

Sex-Dependent Shared and Non-Shared Genetic Architecture Across Mood and Psychotic Disorders

Supplement 1

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Supplementary Methods

Power analyses

Power analyses were carried out using the ‘GeneticsDesign’ Bioconductor package in R. At the listed within-disorder and cross-disorder sample sizes, and a MAF of 0.05, this study had 83%-99% power to detect disease risk interaction effects within-disorder at an odds ratio of ≥ 1.2 , and 88% power to detect effects cross-disorder at an odds ratio of ≥ 1.1 . Power estimates for varying effect sizes and for the different data configurations are presented in **Table S3** and **Figure S2**.

IBD Filtering

IBD analyses were performed using PLINK (1) to identify duplicate samples and/or cryptic relatedness. For sample pairs in which PI_HAT > 0.1 , one sample was randomly excluded if both samples were cases or both controls, or the control sample was excluded if one sample was a case and the other a control. IBD filtering was first applied within each study cohort and subsequently across study cohorts within a disorder. For cross-disorder analyses, IBD filtering was applied across all cohorts across all three disorders.

Sex interaction versus sex stratification

An interaction test is powered to detect a difference between the sexes in genetic risk and needed to determine whether differences in effect sizes are statistically different between the sexes (2). On the other hand, a stratified analysis is required in order to characterize the effect size itself, and the direction of effect within each sex. A sex-stratified analysis followed by a Z-score difference test (Eq. 1) is equivalent to a formal test for G×S interaction when there is no interaction between covariates and the strata, and the trait variance are equivalent in the two strata. Thus, different information can be gained from both types of analyses.

$$\text{Eq. 1: } [Z - \text{score}] = \frac{\text{Beta}_{\text{female}} - \text{Beta}_{\text{male}}}{\sqrt{\text{SE}_{\text{female}}^2 + \text{SE}_{\text{male}}^2}}$$

Here, we focused on the interaction analysis. However, to characterize the quality of the suggestive G×S interaction signals ($p < 1 \times 10^{-6}$), included in the tables with G×S interaction results (**Tables 1-2, Tables S6-S9**), we also report sex-specific association statistics. Miami plots show the genome-wide sex-specific associations (**Figure S3**). None of these G×S SNPs showed a genome-wide significant sex-specific signal. Furthermore, a scatter plot of $-\log_{10}(p\text{-values})$ for sex-specific genome-wide associations indicated little overlap in the top signals across sexes (**Figure S4**).

Linkage Disequilibrium Score Regression

Estimates of h_{SNP}^2 were transformed to the liability scale assuming lifetime prevalence of the disorder in the population (K) of $K = 0.01$, $K = 0.01$, and $K = 0.10$ for SZ, BD, and MDD females, respectively, and $K = 0.01$, $K = 0.01$, and $K = 0.05$ for SZ, BD, and MDD males, respectively, based on a Danish population study (3). Estimates of h_{SNP}^2 increased minimally across a range of MAF cutoffs (MAF $> 1\%$, 2% , 5%), indicating rarer variants contributed little to the heritability estimates (**Table S7**).

For traits with non-zero h_{SNP}^2 estimates in both sexes (significantly greater than zero; $z = h_{SNP}^2/\text{SE}$), we tested whether the estimates were significantly different between the sexes by calculating Z-scores using the Equation above (replacing Beta with h_{SNP}^2), and obtaining

corresponding *p*-values from the standard normal distribution, followed by Bonferroni-correction for multiple testing based on 3 independent tests/disorders (*p*-value threshold = 0.017).

We also used linkage disequilibrium score regression (LDSC) (4) to estimate bivariate genetic correlations (r_g) between the sexes and between the three disorders. LDSC genetic correlations attributable to genome-wide SNPs (r_g) were estimated within (males/females) and across disorders (sex-interaction; males/females). The intent of these comparisons was to evaluate the extent of shared common variant genetic architectures in order to suggest hypotheses about the fundamental genetic basis of sex differences in these three disorders. These r_g are mostly based on studies of independent subjects and the estimates should be unbiased by confounding of genetic and non-genetic effects (except if there is genotype-by-environment correlation). When GWAS studies include overlapping samples, r_g estimates remain unbiased but the intercept of the LDSC regression increases as it is an estimate of the correlation between association statistics attributable to sample overlap. Subject overlap in itself does not bias r_g (4, 5). Therefore, we used the data with only within-cohort/within-disorder IBD filtering for these analyses.

For between-sex, within-disorder correlations, we used one-tailed tests comparing to a standard normal distribution, to determine whether r_g was significantly greater than zero ($z=r_g/\text{SE}$) and significantly less than 1 ($z=(1-r_g)/\text{SE}$). Bonferroni-correction was applied to adjust for multiple testing based on 3 tests/disorders. Next, we determined whether the between-trait, within-sex correlations were different for males and females (see Equation above). Given the non-independent genetic correlations across disorders, rendering Bonferroni-correction overly conservative, we applied false discovery rate (FDR) correction to adjust for multiple tests.

All estimates of h_{SNP}^2 and r_g are based on the autosomal contributions only, as LDSC currently does not allow for estimation of h_{SNP}^2 and r_g from the X chromosome, due to its more complex composition.

We provided the within-disorder meta-analysis sex-stratified summary statistics, calculated based on the PGC-only samples, to Martin *et al* (6), who evaluated sex differences in heritability estimates and genetic correlations of multiple psychiatric disorders and relevant quantitative phenotypes in an expanded set of analyses.

SNP-by-sex interaction analyses

PLINK (1) was used to perform a genome-wide genotype-by-sex (G×S) interaction analysis of each study cohort, followed by standard-error weighted (i.e., inverse variance) meta-analysis of the G×S interaction results using METAL (7). G×S interaction analyses were performed using logistic regression with a main effect for each SNP, a main effect for sex, and SNP-by-sex interaction terms, using an additive model for each SNP. The first 10 ancestry principal components (PCs) were included as covariates to adjust for population stratification. A secondary regression model included additional statistical controls in the form of 10 SNP-by-PC interaction terms and 10 sex-by-PC interaction terms in addition to the terms above (8). The “dosage” information score for imputed genotype was used to account for uncertainty of imputation. For all analyses, SNPs with poor imputation quality (IMPUTE2 INFO score < 0.6) or low minor allele frequency (MAF < 0.01 for SNP-by-sex interaction analysis) were excluded.

X chromosome

The X chromosome is usually excluded from GWAS because the data has a different, sex-specific structure and, therefore, requires special analytical tools.(9) While there are two copies

of each autosomal chromosome, males carry only one copy of the X chromosome whereas females, again, carry two copies. Therefore, at each SNP, females can carry one of three possible genotypes; that is, they can have 0, 1 or 2 copies of a specific allele. In contrast to this, there are only two possible genotypes for males, corresponding to 0 or 1 copies of a specific allele. Only for the so-called pseudo-autosomal regions, there exist homologous loci on the Y chromosome, and males can have up to 2 copies of a specific allele. In addition, one of the two female X chromosomes might be inactivated. In each cell, one of the two female X chromosomes is randomly selected to be silenced (10). This means that the expression levels of this chromosome are much lower than for the second chromosome in the cell. This mechanism of dose compensation should result in comparable expression levels for males and females despite the different number of chromosome copies. However, this inactivation is incomplete: while some genes or regions will be completely inactivated, some genes might show expression levels that are reduced only slightly or not at all. Therefore, to analyze X-chromosomal data, special quality control (separately for males and females) and test statistics are required (11). The choice of the best statistical test depends on the underlying genetic model and the inactivation patterns at a specific locus (12).

Omnibus test

As opposite risk effects of SNPs in cross-disorder analyses (i.e., a particular allele is associated with increased risk of one disorder and decreased risk of another disorder) might cancel each other out, we also performed a 3 degrees-of-freedom omnibus test (13-15) as a second analytical approach. This test was performed by summing the χ^2 values for each individual disease meta-analysis, which enables detection of opposing allelic effects across disorders.

Association analysis based on SubSETs (ASSET) (16) is designed to be powerful for pooling association signals across multiple studies when true effects may exist only in a subset of the studies and could be in opposite directions across studies. The method explores all possible subsets of studies and evaluates fixed-effect meta-analysis test statistics for each subset. The final test statistic is obtained by maximizing the subset-specific test statistics over all possible subsets and then evaluating its significance after efficient adjustment for multiple testing, taking into account the correlation between test statistics across different subsets due to possible subject overlap (although here we removed this overlap using the IBD filtering described above). The method not only returns a *p*-value for significance for the overall evidence of association of a SNP across studies, but also outputs the "best subset" containing the studies that contributed to the overall association signal. For detection of association signals with effects in opposite directions, ASSET allows subset search separately for positively- and negatively- associated studies and then combines association signals from two directions using a chi-square test statistic.

Inclusion of East Asian ancestry SCZ cohorts, which represent a relatively small component of the SCZ dataset (7.56% of PGC; 7.03% of PGC+iPSYCH), did not substantially improve SNP-by-sex interaction results. For this reason, and given that the gene- and pathway-based analyses reported below required the application of an ancestry-specific reference panel, all subsequent analyses utilized only European ancestry cohorts.

Identification of credible SNPs

Linkage disequilibrium (LD)-independent SNPs with genome-wide significance ($p < 5 \times 10^{-8}$) and suggestive G×S signals ($p < 1 \times 10^{-6}$) were used as index SNPs to obtain credible SNPs (i.e., potentially causal in disease risk). All SNPs associated with $p < 1 \times 10^{-6}$ and SNPs in LD ($r^2 > 0.6$) with the index SNP were selected. Correlations (LD structure) among this set of SNPs were calculated based on the 1000 Genomes Phase 1 European (CEU) reference panel. FINEMAP v1.4 (17) and CAVIAR v2.2 (18) (-r 0.95, posterior probability; -c 2, maximum number of causal SNPs) were applied to summary association statistics and LD structure for each index SNP locus (plink --bfile 1kgp1_ref_file --clump metal_output_file --clump-p1 1e-4 --clump-p2 0.05 --clump-r2 0.1 --clump-kb 250), and credible SNPs for each index SNP were identified. We summarize the posterior probabilities of all SNPs in the fine-mapping loci (**Table S10**) and highlight the SNPs that are most likely to have a causal effect on mood and psychotic disorders. It is noteworthy that the SNPs with the highest posterior probability of causality are not necessarily the most statistically significant SNPs in the original G×S analysis.

Gene-based test in MAGMA

Briefly, the gene-based test evaluates whether the number of associated SNPs in/around a particular gene is greater than would be expected given the size and structure of that gene, as opposed to a SNP-based test, which does not take into account gene size and structure. The gene-based test in MAGMA (19) is based on a multiple linear principal components regression model, using an F-test to compute the gene p -value. This model first projects the SNP matrix for a gene onto its principal components (PCs), pruning away PCs with very small eigenvalues, and then uses those PCs as predictors for the phenotype in the linear regression model. This improves power by removing redundant parameters, and guarantees that the model is identifiable in the presence of highly collinear SNPs. Although application of the linear regression model to a binary phenotype violates some assumptions of the F-test, comparison of the F-test p -values with p -values based on permutation of the F-statistic has shown that the F-test remains accurate.

We applied an adjusted genome-wide significant p -value threshold of $p < 2.6 \times 10^{-6}$, which accounts for 19,427 autosome and sex chromosome genes evaluated in the test (**Table S11**).

Pathway gene set enrichment analyses

Using MAGMA (19), two sets of pathway/gene set enrichment analyses were carried out. Hypothesis-free analyses were performed for Gene Ontology (GO) pathways (20, 21) plus curated gene sets (including gene sets from BioCarta, KEGG, and Reactome) from the Molecular Signatures Database v6.2 (MSigDB; <http://software.broadinstitute.org/gsea/msigdb/genesets.jsp>) (22). Pathways analyzed contained a minimum of 10 genes because statistics for smaller gene sets tend to be over-dispersed (23), reducing down the number of MSigDB gene sets from 5917 GO + 4762 curated = 10,679 pathways to 10,353. Data-driven analyses included an additional 9 gene sets/pathways compiled from prior studies: immune/neurotrophic, synaptic, and histone methylation gene sets reported to be enriched across the PGC SZ, BD, and MDD cohorts (23), and six central nervous system (CNS) pathways that were enriched in the largest SZ GWAS to date (CLOZUK+PGC) (24): mouse phenome (MP) abnormal behavior, MP abnormal long-term potentiation, MP abnormal CNS electrophysiology, 5HT2C receptor complex, FMRP targets, and Voltage-gated Ca²⁺ channels. The number of genes in each (top) pathway are listed in **Tables S12-S13**.

