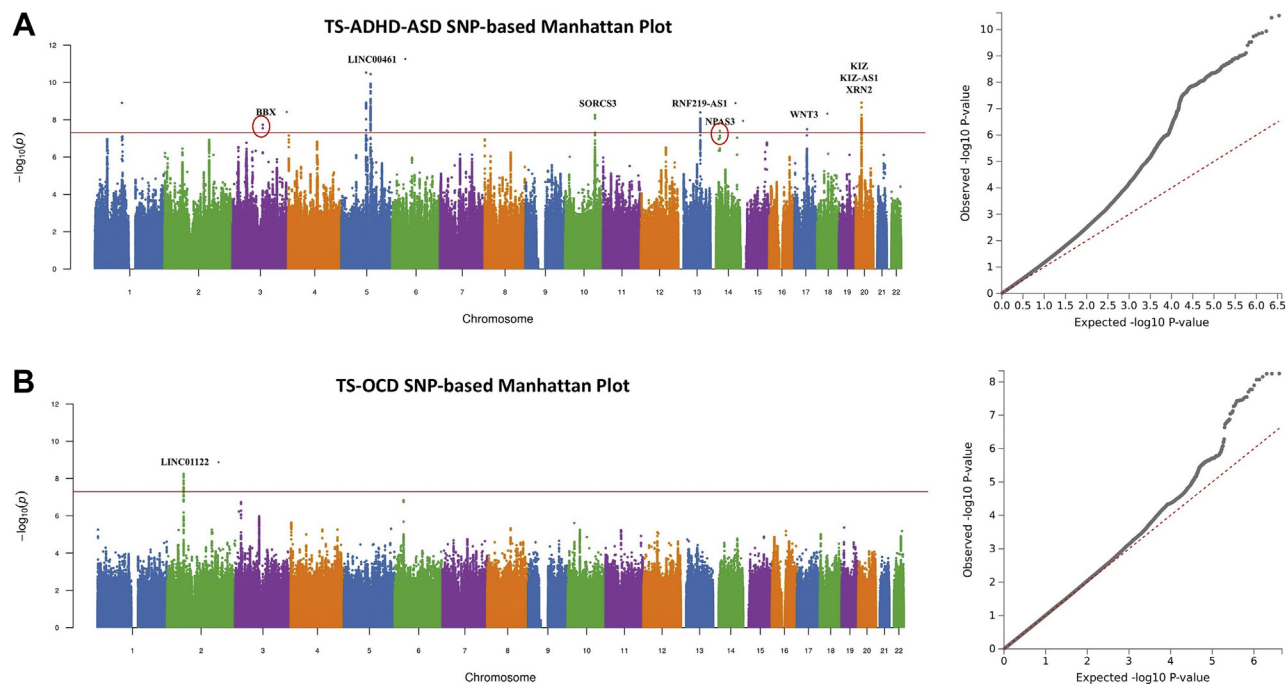
### Cross-Disorder GWAS Meta-analysis for TS, ADHD, ASD, and OCD

We carried out systematic SNP-based GWAS meta-analyses across TS, ADHD, ASD, and OCD using ASSET (24). Combining all four datasets described above, 93,294 nonoverlapping samples (51,311 controls) were available. We followed a different approach than the PGC eight-disorder meta-analysis study (15) and guided all subsequent analysis based on the genetic architecture of the studied disorders as revealed by exploratory factor analysis rather than analyzing everything jointly. We first pursued meta-analysis of the TS, ADHD, and ASD datasets, yielding 6,815,585 overlapping SNPs. No obvious inflation was observed ( $\lambda_{TS-ADHD-ASD} = 1.20$ ,  $\lambda_{1000} = 1.00$ ). We identified seven independent regions with high evidence of pleiotropy ( $m$ -value  $> 0.9$ ) across all three disorders (Figure 2; Table 2; Tables S3, S4, and S5 in Supplement 2). Despite reduced sample size, thanks to our more focused approach, we were able to identify here six genome-wide significant regions harboring highly pleiotropic loci across TS-ADHD-ASD that were not identified as either TS-ADHD-ASD pleiotropic (at  $m$ -value threshold  $> 0.9$ ) or genome-wide significant in the PGC eight-disorder analysis (Table 2; Tables S5 and S6 in Supplement 2).

Because OCD was the disorder that was most closely correlated with TS but was not found to lie in the TS-ADHD-ASD factor, we also pursued pairwise analysis for the TS and



**Figure 1.** Genetic architecture and causality relationships across disorders of interest. **(A)** Investigating the existence of a common factor  $F$  across all four disorders using genomic structural equation modeling. Path graph shows loads and corresponding standard errors in parenthesis. Circular arrows denote the residual genetic variance not explained by the common factor. See Table S1 in Supplement 2. **(B)** Network plot indicating the causality across four disorders estimated using generalized summary data-based Mendelian randomization. Solid arrows indicate a significant causality relationship, while dash arrows indicate insignificant relationships. Numbers on the arrow indicate effect size and estimation standard error (in parenthesis). See Table S2 in Supplement 2. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder; TS, Tourette syndrome; u, residual variance not explained by common factor  $F$ .



