SUPPLEMENTARY MATERIALS

LIST OF ABBREVIATIONS

AJ, Ashkenazi-Jewish European-derived isolate samples collected from the US and Israel; EU, European-ancestry, non-isolate samples collected from the US, Canada and Europe; FC, French-Canadian European-derived isolate samples collected from Quebec, Canada; SA, South African samples collected from all provinces in South Africa.

SUPPLEMENTARY METHODS

Subjects and Genotyping

TS: The initial TS sample, prior to quality control (QC) analyses, consisted of 1764 individuals recruited from 20 sites in the US, Canada, UK, Netherlands, and Israel, and included subjects of general European (EU) ancestry as well as two EU-derived population isolates of Ashkenazi Jewish (AJ) and French Canadian (FC) descent (1). Inclusion criteria required a TS Classification Study Group (TSCSG) diagnosis of definite TS (a DSM-IV-TR diagnosis of TS plus tics observed by an experienced clinician), and available genomic DNA extracted either from blood or cell lines. Exclusion criteria consisted of a history of intellectual disability, tardive tourettism or other known genetic, metabolic or acquired tic disorders. Subjects from 17 of the 20 sites (77% of total participants) were assessed for a lifetime diagnosis of TS, OCD and attention-deficit hyperactivity disorder using a standardized and validated semi-structured interview that has high validity and reliability for TS ($\kappa = 1.00$) and OCD ($\kappa = 0.97$). Of those who were examined for OCD comorbidity, 45% had the disorder. Genotyping of 1508 of the 1764 TS cases was conducted on the Illumina Human610-Quadv1_B SNP array (Illumina, Hap610_Broad) at the Broad Institute of Harvard and MIT (Cambridge, MA, USA). An additional 344 EU cases were genotyped on the Illumina HumanCNV370-Duo_v1 (Illumina, Hap370_Yale) at the Yale Center for Genome Analysis (New Haven, CT, USA), including 88 duplicate EU samples that overlapped with those genotyped on the Hap610_Broad platform to allow for cross-platform checks of concordance.

OCD: The initial pre-QC OCD sample consisted of 1817 OCD cases and 313 parent-child trios (including 29 affected siblings) recruited from 21 sites in the North, Central and South America, Europe, the United Arab Emirates, and South Africa (2). Inclusion criteria required a DSM-IV diagnosis of OCD. For this study, only subjects of EU, AJ, and Afrikaner (SA) descent were included. Presence or absence of a chronic tic disorder (TS or CT) was assessed in

approximately 76% of the OCD probands; approximately 12% of those who were assessed for tics had comorbid TS or CT. Genotyping of the 1817 OCD cases and 313 trios was conducted on the Illumina Human610-Quadv1_B SNP array (Illumina, Hap610_Broad) at the Broad Institute of Harvard and MIT (Cambridge, MA, USA).

Controls: The pre-QC EU control sample consisted of 5654 European Caucasian controls who were primarily derived from cohorts of previously genotyped, unselected population controls (1, 2). These included 3212 controls from the Illumina Genotype Control Database genotyped on the Illumina HumanHap550v1/v3 platforms (www.Illumina.com, Illumina, San Diego, CA, USA, Hap550_iControl), 1288 controls from the Studies of Addiction: Genetics and Environment (SAGE) cohort (3-5) genotyped on the Illumina Human-Hap1Mv1_C (Hap1M_SAGE), 653 Dutch ancestry controls genotyped on the Illumina HumanHap550v1 (Hap550_Dutch) (6), and 501 Italian ancestry controls from the HYPERGENES Consortium genotyped on Illumina Human-Hap1M-Duo (Hap1M_Italian). Ancestry-matched controls for the FC (N=297) and SA (N=187) population isolates were collected in parallel with their respective cases (1, 2). An additional 298 German and Dutch EU controls were genotyped simultaneously with the case samples on the Illumina Human610-Quadv1_B SNP array (Illumina, Hap610_Broad) at the Broad Institute, including 48 duplicates from the Hap550_Dutch control cohort, to facilitate cross-platform and cross-facility comparisons. All controls were unscreened except for the controls from Bonn, Germany, who had absent lifetime history of all Axis I disorders.

Quality Control

Quality control (QC) analyses were performed using PLINK v1.07 (7) and EIGENSTRAT (8), with particular attention paid to cross-platform comparisons of concordance, allele frequency and differential missingness, given the complexity of the study design and use of control samples that had been previously genotyped on different Illumina platforms (Figure S1). SNP QC was initially performed within each platform separately. We removed monomorphic and CNV-targeted SNPs, non-autosomal SNPs, SNPs with genotyping rate < 98%, and strand-ambiguous SNPs with significant allele frequency differences or aberrant LD correlations with adjacent SNPs based on the entire HapMap2 reference panel (9). Concordance was checked between 82 duplicate samples successfully genotyped both on Hap610_Broad and Hap370_Yale, 41 duplicate samples successfully genotyped on Hap610_Broad and Hap550_Dutch, as well as among the HapMap samples genotyped on all 4 Illumina platforms,

SNPs with >1 discordant calls were removed. No SNPs were identified with significant association between the two genotyping batches on Hap610_Broad (Figure S1).

Sample QC was performed within each platform separately, along with the SNP QC. Samples with call rates <98% were removed. In addition, the samples from one recruiting site were observed to have a significantly higher missing rate compared to other samples on the same genotyping platform (Hap370_Yale), possibly due to site-specific low DNA quality; therefore, all samples from this site were removed. Genomic sex status was determined through the homozygosity rate (F statistic) on the X chromosome. A genomic male was defined as F>0.75, while a genomic female was defined as F<0.25. Any samples with an F statistic between 0.25 and 0.75 were defined as having ambiguous genomic sex and were removed from the study. In addition, samples with discrepant sex between reported phenotypic and estimated genomic sex were removed (Figure S1).

After SNP and sample QC within each platform, all six platforms were merged into a single dataset, and SNPs that were not present on the 3 common platforms (Hap610_Broad, Hap550_iControl, and Hap1M_SAGE) or SNPs that were mismatched or tri-allelic were removed. SNP allele frequencies were compared across different platforms, and any SNP with an absolute allele frequency difference >0.15 between two platforms were removed. SNPs were also removed in all samples if they generated >1% Mendelian errors in the OCD trios (Figure S1).

Estimate of pair-wise identity-by-descent (IBD) was conducted with an LD-pruned set of SNPs using PLINK. Any pair of samples with either a pi-hat>0.1 or Z1>0.2 were determined to be duplicates or relatives, and the individual with the lower SNP call rate in each pair was removed. Multidimensional scaling (MDS) analysis was applied for the exclusion of samples of non-European descent. Remaining EU and European-derived isolate samples were separated into four strata (EU, AJ, FC, and SA) based on observed genetic ancestry and source population (Figures S1 and S2). Within each of the MDS-defined genetic subpopulations, additional outliers were removed for excess low-level relatedness (Z1>0.1 with ≥20 other samples within each subpopulation), abnormal average heterozygosity ($|F_{het}| > 0.05$) or inadequate case-control matching.

Subpopulation-specific SNP QC included removal of SNPs with Hardy-Weinberg equilibrium (HWE) $P<10^{-5}$ in controls. In addition, we examined differential missingness tests between cases and controls. Given the decreased power of detecting differential missingness between

cases and controls for rare SNPs, different thresholds were applied for SNP removal. For SNPs with MAF≥0.2, SNPs were excluded with Chi-square test $p<10^{-5}$ (1df). For SNPs with MAF<0.2, but ≥0.1, SNPs were excluded with $p<10^{-4}$. Lastly, for SNPs with MAF<0.1, SNPs were excluded with $p<10^{-3}$. In addition, a haplotype-based test for non-random missingness by genotype was performed, and SNPs were excluded if the flanking SNP haplotypes were associated with missingness at the reference SNP site at $p<10^{-10}$. Any SNP that failed either the differential missingness test or the HWE test in one subpopulation was subsequently removed from all populations prior to the imputation.