Ensembl gene definitions were used as the reference gene annotation and map. The different pathway sets were combined into one database and identical pathways merged. SNPs were assigned to genes based on human genome build 37 positions if they lay within 10 kb upstream or 10 kb downstream of the gene, to capture transcriptional regulatory elements. SNPs that mapped to more than one gene, were assigned to all such genes. Analyses were run according to the standard protocols for MAGMA, both with and without the MHC region (chromosome 6, between base pair position 25,000,000 and 35,000,000). MAGMA (19) is a “best SNP per gene” method that counts the number of genes in a pathway where a number of independent SNPs exceed a predefined significance, and adjusts for LD and genomic structure with corrected statistics derived by Monte Carlo simulation. This gene-set analysis also uses a regression structure to allow generalization to analysis of continuous properties of genes and simultaneous analysis of multiple gene sets and other gene properties. To determine whether any pathway gene sets annotate the top GWAS genes at a frequency greater than that would be expected by chance, a *p*-value was calculated using the hypergeometric distribution (25). Pathway enrichment *p*-values were FDR-corrected (26) based on number of pathways tested.

Brain expression analysis

Brain expression (RNA Sequencing, RNA-Seq) data from the Genotype-Tissue Expression project (GTEx; 44 tissues, N>70; <http://www.gtexportal.org> (27, 28)), the Human Brain Transcriptome project (HBT; <http://hbaflas.org> (29, 30)), the Allen Brain Atlas (<http://human.brain-map.org> (31)), and the Stanford Brain RNA-Seq database (http://web.stanford.edu/group/barres_lab/brain_rnaseq.html (32, 33)) were evaluated to validate and interpret the G×S interaction results (variants with a G×S interaction *p*-value < 1×10^{-6}).

The expression levels from the Allen Brain Atlas were averaged across the 6 brain tissue samples and up to 6 probes per gene. As the experiments contained in the Stanford Brain RNA-Seq database (32, 33), i.e. expression of genes in neurons, astrocytes, and oligodendrocytes specifically, were done in mice, genes were mapped to human orthologous genes using Ensembl.

Expression quantitative trait locus analyses

All variants with a G×S interaction *p*-value < 1×10^{-6} were analyzed further to test whether their genotype was associated with RNA(-Seq) expression. The most significant SNP from each locus having *p* < 1×10^{-6} in G×S interaction analyses was assessed for the possibility of genotype-specific gene expression patterns (or expression quantitative trait loci, eQTLs). To assess variants for their influence on expression of their closest genes in brain tissue, we conducted eQTL look-ups of the most associated SNPs in each locus (*p* < 1×10^{-6}) and report GWAS SNPs in LD ($r^2 > 0.8$) with the top eQTLs in the following data sets: GTEx (27, 28), PsychENCODE (PEC; PFC, N=427; <https://www.synapse.org/pec> ; <http://resource.psychencode.org>) (34, 35), CommonMind Consortium (CMC; dorsolateral prefrontal cortex [DLPFC], Sage Synapse accession syn5650509, N=467; <https://www.synapse.org/cmc>) (36), the Lieber Institute for Brain Development (LIBD; DLPFC), accessed via the eQTL Browser (<http://eqtl.brainseq.org/>) (37, 38). For SNPs showing significant eQTLs in the GTEx dataset, we looked for replication in the other datasets. Expression QTLs that reached a threshold of $\alpha = 0.05$ in the GTEx dataset and replicated (defined as a threshold of $\alpha = 0.05$ in the same direction) in PEC, CMC, and/or LIBD are reported.

Evaluation of G×S interaction for sex-dependent and cross-disorder SNPs from prior studies

To assess overlap of G×S signals between the current study and prior published studies, G×S interaction results were compared to previously reported sex-dependent or sex-specific effects on psychiatric illness risk ($p < 5 \times 10^{-8}$) from sex-stratified analyses by the PGC (2, 39, 40), ASD collection (41), 23andMe (42), and UK Biobank (43) (see Supplementary Methods).

Additionally, G×S interaction effects were evaluated for SNPs with genome-wide significant main additive effects across sexes in the recent PGC cross-disorder group (CDG) study of eight disorders (includes the PGC SCZ, BIP, and MDD datasets analyzed in this study) (44).

For the UK Biobank GWAS, genome-wide sex-stratified summary statistics are available for download for a range of mental illness diagnoses. Lookups were performed for SNPs with a significant Z difference score ($p < 5 \times 10^{-8}$) between the sexes only. The Z difference score was calculated as described above. Additionally, G×S interaction effects were evaluated for genome-wide significant SNPs (main additive effect across sexes) from the recent PGC-CDG study of eight disorders (this study includes the PGC data analyzed here) (44).

Supplementary Results

Brain expression analysis

Tissue and brain expression data were examined for genes located adjacent to SNPs with significant or suggestive evidence for G×S interactions ($p < 1 \times 10^{-6}$; i.e. the SNPs listed in **Tables 1-2**). As shown in **Figures S11-S13**, the *NKAIN2* gene containing the omnibus genome-wide significant SNP (rs117780815) is specifically expressed in brain in the adult, being highest in spinal cord followed by hippocampus and substantia nigra, while expression during neurodevelopment is highest in prenatal cortex and neocortex. *MOCOS* expression is highest in tibial nerve in adulthood, and prenatally in cortex, hippocampus, and amygdala. *IDO2* expression in adulthood is highest in cortex, and in childhood frontal cortex and amygdala. *SLTM* expression is highest in adulthood in hypothalamus, and in prenatal and childhood cortex. *TUSCI* is fairly consistently expressed across the brain and across development from prenatal development through childhood to adulthood. *FHL2* brain expression is relatively low prenatally, highest in mediodorsal nucleus of the thalamus in early childhood, and in neocortex in adulthood. *SPAG17* expression is highest prenatally in hippocampus and amygdala, through childhood in hippocampus, and in the adult hypothalamus. *ZNF385C* expression is highest in the cerebellum (including cortex), throughout prenatal development, childhood, and adulthood. Among seven brain cell types, *NKAIN2* expression is highest in oligodendrocytes, *MOCOS* in endothelial cells and microglia, *IDO2* and *FHL2* in oligodendrocyte precursor cells, *SLTM*, *SPAG17* and *ZNF385C* in astrocytes, and *TUSCI* in neuron (**Figure S15**).

Evaluation of sex-specific expression detected different expression levels between males and females of several of the genes in some brain regions (**Figure S21**).

Evaluation of G×S interaction for sex-dependent and cross-disorder SNPs from prior studies

Of four SNPs with nominally significant SNP-by-sex interactions ($p < 0.05$) identified in a 23andMe study of MDD (42), two SNPs exhibited nominally significant G×S interactions in our analyses (**Table S14**) of MDD (rs2042772; $p = 0.037$) and BIP (rs4543289; $p = 0.034$). SNPs with significant sex-dependent effects ($p < 5 \times 10^{-8}$) in prior within-disorder studies of ADHD, OCD, PTSD, and ASD (2, 39-41) or UK Biobank psychiatric phenotypes (43) had non-significant ($p_{FDR} > 0.05$) G×S interaction p -values in this study. Among the genome-wide significant results in a PGC cross-disorder (non-sex-stratified) analysis of 8 psychiatric disorders

(44), rs7521492 had a *p*-value of 4.2×10^{-4} in our G×S omnibus test of SCZ, BIP and rMDD ($p_{\text{FDR}} = 0.034$); rs11688767 had a *p*-value of 3.2×10^{-4} in our meta-analysis of rMDD ($p_{\text{FDR}} = 0.034$). Of note, *CSMD1*, identified in the PGC-CDG cross-disorder analysis (44), was among our top cross-disorder G×S results (regular meta-analysis). However, the most significant SNP in each analysis differed.

Supplementary Tables

Table S1. PGC cohort characteristics

See TableS1_PGC_cohort_characteristics.xlsx

The cohorts have been previously described in references (45-47).

Note: Due to the nature of the sample composition, 3 SCZ trio cohorts and 2 BIP trio cohorts were excluded from analyses (and from this table).

*No X chromosome data; #Recurrent MDD data available.

Table S2. iPSYCH cohort characteristics

See TableS2_iPSYCH_cohort_characteristics.xlsx

The cohort has been previously described in Pedersen *et al* (2018) (48). For this study, the large control dataset was semi-randomly split into subsets to match with the patients for each disorder. The number of controls in each set was decided upon based on the percentage of patients with that disorder.

Table S3. Power analyses

See TableS3_Power.xlsx

Power analyses for varying effect sizes and different data configurations were carried out using the ‘GeneticsDesign’ Bioconductor package in R. At the listed within-disorder and cross-disorder sample sizes, and a MAF of 0.05, this study had 83%-99% power to detect disease risk interaction effects within-disorder at an odds ratio of ≥ 1.2 , and 88% power to detect effects cross-disorder at an odds ratio of ≥ 1.1 .

Table S4. SNP-based heritability

See TableS4_SNP-based_heritability_LDSC.xlsx

Estimates of SNP-based heritability, h^2 (standard error, SE), were obtained for three minor allele frequency (MAF) cutoffs using Linkage Disequilibrium Score Regression (LDSC) with population prevalences of $K = 0.0124$, $K = 0.0107$, $K = 0.1018$, and $K = 0.0563$ for SCZ, BIP, MDD, and rMDD females, respectively, and $K = 0.0173$, $K = 0.0076$, $K = 0.0563$, and $K = 0.0256$ for SCZ, BIP, MDD, and rMDD males, respectively (3), to transform from the observed heritability scale to the liability scale. Primary model refers to the regression model without additional interaction covariates; secondary model refers to the extended model with additional interaction covariates.

Abbreviations: BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S5. SNP-based genetic correlations

See TableS5_SNP-based_rg_LDSC.xlsx

Estimates of SNP-based genetic correlations, r_g (standard error, SE), were obtained using Linkage Disequilibrium Score Regression (LDSC) with MAF threshold 0.01 and population prevalences of $K = 0.0124$, $K = 0.0107$, $K = 0.1018$, and $K = 0.0563$ for SCZ, BIP, MDD, and

rMDD females, respectively, and $K = 0.0173$, $K = 0.0076$, $K = 0.0563$, and $K = 0.0256$ for SCZ, BIP, MDD, and rMDD males, respectively (3). Primary model refers to the regression model without additional interaction covariates; secondary model refers to the extended model with additional interaction covariates.

Abbreviations: BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S6. Meta-analysis Autosomal G×S interaction loci in PGC+iPSYCH

See TableS6_MetaAnalysisSTDERR_auto_PGC+iPSYCH.xlsx

Cross-disorder and within-disorder meta-analyses were carried out using METAL, incorporating cohort-level summary statistics from PLINK. Listed are LD-independent SNPs with interaction p -values $< 1 \times 10^{-6}$ in SCZ, BIP, (r)MDD, and cross-disorder. Loci were clumped using ‘*plink --bfile 1kgp_ref_file --clump metal_output --clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.6 --clump-kb 3000*’. Primary model refers to the regression model without additional interaction covariates; secondary model refers to the extended model with additional interaction covariates.

Abbreviations: BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S7. Omnibus test Autosomal G×S interaction loci in PGC+iPSYCH

See TableS7_OmnibusTestASSET_auto_PGC+iPSYCH.xlsx

Omnibus tests were carried out using ASSET, incorporating the within-disorder meta-analysis summary statistics from METAL. Listed are LD-independent SNPs with cross-disorder interaction p -values $< 1 \times 10^{-6}$. Loci were clumped using ‘*plink --bfile 1kgp_ref_file --clump asset_output --clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.6 --clump-kb 3000*’. Primary model refers to the regression model without additional interaction covariates; secondary model refers to the extended model with additional interaction covariates.

Abbreviations: BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S8. Meta-analysis chrX G×S interaction loci in PGC+iPSYCH

See TableS8_MetaAnalysisSTDERR_xchr_PGC+iPSYCH.xlsx

Cross-disorder and within-disorder meta-analyses were carried out using METAL, incorporating cohort-level summary statistics from PLINK. Listed are LD-independent SNPs with interaction p -values $< 1 \times 10^{-6}$ in SCZ, BIP, (r)MDD, and cross-disorder. Model A (**a**) effectively assumes complete and uniform X-inactivation in females and a similar effect size between males and females. Females are considered to have 0, 1, or 2 copies of an allele; males are considered to have 0 or 2 copies of the same allele. Model B (**b**) considers the allelic dosages for females to be 0, 1, or 2 copies, and males to be 0 or 1 copy as in an autosomal analysis. Loci were clumped using ‘*plink --bfile 1kgp_ref_file --clump metal_output --clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.6 --clump-kb 3000*’. Primary model refers to the regression model without additional interaction covariates; secondary model refers to the extended model with additional interaction covariates.

