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Genome-Wide Association Study Meta-Analysis of 9619 Cases With Tic Disorders

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ABSTRACT

BACKGROUND: Despite the significant personal and societal burden of tic disorders (TDs), treatment outcomes remain modest, necessitating a deeper understanding of their etiology. Family history is the biggest known risk factor, and identifying risk genes could accelerate progress in the field.

METHODS: Expanding upon previous sample size limitations, we added 4800 new TD cases and 971,560 controls and conducted a genome-wide association study (GWAS) meta-analysis with 9619 cases and 981,048 controls of European ancestry. We attempted to replicate the results in an independent deCODE genetics GWAS (885 TD cases and 310,367 controls). To characterize GWAS findings, we conducted several post-GWAS gene-based and enrichment analyses.

RESULTS: A genome-wide significant hit (rs79244681, $p = 2.27 \times 10^{-8}$) within *MCHR2-AS1* was identified, although it was not replicated. Post-GWAS analyses revealed a 13.8% single nucleotide polymorphism heritability and 3 significant genes: *BCL11B*, *NDFIP2*, and *RBM26*. Common variant risk for TD was enriched within genes preferentially expressed in the cortico-striato-thalamo-cortical circuit (including the putamen, caudate, nucleus accumbens, and Brodmann area 9) and 5 brain cell types (excitatory and inhibitory telencephalon neurons, inhibitory diencephalon and mesencephalon neurons, and hindbrain and medium spiny neurons). TD polygenic risk was enriched within loss-of-function intolerant genes ($p = .0017$) and high-confidence neurodevelopmental disorder genes ($p = .0108$). Of 112 genetic correlations, 43 were statistically significant, showing high positive correlations with most psychiatric disorders. Of the 2 single nucleotide polymorphisms previously associated with TDs, one (rs2453763) replicated in an independent subsample of our GWAS ($p = .00018$).

CONCLUSIONS: This GWAS was still underpowered to identify high-confidence, replicable loci, but the results suggest imminent discovery of common genetic variants for TDs.

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Tic disorders (TDs) (including Tourette syndrome [TS], chronic tic disorder [CTD], and transient tic disorder [TTD]) are childhood-onset neuropsychiatric disorders characterized by recurrent, nonrhythmic tics that last for at least 1 year (TS, CTD) or less than 1 year (TTD) (1). TS and CTD differ only in the requirement that either motor or vocal tics be present in CTD and that both be present in TS. Clinically, these disorders are more similar than they are different, and they likely represent a single entity expressed along a severity spectrum where TS is the most severe manifestation (2–4). This view is supported by previous genetic studies indicating that (subclinical) tics, CTD, and TS fall along a single etiological spectrum (5,6).

TS/CTD affects ~0.5% to 3% (7) of the global population, leading to substantial academic underachievement (8), increased risk of violence (9), and higher suicide rates (10). Treatment options include behavioral therapy and medication, although no specific TD medication exists, and the medications available have undesirable side effects, resulting in modest treatment outcomes. Better understanding TD etiology may lead to better treatments, and because family history of tics represents the greatest known risk factor, identifying genes and biological pathways that influence risk may accelerate this process.

TS/CTD is highly genetic (~60%–70% heritability) according to twin and family studies (11). First-degree relatives of affected individuals have a roughly 20-fold increased risk of TS/CTD compared with the general population (12,13), which represents one of the highest recurrence risks for a neuropsychiatric disorder. While molecular genetic studies of TS/CTD or TD have been largely underpowered, recent rare-

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variant studies are beginning to identify risk genes. Whole-exome sequencing of trios (mother, father, and affected child) and case/control copy number variant analyses have yielded putative TS/CTD risk genes, including *NRXN1*, *WWC1*, *CELSR3*, *NIPBL, FN1*, *CNTN6*, *OPA1*, and *FBN2* (14–16).

Regarding common genetic variation, the first genome-wide association study (GWAS) of TS (17), with 1496 cases and 5249 controls, found no genome-wide significant (GWS) loci but revealed a significant polygenic signal and genetic overlap with obsessive-compulsive disorder (OCD). A second TS GWAS (6) that included ~3400 additional cases and matched controls identified one GWS hit on chromosome 13 that awaits replication, and several other loci neared significance. A third TS GWAS (18) with 6133 cases and 13,565 controls [including the previous samples by (17) and (6)] found one GWS locus on chromosome 5 but failed to replicate the chromosome 13 association. Overall, replicable associations for TD have remained elusive, highlighting the need for larger TD GWAS meta-analyses with greater statistical power.

Here, we added new genetic data for 4800 TD cases and 971,560 controls to the Yu *et al.* (6) meta-analysis and performed comprehensive post-GWAS analyses to enhance understanding of TD etiology. Given the spectrum view of TDs and to maximize single nucleotide polymorphism (SNP) discovery power, we conducted a combined TD GWAS instead of separate analyses for each TD diagnosis.

METHODS AND MATERIALS

TD Case Samples and Control Samples

We analyzed data from 4 TD case-control cohorts of European ancestry (see Table S1), all of which except iPSYCH included TS/CTD cases. The meta-analysis included previously unpublished data from the NORDiC (Nordic OCD and Related DIsorders Consortium) sample from Sweden (n_{cases} = 188, $n_{controls}$ = 414), the Danish iPSYCH study (n_{cases} = 3041, $n_{controls}$ = 29,808), and 23andMe, Inc. (n_{cases} = 1571, $n_{controls}$ = 941,338), as well as previously published data from the PGC [Psychiatric Genomics Consortium (19)] (n_{cases} = 4819, $n_{controls}$ = 9488). Together, the TD GWAS meta-analysis contained 9619 individuals with a diagnosis of TD (9079 with TS or CTD [F95.1 and F95.2], 171 with TTD [F95.0], 324 with unspecified TD [F95.9], and 45 with other TD [F95.8]) and 981,048 controls with complete phenotypic and genotypic data (after quality control). Cohort descriptions, quality control steps, GWAS analyses for each cohort, and alignment and filtering of each resulting summary statistic are described in detail in Supplemental Note S1.