**Figure 2.** Manhattan plots and QQ plots for cross-disorder genome-wide association study meta-analyses. An asterisk (\*) indicates genes hosting SNPs with  $m$ -value  $> 0.9$  in all disorders analyzed, and a red circle denotes a novel region that was not previously reported associated with the disorder of interest. **(A)** TS-ADHD-ASD genome-wide association study meta-analysis. **(B)** TS-OCD genome-wide association study meta-analysis. See [Tables S3](#) and [S4](#) in [Supplement 2](#). ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder; SNP, single nucleotide polymorphism; TS, Tourette syndrome.

OCD GWAS. A total of 8,112,469 overlapping SNPs were available for analysis across TS and OCD ( $\lambda_{TS-OCD} = 1.00$ ,  $\lambda_{1000} = 1.00$ ). We found 21 genome-wide significant variants in a single region (top result, rs140347666 [ $p = 5.64 \times 10^{-9}$ ,  $m_{TS} = 1$ ,  $m_{OCD} = 1$ ]) (Figure 2; Table 3; Tables S3, S4, and S6 in Supplement 2); all significant SNPs were located in *LINC01122* on region 2p16.1 and had the same direction of effect. All 21 SNPs showed  $m$ -value  $> 0.9$  for both TS and OCD, indicating high homogeneity across both disorders. This region had not been identified as genome-wide significant in the PGC eight-disorder analysis and could be specific to the TS-OCD correlation. However, the PGC eight-disorder meta-analysis (15) had also previously identified six additional regions that were genome-wide significant and had  $m$ -value  $> 0.9$  in both TS and OCD (Table 3; Tables S5 and S6 in Supplement 2).

### SNP-Based Conditional Analysis Between TS-ADHD-ASD and TS-OCD

OCD showed a high genetic correlation with TS that cannot be explained by the same latent genetic factor as the TS-ADHD-ASD group. Therefore, we tried to further explore the group-specific difference between TS-OCD and TS-ADHD-ASD through conditional analysis using multitrait-based conditional and joint analysis. We expected a decreased effect in most of the SNPs after conditioning because of dependency caused by the fact that both groups include TS. However, we also found some SNPs with stronger effects after conditioning, which indicated that they play a role more specific to the

particular group, thus possibly leading to the differentiation of these two clusters. In the TS-OCD GWAS conditioning on TS-ADHD-ASD analysis, only nine significant SNPs in the top region survived (compared with 21 in our original meta-analysis) (Table S8 in Supplement 2). None of them showed an increased effect after conditioning. In contrast, in the TS-ADHD-ASD conditioning on TS-OCD analysis, 55 SNPs in six genomic regions showed a higher effect despite conditioning (including regions 1p34.1, 1p21.3, 4q24, 5q14.3, 5q21.2, and 10q25.1). These included two extra genomic risk regions that were only now revealed in TS-ADHD-ASD as independent from TS-OCD (region 1p34.1, genes *PTPRF*, *KDM4A*, and *ST3GAL3*; and region 4q24, gene *MANBA*) (Table S8 in Supplement 2). Among the six regions, most of them showed high ADHD-ASD specificity with low  $m$ -value for TS. However, we did identify one region hosting SNPs with an increased effect after conditioning, while also having high  $m$ -values for all three disorders analyzed (region 5q21.2).

### Cross-Disorder Gene-Based Association Analysis

We proceeded to perform gene-based analysis for the TS-ADHD-ASD and TS-OCD GWAS meta-analyses as implemented in FUMA (28). Our gene-based analysis highlighted 18 genes as significantly associated in the TS-ADHD-ASD meta-analysis (Table S9 in Supplement 2). Of the 18 genes, 14 (including the top result *SORCS3* [ $p = 4.97 \times 10^{-10}$ ] on chromosome 10) can also be picked up even if we only analyze those SNPs with  $m$ -value  $> 0.9$  for all three

**Table 2. Comparison of Results Across Regions That Are Shown as Genome-wide Significant and Pleiotropic in Either the TS-ADHD-ASD GWAS Meta-analysis (SNP-Based or Gene-Based) or the PGC Eight-Disorder GWAS Meta-analysis**

