Data Supplement for Yu et al., Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies. Am J Psychiatry (doi: 10.1176/appi.ajp.2018.18070857)

Contents

Abbreviations

AJ: Ashkenazi Jewish European-derived isolate samples collected from the US and Israel

CIDR: The Center for Inherited Disease Research

CMVT: Chronic (persistent) Motor or Vocal Tic disorder

CNP: The Consortium for Neuropsychiatric Phenomics

EU: European ancestry

FC: French Canadian European-derived isolate samples collected from Quebec, Canada

GCTA: Genome-wide Complex Trait Analysis

GGRI: The Gilles de la Tourette Syndrome Genome-wide Association Study Replication Initiative

GPC: Genomic Psychiatry Cohort

GSP: The Harvard/MGH Brain Genomics Superstruct Project

GWAS: Genome Wide Association Analysis

LD: Linkage Disequilibrium

LDSC: Linkage Disequilibrium Score Regression

MAF: Minor Allele Frequency

MDS: Multi-dimensional Scaling

PCA: Principal Component Analysis

PRS: Polygenic Risk Score

QC: Quality Control

REML: Restricted Maximum Likelihood

SNP: Single Nucleotide Polymorphism

TAAICG: Tourette Association of America International Consortium for Genetics

TIC: The Tourette International Collaborative - Genetics

TS: Tourette Syndrome

Programs

EIGENSTRAT -- https://github.com/DReichLab/EIG/tree/master/EIGENSTRAT

GCTA -- http://cnsgenomics.com/software/gcta/#Overview

IMPUTE v2 -- http://mathgen.stats.ox.ac.uk/impute/impute_v2.1.0.html

LDSC -- https://github.com/bulik/ldsc

MAGMA -- https://ctg.cncr.nl/software/magma

METAL -- http://csg.sph.umich.edu/abecasis/Metal/

MMM v1.0 -- http://www.helsinki.fi/~mjxpirin/download.html

PLINK v1.9 -- https://www.cog-genomics.org/plink2

ShapeIT -- https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html

Supplementary Methods and Results

Subjects

Primary GWAS meta-analysis

The primary GWAS meta-analysis consisted of 4,819 Tourette cases and 9,488 controls from four European ancestry (EU) GWAS datasets (sample numbers after quality control):

1) 969 cases and 3,923 ancestry-matched controls from the initial Tourette syndrome GWAS (GWAS1) published by the Tourette Association of America International Consortium for Genetics (TAAICG)(1);

2) a second-wave EU ancestry case-control sample of 2,711 cases collected by the TAAICG and the GTS GWAS Replication Initiative (GGRI) (2, 3) and 3,762 ancestry-matched controls described below (GWAS2);

3) an EU ancestry family-based sample consisting of 175 probands from the initial Tourette GWAS plus one or more additional Tourette-affected family members(4) (N=548) and 597 ancestry-matched controls (GWAS2 FAM);

4) 591 independent EU Tourette syndrome probands from the TIC Genetics consortium (TIC) (5) and 1206 unselected ancestry-matched controls.

The GWAS1 sample is described elsewhere (1). The remaining datasets are described below (**Table S1**).

GWAS2: A total of 2,871 EU cases with DSM-5 Tourette syndrome were recruited using email/online recruitment combined with validated, web-based phenotypic assessments for assigning diagnoses of Tourette syndrome, OCD and ADHD(6, 7) (N=1,264), or from Tourette specialty clinics throughout the US, Canada, the Netherlands, Austria, France, Germany, Greece, Hungary, and Italy (N=1,607). Eligible cases met DSM-5 criteria for a lifetime history of Tourette

syndrome; other psychiatric diagnoses were not excluded. Exclusion criteria included a history of intellectual disability, and genetic or neurological disorders that caused tics or movement disorder phenocopies (e.g., epilepsy, known chromosomal abnormalities, etc.). OCD and ADHD were phenotypically assessed by clinicians with expertise in the diagnosis of Tourette syndrome, OCD and ADHD, and diagnoses were assigned based either on DSM-5 criteria alone(2, 3) or by using standardized structured instruments(4, 6) (TAAICG). The same inclusion/exclusion criteria were used for these Tourette syndrome cases and family members as those used in the Tourette GWAS2 case-control sample.

Genomic DNA was extracted either from blood or cell lines, and all subjects were genotyped on the Illumina HumanOmniExpressExome_8v1 SNP array (Illumina, San Diego, CA) at the UCLA Neuroscience Genomics Core (UNGC).

A total of 5,487 EU controls were obtained from cohorts of previously genotyped, unselected population controls (**Table S1**) for the GWAS2 analyses. These included 1,311 EU ancestry controls from the Consortium for Neuropsychiatric Phenomics (CNP)(8), genotyped on the Illumina HumanOmniExpress_12v1 at the UNGC, 1,941 controls from the Harvard/MGH Brain Genomics Superstruct Project (GSP)(9) genotyped on the Illumina HumanOmniExpressExome_12v1 at the Broad Institute of MIT and Harvard, 1008 controls from the NINDS Human Genetics Resource Center genotyped on the Illumina HumanOmniExpressExome_12v1 at the Yale Center for Genomic Analysis, and 1,227 Ashkenazi Jewish controls genotyped from the longevity gene study at Einstein (10) on the Illumina HumanOmniExpress-12v1 at the Center for Inherited Disease Research (CIDR) (11).

In addition, 595 EU ancestry controls were collected from Austria, Germany, Greece, Hungary, Italy, and Quebec, Canada (3), and were genotyped simultaneously with the Tourette syndrome cases on the Illumina HumanOmniExpressExome_8v1 at the UNGC.

GWAS2 FAM: The family sample consisted of 548 Tourette syndrome probands and Tourette-affected first-degree relatives from 207 independent families(4) and 597 ancestry matched controls. One hundred and seventy-five Tourette syndrome family probands came from the original Tourette GWAS1 sample and were genotyped on the Illumina Human610-Quadv1_B SNP array(1). Thirty-two Tourette syndrome probands and 341 additional Tourette -affected family members (total N=373) were genotyped on the HumanOmniExpressExome_8v1 SNP array (Illumina, San Diego, CA) at the UNGC along with the GWAS2 case-control sample. Matching controls were selected from a pool of controls genotyped previously on the HumanOmniExpressExome_8v1(9), HumanHap1Mv1_C, or HumanHap550v1/v3(1).

TIC GWAS: The TIC Genetics (TIC) sample consisted of 789 independent case probands initially recruited for family-based genetic studies. All cases met DSM-IV-TR criteria for Tourette syndrome and were formally assessed for OCD and ADHD using the same semi-structured diagnostic instrument as the TAAICG case and family samples(5) above; 18 case probands met DSM-IV-TR criteria for Chronic Motor or Vocal Tic Disorder. All TIC cases were genotyped at the Yale Center for Genome Analysis. Many subjects were genotyped on multiple platforms, and the genotype from the most advanced platform per sample was used for this study, resulting in 261 cases on the Illumina HumanCNV370-Duo_v1 SNP array, 146 cases on the Illumina HumanOmni1M array, and 382 cases on the Illumina HumanOmniExpress Exome SNP array (numbers include overlapping samples prior to QC).

A total of 1,433 unselected controls collected as part of the Genomic Psychiatry Cohort (GPC) at the University of Southern California were used as the matching controls for GWAS2_TIC data sets. Genotyping was conducted on the Illumina HumanOmniExpressExome_12v1 at the Broad Institute of MIT and Harvard(12).

deCODE Replication Sample

The deCODE sample consisted of 706 Icelandic Tourette syndrome cases (N=475 with a clinical Tourette diagnosis based on ICD-10 code F95.2, N=231 identified by screening using questionnaire data as described below), 466 cases with other tic disorders (Chronic Motor or Vocal Tic Disorder, and unspecified tic disorder, N=164 with clinical F95.X diagnosis, N=302 identified by screening using questionnaire data as described below), and 127,164 unscreened population-matched controls without an ICD-10 diagnosis of Tourette syndrome or another tic disorder. 6,068 of the Icelandic controls were screened along with cases and reported no lifetime subclinical motor or vocal tics. All cases and controls were genotyped at deCODE genetics using Illumina SNP arrays and were imputed using a previously described method (13).

The three tic phenotypes in the Icelandic sample were derived as follows:

1) Tourette Syndrome: Subjects either had confirmed Tourette diagnoses by neurologists based on ICD-10 codes (F95.2), or met DSM-5 criteria for Tourette syndrome derived from a self-report questionnaire in which subjects either answered "Yes" to the question "Have you (or, for parents, "Has your child") been diagnosed with Tourette Syndrome?", or answered "Yes" to both of the following two questions: "Have you (or has your child) ever had involuntary motor tics that started before age 18?" and "Have you (or has your child) ever had involuntary vocal tics that included repeated vocalization, sound making?".

2) Chronic (persistent) Motor or Vocal Tic Disorder: Subjects met DSM-5 criteria for Chronic Tics (presence of motor or vocal tics (but not both) that started before age 18), either confirmed by neurologists (F95.1) or assessed using the same self-report questionnaire, but had not received a prior diagnosis of Tourette syndrome and answered Yes to only one of the two questions above, but not both.

3) Other Tic Disorders: Subjects were either diagnosed with other ICD-10 Tic Disorders by a neurologist (F95.0, F95.9) or endorsed the presence of a motor or vocal tic that either onset after age 18 or could not be confirmed to have been present for more than one year.

GWAS Analysis

General quality control and imputation pipeline

Genotyping quality control (QC) was performed using PLINK v1.9 (14) and EIGENSTRAT (15). Within each genotyping platform, iterative removal of SNPs and samples with low genotyping call rates were first conducted at a call rate of <95% and subsequently at a call rate of <98%. Subjects with ambiguous genomic sex (0.2<F<0.8) or discrepancy between genomic sex and phenotypic sex status were excluded. Strand-ambiguous SNPs, monomorphic SNPs, mitochondrial SNPs, sex chromosome SNPs, and CNV-targeted SNP probes were excluded, as were SNPs with a Hardy-Weinberg equilibrium test $p<1.0x10^{-6}$ among homogeneous controls or $p<1.0x10^{-10}$ among homogeneous cases. After flipping SNPs to the forward-oriented strand using the 1000 Genomes Project Phase 1 as the reference panel, subjects genotyped on different platforms were merged into a single PLINK data set, and only the SNPs that were genotyped on all platforms were retained and subjected to the additional QC steps described below.