Imputation

Pre-imputation QC: Prior to genotype imputation, additional quality control measures were conducted to ensure that the GWAS dataset was compatible with the reference data set (1000 Genomes June 2011 Data Release) (10) and that only the highest quality SNPs were included in the imputation so as not to adversely affect imputation accuracy. SNP positions were converted to NCBI Build 37 (GRCh37) using an Illumina-provided mapping file (Human1MDuov3_B-H_MappingInformation.txt), and 211 SNPs were removed without updated mapping information. For each pair of Illumina genotyping platforms used in the study (1M, 610Quad,550v1, 550v3, 370K), SNP-level concordances were calculated using genotype data from HapMap2 samples previously genotyped on each of these platforms (www.icom, Illumina.com, Illumina, San Diego, CA, USA). For any pair of platforms, any SNP with a concordance <95% and >1 genotype mismatch in any one HapMap population, or <95% concordance in the combined populations were removed. In addition, SNPs with a call rate <80% in any combined HapMap population data set were removed. Additionally, SNP-level concordances with the 1000 Genomes June 2011 Data Release were calculated using Illumina-genotyped samples for the same HapMap population samples. The same criteria for the pair-wise genotyping platform comparisons above were used to remove SNPs, with the exception that removed SNPs were also excluded from being re-imputed.

Imputation: Imputation of genotypes was conducted using the IMPUTE2 software program (version 2.1.2) (11) and haplotypes from all 1,092 individuals in the 1000 Genomes June 2011 Data Release (10) as a reference dataset. To facilitate parallel computation, the genome was divided into 1Mb chunks or chunks containing 10,000 reference panel SNPs, whichever was smaller. As no C/G or A/T SNPs were present in the study set, we allowed the software to

automatically match the strand of the study and reference set genotypes. Default program settings were used except for the following parameters: Ne=20000, iter=30, k=80, hap_specific_family, fix_strand_g, pgs_miss, k_hap=1038. Matching case/pseudo-control genotypes were created from trio samples for imputation along with the qualified case control samples.

Post-imputation QC: Following imputation, the distribution of various quality score metrics of imputed SNPs were first examined within all European-derived ancestry (EU, AJ, FC, and SA) case-control samples together. SNPs were excluded for having an IMPUTE2 info score <0.5 or an IMPUTE2 certainty score <0.9. Samples were then separated into genotyping platforms of origin, and imputed SNPs with a PLINK info<0.6 in any individual platform were excluded. Allele frequencies of imputed SNPs were also compared across pairs of platforms, where platform of origin was used as the phenotype for analysis (e.g., 610Quad cases vs 370K cases, or 610Quad controls vs. 550K controls). SNPs with cross-platform analysis $P<1x10^{-5}$ for SNPs with MAF>0.05 or $P<1x10^{-4}$ for SNPs with MAF≤0.05 were flagged. Third, subpopulation-specific QC of imputed SNPs was conducted, and SNPs were removed for PLINK info score <0.1 or a HWE $P<1x10^{-5}$. Given the size of the EU sample relative to that of the other subpopulations, any imputed SNP that failed QC in the EU stratum was also excluded from the other four groups (AJ, FC, SA, and matched case/pseudo-control sample derived from OCD trios).

The final number of SNPs after post-imputation QC was 7,659,573, including 439,840 genotyped SNPs and 7,219,734 imputed SNPs. The final sample for GWAS consisted of five individual ancestry-matched case control datasets, including a general European ancestry sample (EU: 2033 cases and 4975 controls), an Ashkenazi Jewish sample (AJ: 332 cases and 338 controls), a French Canadian sample (FC: 265 cases and 196 controls) and a South African/Afrikaner sample (SA: 93 cases and 158 controls), along with a matched case/pseudo-control sample derived from the OCD trios (290 cases and 290 pseudo controls).

Subpopulation-specific association analysis and meta-analysis

Following QC, each of the five cleaned datasets (EU, AJ, FC, SA, and trios) were analyzed as separate subpopulations in PLINK using logistic regression under an additive model (Cochran-Armitage trend test) with subpopulation-specific MDS dimensions incorporated as covariates in

each analysis. The genomic control λ (the ratio of the median observed chi-square–statistic to the expectation under the null hypothesis) in each subpopulation-specific analysis showed no evidence of residual population stratification or systematic technical artifact (Figure S3).

Meta-analysis was conducted using METAL, which combined the p-values using the number of cases in each subpopulation-specific stratum for weighting (12). Heterogeneity was assessed using Cochran's Q test and I^2 statistics (13). The effective sample size in the final meta-analysis was 3013 cases and 5957 controls. No evidence of residual population stratification or systematic technical artifact was indicated by the genomic control λ in the meta-analysis (Figure S3).

The standard genome-wide significant threshold of $5x10^{-8}$ was used to identify significant evidence for association (14-16). This threshold is based on the assumption of 1,000,000 independent tests (the estimated effective number of independent tests in the genome if all common SNPs in HapMap were tested with direct genotyping or imputation) with a simple Bonferroni correction for multiple testing to achieve an overall false positive of $p<0.05$, i.e. $p<0.05/1,000,000=$ of $5x10^{-8}$. The actual number of independent tests is generally much lower than the number of SNPs tested in a study due to LD between SNPs, and it varies for different populations, different SNPs with different MAF, different LD patterns, different genotyping arrays, and different type of genetic data (genotyping or sequencing). Additional support for this stringent threshold comes from two studies (15, 16), one using permutation and the other using simulation, where both arrived at the same estimate of ~ $5x10^{-8}$.

eQTL and mQTL enrichment tests

Cerebellar expression quantitative trait loci (eQTLs) and methylation QTLs (mQTLs) were generated from 153 individuals of European ancestry (GSE35974) obtained from the Stanley Medical Research Institute. Detailed information on the data processing, genotype imputation, and QTL association analysis were previously reported (17). We also mapped the eQTLs present in parietal lobe (GSE35977) for these same individuals, as previously reported (18). Frontal cortex cis eQTL data were derived from frozen post-mortem brain tissue from 399 neurologically normal European ancestry subjects from the United States and Great Britain. Detailed methods are described previously based on data from the first 150 of these subjects (19). Cis eQTLs and cis mQTLs are defined as SNPs within 1 Mb of the probe for the target

gene.

We sought to test for enrichment of disease associations among the cis eQTLs ($p < 10^{-6}$) identified in each tissue and the cerebellar cis mQTLs ($p < 10^{-6}$). Each such SNP was annotated with its association p-values from the TS, OCD, and cross-disorder TS/OCD GWAS. To illustrate the enrichment for associations relative to that expected under the null, a Q-Q plot of nominal disease association p-values was generated for each set of cis eQTLs and mQTLs (Table 2 in the main text). A horizontal leftward shift from the diagonal line (of complete concordance between the observed p-values and expected p-values) in the Q-Q plot indicates enrichment. This enrichment can be quantified using the false discovery rate (FDR). Following Storey *et al*. (20, 21), we define the FDR as follows:

$$\widehat{FDR}(p) = \frac{\widehat{\pi_0} mp}{\#\{p_i \leq p\}} \qquad (1)$$

where *m* is the number of SNPs, $\{p_i\}$ is the list of *p*-values included in the analysis, and $\widehat{\pi_0}$ is the estimated proportion of null SNPs, which is quantified as:

$$\widehat{\pi_0}(\lambda) = \frac{\#\{p_i > \lambda\}}{m(1-\lambda)} \qquad (2)$$

for a given tuning parameter λ. We choose, as in Storey *et al*., $\lambda = 0.5$. By taking $-log_{10}$ of both sides of equation (1) and noting that, as is true for most GWAS, $\widehat{\pi_0}$ is generally close to 1, we note that the $-log_{10}(\widehat{FDR}(p))$ is the difference between log_{10} of the empirical quantile and log_{10} of *p*. This numeric difference is correlated to the horizontal leftward shift of the curve from the diagonal line in a Q-Q plot; the larger the difference between log_{10} of the empirical quantile and log_{10} of the observed *p*, the greater the leftward shift from the diagonal line (and the smaller the FDR). In our analyses, we report the number of cis eQTLs in each tissue that satisfy FDR < 0.25 for association with each disease. This FDR threshold of 0.25 is a field standard used in other enrichment analytical approaches for interpreting genome-wide gene expression data such as the widely used Gene Set Enrichment Analysis (22).