GWAS Meta-Analysis

Studies were combined with an inverse-weighted meta-analysis using METAL (20) within Ricopili (21). The genome-wide significance threshold was set to $p = 5.0 \times 10^{-8}$. Possible residual population stratification, systematic technical artifacts, and cryptic relatedness were assessed with the genomic inflation factor (lambda1000) and with the linkage disequilibrium score regression (LDSC) intercept (22). To assess heterogeneity in test statistics across the different cohorts, we calculated Cochran's I^2 statistic.

Proportion of Risk Alleles in Comorbid Subgroups

We assessed what proportion of the TD cases with specific comorbidities have each of the risk alleles of the GWS SNP, as well as of the 10 SNPs with a p value $< 1 \times 10^{-6}$. We conducted this analysis only in the iPSYCH sample because for this cohort, we have specific information on comorbid diagnoses (see Supplemental Note S1 for details of comorbidity rates). We first counted the number of risk alleles across all individuals in a comorbid subgroup (attention-deficit/hyperactivity disorder [ADHD], affective disorder, autism spectrum disorder [ASD], OCD, schizophrenia, schizophrenia spectrum disorder, more than one comorbid diagnosis, and not comorbid with any of the listed disorders) to create contingency tables and then determined with χ^2 tests of homogeneity whether there is a significant association between subgroup and allele count by comparing the observed allele counts in each subgroup to the expected counts if allele frequencies were the same across all subgroups (i.e., the overall allele count). The p value for a significant association was set at a Bonferroni-corrected threshold of .05/11 = .0046.

Replication

We attempted replication of all independent loci that met a threshold of $p < 1.0 \times 10^{-6}$ (n = 11) using an independent TD GWAS dataset from Iceland (deCODE genetics; n_{cases} = 885, $n_{controls}$ = 310,367). A sample description can be found in Supplemental Note S1, and the analysis was conducted as described previously (23). A replication was considered significant at a Bonferroni-corrected significance threshold of $p < .0045$ (.05/11).

We further attempted to replicate 2 SNPs that were reported to be significantly associated with TS in previous studies: rs2504235 on chromosome 13 with a p value of 2.1×10^{-8} (19) and rs2453763 on chromosome 5 with a p value of 4.05×10^{-8} (18). For the replication we used an independent subsample of our GWAS analysis, excluding all previously published PGC samples (cases: n = 4800, controls: n = 971,560) as those samples were also included in the previous analyses.

SNP Heritability and Genetic Correlation Estimation Using LDSC

We used LDSC (22) to measure the proportion of phenotypic variation in our dataset that could be explained by the measured SNPs (SNP-based heritability, h^2_G) and to calculate genetic correlations (r_G) with other phenotypes (see Supplemental Note S3 for details). SNP heritability was estimated assuming a 0.52% population prevalence (7). The analysis was conducted for the meta-analysis and separately for each sample, large enough for LDSC (23andMe, iPSYCH, and PGC). To evaluate the internal consistency of our data, we examined pairwise genetic correlations between each subsample (iPSYCH, 23andMe, PGC). We also examined genetic correlations between the TD meta-analysis and a broad range of 112 traits (see Table S6 for a full list of all included phenotypes). The same genetic correlation analysis was performed separately for the iPSYCH, 23andMe, and PGC samples to evaluate differences in correlation patterns between these 3 cohorts and 112 external GWAS summary statistics.

Gene-Based and Functional Characterization of GWAS Findings

We conducted several downstream analyses to positionally and functionally characterize our SNP findings. Details of all analyses can be found in Supplemental Note S4. In brief, we conducted gene-based tests using MAGMA version 1.08 (24). SNPs were mapped to their corresponding genes based on 3 separate models: 1) the standard MAGMA model (C-MAGMA), 2) a model based on expression quantitative trait loci (eQTL) information [E-MAGMA (25)], and 3) a model based on 3-dimensional chromatin interactions [H-MAGMA (26)]. MAGMA gene-set analysis was conducted with FUMA version 1.4.1 (27) for 10,678 gene sets.

We used stratified LDSC to estimate the polygenic contribution of different annotations to heritability in GWAS (28). We ran stratified LDSC with 1) the full basic model, partitioning the heritability of TD by functional category, and 2) a tissue-specific model (LDSC-SEG), using specifically expressed genes by testing a wide range of overlapping multi-tissue gene expression data.

To assess tissue/cell-type enrichment of TD genes, we adhered to the analysis protocol outlined by Bryois *et al.* (29), using tissue-specific gene expression data from the GTEx (Gene-Tissue Expression Project) (30) and broad cell-type groups across the entirety of the mouse nervous system, together with a high-resolution single-cell type map of the same data. We used both LDSC version 1.0.0 [(22), see description of stratified LDSC further up] and MAGMA (24).

Next, we performed single-cell disease relevance score (scDRS) analysis to quantify the relevance of individual cells to TD by integrating single-cell RNA sequencing data with disease-associated genetic information. Following the approach described in the scDRS article (31), we took the 1000 genes with the most significant test statistics and defined this as the TD gene set to use for single-cell enrichment tests across each of the over 100,000 mouse cells across 120 different cell types (32).