To identify unexpected duplicates and relatives among all data sets, and to validate known relationships among family members, a pair-wise identity-by-descent (IBD) matrix was generated among all samples using high call rate (>99.5%), linkage disequilibrium (LD) independent ($r^2<0.2$), common (minor allele frequency, MAF >5%) SNPs that were present on all platforms. One member of each duplicate or relative pair (pi_hat>0.2) among case-control subjects was removed. Samples who were related to >25 other individuals with only low-level relatedness (pi_hat>0.05) were also removed due to potential contamination. Known and identified relative pairs where both individuals had a diagnosis of Tourette syndrome were removed from the case-control sample and moved to the family-based analysis.

Population stratification and removal of outliers

Population stratification was assessed through multi-dimensional scaling (MDS) analysis. Individuals of non-European ancestry and cases for whom a matching control could not be identified were removed. Extreme outliers on each of the MDS components, identified visually

as those falling outside the PC clusters on each MDS plot (see Figure S1 for an example) were removed. Case-control matching was verified across all MDS components.

Tourette syndrome cases and controls of Ashkenazi Jewish (10) ancestry were identified using principal components analysis and separated out from the general European ancestry (EU) sample for further QC steps specific to genetically homogeneous populations. Within the EU and AJ subpopulations, samples with inbreeding coefficient $|F|>0.05$ were excluded. SNPs with differential missing rate (>0.02) between cases and controls and SNPs with HWE $p<1.0x10^{-6}$ among controls or $p<1.0x10^{-10}$ among cases were also excluded. To investigate potential genotyping platform effects, association tests were performed between controls genotyped on different platforms or at different genotyping centers, using either platform or genotyping center as the phenotype. No systemic genomic inflation was identified in any of these control-control analyses; SNPs with control-control association $p<1.0x10^{-5}$ across platforms or centers were removed. SNPs with MAF<0.01 were removed before imputation.

Imputation was conducted after standard QC procedures; any dataset-specific additional QC steps are described below. The 1000 Genomes Project Phase 1 integrated haplotypes (December 2013 release, with singleton sites removed)(16) was used as the reference panel. ShapeIT was used to phase genotype data, followed by imputation using IMPUTE v2. SNPs with information scores between 0.6 and 1.2, average possibility of most likely genotype >0.9, and MAF>0.01 were retained for association testing.

GWAS1: As described previously (1), GWAS1 association analysis was conducted in three strata defined by ancestry: 1) European ancestry, non-isolate cases from North America and Europe with matching controls identified by MDS (GWAS1_EU); 2) Ashkenazi Jewish cases from the United States and Israel with matching controls identified by MDS (GWAS1_AJ); 3) French Canadian cases and controls recruited in parallel from Canada (GWAS1_FC). The three strata remained mostly the same as in the original GWAS1, with the following changes: a) the 175 probands who had Tourette-affected relatives genotyped in GWAS2 FAM were removed from

GWAS1 and analyzed as part of GWAS2 FAM as described below; b) the TIC cases were extracted and analyzed as separate strata due to having been genotyped on different platforms (detailed information is described below).

TIC cases genotyped on the Illumina HumanCNV370-Duo_v1 SNP array and originally analyzed as part of GWAS1 were separated into an independent stratum for analysis along with their matching controls (GWAS1_TIC). In addition, any TIC cases that had been re-genotyped on denser SNP array platforms were excluded from the GWAS1 stratum and were analyzed as part of the TIC GWAS.

After stringent quality control, 969 cases and 3923 controls were obtained in GWAS1, including 1) 447 cases and 3232 controls in GWAS1_EU; 2) 185 cases and 321 controls in GWAS1_AJ; 3) 241 cases and 178 controls in GWAS1_FC; and 4) 96 cases and 192 controls in GWAS1_TIC. The imputation of the first three strata was conducted jointly, while GWAS1_TIC was imputed separately **(Table S2)**.

GWAS2: Standard QC was applied on the GWAS2 samples. After QC, since the GWAS2 AJ control:case ratio (5.7:1) was much larger than that of the GWAS2 EU samples (1.4:1), excess AJ controls were removed to approximate a 1.4:1 control:case ratio at any given MDS component region to avoid overweighting the analysis toward any EU-based subpopulation. Since >500 subjects harbored varying proportions of AJ and EU genetic ancestry components, rather than analyzing the EU and AJ samples separately, all GWAS2 case-control subjects were analyzed together in a single stratum. The final GWAS2 contains 2711 cases and 3762 controls **(Table S2)**.

GWAS2_FAM: After standard QC, 175 family probands who were genotyped previously with the original Tourette GWAS1 samples on the Illumina Human610-Quadv1_B SNP array and ancestry matched controls were merged with the GWAS2 family data, and only SNPs overlapping the two post-QC SNP arrays were retained. A pairwise IBD matrix was generated among family members and controls. Relationships among family members were validated

based on IBD sharing probabilities Z_0, Z_1, and Z_2 (Z_1>0.9 for parent-child pairs, pi_hat between 0.4 and 0.6 and Z_1 between 0.4 and 0.6 for sib-pairs), and family members with unexpected genetic relationships were removed. MDS analysis was performed on family founders and controls, and population outliers were removed. A total of 548 probands and affected relatives from 207 pedigrees and 597 independent matching controls were obtained for imputation **(Table S2)**.

TIC GWAS: The TIC cases and USC GPC controls were split into two strata: 1) TIC cases genotyped on the Illumina HumanCNV370-Duo_v1 but not included in GWAS1, along with matching GPC controls (TIC_370K); 2) TIC cases genotyped on the Illumina HumanOmni1M or the Illumina OmniExpress with matching GPC controls (TIC_Omni). Only the overlapped SNPs on both Illumina HumanOmni1M and Illumina OmniExpress were kept in the TIC_Omni analysis. After standard QC procedures, 591 cases and 1206 controls were obtained, including 1) 141 cases and 266 controls in TIC_370K; 2) 104 cases genotyped on the Illumina HumanOmni1M, 346 cases genotyped on the Illumina OmniExpress, and 940 controls in TIC_Omni. Imputation was conducted on TIC_370K and TIC_Omni separately **(Table S2)**.

Genome-wide association test and meta-analysis

After imputation and post-imputation filtering as described above in the imputation pipeline, genome-wide association tests were conducted on 4 GWAS1 strata, GWAS2, and 2 TIC GWAS strata separately in PLINK1.9 (14), using logistic regression under an additive model with the first four MDS components and any additional MDS components associated with Tourette syndrome case-control status at $p<0.05$ included as covariates to control for residual population stratification. A linear mixed model was performed on the GWAS2_FAM in MMM v.1.0 (17) to control for familial relatedness.

A primary GWAS meta-analysis was conducted on the GWAS1, GWAS2, GWAS2 FAM, and TIC GWAS datasets using the inverse-variance method in METAL(18). Heterogeneity was assessed using Cochran's I^2 statistics. The genomic control factor (λ) was calculated and quantile-quantile

(Q-Q) plots were generated for each individual GWAS and for the overall meta-analysis using all SNPs with MAF>0.01 to identify any residual population stratification or systematic technical artifact (**Figure S2**). The genome-wide significant threshold for the GWAS (19, 20) was set at $p= 5.0x10^{-8}$.

The final Tourette GWAS meta-analysis consisted of 4,819 genetically-defined European ancestry Tourette syndrome cases and 9,488 ancestry-matched controls. After removing SNPs with INFO scores <0.6 or >1.2, certainty <0.9, and MAF<1%, 8,265,319 SNPs remained for analysis. No evidence for residual population stratification or systematic technical artifact was observed from Q-Q plots and genomic control analyses on SNPs with MAF>1% in each of the 8 individual GWAS datasets (λ=1.018 in GWAS1_EU; λ=1.009 in GWAS1_AJ; λ=1.023 in GWAS1_FC; λ=1.042 in GWAS1_TIC; λ=1.058, λ_{1000} =1.018 in GWAS2; λ=1.006 in GWAS2_FAM; λ=1.018 in TIC_370; λ=1.005 in TIC_omni; **Figure S2**) or in the final GWAS meta-analysis (λ=1.072, λ_{1000} =1.011, **Figure 1**).

A sign test was also conducted on the 42 SNPs that were reported in the previous targeted replication study based on the first Tourette GWAS (3). The 42 SNPs were selected from the top Tourette-associated SNPs in GWAS1, and prioritized in eQTLs or functional SNPs. All 42 SNPs had the same effect direction between the Tourette syndrome GWAS meta-analysis and the first Tourette GWAS (p<0.0001, two-way binomial sign test). To assess for independent replication of these 42 selected SNPs from GWAS1 in the new GWAS2 and TIC samples, we performed a separate targeted meta-analysis using only the GWAS2 and TIC GWAS samples in METAL using the inverse variance method on the 42 GWAS1 SNPs, and found 29 out of 42 SNPs with the same effect direction between the original Tourette GWAS1 and the meta-analysis of GWAS2 and TIC GWAS (p=0.020, two-way binomial sign test).

Defining LD-independent top loci

One SNP, rs2504235, achieved genome-wide significance ($p < 5.0x10^{-8}$) in the primary meta-analysis, and 480 SNPs had association p-values $< 1.0x10^{-5}$ **(Table S3)**. LD clumping was

performed to identify LD-independent loci (r^2<0.2) from the markers with association p-values <$1.0x10^{-5}$ in PLINK1.9, using 1000 Genomes Project Phase 1 European ancestry populations as the reference panel for LD structure. The LD clumping window was 2Mb. To avoid any long LD blocks or SNP pairs with low r^2 but high D', conditional association tests were conducted on any identified LD independent loci within 10Mb by using one locus as a covariate. If the association p-value increased to p>0.001 after including a nearby locus as the covariate in the logistic regression, the less significant locus was removed from the top independent loci list.

After LD clumping and conditional association tests, the regional plot for each identified LD independent top locus was manually checked, and one locus was removed due to low imputation quality (information score (INFO) =0.63) and a lack of supporting evidence from nearby SNPs. After checking the regional plots, a total of 39 LD independent top loci were identified (**Table S4**).

Targeted Replication

The Icelandic deCODE genetics case-control samples were used to independently replicate the top SNPs from the primary GWAS meta-analysis. The single locus replication threshold was set at p<0.001 after Bonferroni correction for 39 independent tests. None of the individual SNPs were replicated in the deCODE sample (**Table 1; Table S4, Figure S6**).

A sign test was also conducted to examine consistency in the direction of effect across the 39 SNP risk alleles between the deCODE sample and the primary meta-analysis. Twenty-three of 39 putative Tourette risk alleles had the same direction of effect in the deCODE sample, though this was not statistically significant (two-way sign test p= 0.34).