Region	SNP-Based Results		Gene-Based Results		Cross-Disorder Group of the Psychiatric Genomics Consortium <i>et al.</i> , 2019 (15)	Original TS GWAS	Original ADHD GWAS	Original ASD GWAS
	Leading SNP <i>p</i> Value/OR		Gene	<i>p</i> Value	Leading SNP <i>p</i> Value/OR	Leading SNP <i>p</i> Value	Leading SNP <i>p</i> Value	Leading SNP <i>p</i> Value
2p15 <sup>a</sup>	1.22 × 10 <sup>-7</sup> /1.05		<i>WDPCP</i> <sup>b,c</sup>	6.08 × 10 <sup>-8</sup>	2.40 × 10 <sup>-6</sup> /0.94	9.34 × 10 <sup>-4</sup>	7.27 × 10 <sup>-5</sup>	8.61 × 10 <sup>-6</sup>
			<i>MDH1</i> <sup>b,c</sup>	7.59 × 10 <sup>-7</sup>				
2q24.1 <sup>a</sup>	1.22 × 10 <sup>-7</sup> /1.05		<i>PKP4</i> <sup>b,c</sup>	8.43 × 10 <sup>-8</sup>	2.07 × 10 <sup>-8</sup> /1.03 <sup>c</sup>	2.30 × 10 <sup>-5</sup>	3.36 × 10 <sup>-5</sup>	9.30 × 10 <sup>-7</sup>
3q13.12 <sup>a</sup>	1.86 × 10 <sup>-8</sup> /1.05 <sup>b,c</sup>				9.46 × 10 <sup>-7</sup> /1.05	9.44 × 10 <sup>-6</sup>	2.20 × 10 <sup>-6</sup>	1.51 × 10 <sup>-4</sup>
3p21.31 <sup>a</sup>	1.71 × 10 <sup>-7</sup> /0.96		<i>CCDC36</i> <sup>b,c</sup>	1.69 × 10 <sup>-7</sup>	4.06 × 10 <sup>-8</sup> /1.03 <sup>c</sup>	1.80 × 10 <sup>-5</sup>	6.74 × 10 <sup>-7</sup>	3.51 × 10 <sup>-5</sup>
			<i>USP4</i> <sup>b,c</sup>	5.54 × 10 <sup>-7</sup>				
			<i>CCDC71</i> <sup>b,c</sup>	1.00 × 10 <sup>-6</sup>				
			<i>NICN1</i> <sup>b,c</sup>	1.09 × 10 <sup>-6</sup>				
4p13 <sup>d</sup>	9.29 × 10 <sup>-5</sup> /1.04				3.00 × 10 <sup>-10</sup> /0.97 <sup>b,c</sup>	2.28 × 10 <sup>-4</sup>	4.38 × 10 <sup>-4</sup>	3.08 × 10 <sup>-5</sup>
4q24 <sup>a</sup>	1.51 × 10 <sup>-7</sup> /0.96		<i>MANBA</i> <sup>e</sup>	1.12 × 10 <sup>-7</sup>	1.11 × 10 <sup>-10</sup> /0.87 <sup>c</sup>	3.03 × 10 <sup>-4</sup>	6.48 × 10 <sup>-8</sup>	1.39 × 10 <sup>-5</sup>
			<i>CXXC4</i> <sup>b,c</sup>	1.35 × 10 <sup>-6</sup>				
5q14.3 <sup>a</sup>	2.98 × 10 <sup>-11</sup> /0.95 <sup>b,c</sup>				1.64 × 10 <sup>-9</sup> /0.92 <sup>c</sup>	3.71 × 10 <sup>-5</sup>	1.81 × 10 <sup>-8c</sup>	1.92 × 10 <sup>-6</sup>
5q21.2 <sup>e</sup>	3.56 × 10 <sup>-11</sup> /1.06 <sup>b</sup>				1.55 × 10 <sup>-16</sup> /1.03 <sup>b,c</sup>	8.66 × 10 <sup>-4</sup>	1.08 × 10 <sup>-7</sup>	3.25 × 10 <sup>-7</sup>
7q11.22 <sup>a</sup>	7.17 × 10 <sup>-7</sup> /0.96		<i>CALN1</i> <sup>b,c</sup>	1.15 × 10 <sup>-6</sup>	3.22 × 10 <sup>-6</sup> /0.98	4.01 × 10 <sup>-4</sup>	3.96 × 10 <sup>-6</sup>	4.02 × 10 <sup>-6</sup>
10q25.1 <sup>e</sup>	5.61 × 10 <sup>-9</sup> /1.06 <sup>c</sup>		<i>SORCS3</i> <sup>b,c</sup>	4.97 × 10 <sup>-10</sup>	9.97 × 10 <sup>-13</sup> /1.03 <sup>b,c</sup>	1.67 × 10 <sup>-4</sup>	1.76 × 10 <sup>-8</sup>	1.15 × 10 <sup>-4</sup>
13q22.3 <sup>a</sup>	4.03 × 10 <sup>-9</sup> /0.95 <sup>b,c</sup>		–	–	1.16 × 10 <sup>-7</sup> /0.97	2.46 × 10 <sup>-3</sup>	5.07 × 10 <sup>-7</sup>	1.76 × 10 <sup>-5</sup>
14q13.1 <sup>a</sup>	3.99 × 10 <sup>-8</sup> /0.94 <sup>b,c</sup>		–	–	5.11 × 10 <sup>-10</sup> /0.94 <sup>c</sup>	3.04 × 10 <sup>-4</sup>	1.02 × 10 <sup>-5</sup>	3.08 × 10 <sup>-4</sup>
16p13.3 <sup>d</sup>	3.72 × 10 <sup>-5</sup> /0.96		–	–	5.59 × 10 <sup>-11</sup> /0.97 <sup>b,c</sup>	2.81 × 10 <sup>-5</sup>	1.06 × 10 <sup>-5</sup>	1.92 × 10 <sup>-4</sup>
17q21.31 <sup>a</sup>	3.22 × 10 <sup>-8</sup> /0.95 <sup>b,c</sup>		<i>WNT3</i> <sup>b,c</sup>	4.52 × 10 <sup>-7</sup>	3.28 × 10 <sup>-6</sup> /0.92	6.53 × 10 <sup>-5</sup>	3.79 × 10 <sup>-4</sup>	2.89 × 10 <sup>-7</sup>
			<i>KANSL1</i> <sup>b,c</sup>	7.98 × 10 <sup>-8</sup>				
			<i>CRHR1</i> <sup>b,c</sup>	2.32 × 10 <sup>-7</sup>				
			<i>MAPT</i> <sup>b,c</sup>	8.72 × 10 <sup>-7</sup>				
18q21.2 <sup>d</sup>	1.17 × 10 <sup>-5</sup> /0.97		–	–	4.26 × 10 <sup>-12</sup> /1.03 <sup>b,c</sup>	3.29 × 10 <sup>-4</sup>	1.89 × 10 <sup>-5</sup>	7.05 × 10 <sup>-5</sup>
20p11.23-p11.24 <sup>a</sup>	1.71 × 10 <sup>-9</sup> /1.05 <sup>b,c</sup>		<i>XRN2</i> <sup>c</sup>	2.33 × 10 <sup>-9</sup>	2.72 × 10 <sup>-10</sup> /1.05 <sup>c</sup>	1.08 × 10 <sup>-3</sup>	1.33 × 10 <sup>-6</sup>	2.04 × 10 <sup>-9c</sup>