Abbreviations: BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S9. Omnibus test chrX G×S interaction loci in PGC+iPSYCH

See TableS9_OmnibusTestASSET_xchr_PGC+iPSYCH.xlsx

Omnibus tests were carried out using ASSET, incorporating the within-disorder meta-analysis summary statistics from METAL. Listed are LD-independent SNPs with cross-disorder interaction *p*-values $< 1 \times 10^{-6}$. Loci were clumped using ‘*plink --bfile 1kgp_ref_file --clump asset_output --clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.6 --clump-kb 3000*’. Omnibus tests were carried out using ASSET, incorporating the within-disorder meta-analysis summary statistics from METAL. Listed are LD-independent SNPs with cross-disorder interaction *p*-values $< 1 \times 10^{-6}$.

Abbreviations: BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S10. Credible SNPs for G×S loci in PGC+iPSYCH

See TableS10_CredibleSNPs_FineMapping_PGC+iPSYCH.xlsx

Fine mapping was carried out using both FINEMAP and CAVIAR. Fine mapping using FINEMAP was carried out with settings: *--sss --corr-config 0.95 --n-causal-snps 5 --n-configs-top 50000 --prior-k0 0 --prior-std 0.05*. If there were less than 5 SNPs in the locus, *--n-causal-snps* was set to the number of SNPs in the locus according to LD. The most likely causal SNPs per locus are highlighted in bold font. The shotgun stochastic search (*--sss*) conducts a pre-defined number of iterations within the space of causal configurations. In each iteration, the neighborhood of the current causal configuration is defined by configurations that result from deleting, changing or adding a causal SNP from the current configuration. The next iteration starts by sampling a new causal configuration from the neighborhood based on the scores normalized within the neighborhood. Fine mapping using CAVIAR was carried out with settings: *-r 0.95 -c 5 -f 1*. If there were less than 5 SNPs in the locus, *-c* was set to the number of SNPs in the locus according to LD. Analyses used European ancestry only summary statistics. Loci with *p* $< 1 \times 10^{-6}$ were analyzed (index SNPs determined based on clumping using LD threshold 0.1). The most likely causal SNPs per locus are highlighted in bold font. Primary model refers to the regression model without additional interaction covariates; secondary model refers to the extended model with additional interaction covariates.

Abbreviations: PP_group = posterior probability that there is at least one causal signal among SNPs in the same group with this SNP; PP_causal = posterior probability that the SNP is causal; BP = base pair position; BIP = bipolar disorder; CHR = chromosome; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia; SNP = Single Nucleotide Polymorphism rs ID.

Table S11. Gene-based test in PGC+iPSYCH

See TableS11_Gene-BasedTest_PGC+iPSYCH.xlsx

Gene-based analyses were carried out in MAGMA on the genomic control output with INFO score > 0.6 , European ancestry only, and autosomal SNPs only, with the MHC region included. Genes with *p*-values $< 1 \times 10^{-4}$ are shown. There was no difference in the *p*-values when the MHC region was excluded. There were minor differences in *p*-values when using INFO score > 0.8 ,

but with the same top 10 genes. *Significant at genome-wide threshold for gene-based test of 0.05 / 19,427 genes = 2.6×10^{-6} . Primary model refers to the regression model without additional interaction covariates; secondary model refers to the extended model with additional interaction covariates.

Abbreviations: BP = base pair position; Chr = chromosome; N SNPs = number of SNPs in gene; N Param = number of parameters; N = sample size; Z = Z-statistic; BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S12. MSigDB pathway gene set enrichment analyses in PGC+iPSYCH

See TableS12_MSigDB_pathway_GSEA_PGC+iPSYCH.xlsx

Enrichment analyses were carried out in MAGMA on the genomic control output with INFO score > 0.6, European ancestry only, and autosomal SNPs only. Analyses were run both with (top subtable) and without (bottom subtable) inclusion of the Chromosome 6 Major Histocompatibility Complex (MHC) region. Each (sub)table displays the top 10 gene sets based on the uncorrected *p*-value. Hyperlinks link to the GSEA/MSigDB website with a description of the pathway. Primary model refers to the regression model without additional interaction covariates; secondary model refers to the extended model with additional interaction covariates.

Abbreviations: BIP = bipolar disorder; P_{BONF} = Bonferroni-corrected *p*-value; P_{FDR} = False Discovery Rate-corrected *p*-value; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia; SE = Standard Error.

Table S13. Selected pathway gene set enrichment analyses in PGC+iPSYCH

See TableS13_Selected_pathway_GSEA_PGC+iPSYCH.xlsx

Analyses were run with (top) and without (bottom) inclusion of the Chromosome 6 MHC region in MAGMA. These analyses were carried out on the genomic control output with INFO score > 0.6, European ancestry only, and autosomal SNPs only. * Significant after adjusting *p*-values for multiple testing. Primary model refers to the regression model without additional interaction covariates; secondary model refers to the extended model with additional interaction covariates.

Abbreviations: BIP = bipolar disorder; CNS = central nervous system; MP = Mouse Phenome; P_{FDR} = False Discovery Rate-corrected *p*-value; PGC-NPA = Psychiatric Genomics Consortium – Network and Pathway Analysis Working Group; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia; SE = Standard Error.

Table S14. Lookup of interaction for SNPs showing sex-stratification or G×S interaction in 23andme, PGC, and UK Biobank

See TableS14_Prior_GWAS_SNP_Lookups.xlsx

Interaction results for the SNPs identified in sex-stratified analyses of other disorders and phenotypes, as well as SNPs identified in the recent PGC Cross-Disorder GWAS. Reported are replications/validations with nominal *p*-values < 0.01 in the interaction study.

Abbreviations: BP = base pair position; CHR = Chromosome; SE = Standard Error; SNP = Single Nucleotide Polymorphism rs ID.

Supplementary Figures

Figure S1. Experimental Design.

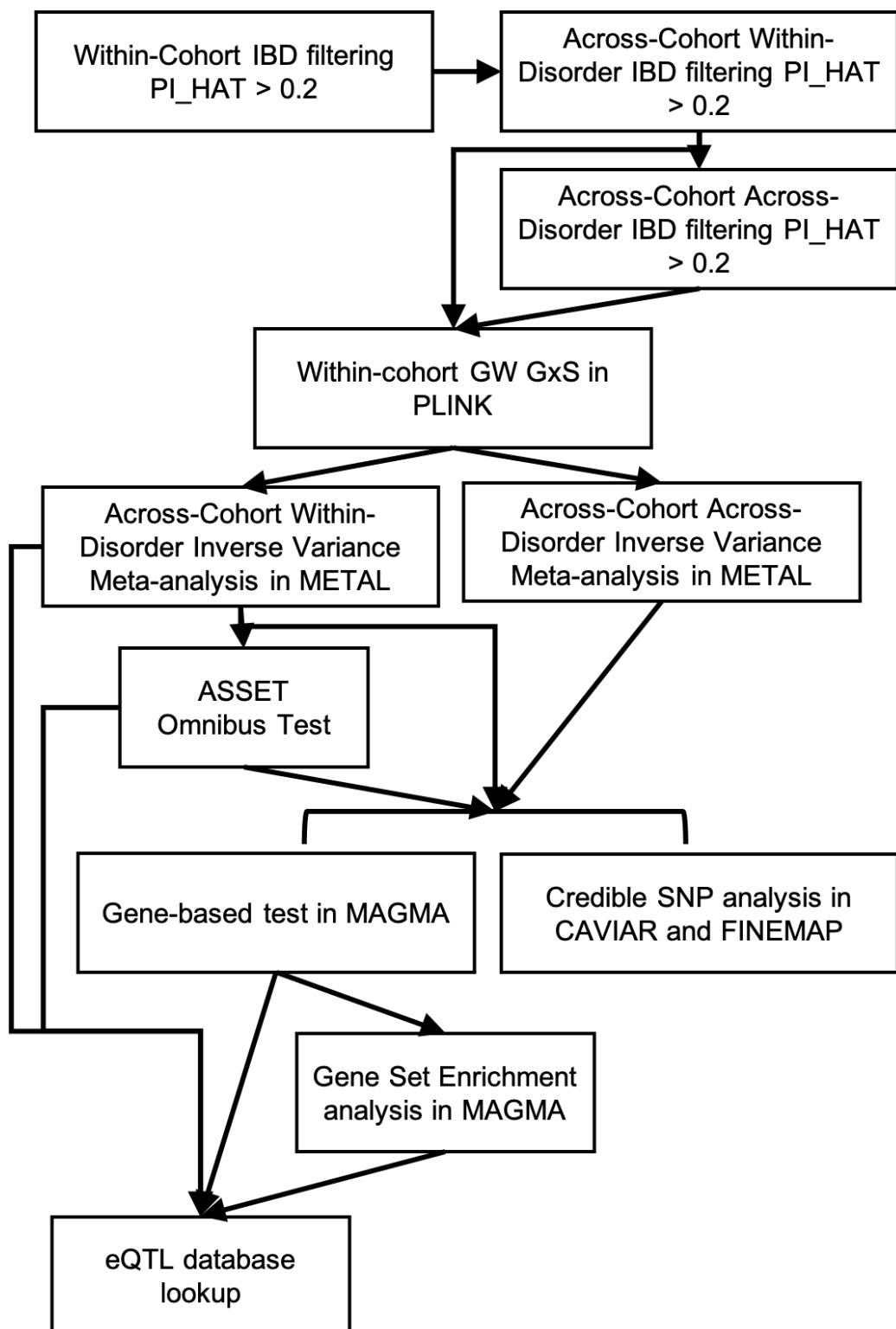


Figure S2. Power analyses.

Abbreviations: MAF = Minor Allele Frequency; OR = Odds Ratio.