The deCODE results for the top SNPs were meta-analyzed in METAL with the primary GWAS meta-analysis using the inverse-variance method.

Heritability Analyses

The SNP-based genetic heritability of Tourette syndrome was estimated using two methods: 1) Genome-wide complex trait analysis (GCTA), a program to estimate the additive genetic variance component using restricted maximum likelihood (REML) from genome-wide genotype data; 2) LD score regression (LDSC), a program to estimate genetic heritability from GWAS summary statistics while accounting for linked genetic variants.

Heritability estimation by GCTA

Additional QC for GCTA: Stringent quality control for GCTA was conducted on European non-isolate samples outlined in Davis et al. (21). The QC procedure started with the cleaned data sets of GWAS1_EU and non-AJ GWAS2 samples, as well as the cleaned SNP sets used for imputation. We first removed one individual from any pair of individuals whose IBD PI_HAT estimate was > 0.05 in a manner that maximized the number of remaining case individuals. We also removed individuals with missing call rate >1%. We then performed the following QC for removing SNPs: 1) SNPs whose missing rate differed between cases and controls with p-value <0.05; 2) SNPs whose HWE p-values were <0.05; and 3) SNPs with the platform effect p-value <0.001. The platform effect p-value was calculated by performing association tests between controls genotyped from two different genotyping platforms or genotyping centers in each GWAS; we assigned one control group to “cases” and another control group to “controls” and performed association tests on SNPs with principal component (PC) factors as the covariates to adjust for population stratification. As there were three control groups in both GWAS1 and GWAS2, we performed three platform tests for every pair of control-control analyses. After all QC was completed, the final GWAS1 dataset for GCTA analysis consisted of 559 cases and 3,400 controls with 389,551 SNPs; the GWAS2 dataset for GCTA consisted of 2,147 cases and 2,564 controls with 474,099 SNPs. We used the top 10 PCs as covariates and used only SNPs with MAF > 1% when estimating heritability using GCTA with disease prevalence of 0.8%. To verify that these additional QC procedures minimized bias in heritability estimation, we applied GCTA to a dataset that consisted of two control groups where one control group was considered as

"cases" while the other control group was considered as "controls." Heritability of zero would be expected from this dataset if no bias was introduced to heritability estimation. We found that for both GWAS1 and GWAS2, zero heritability was observed with the additional QC while non-zero heritability with significant p-values was observed without the QC.

Tourette syndrome heritability by ascertainment method: To compare the relative polygenic burden of Tourette syndrome samples collected using different ascertainment methods, the Tourette GWAS1 and GWAS2 datasets were separated into 3 groups: 1) GWAS1 cases recruited from Tourette syndrome specialty clinics throughout the US, Canada and Europe, in which approximately 25% of cases were derived from affected sibling pairs (one proband per family)(4); 2) GWAS2 cases recruited from Tourette syndrome specialty clinics throughout the US, Canada, and Europe (GWAS2 clinic-based)(3, 4); 3) GWAS2 cases recruited via email from the membership of the Tourette Association of America (TAA) and assessed using a web-based phenotyping tool developed and validated by the TAAICG (GWAS2 web-based)(6, 7). The SNP-based heritability of each ascertainment group was estimated separately, as well as jointly, on the liability scale using a Tourette syndrome population prevalence of 0.8%.

Tourette syndrome SNP-based heritability (h^2_g) estimated from GWAS1 was 0.56 (SE=0.10; $p=1.2x10^{-9}$), similar to what was reported in the first Tourette GWAS paper (h^2_g=0.58, SE=0.09, $p=5.6x10^{-12}$ from 617 cases and 4,116 controls). This small difference was likely due to the exclusion of the samples that were moved to GWAS2_FAM. Tourette h^2_g estimated from GWAS2 was 0.29 (SE=0.04; $p=5.5x10^{-14}$ from 2,146 cases and 2,564 controls), significantly lower than the heritability estimated from GWAS1, although the level of significance level was stronger due to the larger sample size.

To explore the hypothesis that the lower SNP-based heritability of GWAS2 might have arisen from the inclusion of Tourette syndrome cases ascertained using a web-based screen of cases diagnosed in the community(6, 7), the GWAS2 case-control sample was divided into two

subsets (clinic-based cases vs. web-based cases), and the heritability analyses were repeated (**Table 2**).

To explore the alternative hypothesis that differences between the SNP-based heritability estimates for GWAS1 versus GWAS2 were based on preferential ascertainment for highly familial cases in the GWAS1 sample, polygenic risk score (PRS) analyses were conducted as described below. Of note, approximately 25% of GWAS1 cases had a positive family history of a first-degree relative with Tourette syndrome or chronic motor/vocal tic disorder (chronic tics), including multiple affected sibpair families, while GWAS2 cases were not ascertained with regards to either the presence or absence of a family history of Tourette or chronic tics. In this context, GWAS1 probands with a strong family history of Tourette or chronic tics might carry a higher polygenic burden, while probands without a family history of Tourette/Chronic tics might have fewer affected relatives either due to a lower Tourette polygenic burden or as a result of recent rare, large effect-size *de novo* mutations or CNVs with large effect, which would not be captured by the REML method using common genotype variants in GCTA.

Heritability estimation by LDSC

Estimation of Tourette syndrome heritability from the primary GWAS meta-analysis and calculation of genetic correlations between individual GWAS datasets: Genomic inflation observed on genome-wide association Q-Q plots can be divided into two contributions: 1) a component representing true polygenicity of the Tourette syndrome phenotype (a "true positive" increase in aggregate association test statistics) and 2) an artifactual component representing confounding due to technical artifact or residual population stratification (a "false positive" increase in association test statistics). Linkage Disequilibrium (LD) score regression (LDSC) based on the chi-square summary statistics from the primary GWAS meta-analysis was performed to distinguish between these two components (22). Pre-computed 1000 Genome Projects European population LD-scores (https://github.com/bulik/ldsc) were used for SNPs with MAF>0.01 and information score >0.9. The deviation of the intercept above 1 represents the degree of genomic inflation due to confounding, with (intercept-1)/(mean(chi^2)-1)

indicating the proportion of genomic inflation due to confounding, while the remaining genomic inflation represents the contributions of polygenicity. Similarly, the slope of the LD score regression represents the genetic heritability of the trait, as estimated in LDSC. Furthermore, by including two GWAS datasets in a bivariate regression, the genetic correlations between GWAS1, GWAS2, and TIC GWAS were calculated in LDSC.

The LD score regression intercept using the Tourette meta-analysis summary statistics was 1.017, suggesting the presence of minimal residual confounding. In contrast, the mean of chi-square summary statistics was 1.118, and, using the equation above, the proportion of genomic inflation due to the effects of confounding is (1.017-1)/(1.118-1) = 14%, indicating that 86% of the observed genome-wide inflation of test statistics is due to the contribution of a polygenic genetic architecture (**Supplementary Figure S3**).

Partitioning heritability by functional annotation and tissue-specific gene expression: Using Tourette syndrome SNP-based heritability (h^2_g) as a genome-wide genetic probe to localize functional elements and specific cell or tissue types significantly enriched in Tourette genetic risk, we partitioned Tourette syndrome h^2_g in the primary GWAS meta-analysis both by general functional genomic annotations **(Figure S8)** and cell-type-specific annotations using LD Score regression **(Figure S9)** (23).

Enrichment was defined as the proportion of heritability contributed by the tested category divided by the proportion of all SNPs in this category. A total of 53 functional categories were tested, including 24 publicly available non-cell-type-specific main annotations (e.g., Enhancers, Promoters, 5' UTR, 3'UTR, coding regions, introns, conserved regions across placental mammals and multiple epigenomic marks of transcription factor binding sites or location of various histone modifications) as well as ChIP-Seq peaks from 10 different cell-types(23).

Cell type-specific enrichment was also conducted on 10 cell type groups coming from 220 cell type specific annotations for the 4 histone marks: H3K4me1, H3K4me3, H3K9ac, and H3K27ac

(23). The 10 cell type groups included adrenal and pancreas, central nervous system (CNS), cardiovascular (CV), bone and connective tissue, gastrointestinal, immune and hematopoietic, kidney, liver, skeletal muscle, and other (which included adipose nuclei, breast luminal epithelial, breast myoepithelial, breast vHMEC, fetal placenta, ovary, primary penis foreskin keratinocytes, primary penis foreskin melanocytes, and placental amnion).

Polygenic Risk Score Analyses

Polygenic risk score (PRS) analyses were performed to answer 4 questions: 1) the genetic relationships between Tourette syndrome and other tic disorders in a population-based sample; 2) the consistency and the prediction power of polygenic effects across data sets; 3) the effect of ascertainment and family history on PRS; and 4) the relationship between PRS and tic symptom severity.

Genetic relationships between Tourette and other tic disorders in the deCODE sample

To examine the genetic relationship between Tourette GWAS-derived PRS and individuals with various tic disorder diagnoses in Iceland, Tourette polygenic risk scores in Icelandic Tourette cases and screened controls were generated from a framework set of stable Illumina chip high-quality markers covering the whole genome (620,000 SNPs) in LDpred (24). SNP effect sizes from the Tourette GWAS meta-analysis discovery sample were weighted based on varying pre-defined fractions of causal markers (0.001, 0.003, 0.01, 0.03, 0.1, 0.3, and 1.0) and SNP LD information of the European reference panel derived from whole genome sequencing data of 8,453 Icelanders as described previously (13). Logistic regression was performed to predict the effect of Tourette PRS on case/control status in the sample, controlling for sex, year of birth, and the first 20 principal components. The effects were calculated as beta coefficients, and R^2 values were calculated by comparing fitted models predicting phenotype with and without PRS scores. The best fit parameter for the fraction of causal variants was determined to be 0.3 by comparing Icelandic Tourette syndrome cases to screened tic-negative Icelandic controls ($p=5.3x10^{-9}$) **(Figure S5)**. This best-fit parameter was then used to calculate Tourette PRS in the rest of the population-based sample for subsequent analysis. For visualization purposes, all

Tourette PRS in the Icelandic samples were scaled to 0, such that each increase of 1 standard deviation in PRS score indicates a doubling of the risk for Tourette syndrome (**Figure 2**).

PRS analyses to evaluate of consistency and prediction power across data sets

The Tourette syndrome GWAS meta-analysis contained 8 data sets. For the samples in each dataset (target sample), polygenic risk scores were calculated based on a meta-analysis of the other 7 data sets (discovery sample leaving out the target sample). In each discovery sample, the GWAS meta-analysis was performed on SNPs with INFO>0.95, certainty>0.9, and MAF>0.05, followed by LD-pruning (r^2<0.2). The polygenic risk score of the target sample was generated as the sum of the number of risk alleles weighted by the effect size estimated from the discovery sample, using LD-pruned SNPs with pre-defined GWAS association significance levels (p<0.001, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, and 1 respectively).