It is important to note that the FDR is quite different from the more familiar false-positive rate threshold set by p-values (15). The p-value false-positive rate sets a significance threshold that defines the number of "truly negative"/null results that are declared to be positive. In the setting of GWAS, where the number of true positives is likely to be very low, yet the number of independent tests is very high (~1 million), if 1/20 tests are false positive ($p<0.05$), one would expect 50,000 false positives and very few, if any, true positives. In stark contrast, rather than

thresholding the proportion of truly negative results that are called significant, the FDR specifies the proportion of significant results that are actually negative. In doing so, the FDR takes into account the expectation that the overwhelming majority of nominal p-values will be false positives and sets a threshold (in this case FDR<0.25, which is a field standard in genome biology) at which 75% of the results are true.

Polygenic Score Analysis

The polygenic score analysis is used to measure the cumulative effect of many common genetic variants, including variants with small effects. With a limited sample size, it is difficult to detect individual genetic variants at the standard GWAS significance threshold (5×10^{-8}). However, these weakly associated variants can be enriched in aggregate among the top SNPs that are identified using less stringent thresholds (23). We selected nominally-associated alleles (score alleles) based on various thresholds from TS and/or OCD discovery samples, calculated the polygenic risk score of these alleles in an independent target sample, and estimated how much of the phenotypic variance can be explained by the polygenic risk score.

Five discovery samples were designated in our study: 1) all European samples from the TS GWAS to investigate TS-associated variants (TS EU); 2) the European OCD GWAS samples without known comorbid TS/CT to investigate OCD-associated risk alleles (OCD EU without known TS/CT); 3) All OCD European samples plus the TS European cases with co-morbid OCD to investigate whether the polygenic components for OCD without tics and those for OCD with co-occuring TS/CT are the same (All OCD EU); 4) All European samples from the TS and OCD combined GWAS (TS or OCD) to investigate risk variants contributing to both TS and OCD (Combined TS/OCD EU); 5) randomly selected samples from OCD EU to control for differences in sample size between the OCD EU and TS EU samples (Downsized OCD EU).

We calculated the polygenic scores in two target samples: 1) TS French Canadian cases and controls as the independent TS target sample; 2) probands in the OCD European trios and the pseudo-controls derived from the non-transmitted alleles from the parents as the independent OCD target sample. It is well known that non-random genotyping error can often occur in trio samples, especially for rare SNPs, where heterozygotes are more likely to be misclassified as homozygotes of the common allele (24). To reduce the bias caused by non-random genotyping error, the score alleles in our study were limited to the common SNPs with MAF no less than 5%

in the overall European samples and the SNPs with 100% genotyping call rate in the trios.

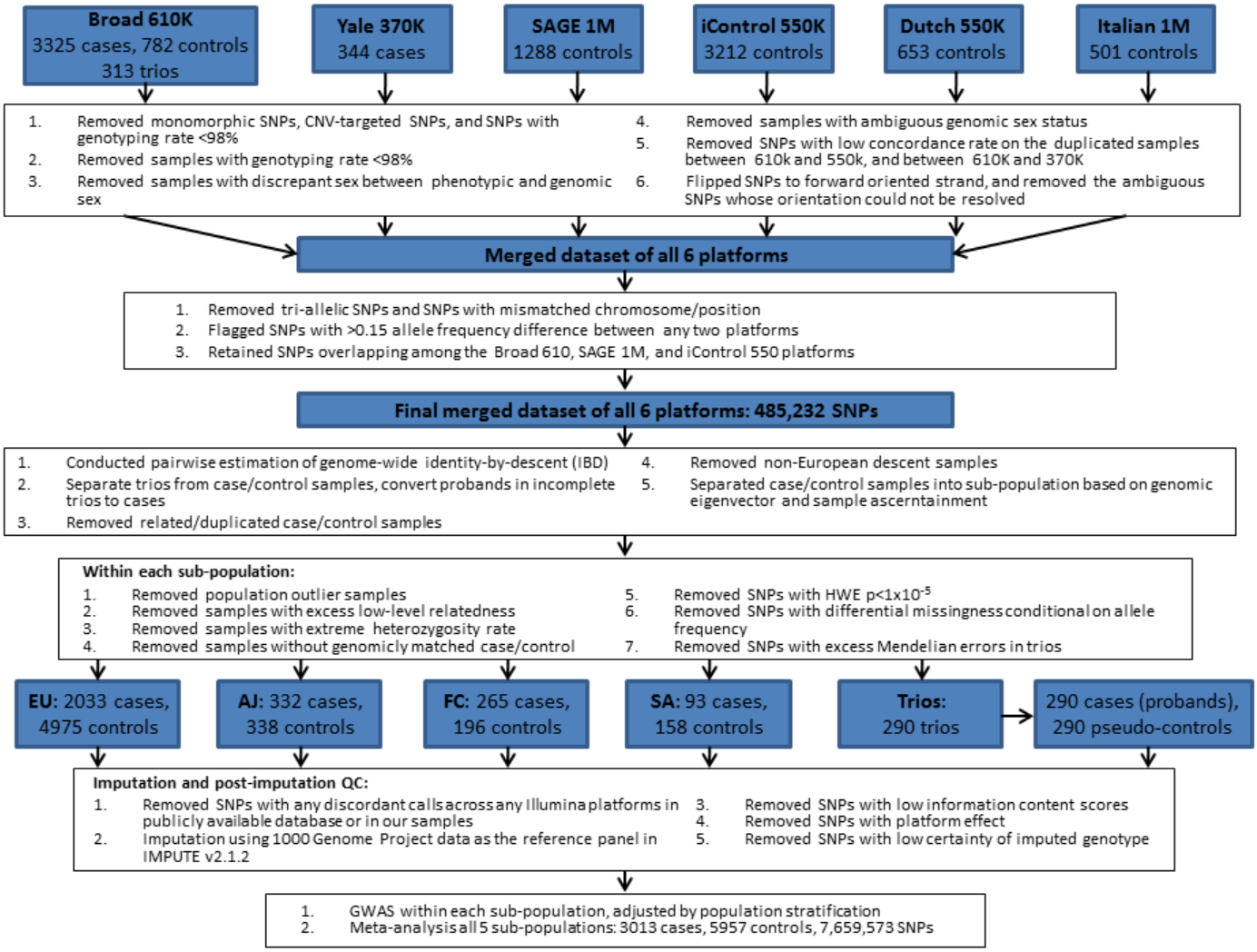
Within each discovery sample, we first pruned the SNPs by removing any SNP in strong linkage disequilibrium (LD) (pairwise r^2>0.2) with any other more significantly associated SNP within a 500kb sliding window, resulting in a set of LD-independent SNPs. Among the LD-independent SNPs, we then selected 6 sets of nominally-associated alleles as the score alleles based on the association test statistics in each discovery sample: SNPs with p<0.01, p<0.1, p<0.2, p<0.3, p<0.4, and p<0.5. In the target sample, we calculated the polygenic score for each individual as the number of score alleles weighted by the log of the odds ratio estimated from the discovery sample. The association between the polygenic score and disease status is tested in a logistic regression model, adjusted by the number of missing genotypes on the score alleles in the target sample. The proportion of phenotypic variance explained by the polygenic score is estimated as Nagelkerke's pseudo R^2.

To evaluate whether the phenotypic variance in OCD trios explained by the score alleles from "OCD EU without known TS/CT" discovery sample was significantly different from the variance explained by the score alleles from "All OCD EU" discovery sample, we applied 100 permutation tests to obtain an empirical p-value. In each permutation, we randomly shuffled the TS/CT phenotype status of the OCD cases in the "All OCD EU" discovery sample, and then removed the OCD cases with "comorbid TS/CT" (now assigned randomly) to form a permuted discovery sample, which contains the same number of OCD cases as the "OCD without known TS/CT" discovery sample regardless of TS/CT status. The phenotypic variance explained by the score alleles from the permuted discovery sample was estimated in the same way as described above, and the difference in the explained variance by the permuted discovery sample and by the "All OCD EU" discovery sample was calculated. The difference in explained variance by the "OCD EU without known TS/CT" discovery sample and by the "All OCD EU" discovery sample was compared with the permuted data to obtain the empirical p-value.