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; GWAS, genome-wide association study; OR, odds ratio; PGC, Psychiatric Genomics Consortium; SNP, single nucleotide polymorphism; TS, Tourette syndrome.

<sup>a</sup>Novel regions that are only identified as genome-wide significant and pleiotropic in this study (i.e., crossing genome-wide significance threshold and *m*-value > 0.9 across TS-ADHD-ASD).

<sup>b</sup>SNP/gene that is genome-wide significant and pleiotropic.

<sup>c</sup>Genome-wide significant.

<sup>d</sup>Regions where criteria are satisfied only in the PGC eight-disorder GWAS meta-analysis.

<sup>e</sup>Regions identified in both studies.

disorders. Out of these 14 pleiotropic genes, only one is located in a genome-wide significant risk region identified as pleiotropic for TS, ADHD, and ASD from the previous PGC eight-disorder analysis (*SORCS3*) (Figure 3; Table 2; Table S6 in Supplement 2). The rest of the identified regions could thus be of particular importance for early-onset disorders. In contrast, for TS-OCD, we tested a total of 18,790 genes, of which four turned out to be significant. Gene *CADM2* on chromosome 3 was the top one (Figure 3; Table 3; Tables S6 and S9 in Supplement 2). All the genes showed evidence of a pleiotropic effect, as they were also identified as significant when we only analyzed SNPs with *m*-value > 0.9 for both disorders.

### Pathway Analysis, Tissue Enrichment, and Partitioned Heritability Analysis

Partitioned heritability analysis revealed enrichment of the cross-disorder GWAS results in conserved regions for both

TS-ADHD-ASD and TS-OCD (Table S7 in Supplement 2). Furthermore, we identified significant enrichment in brain frontal cortex cell type in the TS-OCD GWAS. Partitioning heritability by brain cell-specific chromatin states, we found enrichment in fetal brain, brain germinal matrix, and cortex in TS-ADHD-ASD. In contrast, enrichment in chromatin states specific to the anterior caudate and dorsolateral prefrontal cortex were found in TS-OCD GWAS results (Table S7 in Supplement 2).

To better visualize our results while investigating the pathways and interactions among the top risk genes across TS, ADHD, ASD, and OCD, we constructed Gene Ontology-based networks for the top 200 genes from each gene-based association analysis as well as genes annotated from the SNP-based GWAS meta-analyses. Results are shown in Figure 4 and Figure S1 in Supplement 1. Pathways related to neuronal development, axonogenesis, and synaptic structure

**Table 3. Comparison of Results Across Regions That Are Shown as Genome-wide Significant and Pleiotropic in Either the TS-OCD GWAS Meta-analysis (SNP-Based or Gene-Based) or the PGC Eight-Disorder GWAS Meta-analysis**