The percentage of phenotypic variance explained by PRS in each target sample (in the form of the Nagelkerke R^2) was estimated by comparing a full logistic regression model that included the PRS and all 10 principal components (in order to control for population stratification) to the reduced model that included only the principal components. This procedure was repeated 8 times to calculate the Tourette PRS in each of the 8 contributing datasets (a "leave one out" approach).

Using this "leave one out" approach, significantly higher PRS was found in Tourette cases compared to controls in all 8 data sets, with odds ratios ranging from 1.09 to 1.23. The percentage of phenotypic variance explained by PRS (R^2) ranged from 2.3% to 5.4% **(Figure S4).**

Ascertainment and family history effect on PRS

To maximize the number of samples and minimize the genotyping platform effects, we merged 5 data sets that were genotyped on higher density platforms than the Illumina HumanCNV370-Duo_v1, including GWAS1_EU, GWAS1_AJ, GWAS1_FC, GWAS2, and GWAS2_FAM. Related family members in GWAS2_FAM were removed so that only independent case-control samples

were kept. The overlapped SNPs that crossed all data sets were retained. MDS was carried out to identify European (EU) samples from Ashkenazi Jewish samples, and the EU samples were used for a Hardy Weinberg Equilibrium test, and SNPs with P $<1.0x10^{-6}$ among merged EU controls and P$<1.0x10^{-10}$ among merged EU cases were removed. Genome wide association tests were performed on EU controls across different genotyping platforms by arbitrarily assigning controls from one platform as "affected", and controls from the other platforms as "unaffected". The genomic inflation factor λ was calculated for each control-control GWAS, and no significant inflation was observed. Any SNPs with control-control GWAS P$<1.0x10^{-5}$ were removed. SNPs with differential missing call rates between merged cases and controls >0.02 were also removed. After additional QC steps, a total of 227,746 SNPs from 4486 cases and 9134 controls were kept for imputation. After imputation, common SNPs with INFO >0.95, MAF >0.05, and certainty >0.9 were kept for polygenic risk score analyses.

Polygenic risk score (PRS) per sample was calculated using the cross-validation method. The overall samples were randomly split into 10 subsets under two conditions: 1) the number of cases and controls from each GWAS sample set (i.e. GWAS1_EU, GWAS1_AJ, GWAS1_FC, GWAS2, GWAS2_FAM) were evenly divided across the 10 subsets; 2) the samples were evenly distributed into 10 subsets based on the scale of the first Principal Component. These additional restrictions guaranteed the 10 subsets a similar mixing of ascertainment, family history, genotyping platform, and population stratification. For each subset as a target sample, PRS per sample was calculated as the sum of the number of risk alleles of genome wide (no association p-value threshold applied, i.e., GWAS p≤1) LD-independent SNPs (r^2<0.2), weighted by the SNP effect size derived from the meta-analysis of the other 9 subsets (the discovery sample). The PRS of each subset is expected to come from the same distribution because of the conditional randomization described above. However, due to random fluctuations, the polygenic risk scores of some subsets may be different from the other subsets after correcting for population stratification. To make the PRS comparable across 10 subsets, we further adjusted PRS by population stratification and subset effect, and standardized the adjusted PRS (aPRS) to Norm (0, 1) for interpretation purposes.

To evaluate whether adjusted Tourette PRS differed in cases with or without a family history of chronic (persistent) tic disorders, we divided the Tourette GWAS cases into three groups based on the presence or absence of Tourette syndrome or chronic tics in a first-degree relative (parent or sibling), as assessed in the parent/sibling by the same formal diagnostic interview used for the proband(4):

1) Tourette syndrome cases with a positive first-degree family history of Tourette syndrome (Tourette family-history positive, N=417, representing 250 cases from affected sib-pair families and 167 cases from trios with at least one Tourette-affected parent);

2) Tourette syndrome cases with a positive first-degree family history of chronic tics, but without a positive first-degree relative with Tourette syndrome (Chronic tic family-history positive, N=111);

3) Cases without a family history of Tourette syndrome or Chronic tics or any other type of tic disorder (Tourette syndrome/Chronic tics family-history negative, N=346).

Tourette cases with a positive family history (in a parent or sibling) of other tic disorders (Transient/Provisional Tic Disorder or Tic Disorder, Unspecified) and no additional history of Tourette or Chronic tics in another parent/sibling were excluded from this analysis. Since the mean adjusted PRS (aPRS) in Tourette syndrome family-history positive cases (aPRS, 0.23 (SE=0.05)) was not significantly different from the mean aPRS in Chronic tic family-history positive cases (aPRS, 0.19 (SE=0.09); (Tourette family-history positive vs. Chronic tic family-history positive, $F_{df=1}$=0.12, p=0.73), these two case groups were combined into a group of 528 Tourette syndrome cases with a first-degree relative family history of either Tourette or Chronic tics (Tourette/Chronic tic family-history positive cases) for comparison to the aPRS of Tourette/Chronic tic family-history negative cases (aPRS, 0.06 (SE=0.06)) using an ANOVA test **(Figure S7)**.

Relationship between Tourette PRS and tic symptom severity

Tic symptom severity was measured using the lifetime worst-ever Yale Global Tic Severity Scale (YGTSS) score, ranging from 0 to 50, with 0 being no tic symptoms and 50 being the most severe tic symptoms (6). As studies in other neurodevelopmental disorders such as autism have shown that *de novo* rare variants with large effects play an important role in simplex families (25), to avoid the confounding effects from *de novo* rare variants with large effects, we restricted our analyses to cases with a positive family history of Tourette or Chronic tics (in first-degree relatives that were also formally assessed at the same time as the cases) to investigate the relationship between Tourette aPRS and YGTSS in a linear regression model, with YGTSS as the outcome variable and adjusted standardized PRS (aPRS) described in the previous section as the predictor, adjusted by the first four principal components from the GWAS.

Gene-based analyses and gene set analysis

Gene-based analysis: Gene-based analysis was performed in MAGMA v1.06(26) using the primary GWAS meta-analysis summary statistics. SNPs with MAF>0.01 and INFO>0.9 were assigned to genes based on their genomic position in NCBI genome build 37.3 including 50kb upstream and downstream flanking regions. Gene-based statistics were derived using the association summary statistics for all SNPs assigned to each gene after accounting for linkage disequilibrium based on European panel 1000 Genomes data (phase 3) as reference, and the correlations between neighboring genes were calculated. The resulting gene-based association p-values were adjusted using a Bonferroni correction for 18,079 genes mapped by SNPs tested in the primary meta-analysis **(Figure S10)**.

Gene set analysis: Test statistics and gene correlations were then used for gene set analyses. Competitive gene-set analysis was performed in MAGMA for curated gene sets (C2 sub-collection, Canonical pathways (CP)) and Gene Ontology terms (including three categories: biological processes (bp), cellular components (cc), and molecular functions (mf)) from MsigDB 6.0 (http://software.broadinstitute.org/gsea/msigdb/collection_details.jsp). Three additional specified gene-sets were tested: 1) 107 previously identified ASD susceptibility genes; 2) 2,048

evolutionarily constrained genes (pLI>0.9) that were mapped to SNPs in the primary GWAS meta-analysis (27); 3) 49 genes with deleterious rare variants (large CNVs with >500kb or *de novo* loss of function mutations) in Tourette probands from previous studies (2, 28). Bonferroni correction was applied for the number of gene sets tested (N_total=10,658, including 4,738 Curated gene sets, 5917 GO terms, and 3 specified gene sets).

Tissue expression enrichment test: Test statistics and gene correlations were also used for tissue expression enrichment analyses in 53 distinct human tissues from 714 donors using GTEx RNA-seq data (GTEx_Analysis_2016-01-15_v7_RNASeQCv1.1.8_gene_tpm.gct) (29, 30). Gene expression values (RPKM) were log2 transformed with a pseudocount of 1 after Winsorization at 50 to avoid overweighting extreme values, and the average gene expression across GTEx subjects was used for each tissue. Statistical significance for the gene expression enrichment test was calculated using the Bonferroni method correcting for 53 tissue types ($p= 0.05/53 = 9.4x10^{-4}$) **(Figure 3)**.

Supplementary Tables

Table S1. Samples included in the Tourette syndrome GWAS primary meta-analysis

Sample	Illumina Platform	Pre-QC		Post-QC	
		# cases	# controls	# cases	# controls
TAAICG-GGRI	HumanOmniExpressExome_8v1	3,333	595	3,084	482
TAAICG	Human610-Quadv1_B	1,368	583	1,048	432
TIC Genetics (TIC)	HumanCNV370-Duo_v1	261	0	237	0
	HumanOmni1M	146	0	104	0
	HumanOmniExpressExome_8v1	382	0	346	0
Consortium for Neuropsychiatric Phenomics (CNP) Controls	HumanOmniExpress_12v1	0	1,311	0	631
Genomics Superstruct Project (GSP)	HumanOmniExpressExome_12v1	0	1,941	0	1,527
NINDS controls (NINDS)	HumanOmniExpressExome_12v1	0	1,008	0	839
Ashkenazi Jewish controls at CIDR (AJ_ctl)	HumanOmniExpress-12v1	0	1,227	0	352
Genomic Psychiatry Cohort (GPC) at the University of Southern California	HumanOmniExpressExome_12v1	0	1,433	0	1,206
Illumina Genotype Control Database (iControl)	HumanHap550v1/v3	0	3,212	0	2,319
Studies of Addiction: Genetics and Environment (SAGE) cohort	HumanHap1Mv1_C	0	1,288	0	1,146
Dutch ancestry controls (Dutch_ctl)	HumanHap550v1	0	653	0	554

Table S2. Post-QC data sets in the Tourette syndrome primary GWAS meta-analysis

Data set	Cases	Controls
GWAS1	**969**	**3,923**
GWAS1_TIC	96	192
GWAS1_AJ	185	321
GWAS1_EU	447	3,232
GWAS1_FC	241	178
GWAS2 Case-Control	**2,711**	**3,762**
GWAS2_FAM	**548**	**597**
GWAS2_TIC	**591**	**1,206**
TIC_370K	141	266
TIC_Omni	450	940
Primary meta-analysis	**4,819**	**9,488**
Targeted Replication		
deCODE	**706**	**6,068**