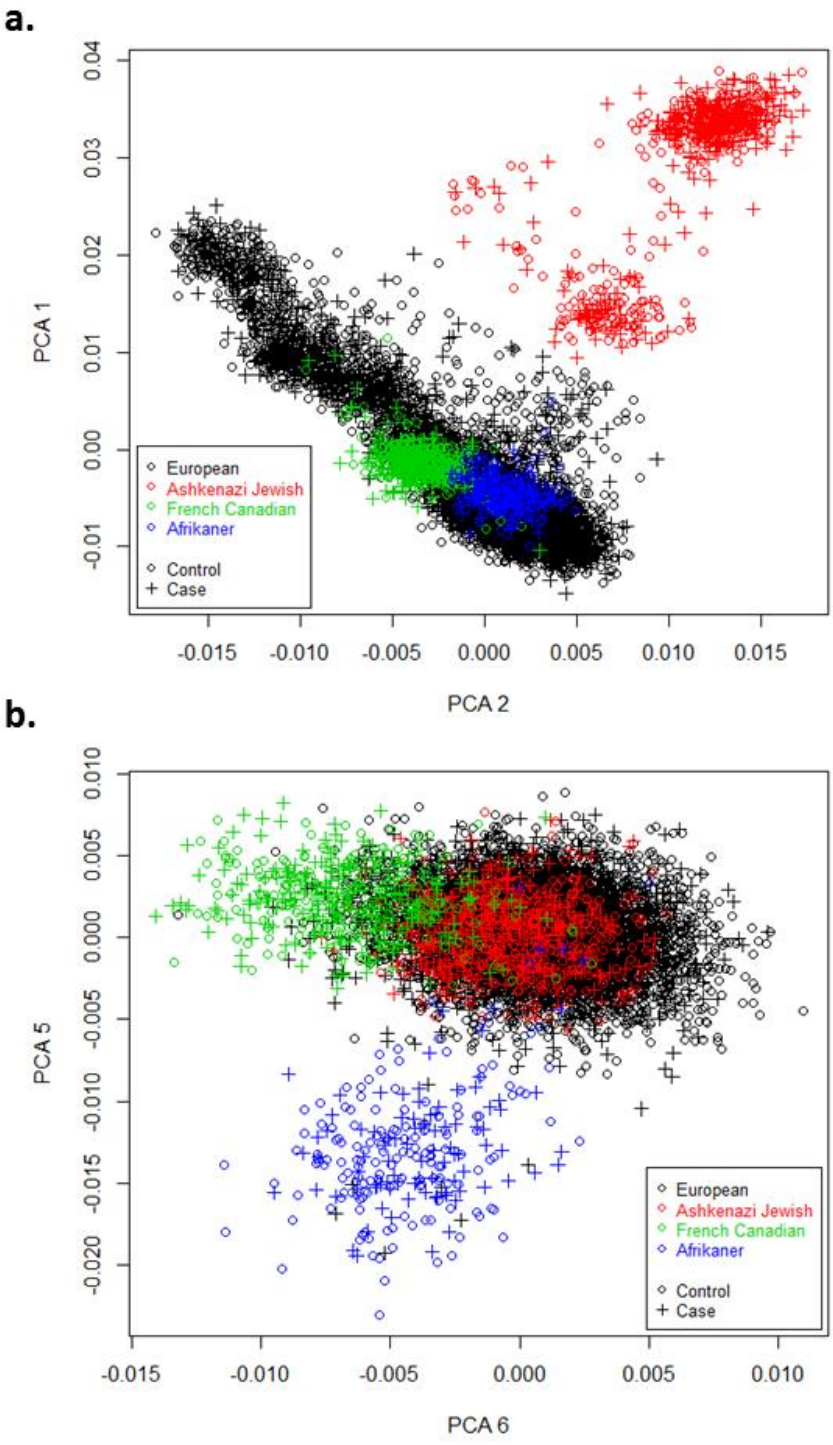
Under the assumption that the score alleles are associated with disease, we expect to see an elevated polygenic risk score among the transmitted alleles compared to the untransmitted alleles in OCD trios. This increase in risk score (risk score elevation) for the transmitted alleles was quantified by calculating the difference in risk scores between transmitted alleles and untransmitted alleles and divided by the absolute value of the risk score among untransmitted alleles for standardization. The risk score elevation derived from each discovery sample ("OCD EU without known TS/CT", "All OCD EU including co-occurring TS/CT", and "Combined EU"

was then compared across discovery samples using two-sided paired t-tests.

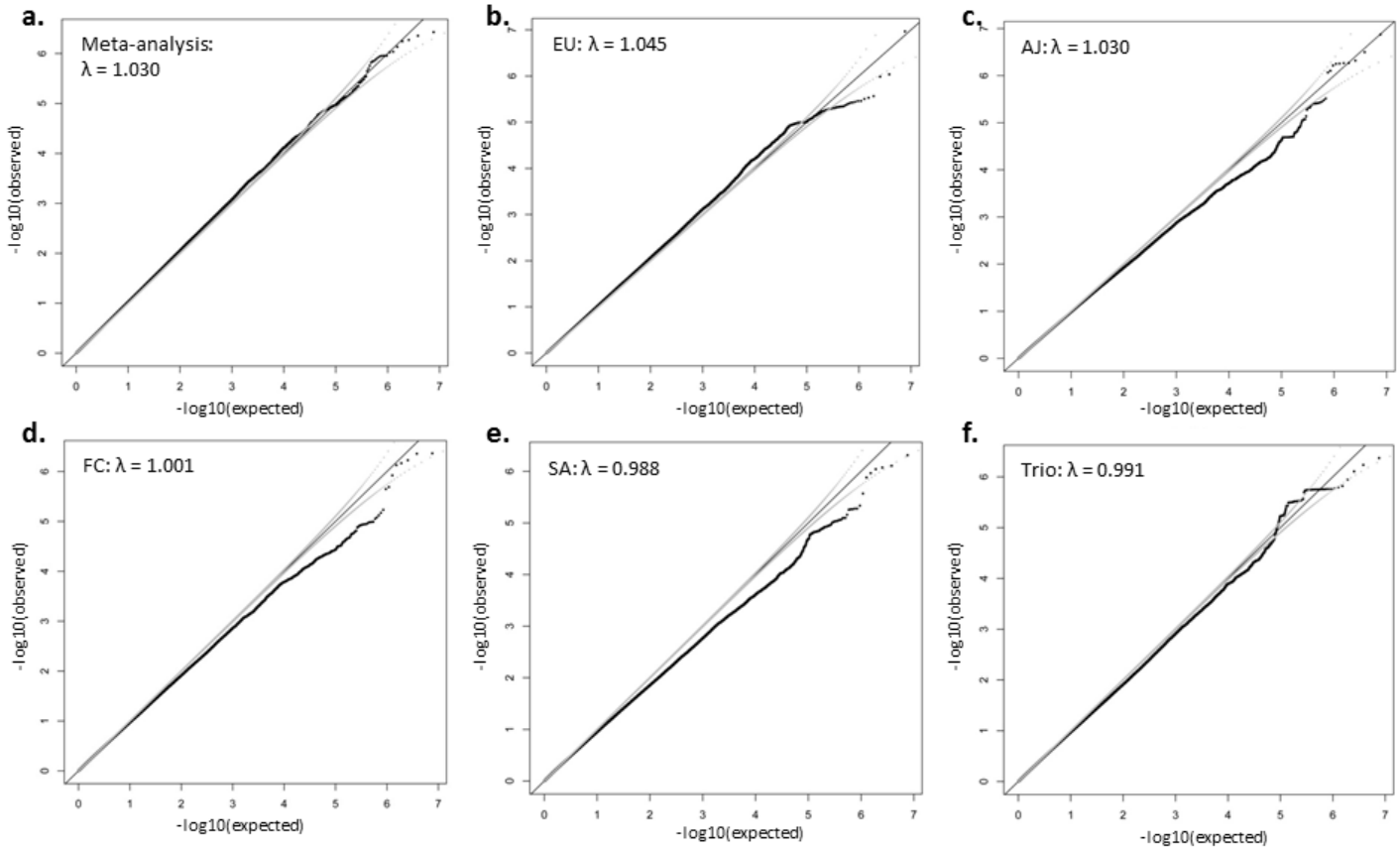
SUPPLEMENTARY FIGURES



Supplementary Figure S1. Quality control and imputation pipeline for the combined TS/OCD GWAS.