Region	SNP-Based Results		Gene-Based Results		Cross-Disorder Group of the Psychiatric Genomics Consortium <i>et al.</i> , 2019 (15)		Original TS GWAS	Original OCD GWAS
	Leading SNP	$p$ Value/OR	Gene	$p$ Value	Leading SNP	$p$ Value/OR	Leading SNP	$p$ Value
1p31.1 <sup>a</sup>		$1.32 \times 10^{-4}/1.34$				$3.63 \times 10^{-11}/1.03^{b,c}$	$1.69 \times 10^{-4}$	$2.26 \times 10^{-4}$
2p16.1 <sup>d</sup>		$5.64 \times 10^{-9}/0.89^{b,c}$				$2.34 \times 10^{-14}/0.97^c$	$4.76 \times 10^{-8}$	$2.03 \times 10^{-4}$
3p12.1 <sup>d</sup>		$1.06 \times 10^{-6}/1.12$	<i>CADM2</i> <sup>b,c</sup>	$3.99 \times 10^{-7}$		$5.74 \times 10^{-5}/1.05$	$8.36 \times 10^{-5}$	$1.15 \times 10^{-4}$
4p13 <sup>a</sup>		$4.03 \times 10^{-4}/1.11$				$5.59 \times 10^{-9}/0.96^{b,c}$	$2.28 \times 10^{-4}$	$6.04 \times 10^{-5}$
6p21.33 <sup>e</sup>		$1.48 \times 10^{-7}/0.81$	<i>LY6G6F</i> <sup>b,c</sup>	$7.64 \times 10^{-7}$		$3.63 \times 10^{-14}/0.97^{b,c}$	$1.56 \times 10^{-5}$	$1.55 \times 10^{-5}$
			<i>MEGT1</i> <sup>b,c</sup>	$7.98 \times 10^{-7}$				
			<i>APOM</i> <sup>b,c</sup>	$1.54 \times 10^{-6}$				
14q32.33 <sup>a</sup>		$6.22 \times 10^{-4}/0.93$	–	–		$5.20 \times 10^{-9}/1.03^{b,c}$	$6.36 \times 10^{-4}$	$1.40 \times 10^{-4}$
16p13.3 <sup>a</sup>		$9.21 \times 10^{-5}/0.92$	–	–		$5.59 \times 10^{-11}/0.97^{b,c}$	$2.81 \times 10^{-5}$	$9.12 \times 10^{-5}$
18q21.2 <sup>a</sup>		$5.74 \times 10^{-4}/0.86$	–	–		$4.26 \times 10^{-12}/1.03^{b,c}$	$3.29 \times 10^{-4}$	$3.99 \times 10^{-4}$
22q13.2 <sup>a</sup>		$1.23 \times 10^{-5}/0.90$	–	–		$5.36 \times 10^{-14}/1.04^{b,c}$	$6.84 \times 10^{-6}$	$9.92 \times 10^{-4}$

GWAS, genome-wide association study; OCD, obsessive-compulsive disorder; OR, odds ratio; PGC, Psychiatric Genomics Consortium; SNP, single nucleotide polymorphism; TS, Tourette syndrome.

<sup>a</sup>Regions where criteria are satisfied only in the PGC eight-disorder GWAS meta-analysis.

<sup>b</sup>SNP/gene that is genome-wide significant and pleiotropic.

<sup>c</sup>Genome-wide significant.

<sup>d</sup>Novel regions that are only identified as genome-wide significant and pleiotropic in this study (i.e., crossing genome-wide significance threshold and  $m$ -value > 0.9 across TS-OCD).

<sup>e</sup>Regions identified in both studies.

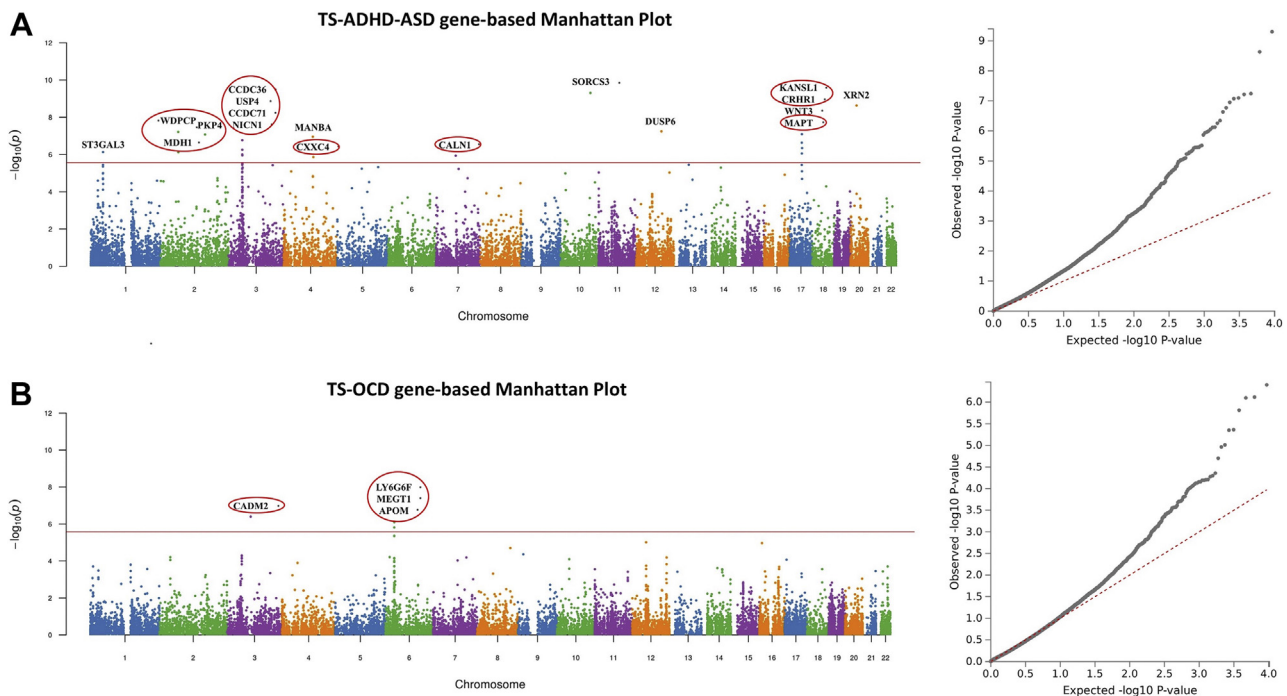
and organization were highlighted among the most significant in our analysis. These results were further strengthened by tissue specificity analyses, which showed enrichment of our top associated loci in genes expressed in brain tissues (Figures S2 and S3 in Supplement 1). In the tissue specificity analysis with 53 tissue types (Figure S3 in Supplement 1; Table S10 in Supplement 2), significant enrichment was found for genes expressed in various brain regions, including the frontal cortex, basal ganglia, hypothalamus, cerebellum, amygdala, and hippocampus for TS-ADHD-ASD and the cortex and frontal cortex for TS-OCD (Figure S3 in Supplement 1). In the 30 tissue types analysis, enrichment in expression in the brain and pituitary arose as significant (Figure S2 in Supplement 1) for TS-ADHD-ASD. Enrichment in genes expressed in the adrenal gland for TS-ADHD-ASD was also highlighted, reaching borderline significance ( $p = 1.89 \times 10^{-3}$ , with a significance threshold of  $p < 1.67 \times 10^{-3}$ ) (Figures S2 and S3 in Supplement 1; Table S10 in Supplement 2).