We conducted summary-data-based Mendelian randomization (SMR) analysis, which combines data from GWAS and eQTL studies to pinpoint genes linked to a complex trait due to pleiotropy. Essentially, it tests whether an SNP's impact on a phenotype is influenced by gene expression. This tool aids in prioritizing genes associated with GWAS findings for further functional investigations. We ran a supplemental SMR analysis focused on cis eQTLs specific to individual cell types from the brain from Bryois *et al.* (33).

Lastly, we checked for overlap between GWAS results and previous exome sequencing study results via gene set enrichment tests using MAGMA (24). We utilized 4 previously published sets of relevant genes (see Supplemental Note S4 for details).

RESULTS

GWAS Meta-Analysis

After stringent quality control and GWAS analysis of each separate cohort (NORDiC, iPSYCH, 23andMe), the individual summary statistics were well controlled for population and other types of stratification (Table S1 for lambda and LDSC-intercept estimates as an indicator for possible inflation). We meta-analyzed the 3 new datasets with the previously published PGC TS/CTD GWAS, totaling 9610 TD cases and 981,048 controls, including 6,085,641 SNPs. We found one GWS association with SNP rs79244681 ($p = 2.269 \times 10^{-8}$, odds ratio = 1.2680, SE = 0.0425), within the gene *MCHR2-AS1* (MCHR2 antisense RNA1) on chromosome 6. See Figure 1A for a Manhattan plot. The genetic inflation factor lambda ($\lambda = 1.164$), lambda1000 ($\lambda_{1000} = 1.009$), and the LDSC intercept ($LDSC_{Intercept} = 1.0254$, SE = 0.0092) did not show excessive inflation, while the QQ plot (Figure 1B) was as

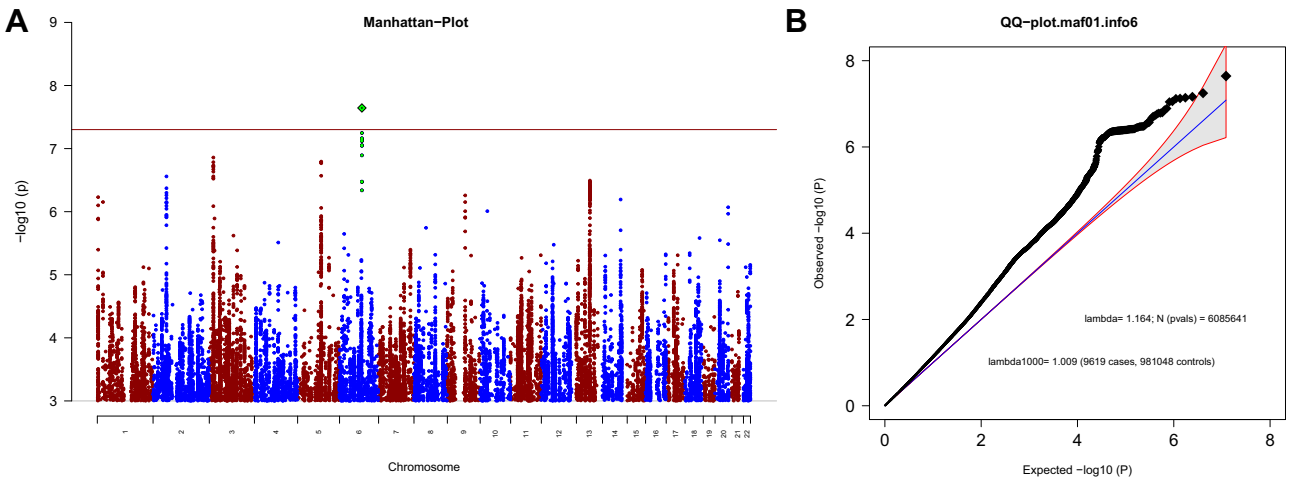

Figure 1. Genome-wide association results of the tic disorder meta-analysis. **(A)** Manhattan plot with the x-axis showing the position in the genome (chromosomes 1–22) and the y-axis representing $-\log10(p)$ values for association of variants with tic disorder. The horizontal red line represents the threshold for genome-wide significance, with each dot representing 1 single nucleotide polymorphism (SNP) tested (cutoff at $-\log10(p) < 1 \times 10^{-3}$) and the green diamond indicating the lead SNP in the region harboring the 1 genome-wide significant SNP. **(B)** Quantile-quantile plot with expected $-\log10(p)$ under the null hypothesis on the x-axis and observed $-\log10(p)$ on the y-axis. The shading indicates the 95% CI, and lambda is the genomic inflation factor, with lambda1000 being the genomic inflation factor adjusted for a GWAS with 1000 cases and 1000 controls.