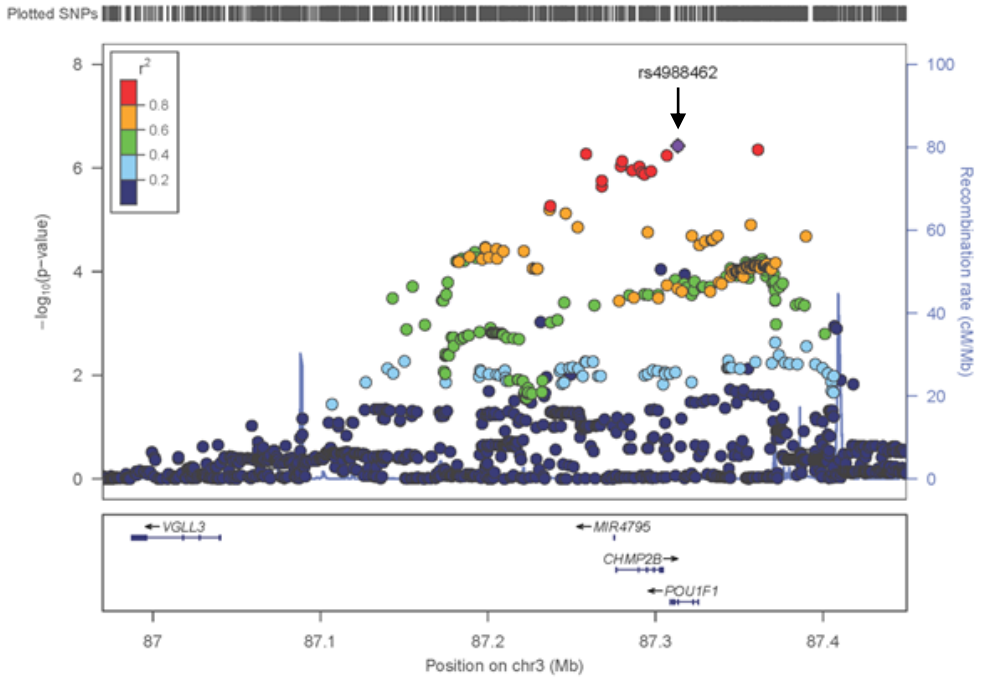


Supplementary Figure S2. MDS plot of case-control samples in the combined TS/OCD GWAS. a) The European samples (EU) clustered together in a homogeneous cloud along the Northern-Southern European cline (black); the Ashkenazi Jewish (AJ) samples clustered together in the top right corner, and the half-AJ/half-EU samples located between the EU and AJ clusters (red); the two isolate samples, French Canadian (FC) and Afrikaner (SA), clustered together with the EU samples. b) A demonstration of the separation of the FC and SA samples from the EU samples on the 6th and 5th MDS dimension, respectively.

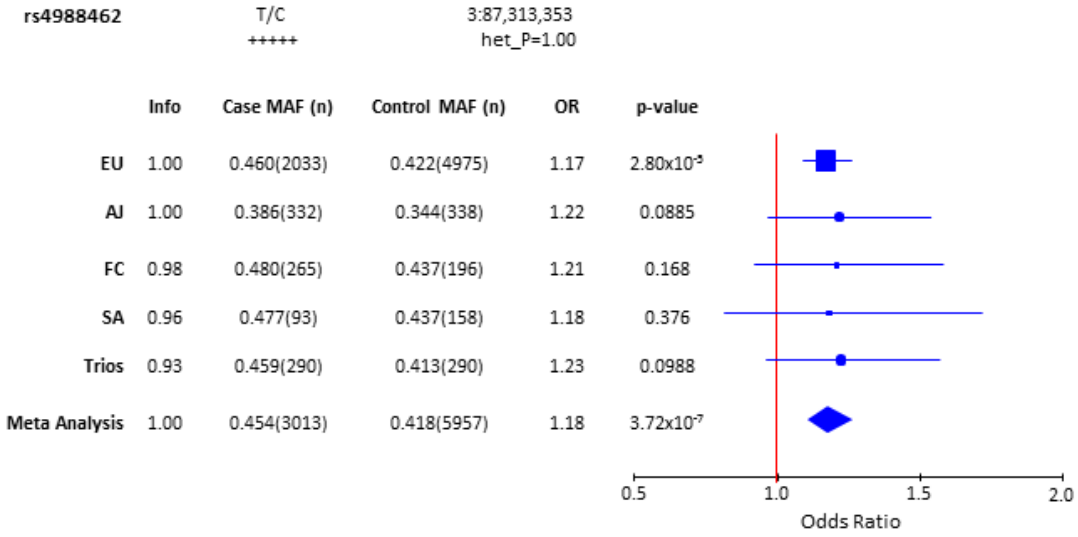


Supplementary Figure S3. Quantile-quantile plots of observed vs. expected –log(p) values for TS and OCD combined meta-analysis and five subpopulation GWAS analyses. The 95% confidence interval of expected values is indicated in grey dotted line. a) meta-analysis, λ=1.030; b) EU, λ=1.045; c) AJ, λ=1.030; d) FC, λ=1.001; e) SA, λ=0.988; f) Trio, λ=0.991.

a.

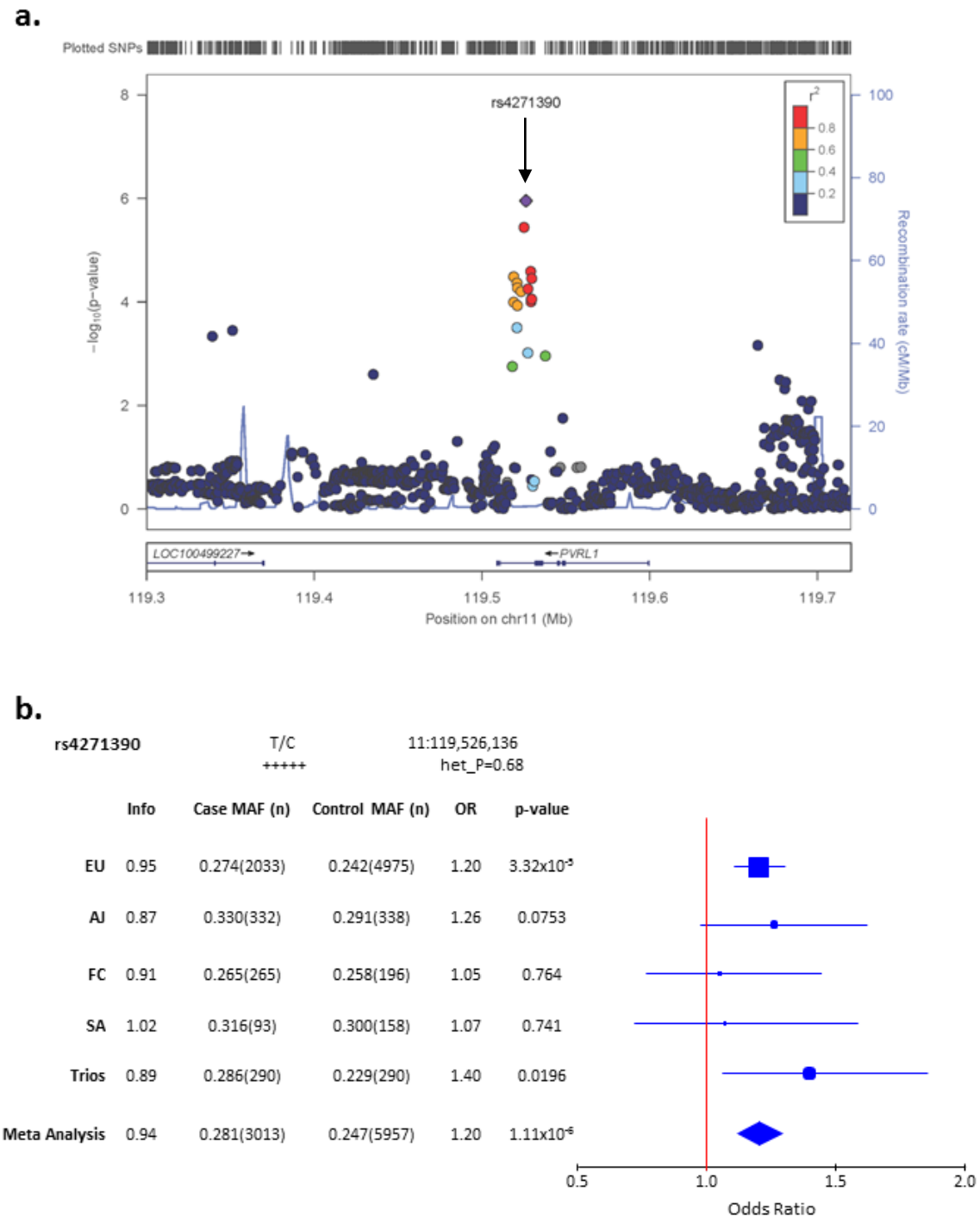


b.