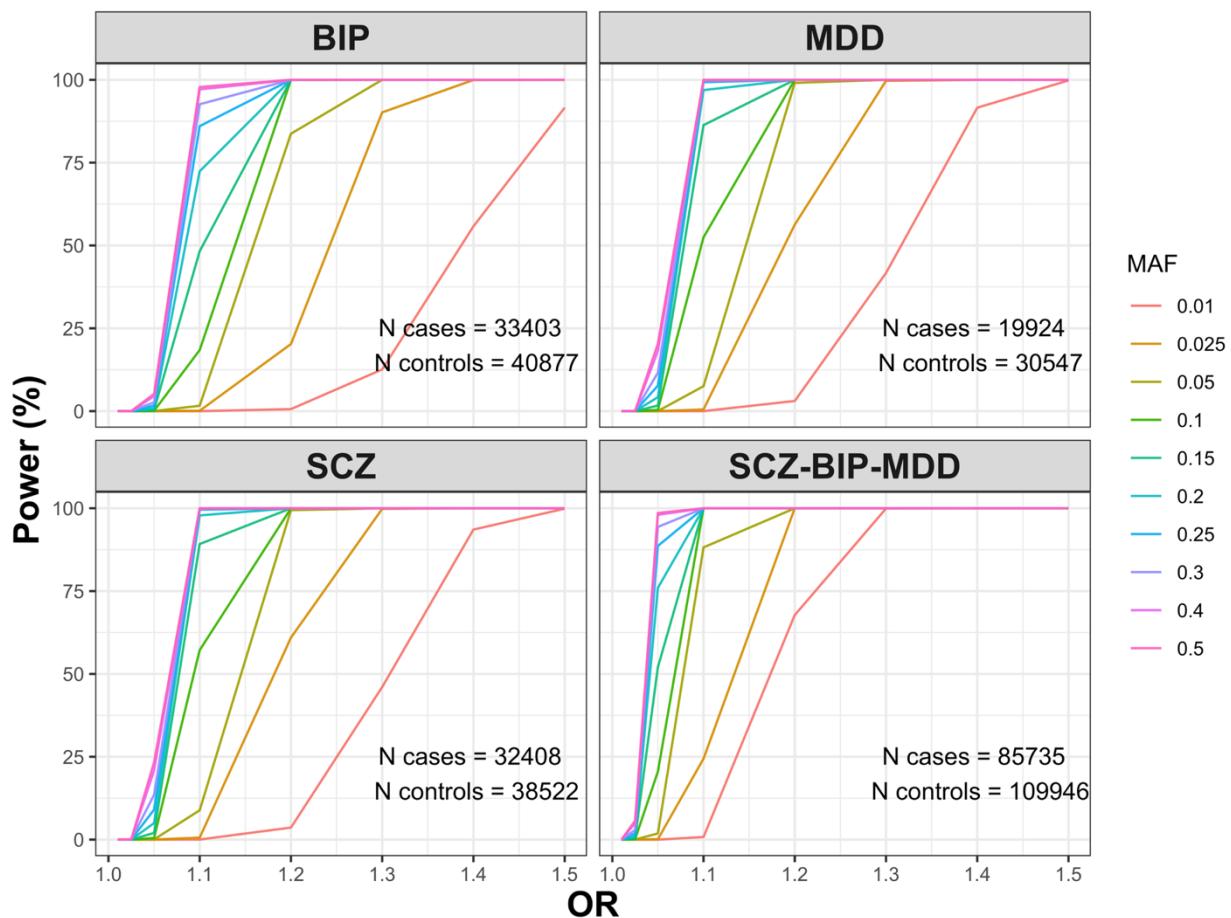
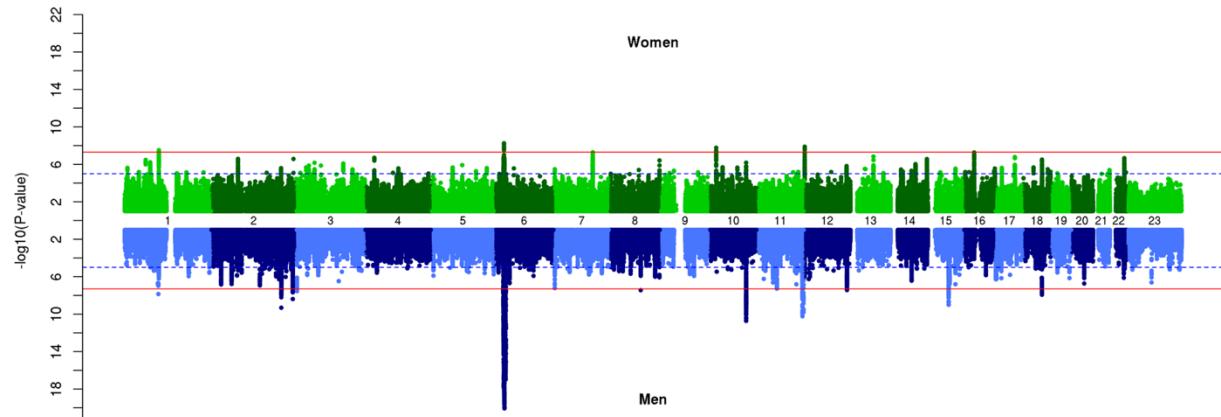
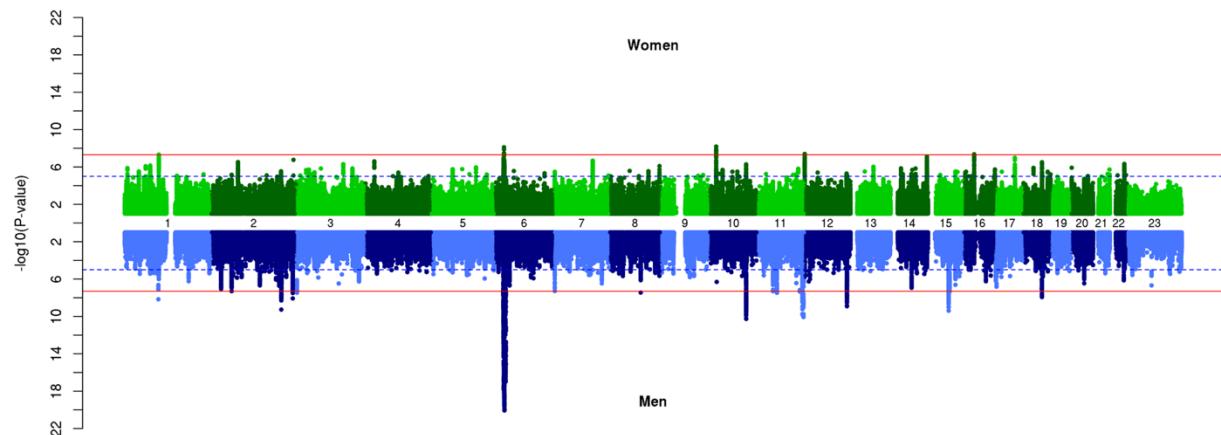
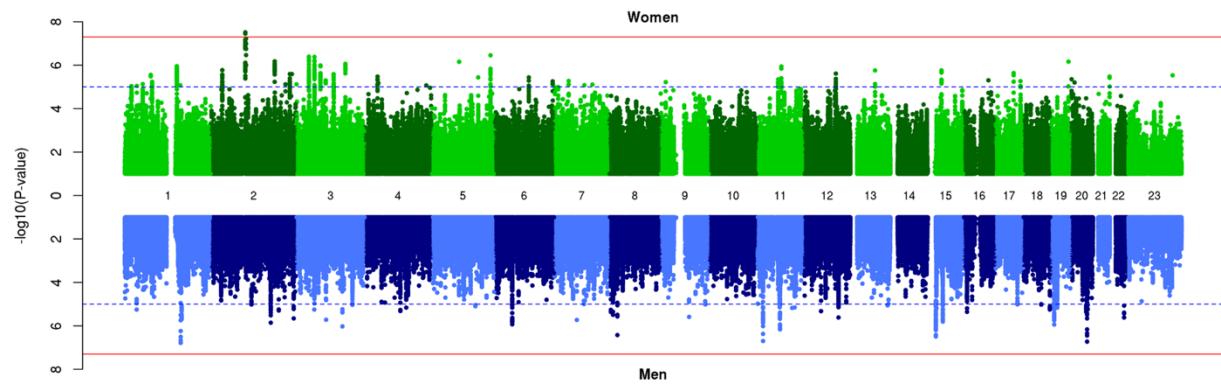
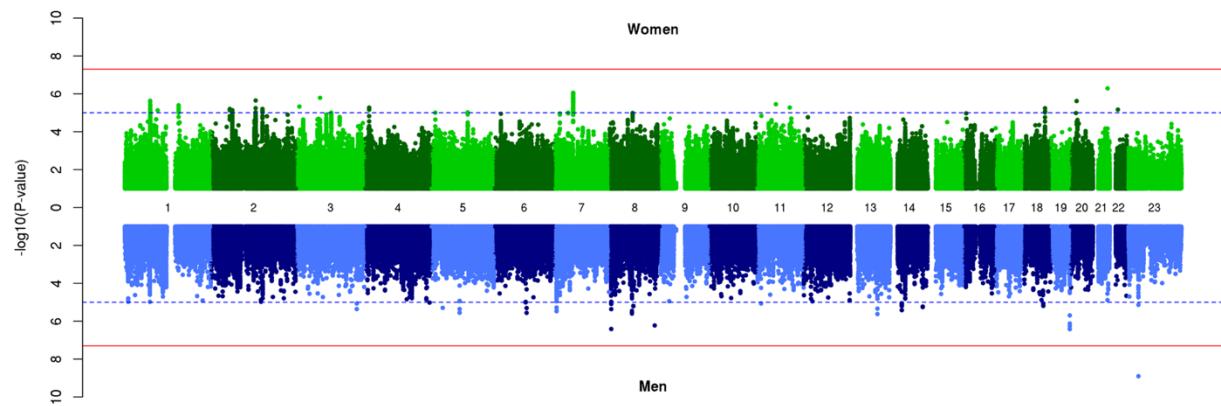
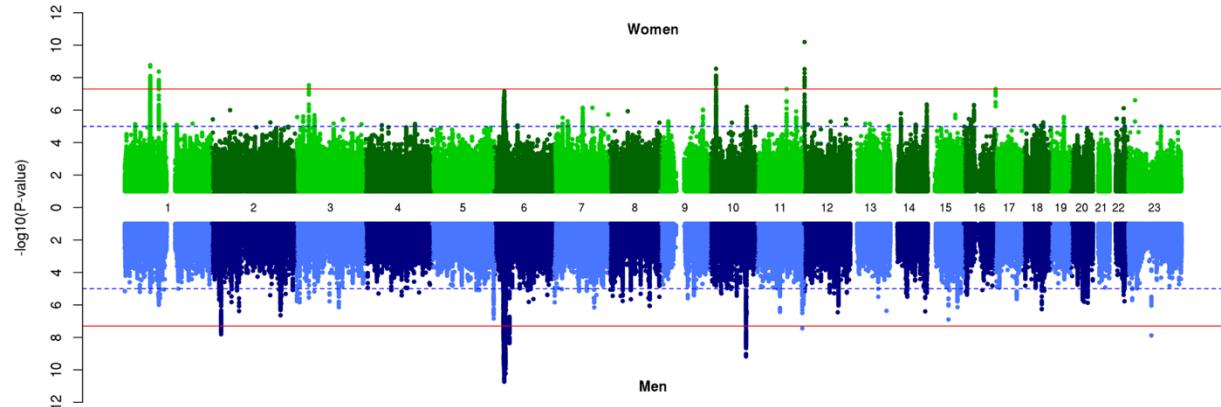


Figure S3. Miami plots for sex-stratified analyses in PGC + iPSYCH

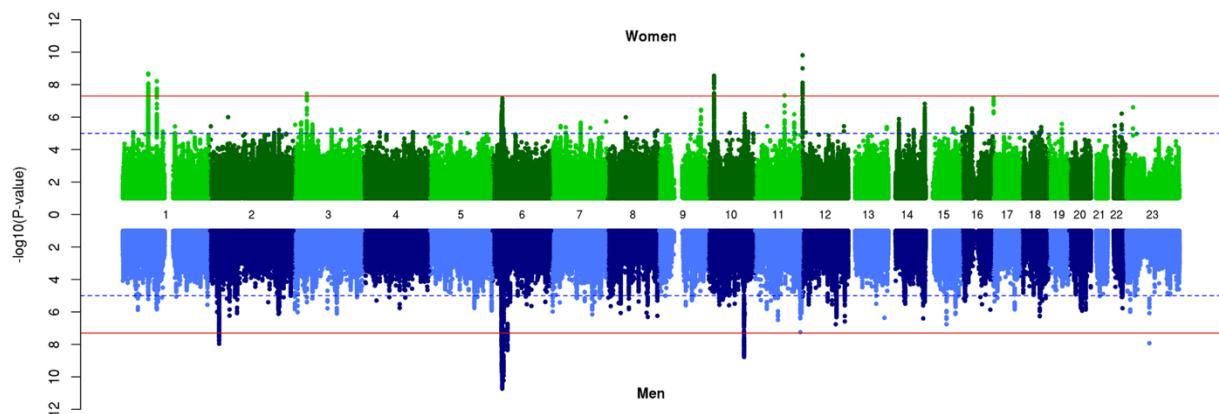
GWAS SNP main effects for men (blue) are plotted downward, and are plotted upward for women (green). Negative log₁₀-transformed *p*-values for each variant (each dot) (y-axis) are plotted by chromosomal position (x-axis). The solid red and dotted blue horizontal lines represent the thresholds for genome-wide significant association ($p = 5 \times 10^{-8}$) and suggestive association ($p = 1 \times 10^{-5}$), respectively. Plotted are the regular meta-analysis results within and across disorders only; omnibus tests were not carried out for sex-stratified analyses. Plots were generated using the ‘plot’ package in R.

Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia

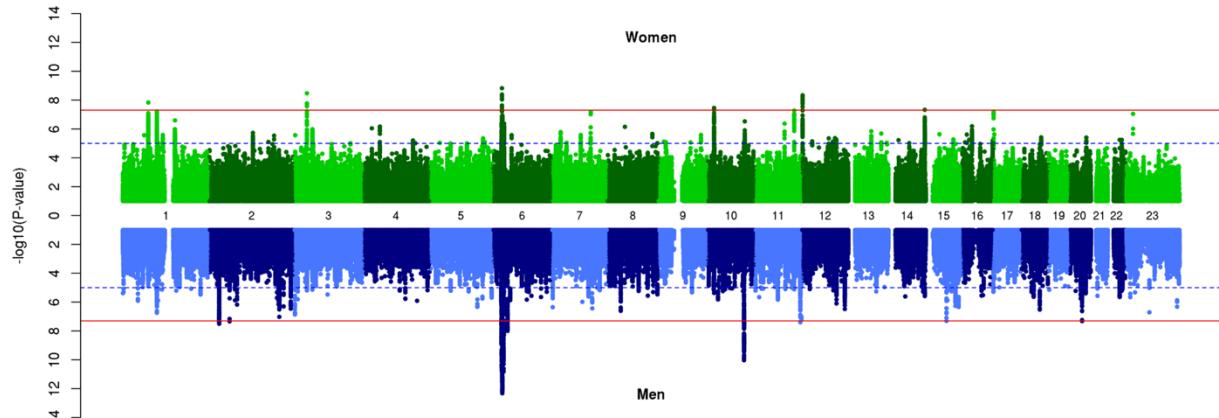
a) Schizophrenia – European ancestry only

b) Schizophrenia – European + East Asian ancestry


c) Bipolar Disorder**d) Major Depressive Disorder****e) Cross-Disorder SCZ-BIP-MDD – European ancestry only**