Next, we incorporated expression quantitative trait locus information into our meta-analyses and performed transcriptome-wide association analyses, aiming to identify genes with expression levels associated across the studied disorders. Results for the TS-ADHD-ASD combined transcriptome-wide analysis are reported in detail in Table S11 in Supplement 1. Two transcript probes satisfying the pleiotropy hypothesis were significant, both located on chromosome 17. Among all significant transcripts, the top result was from the *LRR37A4P* probe ( $p_{SMR} = 1.38 \times 10^{-6}$ ,  $p_{HEIDI} = 1.00 \times 10^{-1}$ ). This corresponds to the transcript of a pseudogene in region 17q21.3, localizing near *KANSL1*. None of the probes were found significant for TS-OCD.

## DISCUSSION

Motivated by high comorbidity rates across studied phenotypes and a long-standing hypothesis of a shared etiological thread across disorders of the impulsivity-compulsivity spectrum, we present a detailed investigation of the shared genetic basis across TS and often-comorbid ADHD, ASD, and OCD. Our analysis is guided by the genetic architecture across the studied disorders as revealed by exploratory factor analysis as well as genetic correlations. Thus, our findings are not affected by analyzing jointly with disorders that are not genetically or clinically correlated. We confirm the existence of a unifying genetic factor across TS, ADHD, and ASD and reproduce the high genetic correlation of TS and OCD that appears to be separate from the TS-ADHD-ASD factor. The identified negative genetic correlation between ADHD and OCD indicates that genetic variants operate in opposite directions in the development of these two disorders. From a clinical perspective, this is quite intuitive because ADHD and OCD may be thought of as lying at opposite extremes of the impulsivity-compulsivity continuum.

The increased power of a transdiagnostic approach is once again highlighted by the discovery of novel genetic associations not previously identified in individual GWASs. Furthermore, our study also highlights the value of increasing homogeneity across studies as we were able to identify here multiple novel pleiotropic loci across the disorders of interest that were not identified by the PGC eight-disorder meta-analysis (15). These loci could therefore be considered as specific for the four disorders on which we focused. For instance, in the TS-ADHD-ASD meta-analysis, we successfully uncovered 16 linkage disequilibrium-independent genomic risk regions (9 through SNP-based and seven through gene-