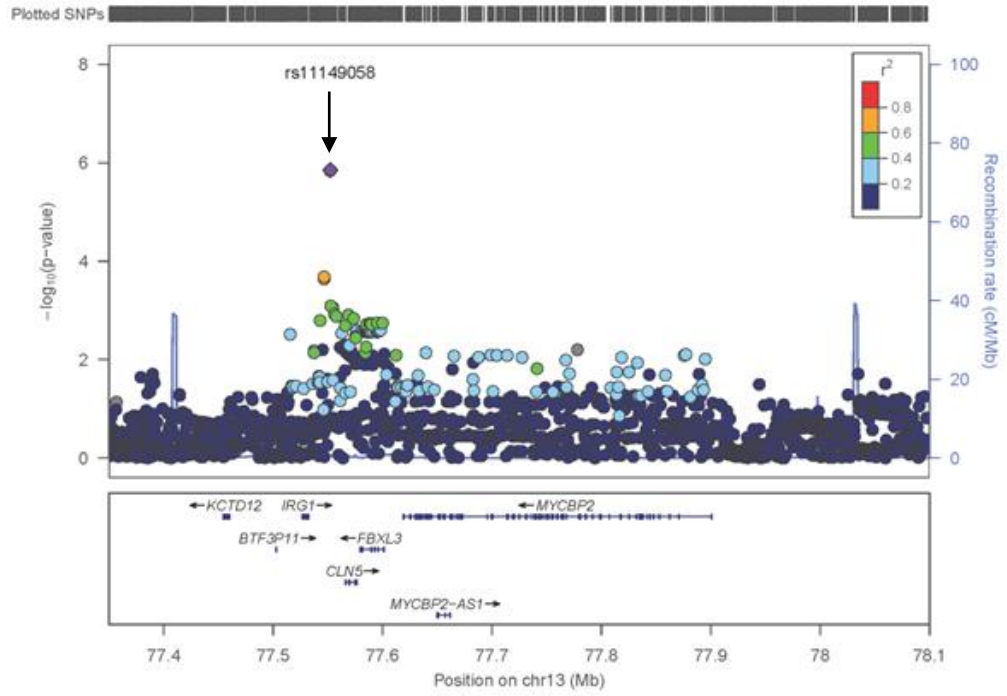
Supplementary Figure S4. Regional association and forest plot of rs4988462 on chromosome 3p11.

a) LocusZoom regional association plot from the meta-analysis. Arrow indicates the top SNP in the region, rs4988462 (in purple); b) Forest plot and heterogeneity tests for each ancestral subpopulation contributing to the association signal for rs4988462.

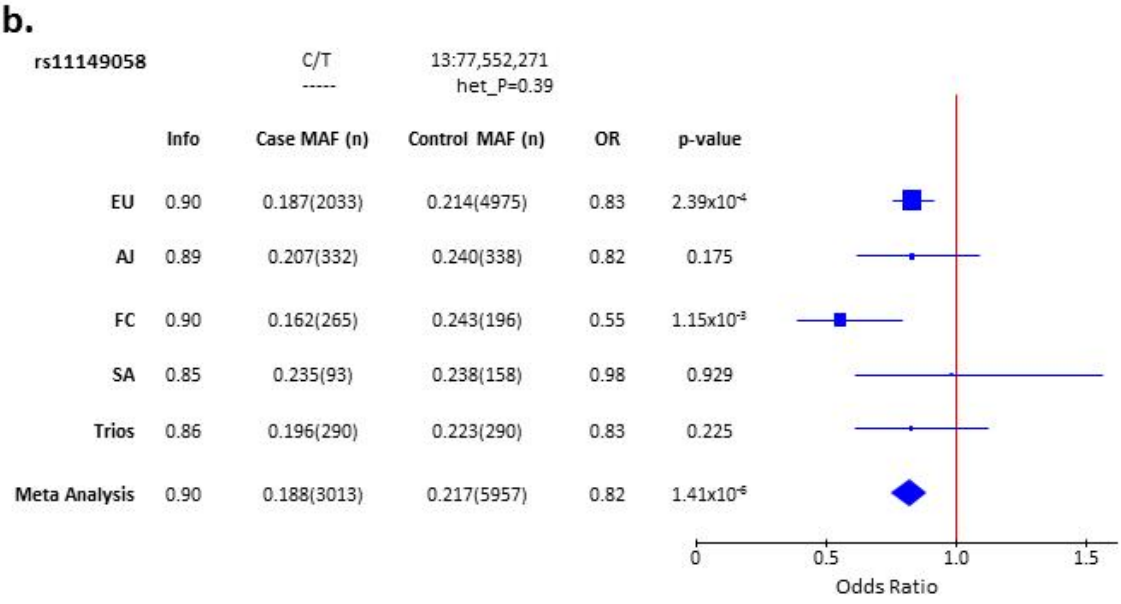


Supplementary Figure S5. Regional association and forest plot of rs4271390 on chromosome 11q23. a) LocusZoom regional association plot from the meta-analysis. Arrow indicates the top SNP in the region, rs4271390 (in purple); b) Forest plot and heterogeneity tests for each ancestral subpopulation contributing to the association signal for rs4271390.

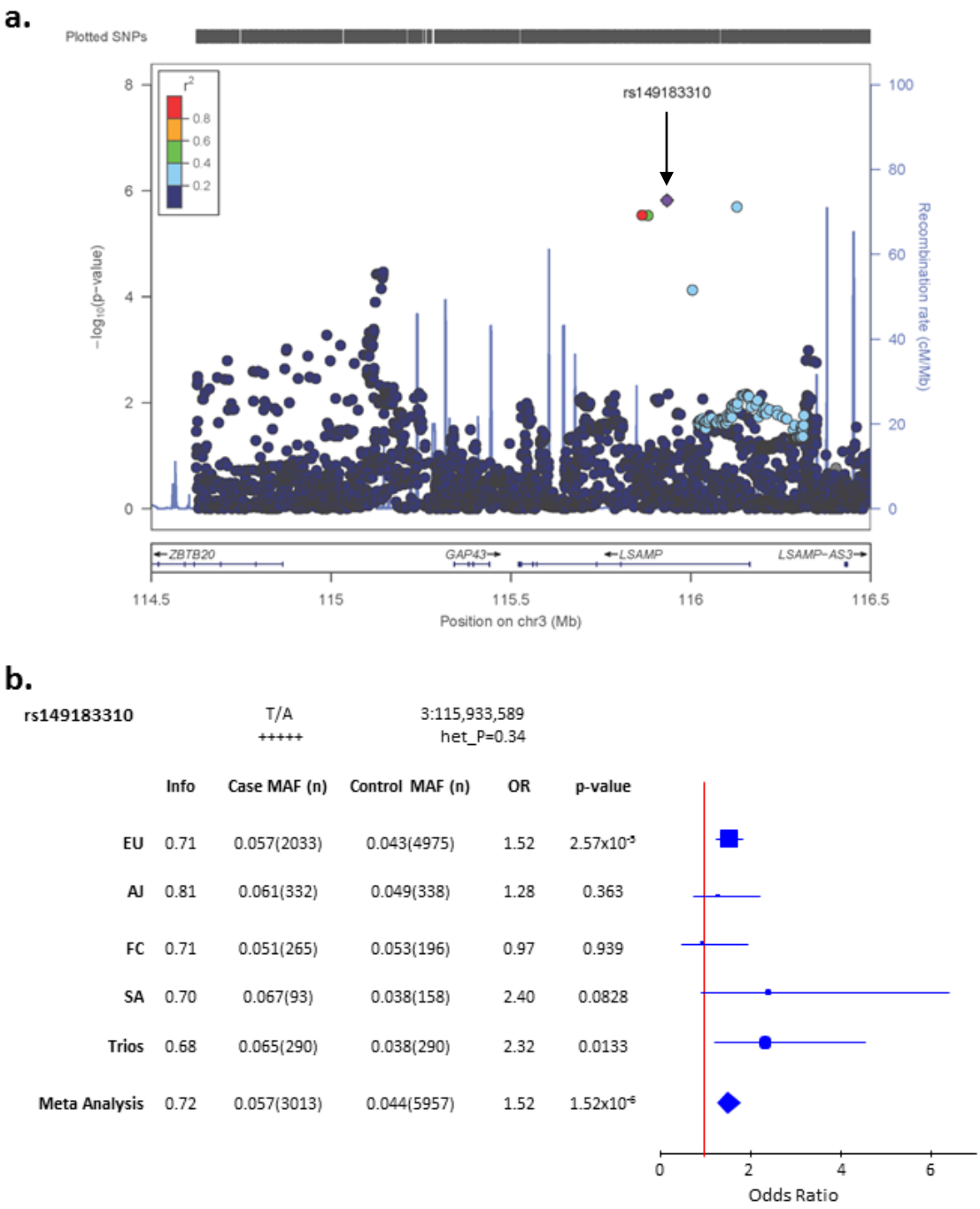
a.