Table S3. Top SNPs and functional annotation in the primary meta-analysis

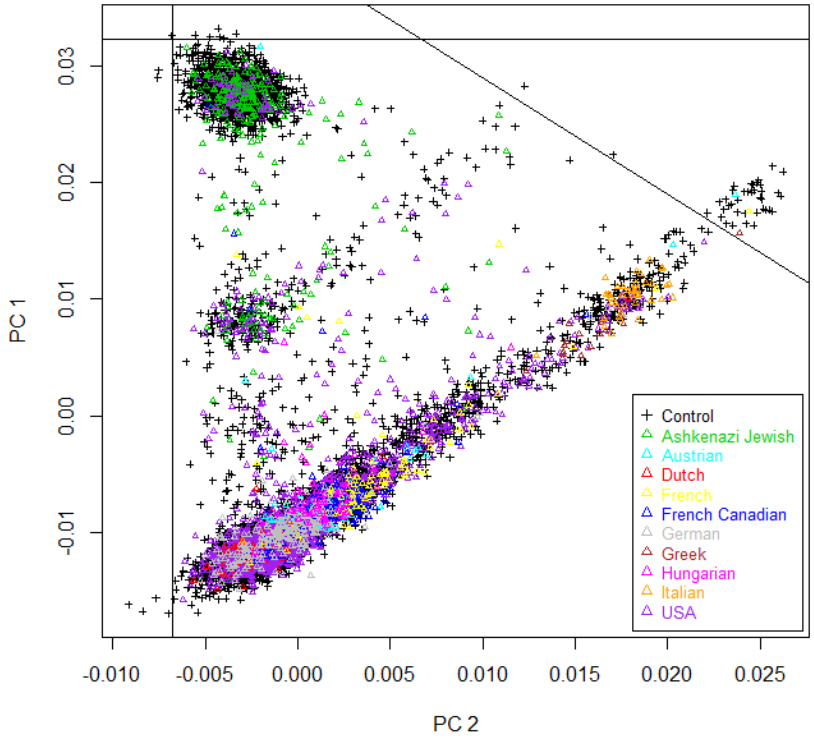
Please see the separate Excel file for Table S3.

Table S4. Top LD-independent loci in the primary Tourette GWAS meta-analysis

Please see the separate Excel file for Table S4.

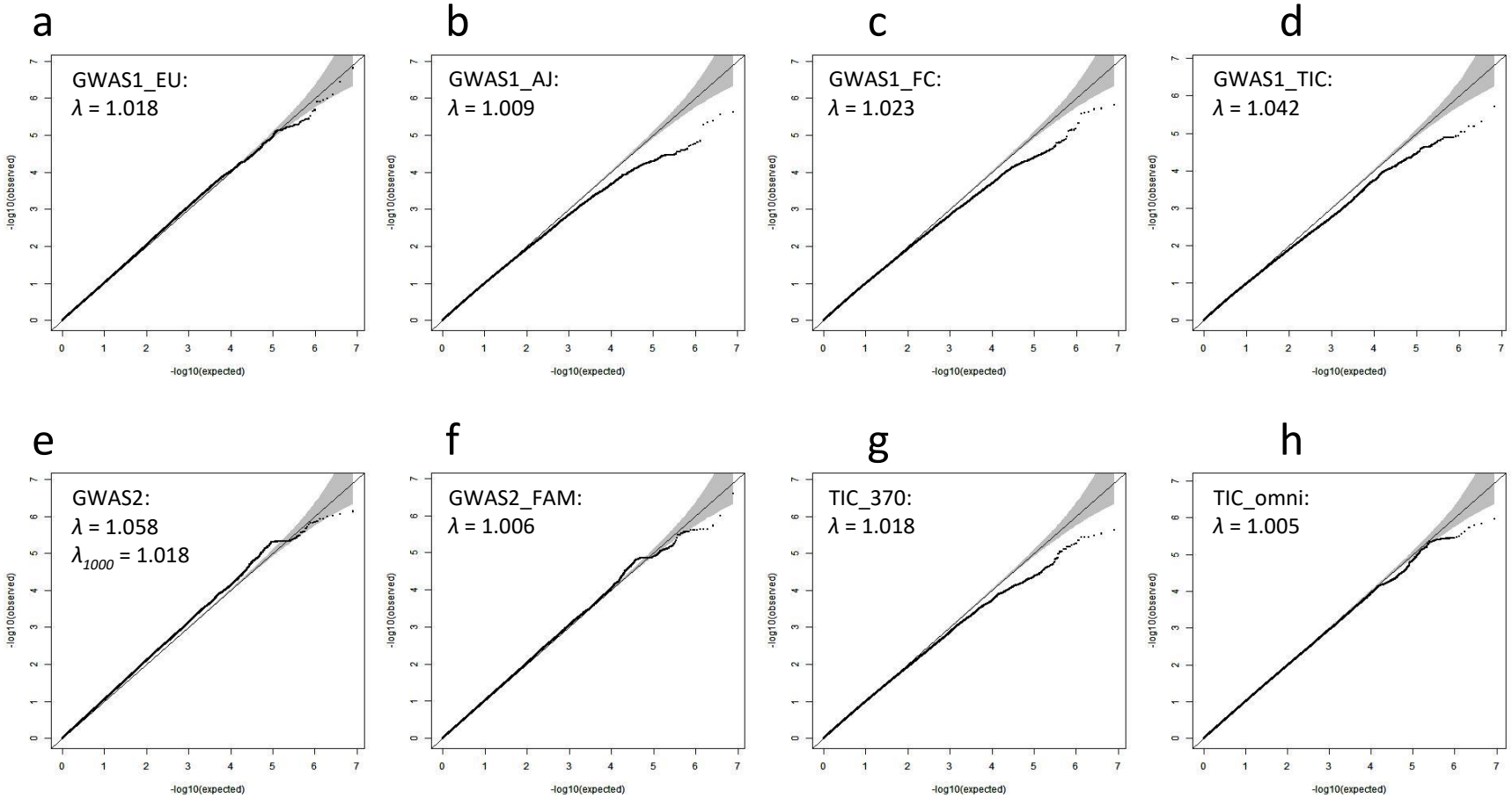
Supplementary Figures

Figure S1. Multidimensional scaling plot of GWAS2 case-control subjects on the first two components.



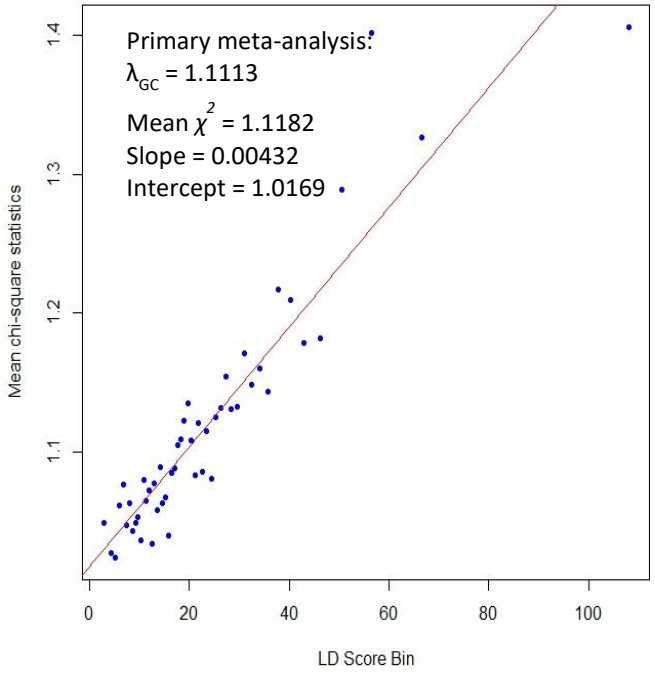
Black crosses represent controls, while triangles in various colors represent Tourette syndrome cases from different recruiting countries as shown in the legend box. The three black lines represent the thresholds for identifying and excluding population outliers or unmatched subjects. The remaining subjects were further investigated on subsequent multidimensional scaling components; additional population outliers and unmatched case-control subjects based on these components were identified and excluded from the final analysis using the same method.

Figure S2. Quantile-quantile (Q-Q) plots of observed vs expected log(*P*) values from all 8 Tourette syndrome GWAS subsets on SNPs with MAF>0.01, INFO>0.6, and certainty>0.9.



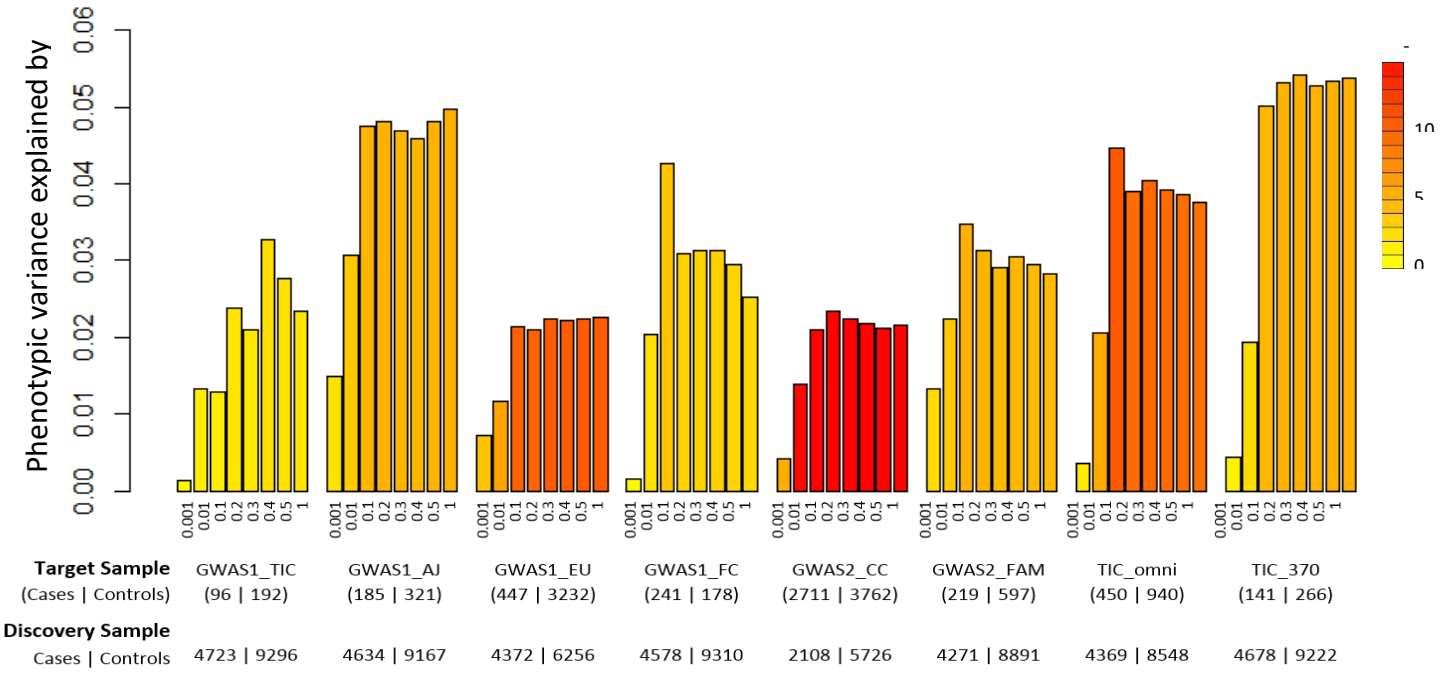
The 8 Tourette syndrome subsets include: (a) GWAS1 non-isolate European ancestry sample (GWAS1_EU) containing 447 cases and 3232 controls; (b) GWAS1 Ashkenazi Jewish sample (GWAS1_AJ) containing 185 cases and 321 controls; (c) GWAS1 French Canadian sample (GWAS1 FC) containing 241 cases and 178 controls; (d) GWAS1 TIC sample (GWAS1_TIC) containing 96 cases and 192 controls; (e) GWAS2 case-control sample (GWAS2) containing 2,711 cases and 3,762 controls; (f) GWAS2 family sample (GWAS2_FAM) containing 548 cases and 597 controls; (g) TIC sample genotyped on Illumina HumanCNV370K (TIC_370) containing 141 cases and 266 controls; and (h) TIC sample genotyped on Illumina HumanOmni1M and HumanOmniExpress (TIC_omni) containing 450 cases and 940 controls. The 95% confidence interval of expected values is indicated in grey. The genomic control λ values of all subsets are reported, and the λ_{1000} value for GWAS2 is calculated to adjust for large sample size.