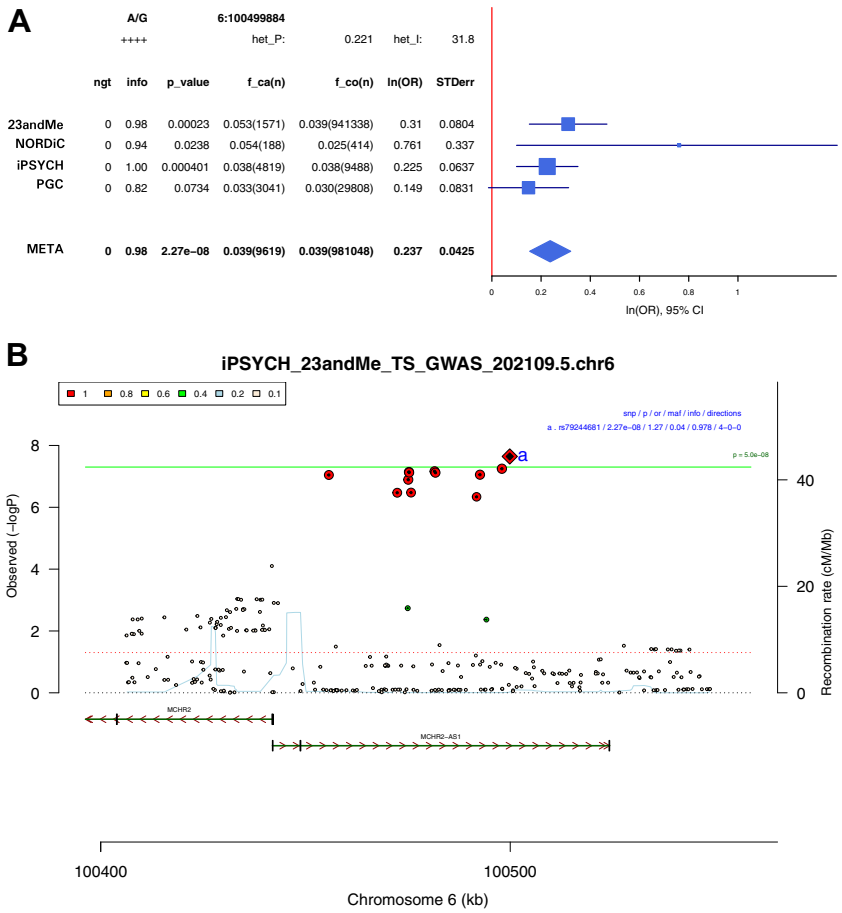

Figure 2. Forest and regional association plots for genome-wide significant single nucleotide polymorphism (SNP) rs79244681. **(A)** Forest plot showing the contribution of each cohort to the meta-analysis. Also shown are the imputation quality score (info), *p* value, A1 allele frequency in cases and the number of cases [f_ca(n)], A1 allele frequency in controls and the number of controls [f_co(n)], the effect of the association [ln(OR)], and the standard error of the effect (STDerr) for each individual dataset and the overall meta-analysis. On the right side, effects [ln(OR)] and 95% CIs are plotted. At the top, the direction of effect for each study is shown (+ for a positive effect of A1, − for a negative effect of A1), and results of a test of heterogeneity (het_P and het_I) of effect across the individual datasets are displayed. **(B)** A regional association plot of the locus including rs79244681. The left axis shows the −log10(*p*) value for each SNP. The recombination rate expressed in cM per Mb (blue line) is shown on the right y-axis, and the position on chromosome 6 (in Mb) is shown on the x-axis. For ease of display, only SNPs with association *p* value < .1 were plotted. The lead SNP in the region is shown as a red diamond, and the color coding indicates linkage disequilibrium to the lead SNP. OR, odds ratio.

expected for a polygenic disorder. Figure 2 shows a forest plot and a regional association plot for the significant SNP. There were a total of 29 independent loci with $p < 5 \times 10^{-6}$ (Table S2). χ^2 tests of homogeneity indicated that the significant SNP did not show a significant difference of risk-allele count across the iPSYCH comorbid subgroups (rs79244681, $\chi^2_7 = 10.867$, $p = .1445$), while 5 of the 10 SNPs with $p < 1 \times 10^{-6}$ did show significant differences across subgroups. All χ^2 test results can be found in Table S3.

Replication

For loci with a lead SNP *p* value $< 1 \times 10^{-6}$ ($n = 11$), we attempted replication with independent Icelandic TD GWAS data from deCODE genetics (885 cases, 310,367 controls). None replicated at a Bonferroni-corrected threshold of $p < .0045$ (.05/11). However, 8 of the 11 loci exhibited consistent directional effects in both GWAS analyses. When meta-analyzing these 11 SNPs with the deCODE GWAS, the 1 significant SNP remained significant with a refined *p* value ($p = 1.11 \times 10^{-8}$) (Table 1).

Of the 2 SNPs that were previously associated with TDs, one [rs2453763 (18)] replicated in an independent subsample of our GWAS ($p = .00018$) while the other [rs2504235 (19)] did not ($p = .3115$).

Heritability and Internal Genetic Correlations

Using LDSC, the SNP-based heritability for TDs was 13.8% (SE = 0.0115), while the iPSYCH, 23andMe, and PGC cohorts showed heritability estimates of 15.9% (SE = 0.0239), 11.6% (SE = 0.0367), and 19.5% (SE = 0.0226), respectively (assuming 0.52% population prevalence for all analyses) (see Table S1). Genetic correlations between the subsamples were high: $r_G = 0.73$ (SE = 0.20, $z = 3.60$, $p = 3 \times 10^{-4}$) between iPSYCH and 23andMe, $r_G = 0.76$ (SE = 0.12, $z = 6.32$, $p = 2.55 \times 10^{-10}$) between iPSYCH and the PGC sample, and $r_G = 1.12$ (SE = 0.21, $z = 5.35$, $p = 9.96 \times 10^{-8}$) between 23andMe and the PGC sample.