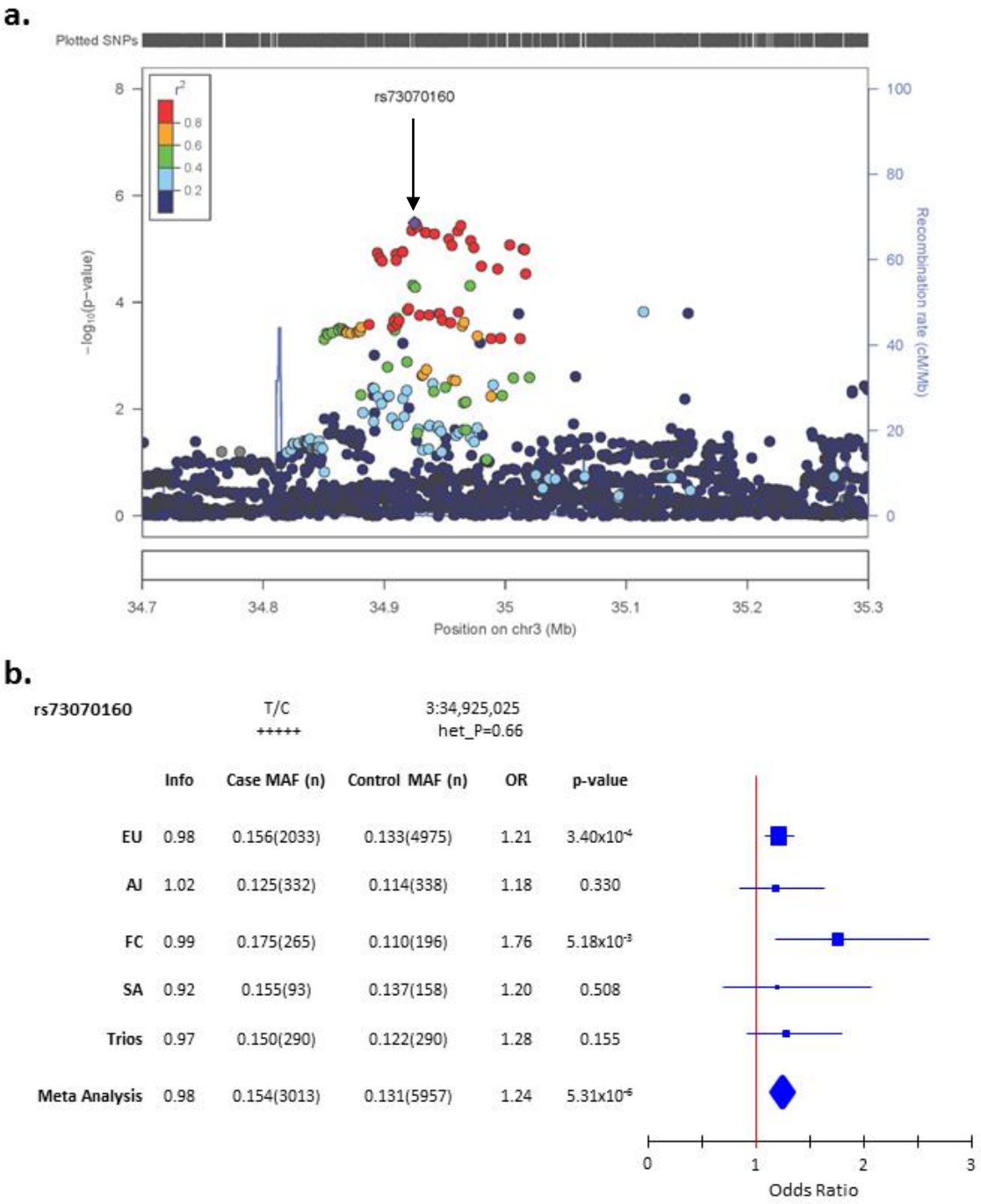
b.



Supplementary Figure S6. Regional association and forest plot of rs11149058 on chromosome 13q22. a) LocusZoom regional association plot from the meta-analysis. Arrow indicates the top SNP in the region, rs11149058 (in purple); b) Forest plot and heterogeneity tests for each ancestral subpopulation contributing to the association signal for rs11149058.

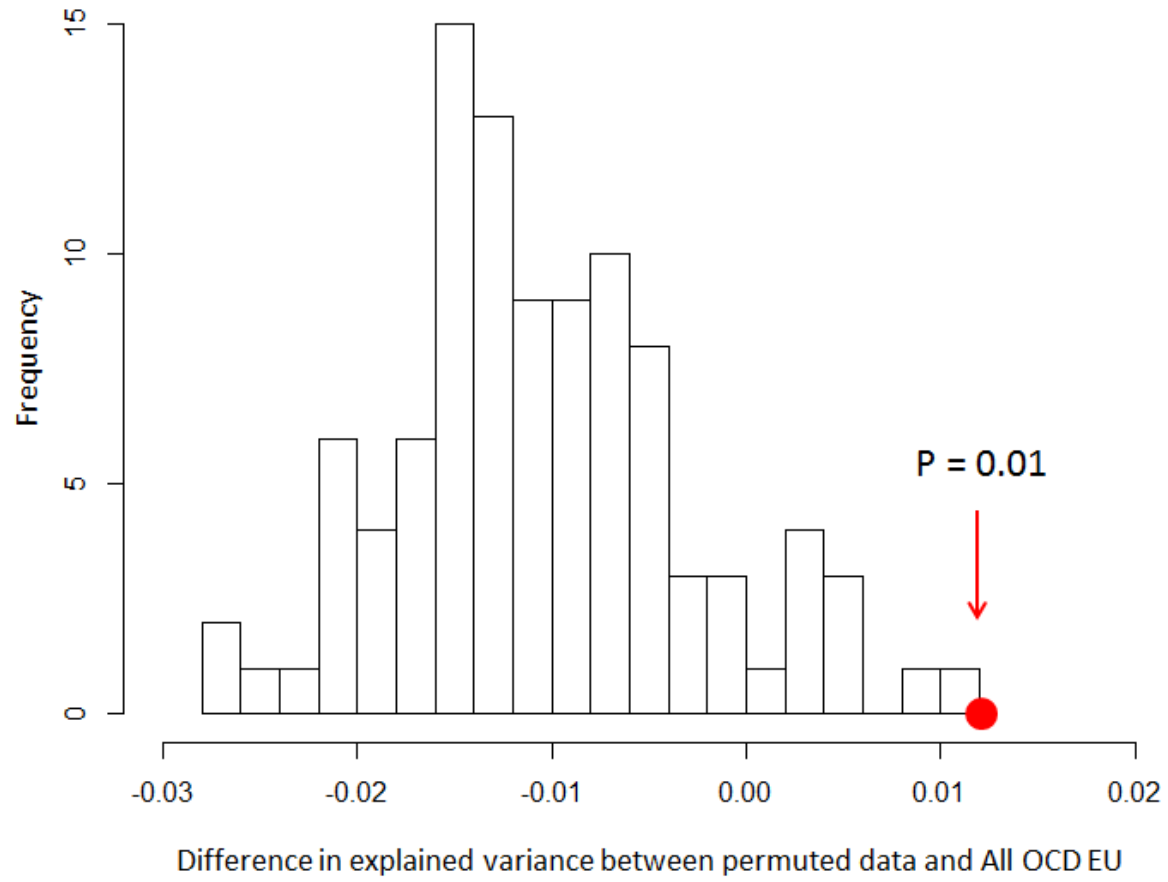


Supplementary Figure S7. Regional association and forest plot of rs149183310 on chromosome 3q13.
a) LocusZoom regional association plot from the meta-analysis. Arrow indicates the top SNP in the region, rs149183310 (in purple); b) Forest plot and heterogeneity tests for each ancestral subpopulation contributing to the association signal for rs149183310.