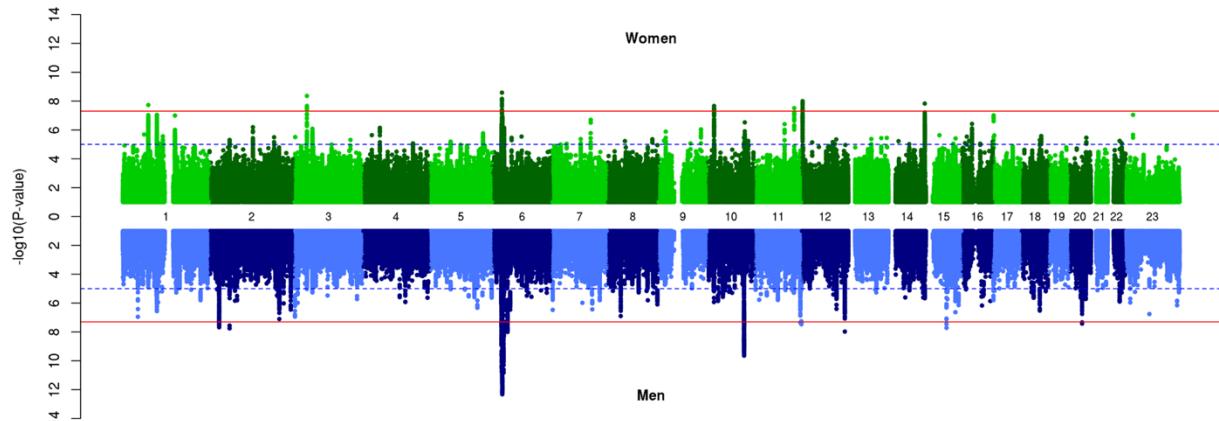
f) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



g) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



h) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry



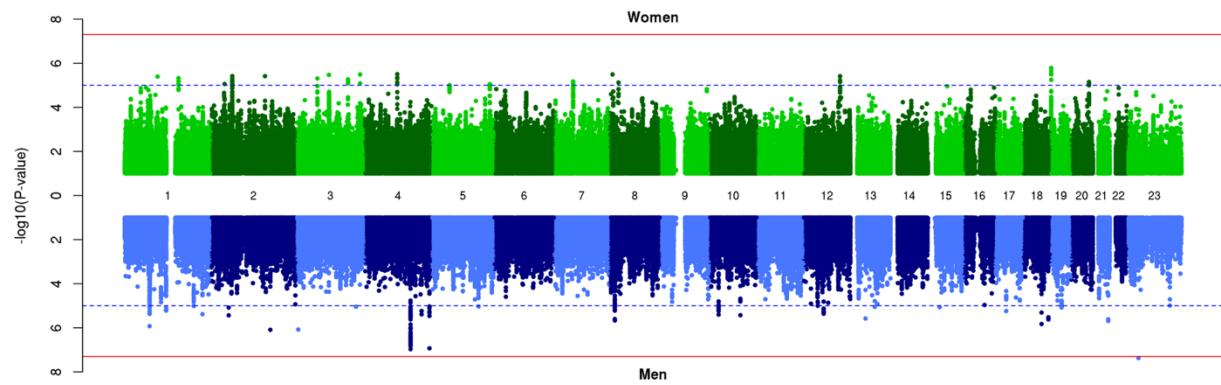
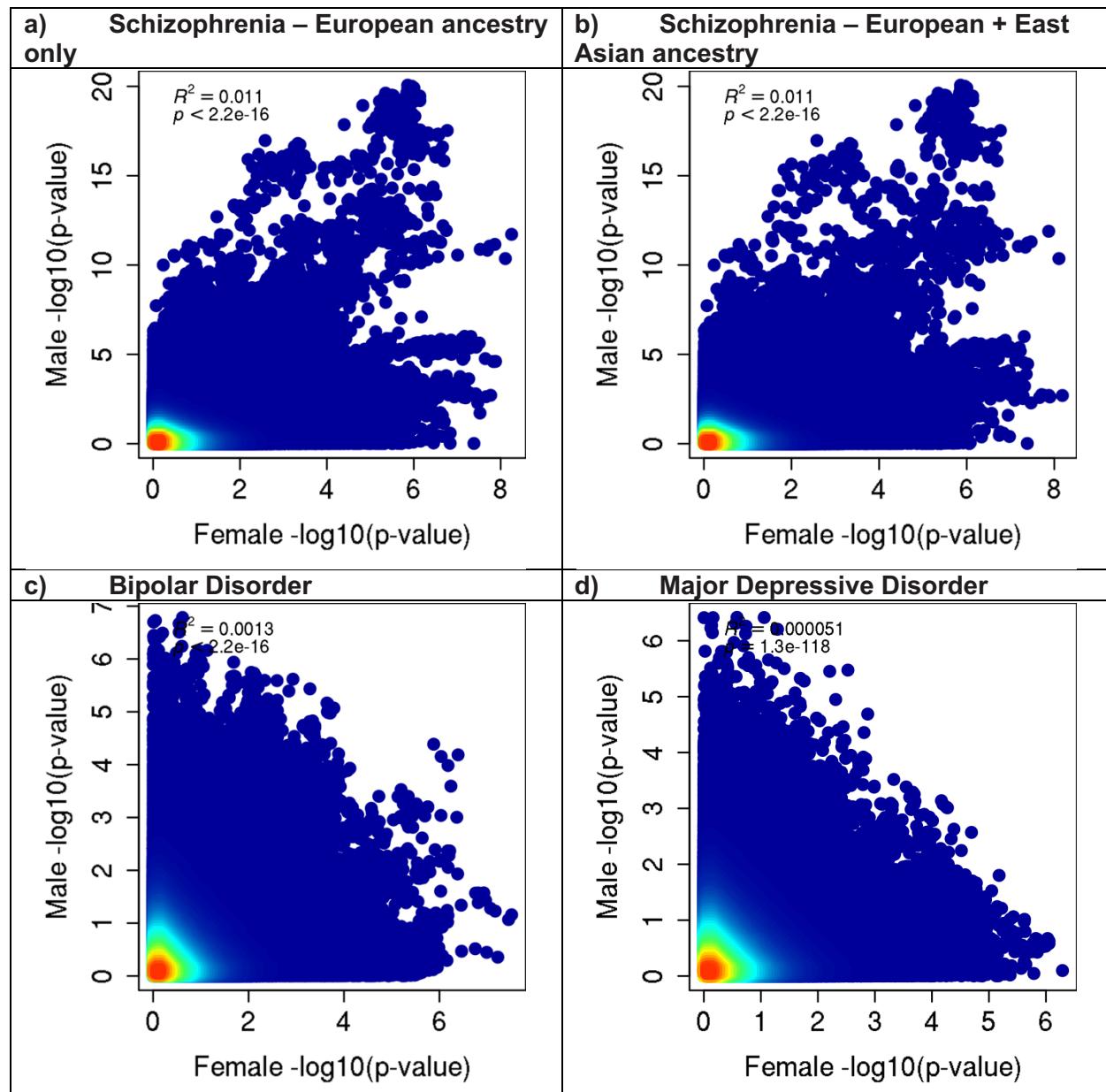
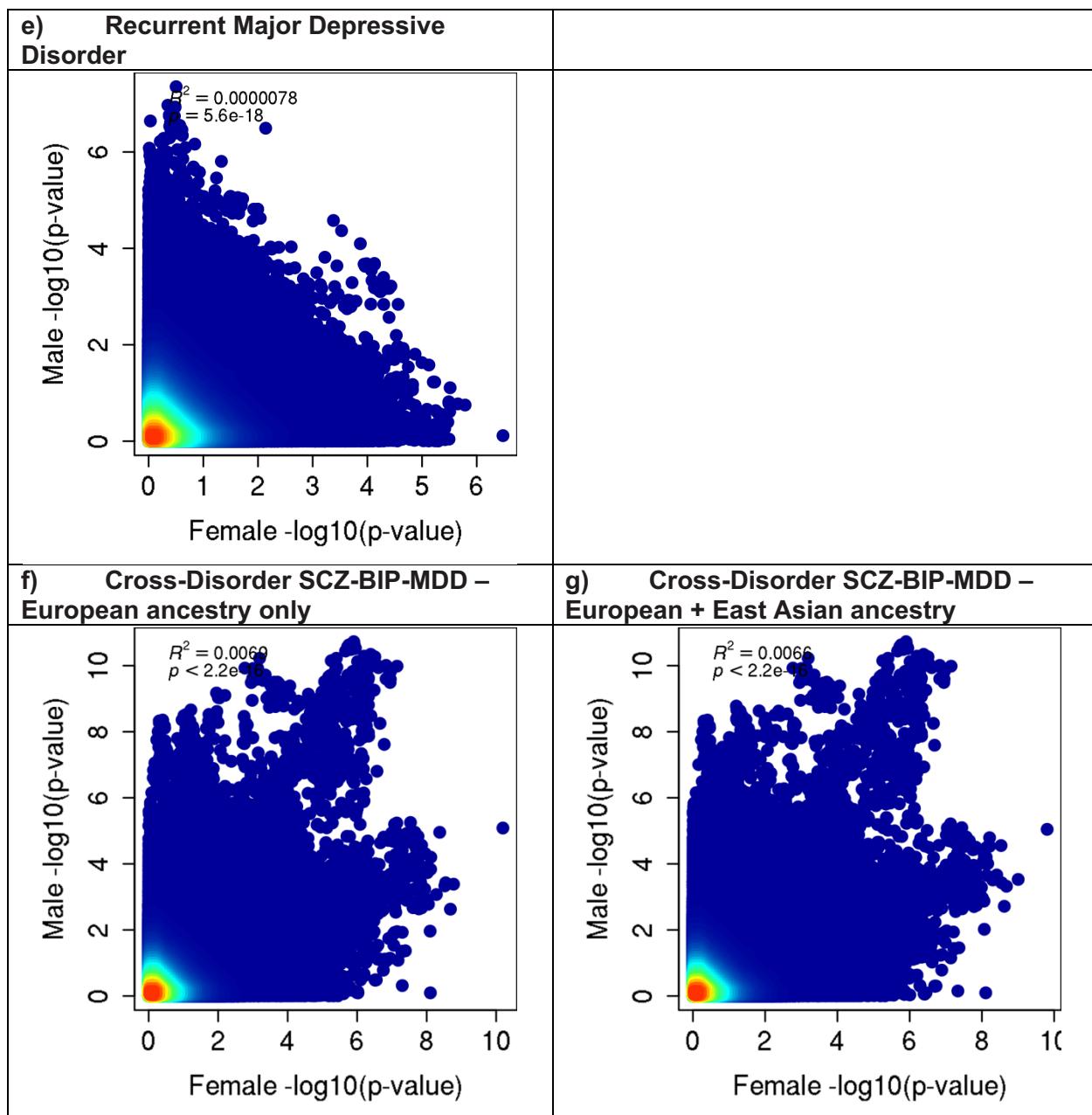
i) Recurrent Major Depressive Disorder

Figure S4. Scatter plots of female vs male associations in PGC + iPSYCH

The scatter plots show little correlation (R) between GWAS SNP main effect p -values from the two sexes, indicating the strength of association differed substantially between the two sexes. Plots were generated using the ‘plot’ package in R.

Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; R^2 = proportion variance explained.