Gene-Based and Gene-Set Analyses

We conducted 3 different gene-based tests in MAGMA, each mapping SNPs to genes differently (Figure 3). The significance threshold was Bonferroni corrected for tests across all 3 methods (.05/43,790 = 1.14×10^{-6}). The standard MAGMA approach (C-MAGMA; 17,665 tests) revealed 2 significant genes (*RBM26*: $z = 4.94$, $p_{Bonferroni} = .018$; *BCL11B*: $z = 5.16$, $p_{Bonferroni} = .005$). H-MAGMA, which links SNPs to genes through gene exons or promoters or through distal intronic or intergenic regions overlapping a chromatin interaction site

Table 1. Results of the 11 Loci With Lead SNP *p* Value $< 1 \times 10^{-6}$

			Main TD GWAS Meta-Analysis				Replication in deCODE			Meta-Analysis With deCODE	
SNP	Chr	A1/A2[a]	FRQ of A1	*p*	β	SE	FRQ of A1	*p*	β	*z*	*p*
rs79244681	6	A/G	0.039	2.27×10^{-8}[b]	0.237	0.043	0.030	.191	0.188	5.714	1.11×10^{-8}[b]
rs4858193	3	C/T	0.264	1.39×10^{-7}	−0.099	0.019	0.350	.864	0.009	−4.932	8.12×10^{-7}
rs10455065	5	C/T	0.515	1.61×10^{-7}	−0.087	0.017	0.577	.823	0.012	−4.890	1.01×10^{-6}
rs2862872	2	G/A	0.613	2.76×10^{-7}	−0.087	0.017	0.623	.111	−0.085	−5.378	7.52×10^{-8}
rs943712	13	A/G	0.532	3.21×10^{-7}	0.085	0.017	0.480	.379	0.046	5.122	3.02×10^{-7}
rs3737289	9	G/A	0.433	5.52×10^{-7}	0.083	0.017	0.500	.512	0.034	4.952	7.34×10^{-7}
rs3795310	1	T/C	0.483	5.89×10^{-7}	0.083	0.017	0.423	.561	0.031	4.917	8.79×10^{-7}
rs2693698	14	G/A	0.555	6.41×10^{-7}	0.083	0.017	0.556	.565	0.031	4.90	9.62×10^{-7}
rs6670211	1	C/A	0.543	7.03×10^{-7}	0.083	0.017	0.577	.087	0.091	5.247	1.54×10^{-7}
rs55885089	20	T/C	0.054	8.51×10^{-7}	0.174	0.035	0.087	.332	−0.094	4.350	1.36×10^{-7}
rs80187201	10	A/G	0.060	9.81×10^{-7}	0.169	0.035	0.082	.139	0.137	5.111	3.20×10^{-7}

β and *z* are the effect size of the A1 allele.

Chr, chromosome; FRQ, frequency; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; TD, tic disorder.

[a]A1 is the effect allele; A2 is the non-effect allele.

[b]Genome-wide significant *p* values.

linking back to the gene body (N = 17,565 tests total), also found 2 significant genes, one overlapping with the C-MAGMA results (*RBM26*: z = 5.33, $p_{Bonferroni}$ = .0022) and one that is unique to this analysis (*NDFIP2*: z = 4.88, $p_{Bonferroni}$ = .0231). E-MAGMA, assigning SNPs to a gene if they were a significant eQTL for this gene in at least one brain tissue type assessed in GTEx (N = 8560 tests total), did not find any significant genes. Gene-based results are provided in Tables S4 to S6. Gene-set analysis in FUMA did not reveal significant associations at a Bonferroni-corrected threshold ($p_{Bonferroni} = 4.68 \times 10^{-6}$).

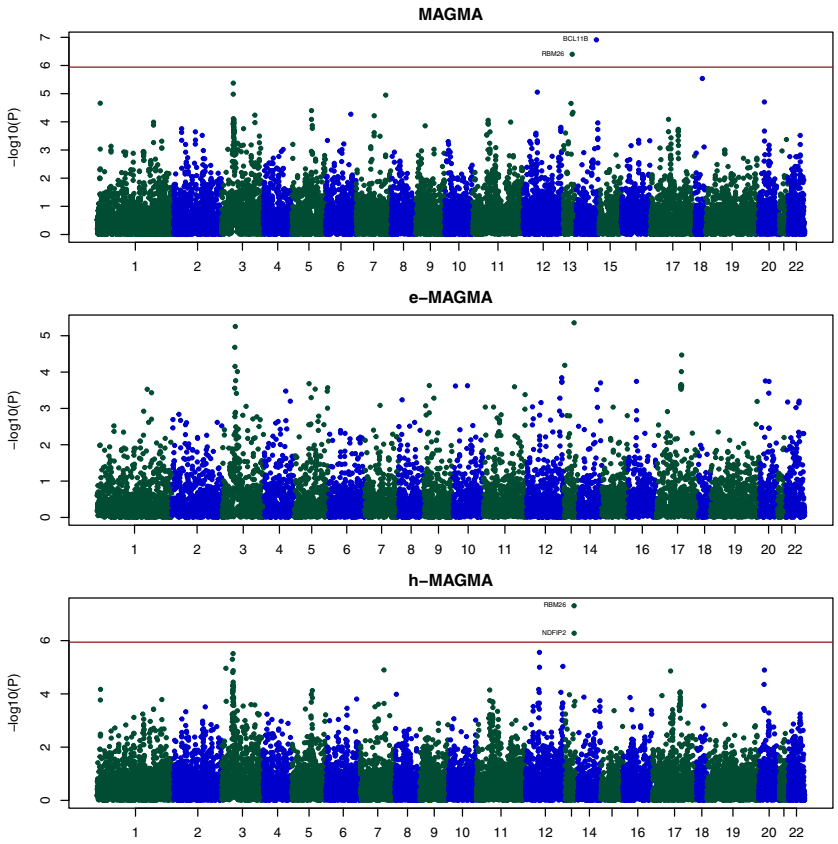

Figure 3. Manhattan plots of gene-association results from MAGMA. Three types of MAGMA were run: conventional MAGMA (MAGMA), expression quantitative trait loci–informed MAGMA (e-MAGMA), and high chromatin–informed MAGMA (h-MAGMA). The horizontal red line indicates Bonferroni-corrected significance ($p = 1.14 \times 10^{-6}$), corrected for 43,790 separate tests across all 3 methods total.