Figure S3. Linear regression between GWAS SNP χ^2 test statistics and Linkage Disequilibrium (LD) Scores.



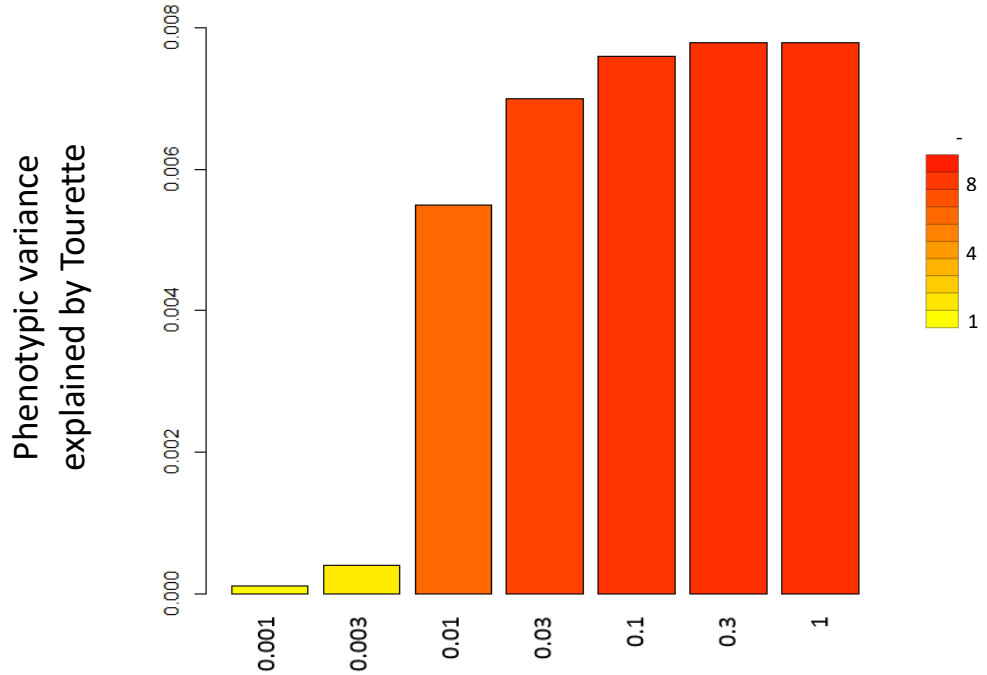
LD Score regression is based on SNPs with MAF >1% and INFO score >0.9. The LD Score is a measure of the amount of genetic variation tagged by the target SNP, defined as the sum of the r^2 values between the target SNP and all surrounding SNPs within a 1 centiMorgan (cM) window. All SNPs were ranked and divided into 50 equal-sized bins based on their LD Score rank. Within each LD Score bin, the mean of χ^2 test statistics for all SNPs was calculated. A non-zero slope suggests a polygenic model for Tourette syndrome genetic architecture. The intercept represents the inflation in the mean of χ^2 statistic due to population stratification, cryptic relatedness, and/or architecture bias. The ratio of the (intercept -1)/(mean χ^2 statistic -1) indicates the proportion of the inflation in the mean χ^2 test statistic that is due to residual confounding (here, (0.017/0.118) = 14%), while the remaining 86% can be attributed to a polygenic signal.

Figure S4. Polygenic risk score analysis of each GWAS dataset contributing to the primary meta-analysis.



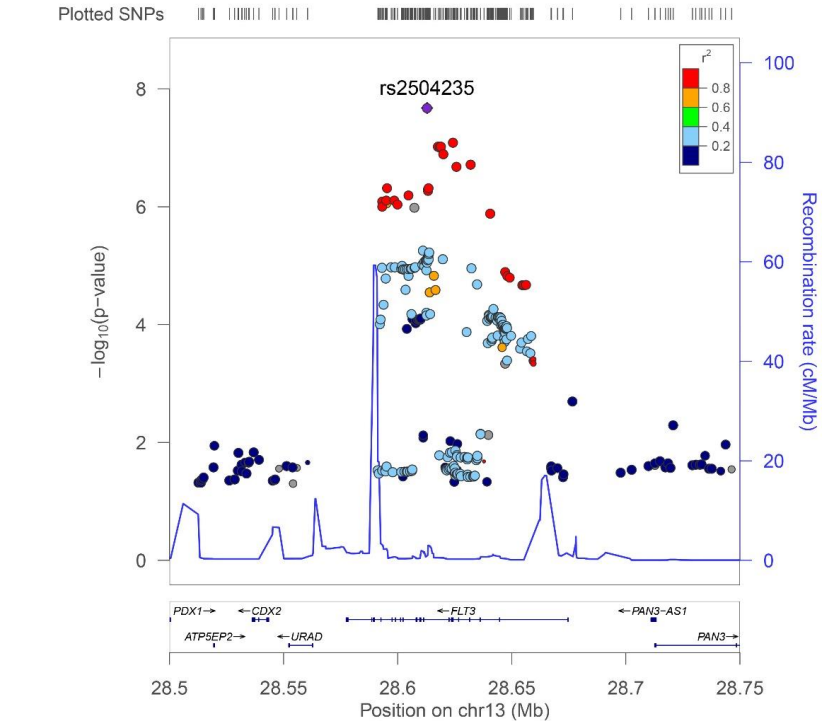
Tourette syndrome polygenic risk scores (PRS) were calculated in each of 8 data sets as the sum of the number of risk alleles weighted by the effect size, which was the risk allele effect derived from the "leave-one-out" meta-analysis (discovery sample of 7 datasets minus each target sample). The SNPs used in calculating Tourette PRS were first filtered by MAF>0.05 and INFO>0.9, and LD pruned (r^2<0.2) with pre-defined association significance levels (p<0.001, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, and 1, respectively) in the discovery sample. The sizes of the discovery and target samples are provided along the x-axis. The proportion of phenotypic variance explained by Tourette PRS in each target sample was estimated by comparing logistic regression in the full model with PRS and GWAS principal components for population stratification to the reduced model without the PRS in the form of Nagelkerke R^2. The color of each bar represents the significance level of the PRS effect on Tourette syndrome status, based on the heat map of -log(p) values on the upper right of the figure.

Figure S5. Polygenic risk score (PRS) analysis in the deCODE sample.

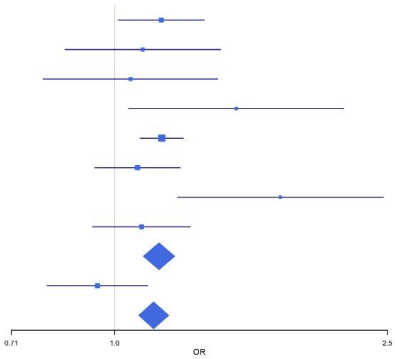


Tourette polygenic risk scores were calculated in the independent deCODE sample using the primary Tourette syndrome GWAS meta-analysis (4,819 cases and 9,488 controls) as the discovery sample in LDpred (24). The posterior effect size was derived from genome-wide summary statistics from the primary Tourette GWAS meta-analysis, LD information, and pre-defined fractions of causal markers (0.001, 0.003, 0.01, 0.03, 0.1, 0.3, and 1 respectively). The polygenic risk scores of deCODE samples were calculated under each assumption of fraction of causal markers. The x-axis labels the predefined fraction of causal markers. The target deCODE sample contains 706 Tourette syndrome cases and 6,068 screened controls. The percentage of phenotypic variance explained by PRS in each target sample was estimated by comparing logistic regression of a full model with PRS, sex, birth year, and the first 20 principal components to a reduced model without PRS in the form of Nagelkerke R^2. The color of each bar represents the significance level of the PRS effect on Tourette syndrome status.

Figure S6. Regional plot and forest plot of the genome-wide significant locus.