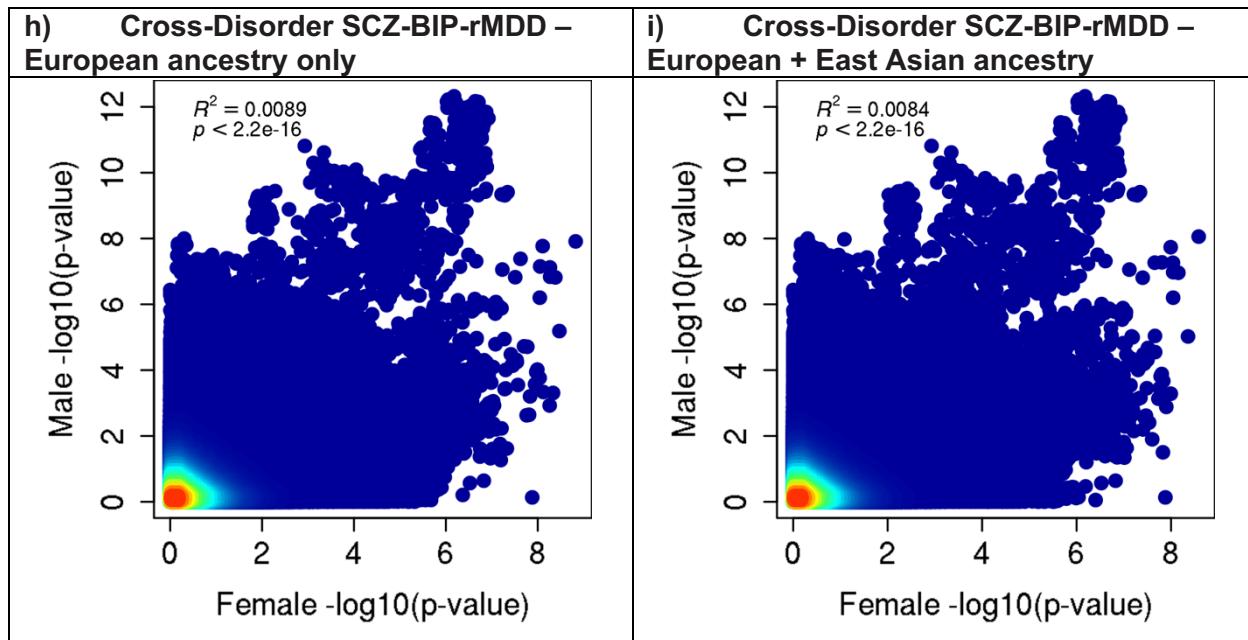
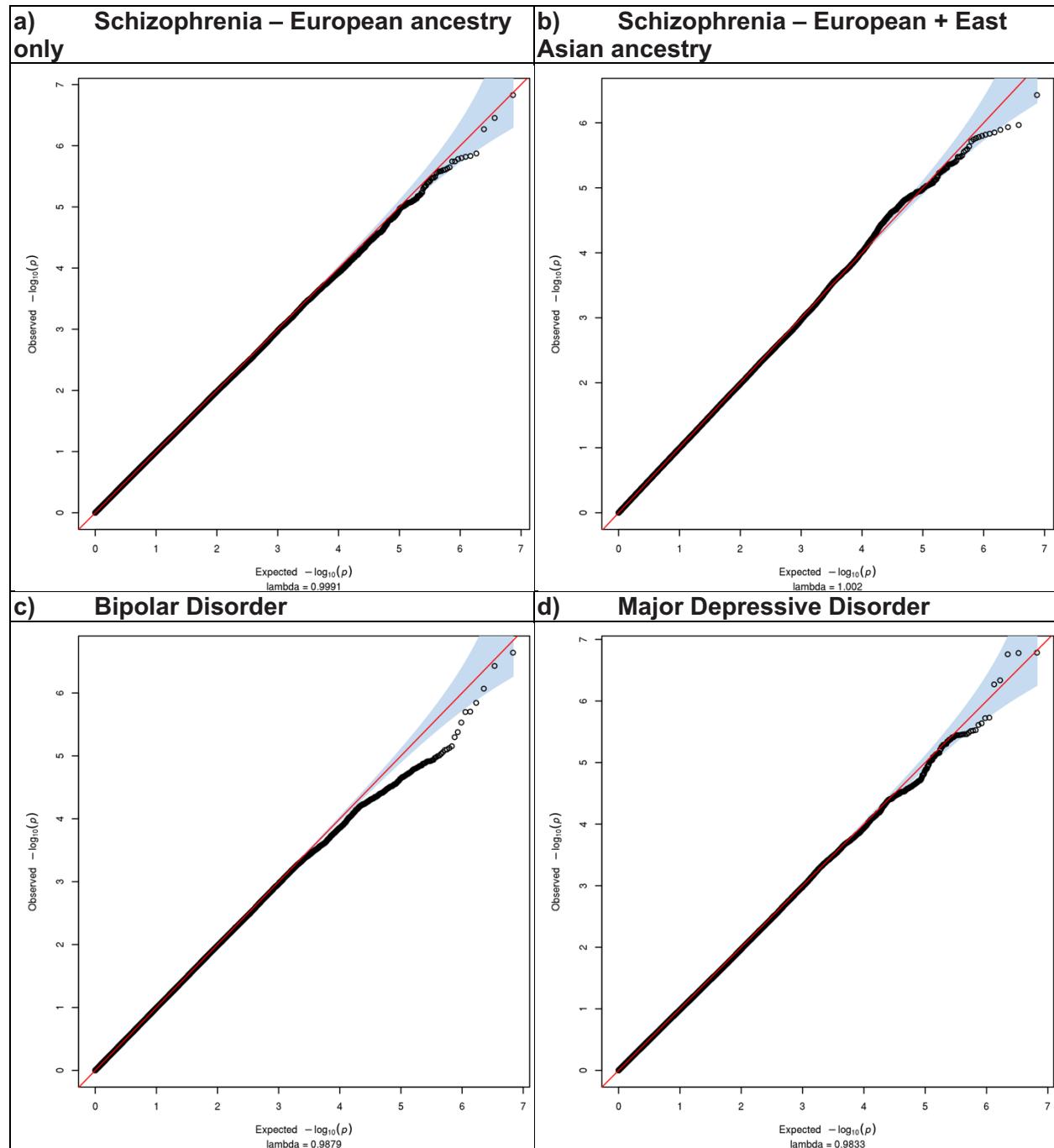
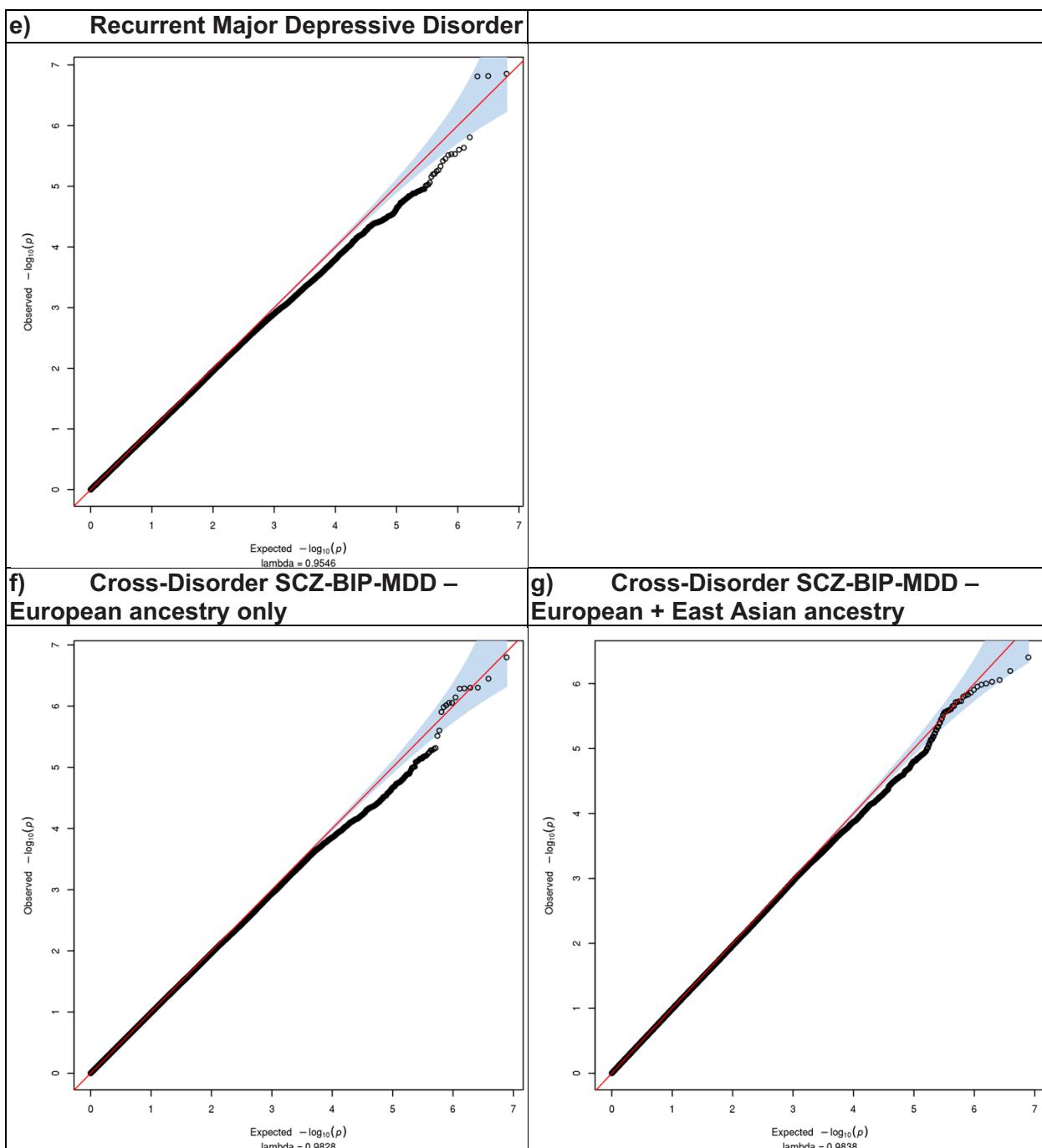


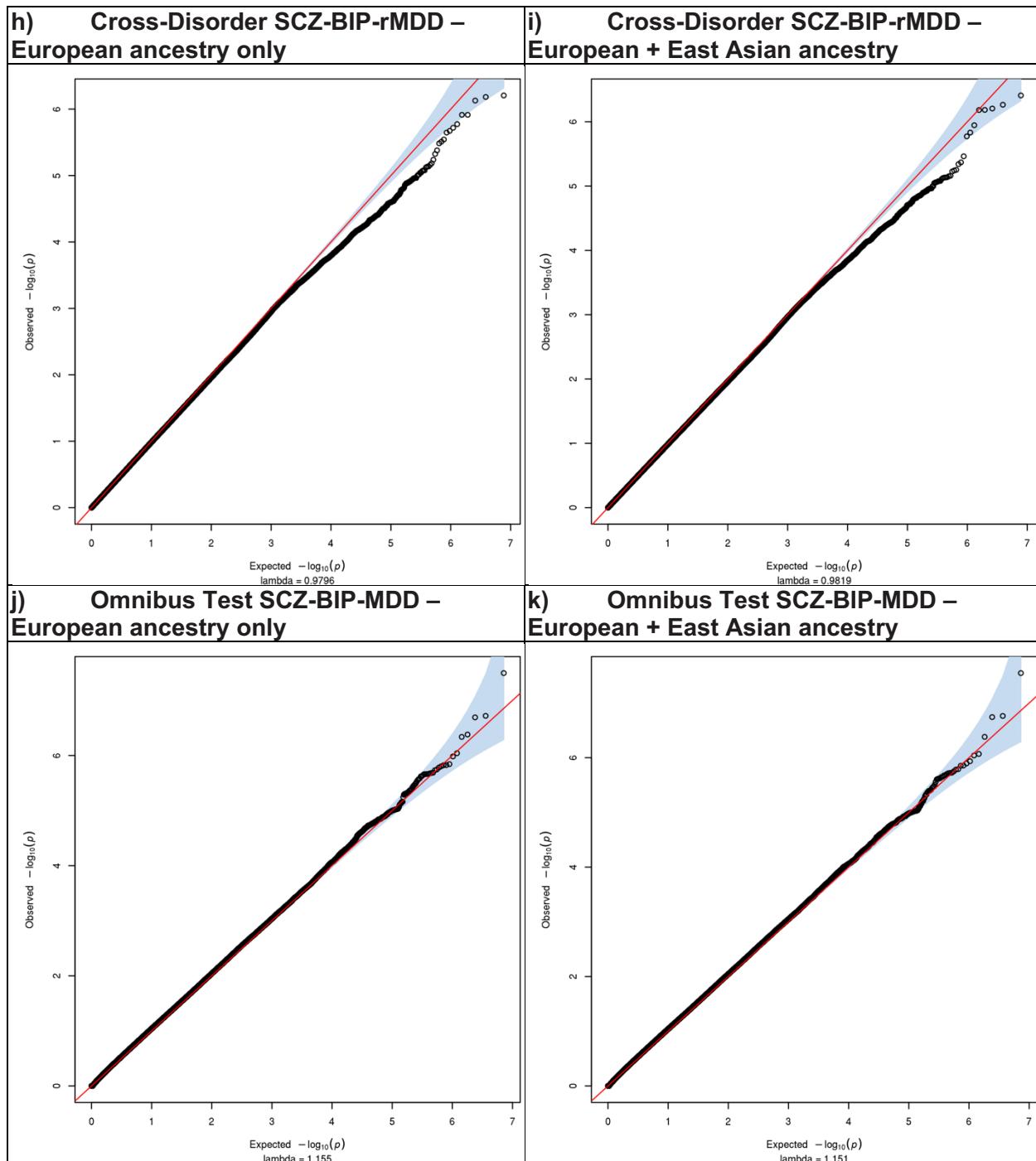
Figure S5. Quantile-Quantile plots for G×S interaction in PGC + iPSYCH

The Quantile-Quantile (Q-Q) plot is used to assess the number and magnitude of observed associations compared with the expectations under no association. The nature of deviations from the identity line provide clues whether the observed associations are true associations or may be due to for example population stratification or cryptic relatedness.

Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia







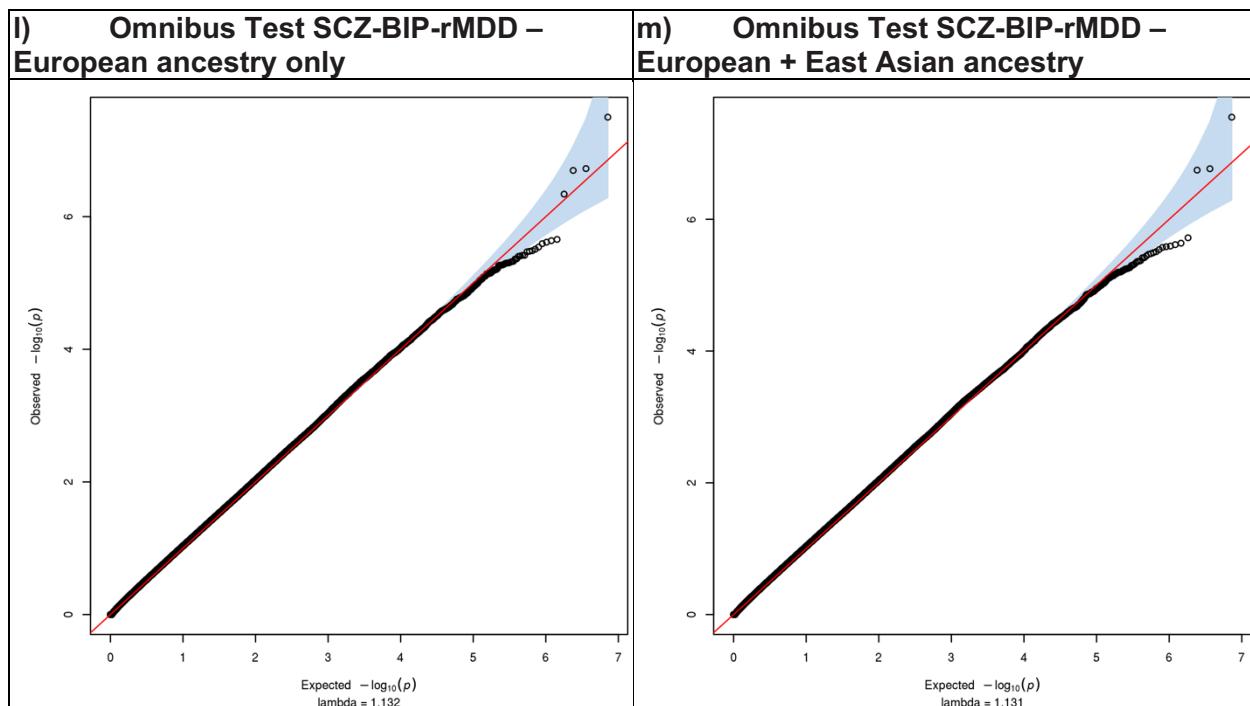
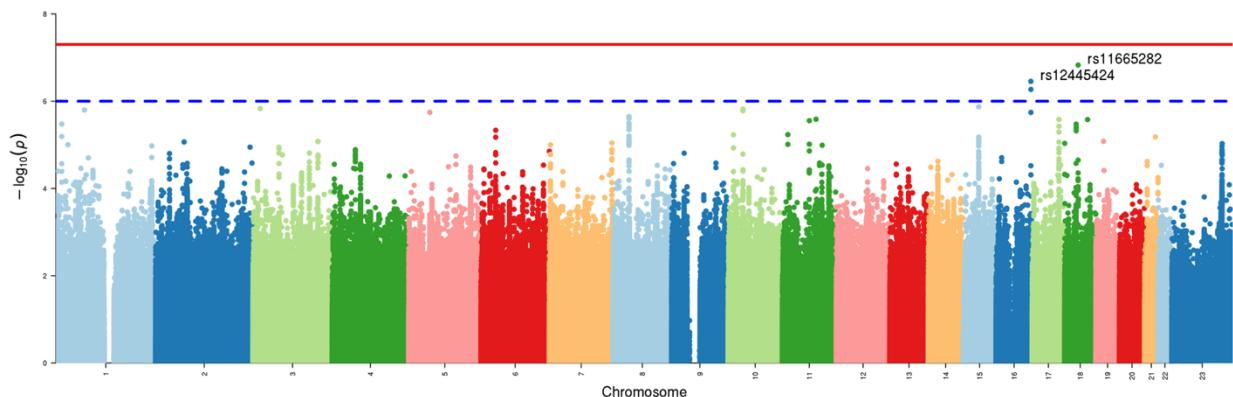


Figure S6. Manhattan plots of the G×S interaction GWAS in PGC + iPSYCH

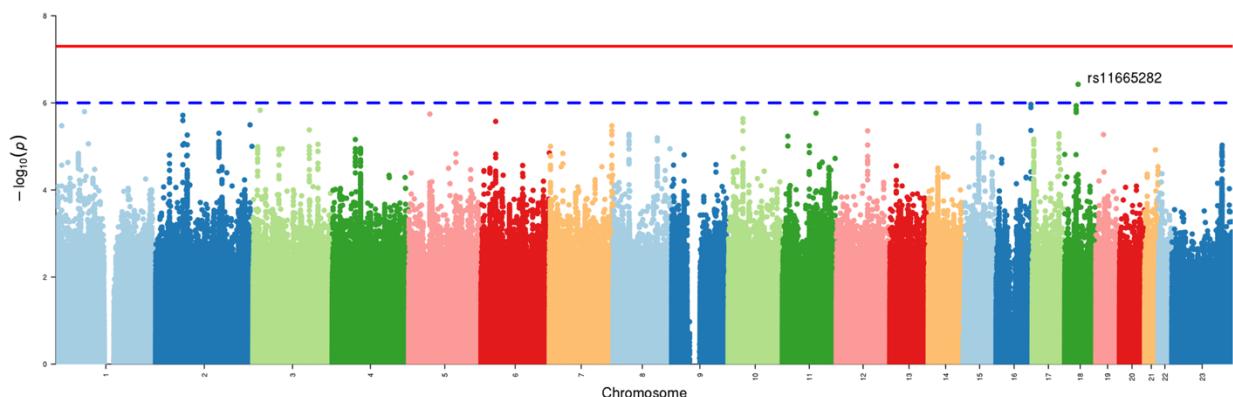
Negative log₁₀-transformed *p*-values for each variant (each dot) (y-axis) are plotted by chromosomal position (x-axis). The red and blue lines represent the thresholds for genome-wide significant association ($p = 5 \times 10^{-8}$) and suggestive association ($p = 1 \times 10^{-5}$), respectively. P-values for X chromosome (23) model B (alleles: females 0, 1, or 2; males 0 or 1) are included.

Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia

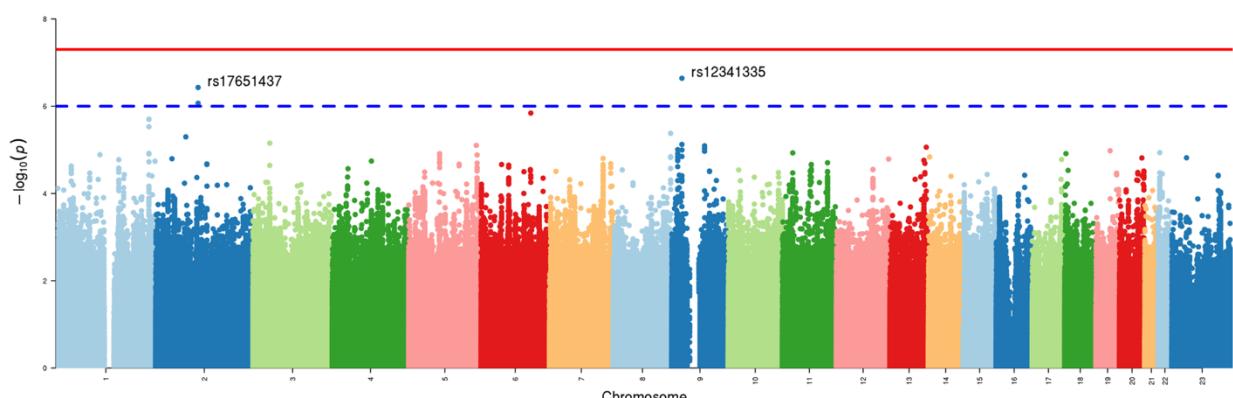
a) Schizophrenia – European ancestry only

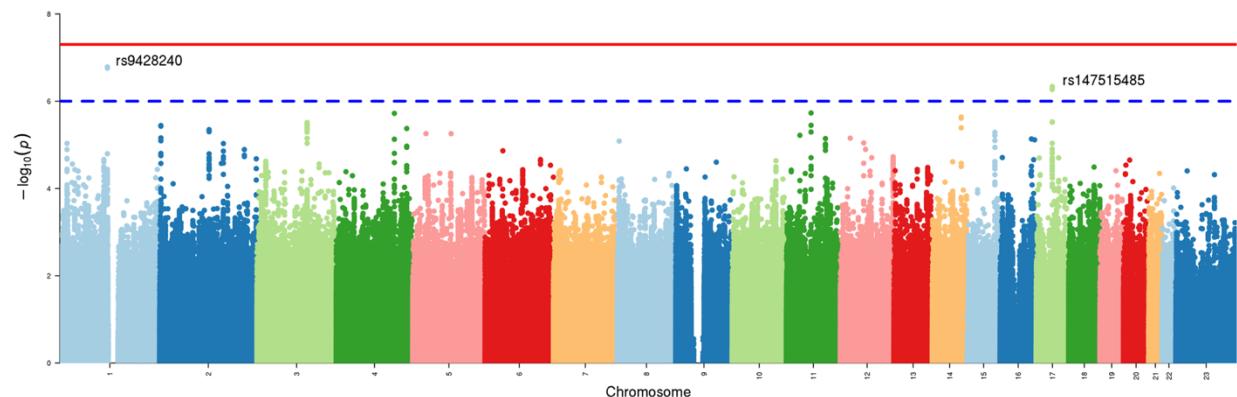
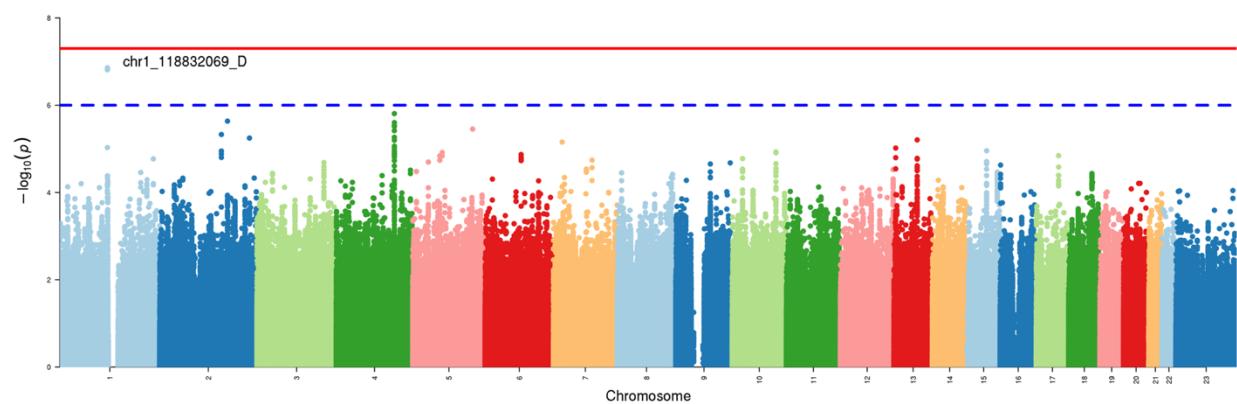
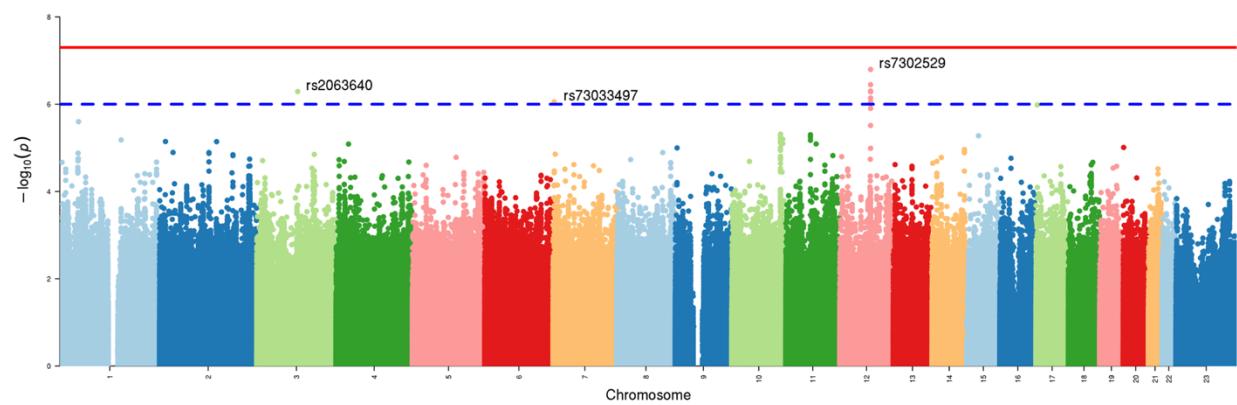