Partitioning Heritability by Functional Category

Using partitioned LDSC, we partitioned the heritability of TDs by functional category. Two categories showed significant enrichment (Bonferroni-corrected threshold of .05/53 tests = 9.42×10^{-4}). Heritability was significantly enriched in conserved regions—2.6% of SNPs belong to the category "Conserved_LindbladToh.bedL2_0" and explained 51% of SNP heritability ($p = 1.41 \times 10^{-07}$), while 33% of SNPs were assigned to the category "Conserved_LindbladToh.extend.500.bedL2_0" and explained 78% of SNP heritability ($p = 2.47 \times 10^{-5}$) (Table S7). Visual cortex and palatine tonsil showed significant enrichment for TD signal at a Bonferroni-corrected p-value threshold of 2.44×10^{-4} ($p = 6.75 \times 10^{-5}$ and $p = 1.11 \times 10^{-4}$, respectively) (Table S8).

Tissue and Cell-Type Enrichment Analyses

We tested whether specific tissues or cell types showed enriched expression of genes from the TD GWAS. No tissue from GTEx or broad cell type (34) met our significance criteria (false discovery rate [FDR]–corrected p values $< .05$ for both MAGMA and LDSC-derived tests). However, 4 brain tissues (putamen, caudate, nucleus accumbens, and frontal cortex Brodmann area 9) were significant in 1 test type (Figure S1). This justified follow-up analysis of 39 broad brain cell types, which revealed 4 broad cell types (di- and mesencephalon inhibitory neurons, telencephalon projecting excitatory neurons, hindbrain neurons, and telencephalon projecting inhibitory neurons) that were significant in 1 test type (Figure S1). We utilized an analogous approach scDRS (31) to test associations between TD GWAS polygenic signal and over 100,000 cells derived from mouse, which were aggregated into 120 cell-type groups, replicating brain-specific enrichment. Notable results came from neurons, which showed heterogeneity, suggesting that signal came from a subset of cells and medium spiny neurons with uniform TD polygenic signal (Figure S2).

A detailed analysis of 265 neuronal cell types (34) failed to identify significant enrichment ($p_{FDR} < .05$). Clustering cell types into 35 cell-type classifications, where each classification contained at least 2 cell types, also did not yield significant results post FDR correction.

Summary-Data-Based Mendelian Randomization

We ran SMR analyses on the TD summary statistics to check for pleiotropy between TD risk variation and tissue/cell type–relevant expression changes in single genes via known QTLs. We ran 2 sets of SMR: 1) eQTLs and splicing QTLs from BrainMeta version 2 (35) (24,076 tests, Bonferroni threshold = $.05/24{,}076 = 2.1 \times 10^{-6}$) and 2) brain cell type–specific eQTLs from Bryois *et al.* (33) (2980 tests, Bonferroni-corrected p-value threshold = $.05/2980 = 1.7 \times 10^{-5}$). Neither set of the SMR analyses produced a gene-based result that passed the preset Bonferroni significance threshold (Tables S9 and S10).

Overlap With Exome Sequence Data

We examined the relationship between GWAS and exome sequencing results for TDs, testing 3 gene types for polygenic risk enrichment: 1) genes defined as intolerant to loss-of-function (LoF) variation (36), 2) genes hit by at least one LoF de novo variant in TS trio studies (15,37), and 3) high-confidence (FDR $< .001$) neurodevelopmental genes defined in a recent study (38).

TS polygenic risk was enriched within LoF-intolerant gene loci ($p = .0017$) and, to a lesser degree, within high-confidence neurodevelopmental genes ($p = .011$) (Figure S3). No significant overlap was found with genes having an LoF mutation in TS trios ($p = .419$). Testing the 10 deciles of LoF intolerance for enrichment with TD summary statistics revealed nominally significant overlap in the most intolerant 2 deciles ($p = .015$ and $p = .032$) (Figure S4). Enrichment was specific to deciles 1 to 5, which represent the more intolerant half of the exome. A pooled test of all genes within deciles 1 to 5 supported this observation ($p = 2.13 \times 10^{-5}$).

Cross-Trait Genetic Correlations

We examined genetic correlations between TDs and 112 different traits and found 43 that exceeded the significance threshold after correcting for multiple testing using the Benjamini-Hochberg procedure to control the FDR at a threshold of .05 (Figure 4 and Table S11). The traits span psychiatric, substance use, cognition, socioeconomic status, personality, psychological, neurological, autoimmune, cardiovascular, anthropomorphic/diet, and fertility categories. TD was significantly correlated with all tested psychiatric disorders, except posttraumatic stress disorder; the highest correlations were with ADHD ($r_G = 0.44$, 95% CI = [0.354–0.526], $p_{FDR} = 2.79 \times 10^{-23}$), followed by major depressive disorder ($r_G = 0.38$, 95% CI = [0.291–0.469], $p_{FDR} = 2.84 \times 10^{-15}$), ASD ($r_G = 0.32$, 95% CI = [0.207–0.433], $p_{FDR} = 3.29 \times 10^{-7}$), depressive disorder ($r_G = 0.32$, 95% CI = [0.251–0.389], $p_{FDR} = 2.28 \times 10^{-17}$), and OCD ($r_G = 0.29$, 95% CI = [0.133–0.447], $p_{FDR} = .001$). Significant positive genetic correlations were also observed for all 15 neuroticism phenotypes, suicide attempt, childhood maltreatment, tiredness, asthma adult-onset, LDL cholesterol, and total cholesterol. Four smoking phenotypes also showed a significant correlation: nicotine dependence, cigarettes per day, smoking initiation (positive), and age of smoking initiation (negative). Significant negative correlations were observed with alcohol dependence, age at first birth, sleep duration, and self-rated health (Table S11 for phenotype details).