Supplementary Figure S8. Regional association and forest plot of rs73070160 on chromosome 3p22.

a) LocusZoom regional association plot from the meta-analysis. Arrow indicates the top SNP in the region, rs73070160 (in purple); b) Forest plot and heterogeneity tests for each ancestral subpopulation contributing to the association signal for rs73070160.



Supplementary Figure S9. Distribution of difference in explained variance between 100 permuted "OCD EU without known TS/CT" discovery samples and the "All OCD EU" discovery sample using OCD trios as the target sample. Difference in explained variance is calculated as the variance explained by the risk score derived from the permuted "OCD EU without known TS/CT" discovery sample (N=1154) subtracted from the variance explained by the risk score from the "All OCD EU" discovery sample (N=1499). Each of the 100 permuted "OCD EU without known TS/CT" discovery samples was generated by shuffling the TS/CT phenotype status of the 1499 OCD cases in the "All OCD EU" discovery sample and then removing the 345 OCD cases randomly assigned the permuted diagnosis of co-occurring TS/CT. Risk scores were then derived from each permuted discovery sample and calculated in the OCD trios. The red dot represents the difference in explained variance between the real "OCD EU without known TS/CT" discovery sample and the "All OCD EU" discovery sample. Only 1 out of 100 permuted "OCD EU without know TS/CT" discovery samples provided the same pseudo R^2 difference as the real dataset, giving an empirical p-value of 0.01. OCD EU without known TS/CT, European ancestry OCD GWAS samples after removing samples with known co-occurring TS/CT; All OCD EU, European ancestry OCD GWAS samples plus additional GWAS samples with co-occurring OCD and TS/CT.

SUPPLEMENTARY TABLES

Supplementary Table S1 (Attached Excel File): Annotated list of SNPs with $p < 1 \times 10^{-3}$ in the TS and OCD combined GWAS final analysis. The p-values of the corresponding SNPs in the individual TS and OCD GWAS analyses are also provided. SNP, Single Nucleotide Polymorphism. CHR, chromosomal location of SNP. BP, hg19 base pair position. A1/A2, A1 = reference allele (minor allele in EU sample); A2 = alternate allele. A1 FRQ, observed frequency of A1 allele in EU subpopulation. TS/OCD combined, meta-analysis result in TS/OCD combined GWAS. TS GWAS, meta-analysis result in TS GWAS. OCD GWAS, meta-analysis result in OCD GWAS. Z, combined Z-statistic for meta-analysis. P, association p-value in meta-analysis. PLINK_hg19_annotion, SNP annotation using Plink. Genes are listed if reference SNP lies within 50 kb based on dbSNP v 137. Gene name is followed by (distance). For SNPs within genes (intronic or exonic), distance = 0 kb. Upper case annotation (i.e. MISSENSE) indicates a coding SNP, while lower case annotation (i.e. missense) indicates a SNP in LD (r2>0.5) with a functional SNP. SCAN Annotation, SNP annotation based on SCANdb (SNP and CNV Annotation Database). SCAN_gene, genes that the reference SNP lies between the 5' and 3' end of its transcript; multiple entries of the same gene indicate multiple alternate transcripts. SCAN_feature: location/function of the reference SNP relative to gene, including nonsense, missense, coding/synonymous, intron, near-gene-3', near-gene-5', utr-3', utr-5', etc. SCAN_left_gene: adjacent flanking gene left of reference SNP, regardless of distance. SCAN_right_gene, adjacent flanking gene right of reference SNP, regardless of distance. Cerebellar eQTL: eQTLs from cerebellar tissue with expression association p-values <0.001. Frontal Cortex eQTL, eQTLs from frontal cortex tissue with expression association p-values <0.001. Parietal Cortex eQTL, eQTLs from parietal cortex tissue with expression association p-values <0.001. Cerebellar mQTL, methylation QTLs from cerebellar tissue with association p-values for gene methylation p<0.001.

Supplementary Table S2 (Attached Excel File): Information (including allele frequency, odds ratio, and p-value) for SNPs with final meta-analysis $p < 1 \times 10^{-3}$ in each of the individual ancestry-specific sub-population analyses for the combined TS/OCD GWAS. SNP, Single Nucleotide Polymorphism. CHR, chromosomal location of SNP. BP, hg19 base pair position. A1/A2, A1 = reference allele (minor allele in EU sample); A2 = alternate allele. Z, combined Z-statistic for meta-analysis . P, association p-value in meta-analysis. Direction, effect direction of the reference allele (A1) in the subpopulations in the order of EU, AJ, FC, SA, and Trios. HetChiSq, Chi-square test statistic of the heterogeneity test. df, degree of freedom of the heterogeneity test. P_Het, p-value of heterogeneity Chi-square test. EU, European Ancestry non-isolate sample. AJ, Ashkenazi Jewish population isolate sample. FC, French Canadian population isolate sample. SA, South Africa population isolate sample. Trio, European Ancestry OCD trio. A1 FRQ, observed frequency of A1 allele in the reported subpopulation. OR, odds ratio of A1 allele in the reported subpopulation. P, association p-value in the reported subpopulation.

Discovery Sample		Target Sample		Best	Best	P-value
Sample Set	# of Cases	Sample Set	# of Cases/Controls	Pseudo R^2	P-value	Threshold
OCD EU without known TS/CT	1154	OCD trios	290/290	0.032	2.1×10^{-4}	< 0.1
All OCD EU	1499	OCD trios	290/290	0.021	0.0023	< 0.1
Combined TS/OCD EU	2033	OCD trios	290/290	0.017	0.0075	< 0.4
Downsized OCD EU	776	OCD trios	290/290	0.014	0.01	< 0.5
TS EU	776	OCD trios	290/290	0.0004	0.66	< 0.2
OCD EU without known TS/CT	1154	TS FC	265/196	-0.012	0.37	< 0.5
Combined TS/OCD EU	2033	TS FC	265/196	0.002	0.40	< 0.1
TS EU	776	TS FC	265/196	0.006	0.06	< 0.3

Supplementary Table S3. Within-disorder and cross-disorder polygenic analyses of TS and OCD. Variance explained (Nagelkerke's pseudo R^2) in two target samples (OCD trios and TS French Canadian (FC) case/control) is based on polygenic scores derived from an aggregated sum of weighted SNP risk allele effect sizes in the TS EU GWAS, OCD EU GWAS, and TS/OCD combined EU GWAS discovery samples for six significance thresholds (P_T < 0.01, 0.1, 0.2, 0.3, 0.4 and 0.5). Negative R^2 values indicate a negative correlation between risk scores and illness status in the target sample. OCD EU without known TS/CT: European ancestry OCD GWAS samples after removing cases with comorbid TS/CT; All OCD EU: European ancestry OCD GWAS samples plus additional GWAS samples with co-morbid OCD and TS/CT; Combined TS/OCD EU: All European ancestry TS GWAS samples and OCD GWAS samples; Downsized OCD EU: randomly selected subset of OCD EU samples to match the number of cases in the TS EU discovery sample; TS EU: European ancestry TS GWAS samples; OCD Trios: the OCD EU trio probands and matched pseudo-control data derived from non-transmitted alleles; TS FC: TS French Canadian cases and matching controls.

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