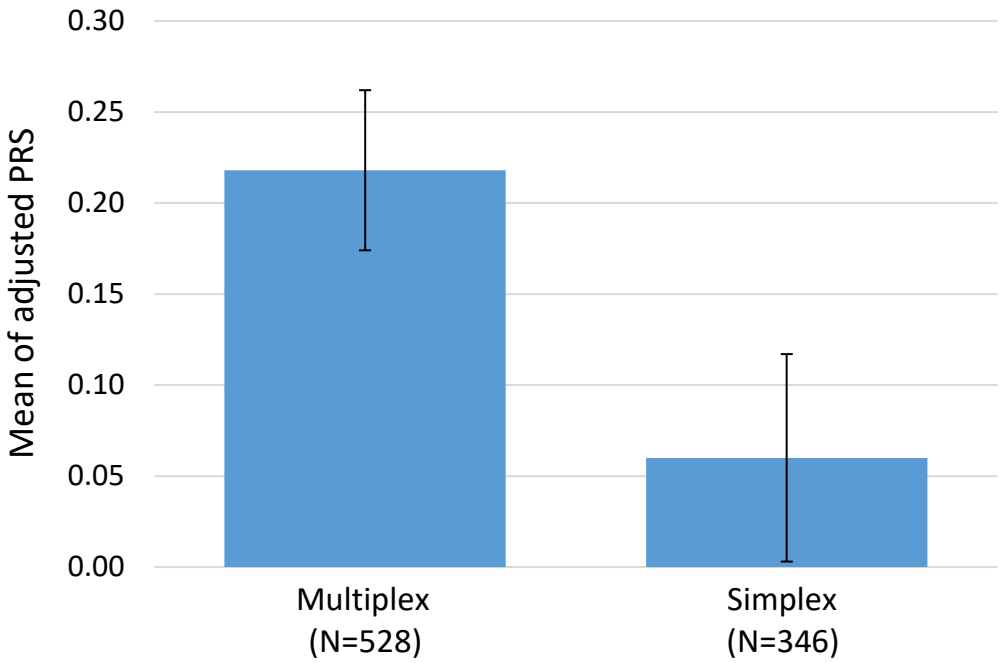


DataSet	Cases	Controls	OR
GWAS1_EU	447	3,232	1.170
GWAS1_AJ	185	321	1.099
GWAS1_FC	241	178	1.055
GWAS1_370K	96	192	1.505
GWAS2_CC	2,711	3,762	1.172
GWAS2_FAM	548	597	1.080
TIC_370	141	266	1.745
TIC_omni	450	940	1.095
Primary Meta	**4,819**	**9,488**	**1.161**
deCODE	706	6,068	0.944
Primary + deCODE	**5,525**	**15,556**	**1.140**



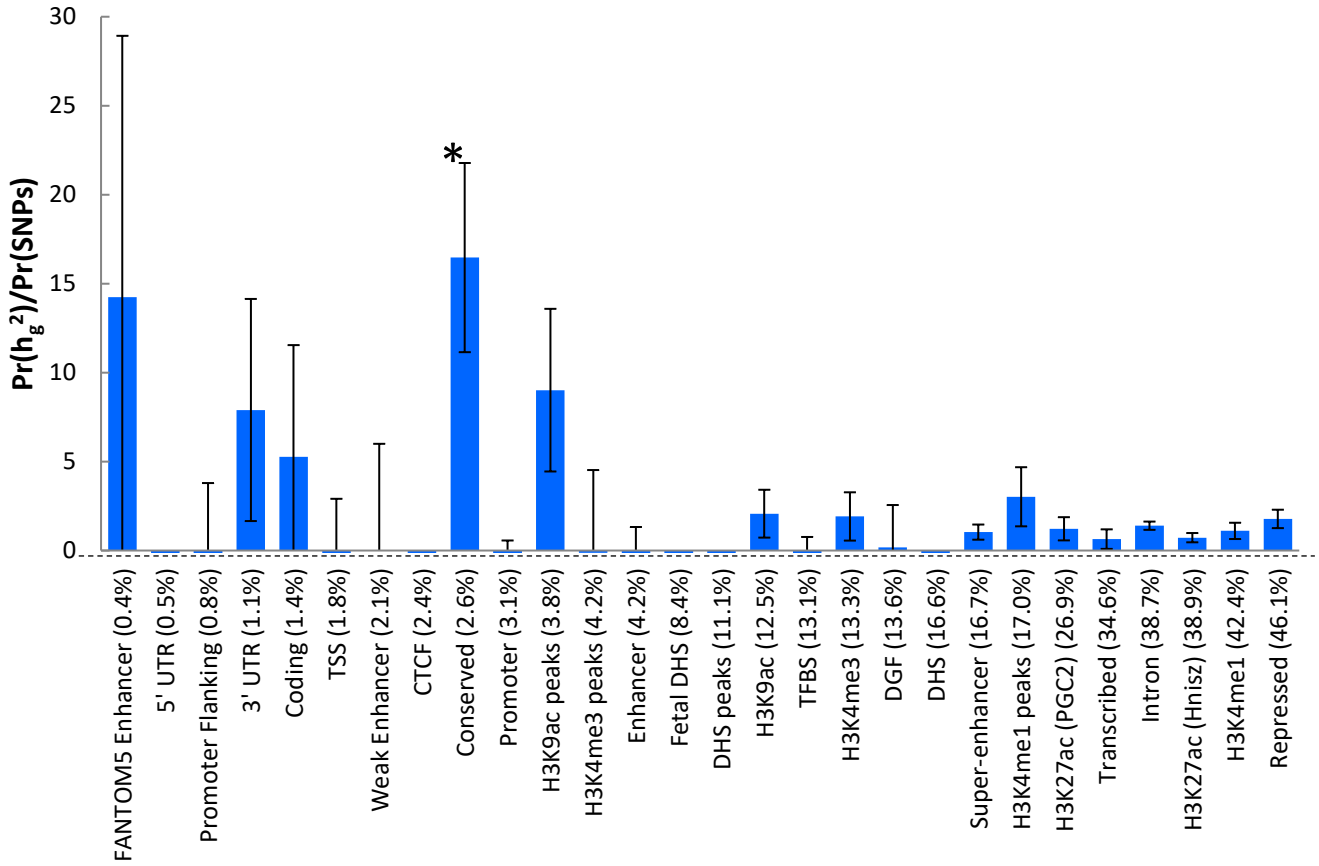
(a) The regional plot of the chromosome 13 GWAS locus surrounding rs2504235. The x-axis represents the chromosomal position (in megabases (Mb)). The y-axis on the left is the significance of association as $-\log_{10}(P)$, and the y-axis on the right is the recombination rate (in cM/Mb). The reference panel for LD and recombination rate estimation is the 1000 Genomes Project European samples (1KG EUR). The index SNP, rs2504235, is in purple, and the color of the other SNPs is based on the degree of LD to rs2504235 (r^2). SNPs not present in 1KG EUR but present in this analysis are in grey. Only SNPs with association P-values <0.05 were plotted. (b) Forest plot of effect size and direction of effect for SNP rs2504235 in the 8 Tourette GWAS datasets and the deCODE Tourette syndrome replication sample. The squares and horizontal lines represent the odds ratio (OR) and 95% confidence interval (CI) of each dataset. The diamonds show the summary OR and 95% CI of the meta-analysis. Size of the squares and the diamonds are proportional to the size of each dataset. LD, linkage disequilibrium.

Figure S7. Mean adjusted Tourette Polygenic Risk Scores (aPRS) for Tourette syndrome cases stratified by the presence (Multiplex) or absence (Simplex) of a positive family history of Tourette or Chronic tics in a first-degree relative (parent or sibling).



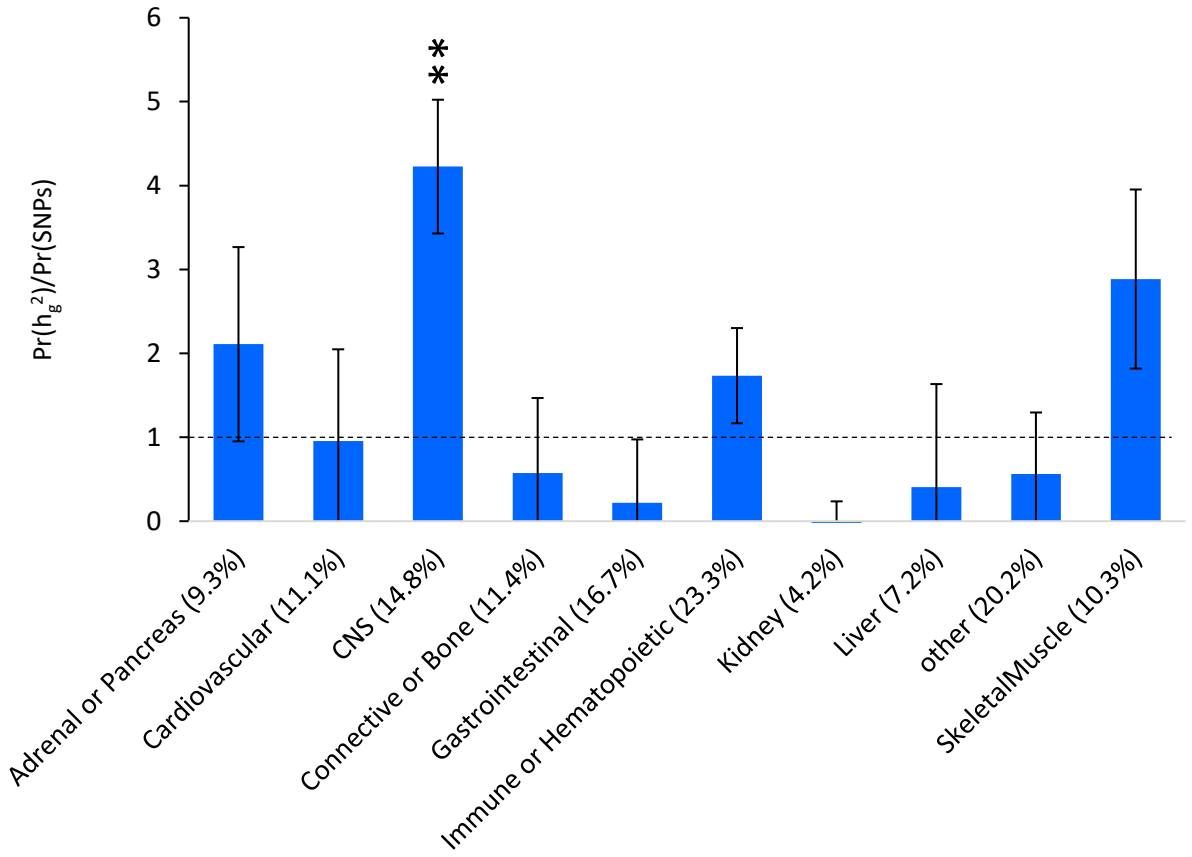
Tourette syndrome aPRS was calculated using a cross-validation method based on the merged case-control data set (see Supplementary Methods above). After adjusting for population stratification and dataset effects, comparison between the two Tourette syndrome case groups was performed using an ANOVA test. Tourette aPRS from Tourette/Chronic tic Multiplex cases was significantly higher than the aPRS from simplex Tourette cases (P=0.027).

Figure S8. Enrichment of Tourette SNP-based heritability (h^2_g) for 24 functional genomic annotations.