We conducted the same genetic correlation analyses separately for iPSYCH, 23andMe, and PGC (Figure S5 and Table S12). The iPSYCH cohort showed higher genetic correlations for some psychiatric disorders, especially ASD, ADHD, and major depressive disorder. Similarly, the 23andMe and PGC samples showed positive genetic correlations for all psychiatric disorders except posttraumatic stress disorder. For most other phenotypes, the results were comparable within small variations.

DISCUSSION

Here, we report results from the largest TD GWAS to date, with 9619 cases and 981,048 controls, including 4800 cases and 971,560 controls not previously published. This increased sample size allowed us to identify 1 GWS locus. While this may seem surprisingly low given how highly heritable TDs are, other highly heritable traits performed similarly at this sample size (39). Nevertheless, the increased power facilitated several

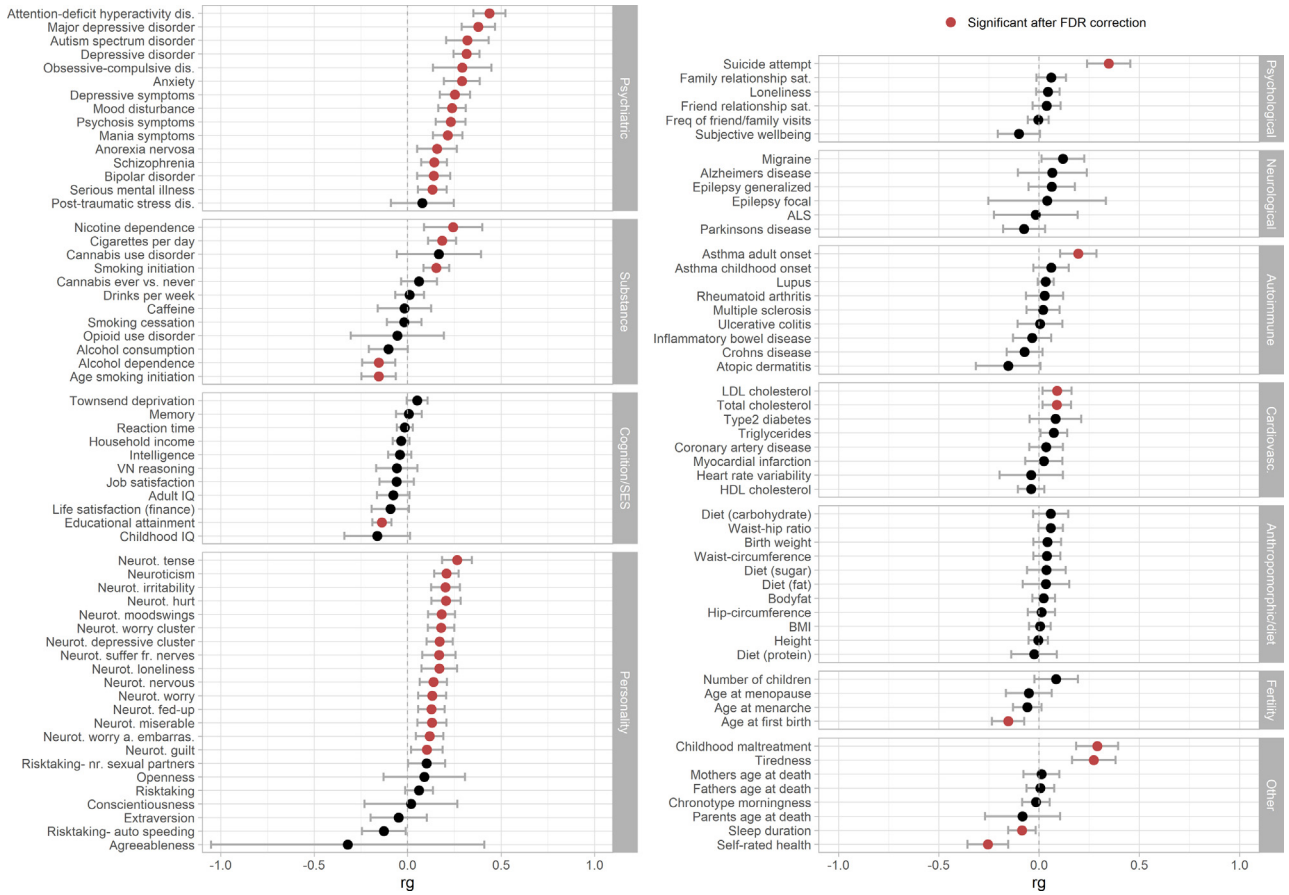

Figure 4. Genetic correlations (r_G) between tic disorders and 112 other traits. Correlations with 112 psychiatric, substance use, cognition/socioeconomic status (SES), personality, psychological, neurological, autoimmune, cardiovascular, anthropomorphic/diet, fertility, and other traits were examined. Error bars represent 95% CIs, and red circles indicate significant associations with a *p* value corrected for multiple testing with the Benjamini-Hochberg procedure to control the false discovery rate (FDR) (< .05). References for all phenotypes can be found in Table S6. ALS, amyotrophic lateral sclerosis; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VN, verbal and numerical.

post-GWAS analyses that were aimed at understanding more about the biology of TDs.