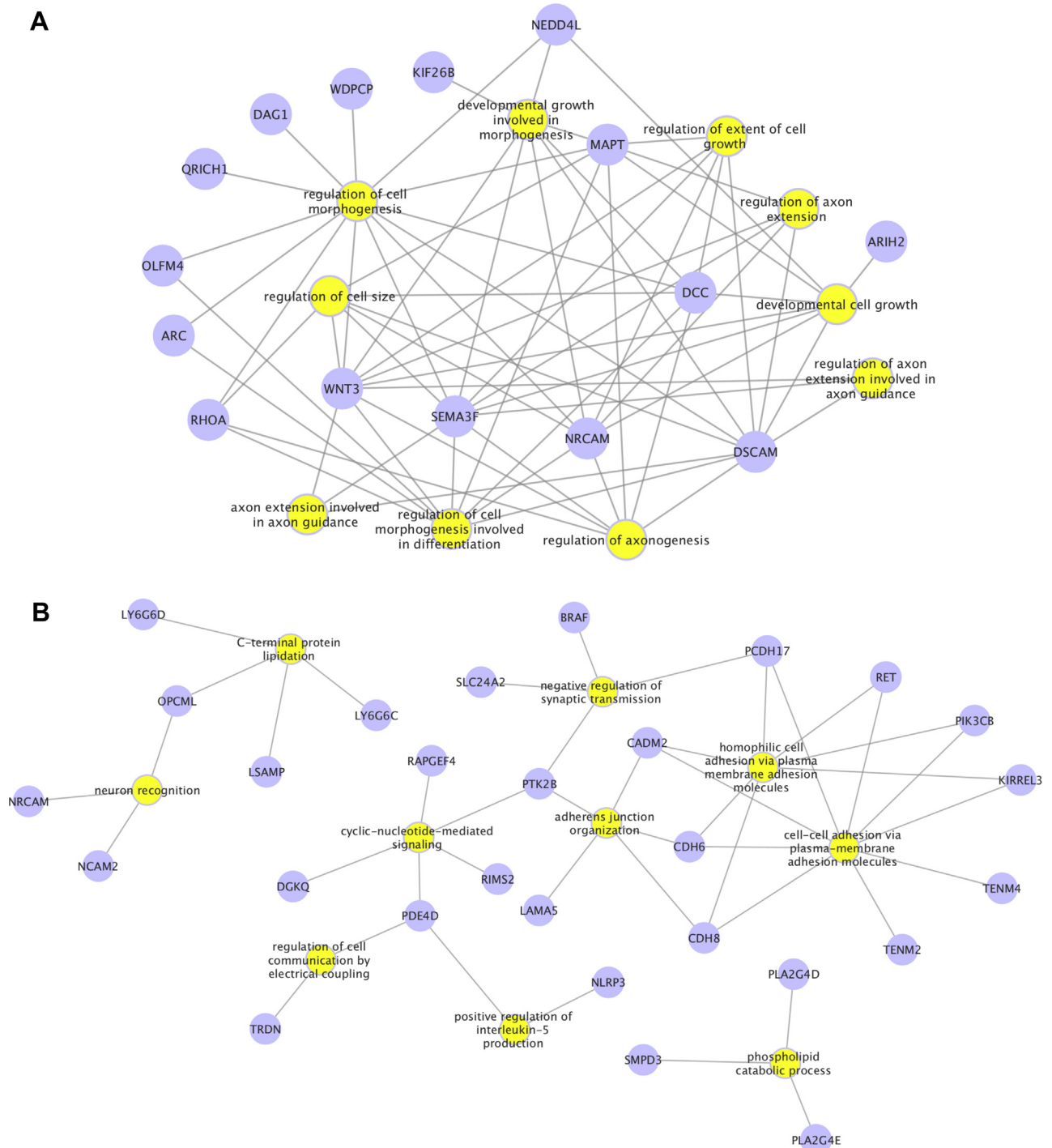
**Figure 3.** Manhattan plots for gene-based genome-wide association study meta-analyses. An asterisk (\*) indicates that genes stay significant when only analyzing SNPs with  $m$ -value  $> 0.9$  in all disorders analyzed, and a red circle denotes novel genes that could not be picked up through gene-based analysis using summary statistics from individual disorders alone. **(A)** TS-ADHD-ASD gene-based analysis. **(B)** TS-OCD gene-based analysis. See Table S9 in Supplement 2. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder; SNP, single nucleotide polymorphism; TS, Tourette syndrome.

based analysis), 13 of which are highly pleiotropic across all disorders analyzed. Of these, 11 were not previously identified as genome-wide significant or pleiotropic by the eight-disorder meta-analysis, suggesting a specific role for the disorders that are the focus of our analysis.

The top significant genomic risk locus showing also high probability for association across TS-ADHD-ASD was in gene *LINC00461* on chromosome 5. This gene is highly expressed in the brain and visual cortex and has been previously involved in tumorigenesis (29). Gene *MIR9-2* is also located within gene *LINC00461*. The expression of this microRNA is almost brain exclusive and has been found crucial during neuronal differentiation (30,31). *LINC00461* was recently reported with high pleiotropic effects across five psychiatric traits (32). Moreover, in the same study, behavior tests of expression knockdown mice confirmed the critical role it plays in neurodevelopment processes (32). Although this top region on chromosome 5 has also been previously highlighted as genome-wide significant by the ADHD individual GWAS as well as results from the PGC eight-disorder GWAS, it was not reported among the most broadly pleiotropic ones and did not have a high  $m$ -value for TS in that study. This is because of the nature of  $m$ -value computation and highlights the importance of fine-resolution cross-disorder comparisons. Because  $m$ -value measures the posterior probability of the SNP effect existing in a given disorder, it is subject to the result of meta-analysis, which is further subject to the data input. Hence, if an SNP effect from the meta-analysis is significantly driven by one or a few disorders

that are highly heterogeneous from the others, we may not capture the evidence of such an effect existing in other disorders even though the overall analysis has an increased power.

Gene-based meta-analysis also proved extremely powerful and led to the identification of multiple novel hits not previously identified by individual GWASs or the PGC eight-disorder meta-analysis (15). In our TS-ADHD-ASD gene-based analysis, we identified 12 novel genes that could not be identified using the individual disorder summary statistics alone. The top result was *SORCS3*. The effect of this gene remained significant even if we analyzed only SNPs with high  $m$ -values in all three disorders, indicating a potential pleiotropic effect. This gene encodes a member of the VPS10 receptor family, which controls intracellular protein signaling in neurons and regulates neuronal viability through many pathways (33). It is highly expressed in brain tissues (34), and it has been previously implicated in neurological disease, including ADHD and ASD etiology (10,12). Multiple studies indicate a relationship between *SORCS3* and the accumulation of amyloid, which is linked to Alzheimer's disease (35,36). It is also associated with major depressive disorder in individuals of European descent (37). Moreover, its interaction with postsynaptic proteins, such as *PICK1*, indicates that the product of *SORCS3* regulates glutamate receptor function (38,39). As one of the major neurotransmitters in the human brain, the glutamate pathway has long been hypothesized to underlie abnormalities in ADHD, ASD, and TS and is a possible therapeutic target for these disorders (40–43).