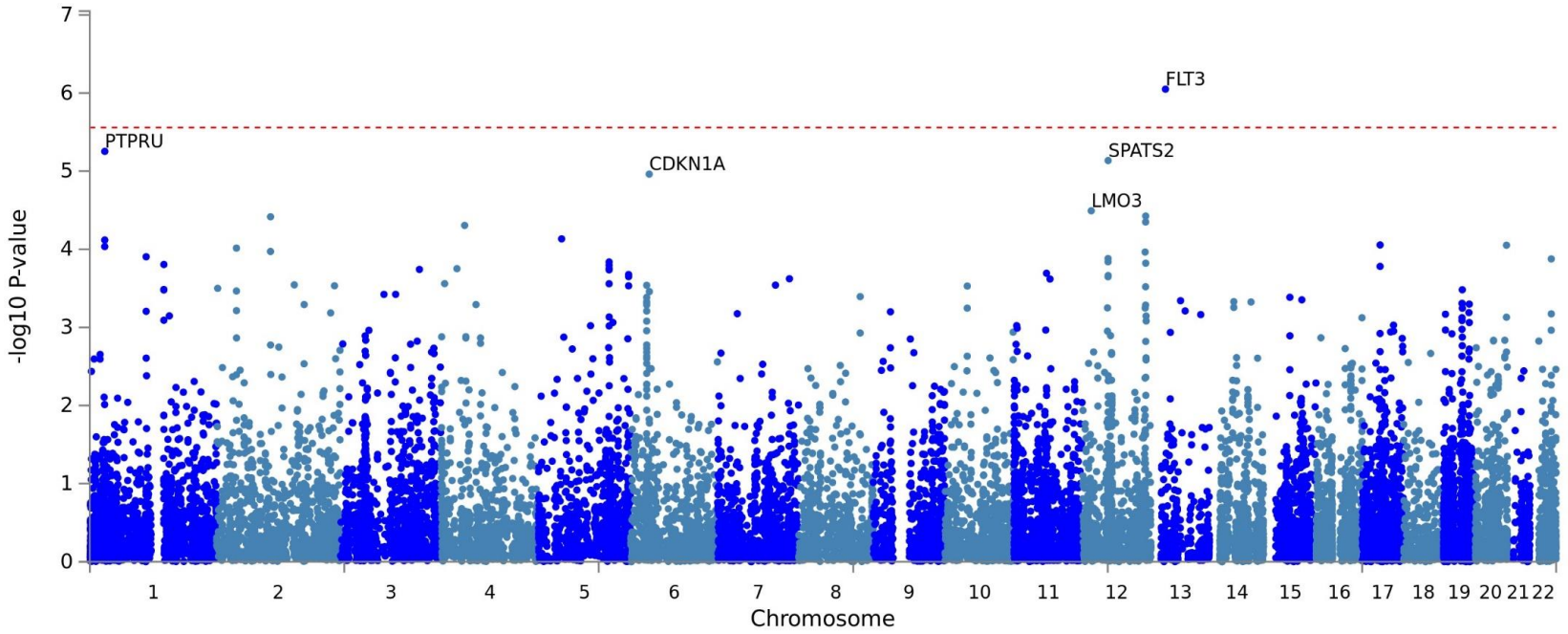
The main annotations are from the "full baseline model" defined by Finucane et al. (20) based on 24 publicly available, non-cell-type specific main annotations. Annotations are ordered by the proportion of SNPs annotated in the category. The black dashed line indicates no heritability enrichment. An asterisk indicates nominal significance at $P < 0.05$, but no annotation survived Bonferroni correction for the 24 hypotheses tested.

Figure S9. Enrichment of Tourette SNP-based heritability (h^2_g) for genome-wide histone modification sites in 10 cell-type groups.



220 cell-type-specific annotations for 4 histone marks (H3K4me1, H3K4me3, H3K9ac, and H3K27ac) were grouped into 10 cell types and examined individually for enrichment of Tourette syndrome SNP-based heritability. The black dashed line indicates no enrichment. An asterisk indicates nominal significance at $P < 0.05$, and two asterisks indicate significance after Bonferroni correction for the 10 cell types tested.

Figure S10. Tourette syndrome gene-based genome-wide association test performed using a multiple linear principal components regression model in MAGMA (23).



The SNPs with MAF>0.01 and INFO>0.9 were assigned to protein-coding genes based on their position according to the NCBI 37.3 build and 50kb upstream and downstream flanking regions. Gene-based statistics were derived using summary statistics for SNPs assigned to each gene after accounting for linkage disequilibrium. The European panel of the 1000 Genomes data (phase 3) was used as the reference panel to account for linkage disequilibrium. One gene, *FLT3*, was identified with significant association after correcting for multiple tests using a Bonferroni correction for 18,079 genes ($p = 8.9 \times 10^{-7}$).

SUPPLEMENTARY REFERENCES

1. Scharf JM, Yu D, Mathews CA, Neale BM, Stewart SE, Fagerness JA, et al. Genome-wide association study of Tourette's syndrome. Mol Psychiatry. 2013;18(6):721-8.

2. Huang AY, Yu D, Davis LK, Sul JH, Tsetsos F, Ramensky V, et al. Rare Copy Number Variants in NRXN1 and CNTN6 Increase Risk for Tourette Syndrome. Neuron. 2017;94(6):1101-11 e7.

3. Paschou P, Yu D, Gerber G, Evans P, Tsetsos F, Davis LK, et al. Genetic association signal near NTN4 in Tourette syndrome. Ann Neurol. 2014;76(2):310-5.

4. Tourette Syndrome Association International Consortium for Genetics. Genome scan for Tourette disorder in affected-sibling-pair and multigenerational families. Am J Hum Genet. 2007;80(2):265-72.

5. Dietrich A, Fernandez TV, King RA, State MW, Tischfield JA, Hoekstra PJ, et al. The Tourette International Collaborative Genetics (TIC Genetics) study, finding the genes causing Tourette syndrome: objectives and methods. Eur Child Adolesc Psychiatry. 2015;24(2):141-51.

6. Darrow SM, Illmann C, Gauvin C, Osiecki L, Egan CA, Greenberg E, et al. Web-based phenotyping for Tourette Syndrome: Reliability of common co-morbid diagnoses. Psychiatry Res. 2015;228(3):816-25.

7. Egan CA, Marakovitz SE, O'Rourke JA, Osiecki L, Illmann C, Barton L, et al. Effectiveness of a web-based protocol for the screening and phenotyping of individuals with Tourette syndrome for genetic studies. Am J Med Genet B Neuropsychiatr Genet. 2012;159B(8):987-96.

8. Bilder RM, Sabb FW, Cannon TD, London ED, Jentsch JD, Parker DS, et al. Phenomics: the systematic study of phenotypes on a genome-wide scale. Neuroscience. 2009;164(1):30-42.

9. Holmes AJ, Hollinshead MO, O'Keefe TM, Petrov VI, Fariello GR, Wald LL, et al. Brain Genomics Superstruct Project initial data release with structural, functional, and behavioral measures. Scientific data. 2015;2:150031.

10. Atzmon G, Rincon M, Schechter CB, Shuldiner AR, Lipton RB, Bergman A, et al. Lipoprotein genotype and conserved pathway for exceptional longevity in humans. . PLoS biology. 2006;4(4):e113.

11. Bae H, Gurinovich A, Malovini A, Atzmon G, Andersen SL, Villa F, et al. Effects of FOXO3 Polymorphisms on Survival to Extreme Longevity in Four Centenarian Studies. The journals of gerontology Series A, Biological sciences and medical sciences. 2017.

12. Pato MT, Sobell JL, Medeiros H, Abbott C, Sklar BM, Buckley PF, et al. The genomic psychiatry cohort: partners in discovery. Am J Med Genet B Neuropsychiatr Genet. 2013;162B(4):306-12.

13. Styrkarsdottir U, Helgason H, Sigurdsson A, Norddahl GL, Agustsdottir AB, Reynard LN, et al. Whole-genome sequencing identifies rare genotypes in COMP and CHADL associated with high risk of hip osteoarthritis. Nat Genet. 2017;49(5):801-5.

14. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. GigaScience. 2015;4:7.

15. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet. 2006;38(8):904-9.

16. Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. Nature methods. 2011;9(2):179-81.

17. Pirinen M, Donnelly P, Spencer CCA. Efficient computation with a linear mixed model on large-scale data sets with applications to genetic studies. Annals of Applied Statistics. 2012;7(1):369-90.

18. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010;26(17):2190-1.

19. Pe'er I, Yelensky R, Altshuler D, Daly MJ. Estimation of the multiple testing burden for genomewide association studies of nearly all common variants. Genet Epidemiol. 2008;32(4):381-5.

20. Dudbridge F, Gusnanto A. Estimation of significance thresholds for genomewide association scans. Genet Epidemiol. 2008;32(3):227-34.

21. Davis LK, Yu D, Keenan CL, Gamazon ER, Konkashbaev AI, Derks EM, et al. Partitioning the heritability of Tourette syndrome and obsessive compulsive disorder reveals differences in genetic architecture. PLoS Genet. 2013;9(10):e1003864.

22. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Patterson N, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015;47(3):291-5.

23. Finucane HK, Bulik-Sullivan B, Gusev A, Trynka G, Reshef Y, Loh PR, et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. Nat Genet. 2015;47(11):1228-35.

24. Vilhjalmsson BJ, Yang J, Finucane HK, Gusev A, Lindstrom S, Ripke S, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. Am J Hum Genet. 2015;97(4):576-92.

25. Leppa VM, Kravitz SN, Martin CL, Andrieux J, Le Caignec C, Martin-Coignard D, et al. Rare Inherited and De Novo CNVs Reveal Complex Contributions to ASD Risk in Multiplex Families. Am J Hum Genet. 2016;99(3):540-54.

26. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: generalized gene-set analysis of GWAS data. PLoS computational biology. 2015;11(4):e1004219.

27. Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536(7616):285-91.

28. Willsey AJ, Fernandez TV, Yu D, King RA, Dietrich A, Xing J, et al. De Novo Coding Variants Are Strongly Associated with Tourette Disorder. Neuron. 2017;94(3):486-99 e9.

29. The Broad Institute of MIT and Harvard. GTEx Portal. 2017; Available from: https://www.gtexportal.org/home/.

30. GTEx Consortium, Data Analysis Laboratory, Coordinating Center -Analysis Working Group, Statistical Methods groups-Analysis Working Group, Enhancing GTEx groups, NIH Common Fund, et al. Genetic effects on gene expression across human tissues. Nature. 2017;550(7675):204-13.