The Manhattan and QQ plots shown in Figure 1 are consistent with a polygenic trait. The 1 GWS hit, rs79244681, is located within *MCHR2-AS1* on chromosome 6, an RNA gene in the long noncoding RNA class with limited characterization. Two previous smaller TS GWASs (18,19) identified 1 GWS locus each: rs2453763 on chromosome 5 (18) and rs2504235 on chromosome 13 (19). SNP rs2453763 (p = .00018) replicated in a subset of our GWAS including non-overlapping samples, while SNP rs2504235 did not (p = .3115). We tested our top findings' replicability with a new dataset from deCODE genetics for the 11 lead SNPs with $p < 1 \times 10^{-6}$. Eight loci showed the same direction of effect in both GWASs, although none reached Bonferroni-corrected significance. Notably, however, the deCODE GWAS was underpowered, with just 885 cases and 310,367 controls. The SNP rs2453763 that reached genome-wide significance in the analysis by Tsetsos *et al.* (18) was also nominally significant in a meta-analysis of our non-overlapping TD GWAS together with deCODE (p = .0004) and was GWS when we combined the present meta-analysis with deCODE and the GWAS from Tsetsos *et al.* ($p < 1.82 \times 10^{-8}$).

Gene-based analyses identified 3 genes associated with TDs (*RBM26*, *BCL11B*, and *NDFIP2*) (see Figure 3). *BCL11B* (BCL11 transcription factor B) was implicated in neurodevelopmental disorders in a recent large meta-analysis of exome sequence data (38).

We next tested whether TD-associated genomic regions were enriched for genes expressed in various tissues and cell types. Despite being underpowered, 4 brain tissues, including 3 from the basal ganglia (putamen, caudate, nucleus accumbens) and 1 from the frontal cortex (Brodmann area 9) were significant in at least one statistical test (Figure S1). These structures are involved in the cortico-striato-thalamo-cortical pathway that has been associated with TS/CTD (40). Using 2 different methods (enrichment analysis with LDSC/MAGMA and scDRS), we identified 5 neuronal cell types associated with TDs, including excitatory and inhibitory telencephalon neurons, di- and mesencephalon inhibitory neurons, hindbrain neurons, and medium spiny neurons. We performed 2 other post-GWAS analyses: 1) partitioning heritability by functional

categories and 2) SMR analyses examining the relationship between TD risk variation and eQTLs. These analyses were underpowered and yielded largely negative findings but showed a significant enrichment of heritability in evolutionarily conserved regions. This consistency with prior psychiatric GWASs suggests that we are nearing the discovery of common genetic variants for TDs.

Then, we examined the relationship between common variation for TDs (through the current GWAS) and rare protein-coding variation (through exome sequencing). Consistent with other neuropsychiatric disorders, we found that TD polygenic risk was enriched in evolutionary constrained genes (i.e., genes intolerant to LoF variation). In addition, TD polygenic risk significantly overlapped with high-confidence neurodevelopmental genes (Figure S2).

Genetic correlations between TDs and 112 different traits revealed 43 significant correlations, including positive correlations with every psychiatric disorder tested except post-traumatic stress disorder (Figure 4). These findings are consistent with clinical manifestations of TDs, where comorbidity with other psychiatric disorders is the norm (e.g., ADHD, OCD, depression). Separate correlation analyses for the 3 largest cohorts in our sample showed higher genetic correlations for psychiatric disorders in the iPSYCH sample, especially for disorders that iPSYCH was primarily ascertained for (ASD, ADHD, major depressive disorder), with comparable results in the other cohorts. Fluctuations in estimates are to be expected because individual sample sizes were small, resulting in larger confidence intervals than for the overall meta-analysis. Furthermore, different comorbidity subgroups in iPSYCH did not show a significant difference in risk-allele frequency of the significant SNP, further indicating that the cohort with higher comorbidity rates (iPSYCH) had a limited influence on the overall results. Interestingly, in a similar GWAS study (with a larger overall sample size), comparable findings were obtained for the closely related disorder OCD (41).

The main limitation of the current study is that despite contributing a substantial number of new cases and controls, most analyses were still underpowered for genetic discovery. The iPSYCH cases were not primarily ascertained for TDs, including higher comorbidity rates and potential diagnostic heterogeneity. Furthermore, a small subset of individuals in iPSYCH were diagnosed with TTD or another TD (see the Supplement for details), potentially introducing additional heterogeneity. Other TDs are likely to be miscoded as TS or CTD cases [see (42)]. While it is plausible that individuals initially diagnosed with, e.g., TTD may later receive a diagnosis of either CTD or TS that may not have been captured in the registry data, we cannot dismiss the possibility that these transient tics were temporary and therefore distinct from a TS/CTD diagnosis. Generally, there is consensus in the field that all tic-related disorders lie on a spectrum, with TS at the severe end of the spectrum (4,43). Given the limited number of individuals with these alternative diagnoses (as opposed to TS or CTD) in our dataset, the overall impact on the results is expected to be minimal. Another limitation may be that the 23andMe cases self-reported being diagnosed with TS, and their diagnoses were not directly verified by a clinician. The samples were all of European ancestry, which limits the generalizability of the findings to other (ancestral) groups.

Conclusions

The combined results of all available TD GWASs to date, including the current one, are probably still underpowered to identify high-confidence, replicable loci. However, the current results are encouraging and suggest that we are at the brink of discovery of common genetic variants for TDs.

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The meta-analyzed summary statistics (excl. 23andMe) are available via the Psychiatric Genomics Consortium download page (https://www.med.unc.edu/pgc/download-results/). The full GWAS summary statistics for the 23andMe discovery dataset will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Datasets will be made available at no cost for academic use. For more information and to apply to access the data, see https://research.23andme.com/collaborate/#dataset-access/.

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