**Figure 4.** Top 10 gene networks from top 200 genes annotated from SNP-based genome-wide association study meta-analyses results. **(A)** TS-ADHD-ASD-based network plot. **(B)** TS-OCD-SNP-based network plot. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder; SNP, single nucleotide polymorphism; TS, Tourette syndrome.

In the case of the TS-OCD meta-analysis, we identified three (one through SNP-based analysis and two through gene-based analysis) genomic risk regions showing pleiotropic effect across TS and OCD. Two of them were not identified by

the PGC eight-disorder meta-analysis. In contrast, the broader study reported six additional risk regions to be pleiotropic across TS and OCD but also other disorders, highlighting the trade-off between power and homogeneity and the importance



of combining different approaches. We found multiple significant hits on gene *LINC01122* in chromosome 2 that showed evidence of pleiotropic effect in both disorders. Note that in the original TS GWAS carried out by Yu *et al.* (14), SNPs in this region were at borderline genome-wide significance ( $\sim 10^{-7}$ ).

Observing a structure that breaks up the studied TS-related phenotypes in TS-ADHD-ASD and TS-OCD correlations, we also tried to identify groupwise differentiating effects through a conditional analysis. An intergenic region in 5q21.2 seems of particular importance: this region not only hosts SNPs with an increased effect in TS-ADHD-ASD conditioning on TS-OCD but also shows high posterior probability of association in all three disorders, indicating a group-specific pleiotropic effect. Duplication of the 5q21.2 region has been previously reported as a clinically significant copy number variation in schizophrenia (44).

Among the top genes that we found associated in the TS-ADHD-ASD GWAS meta-analysis, we observed enrichment for genes expressed in the brain. Our results provide further support for the involvement of the basal ganglia across all disorders analyzed here. Dysfunction of the basal ganglia has been observed in all four studied disorders (45–48). We found significant enrichment in pituitary and hypothalamus expression, and furthermore, the enrichment of adrenal gland expression was also borderline significant. This observation implicates the involvement of the hypothalamus-pituitary-adrenal (HPA) axis, in accordance with previous clinical studies implicating this system in multiple childhood-onset psychiatric traits, including TS and ADHD (49–53). The HPA axis plays a critical role in human stress response through the regulation of cortisol secretion (54). Low-cortisol responsiveness to stress was proposed as a biomarker for certain types of ADHD, indicating possibly altered HPA axis activity in this disorder (55). Altered cortisol levels among individuals with TS have also been reported, with a negative correlation between evening cortisol and patients' tic severity and higher cortisol levels in response to stress (56).

Our analysis provides clues to potential biological distinctions between the studied subgroups of disorders along the impulsivity-compulsivity continuum. While the role of the frontal cortex and basal ganglia was highlighted for both TS-ADHD-ASD and TS-OCD, support for HPA axis involvement and significant enrichment of chromatin states in fetal brain cell types was only observed in TS-ADHD-ASD. Our findings thus point to more significant contributions of neurodevelopment and stress-related processes in the TS-ADHD-ASD dimension in comparison with TS-OCD.

Although we provide results on combined datasets of very large size across TS, ADHD, ASD, and OCD, available datasets varied in size for each of the studied disorders. The unbalanced sample size across the studied datasets is one of the limitations of our study. To mitigate this problem, we placed emphasis on investigating and reporting the SNP posterior probability of association (*m*-value) for each disorder, providing higher confidence for shared effect across multiple disorders. Existing overlap across the studied samples was relatively small (<6% case overlap in the datasets that we studied), and we used ASSET, which takes into account known sample overlap to control the inflation in meta-analysis results.

## Conclusions

In conclusion, through a series of systematic genome-wide association meta-analyses, we uncovered multiple loci that may underlie biological mechanisms across TS and its highly comorbid neurodevelopmental disorders along the impulsivity-compulsivity spectrum (ADHD, ASD, OCD). Despite the trade-off in power compared with the PGC earlier meta-analysis across eight disorders (15), we show that by increasing homogeneity when motivated by clinical observations, we can identify many additional genomic risk loci that could play a more specific role across clinically correlated phenotypes. The existing evidence for a common genetic background across these highly comorbid disorders highlights what seems to become a recurrent theme across the studies on neuropsychiatric disorders: the importance of thinking across diagnostic boxes when attempting to understand neurobiology. Most importantly, moving toward genomic analysis of symptom dimensions across diagnostic categories may prove extremely powerful but would require availability of very large and well-characterized cohorts of patients as well as the harmonization of existing clinical databases spanning the disorder spectrum.

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ZY performed experiments and wrote the manuscript. PP designed the study, coordinated analysis, and wrote the manuscript. HW generated figures and tables for main and supplementary content. All authors participated in study design and analysis, interpretation of results, and critical review of the manuscript.

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