b) Schizophrenia – European + East Asian ancestry

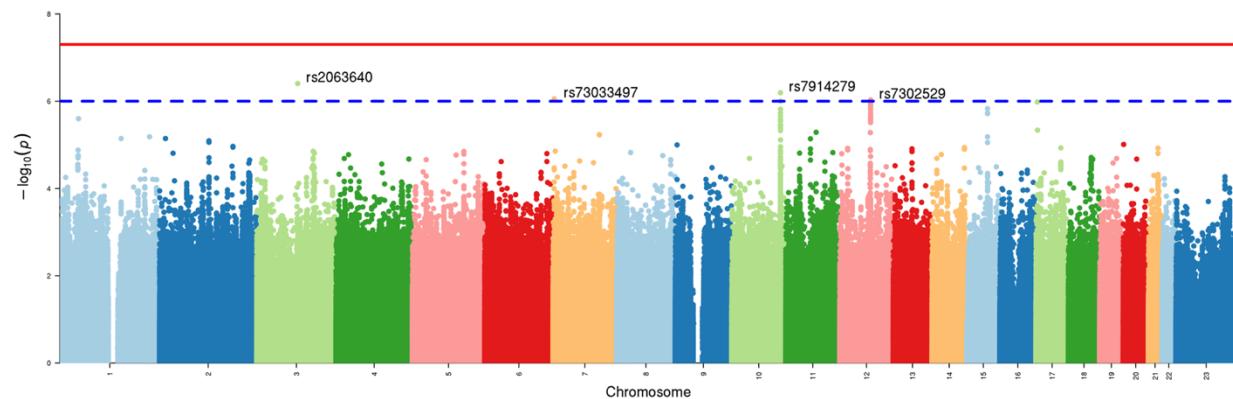


c) Bipolar Disorder

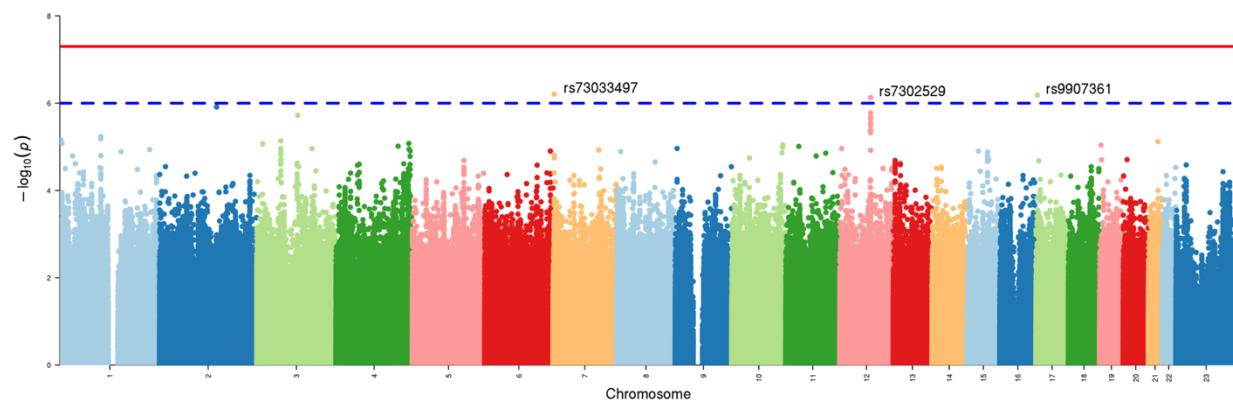


d) Major Depressive Disorder**e) Recurrent Major Depressive Disorders****f) Cross-Disorder SCZ-BIP-MDD – European ancestry only**

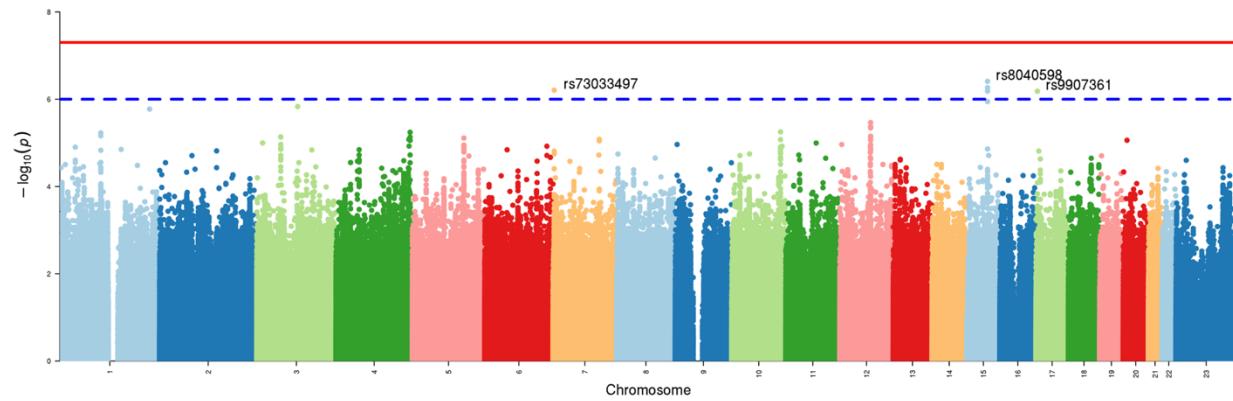
g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry

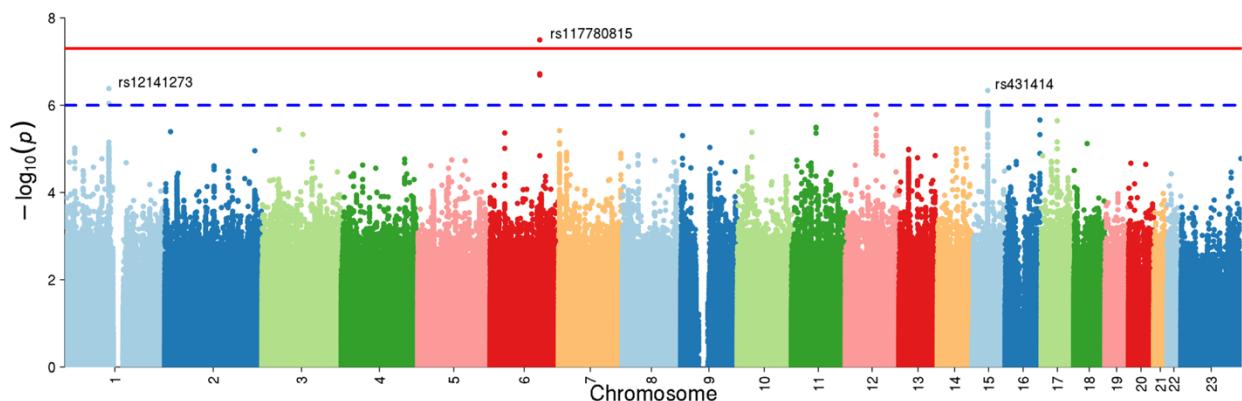
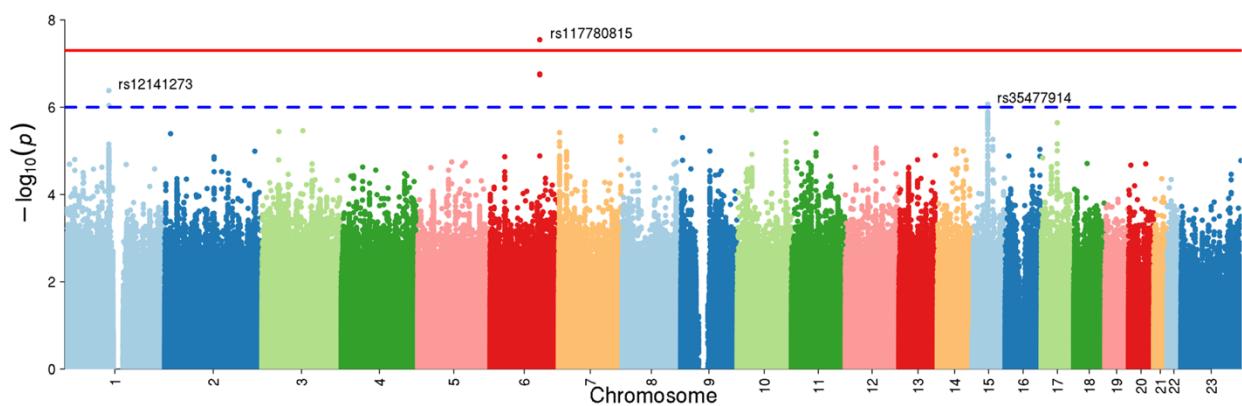
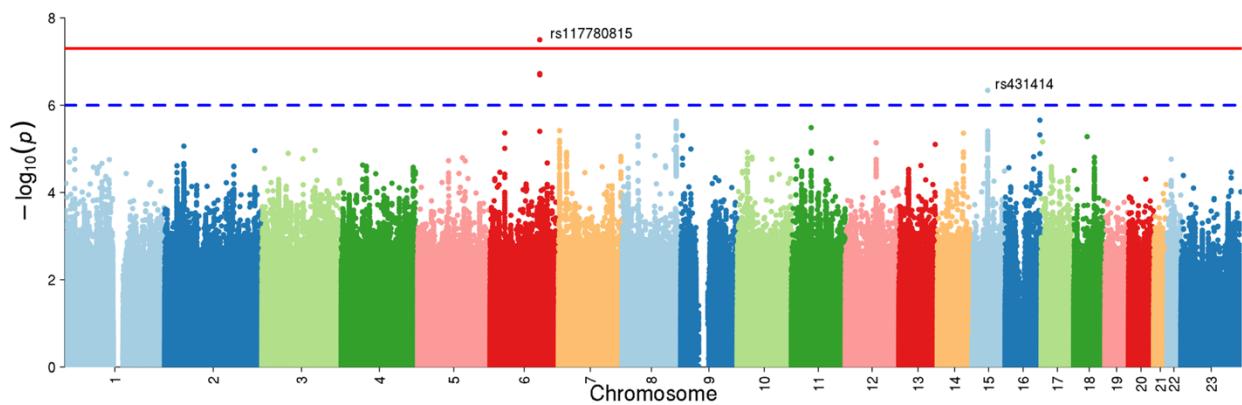


h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry



j) Omnibus Test SCZ-BIP-MDD – European ancestry only**k) Omnibus Test SCZ-BIP-MDD – European + East Asian ancestry****l) Omnibus Test SCZ-BIP-rMDD – European ancestry only**

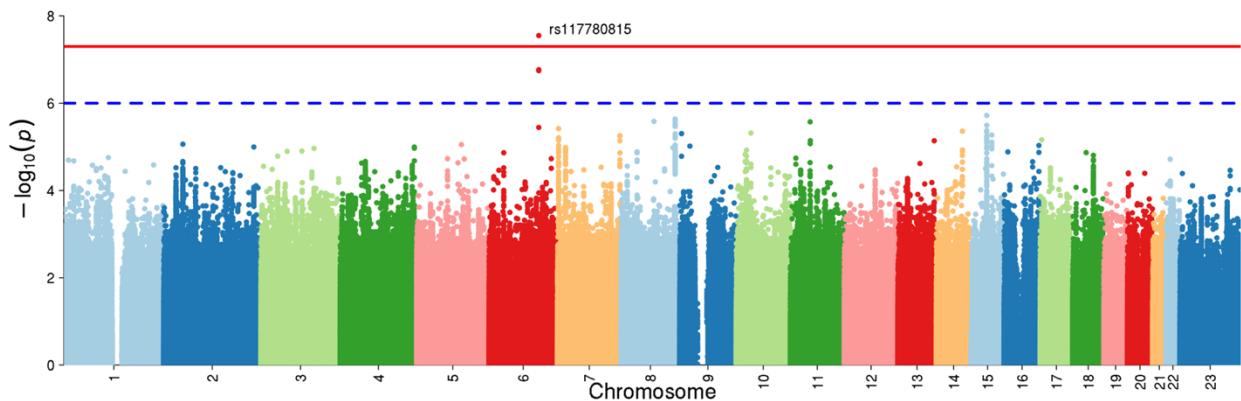
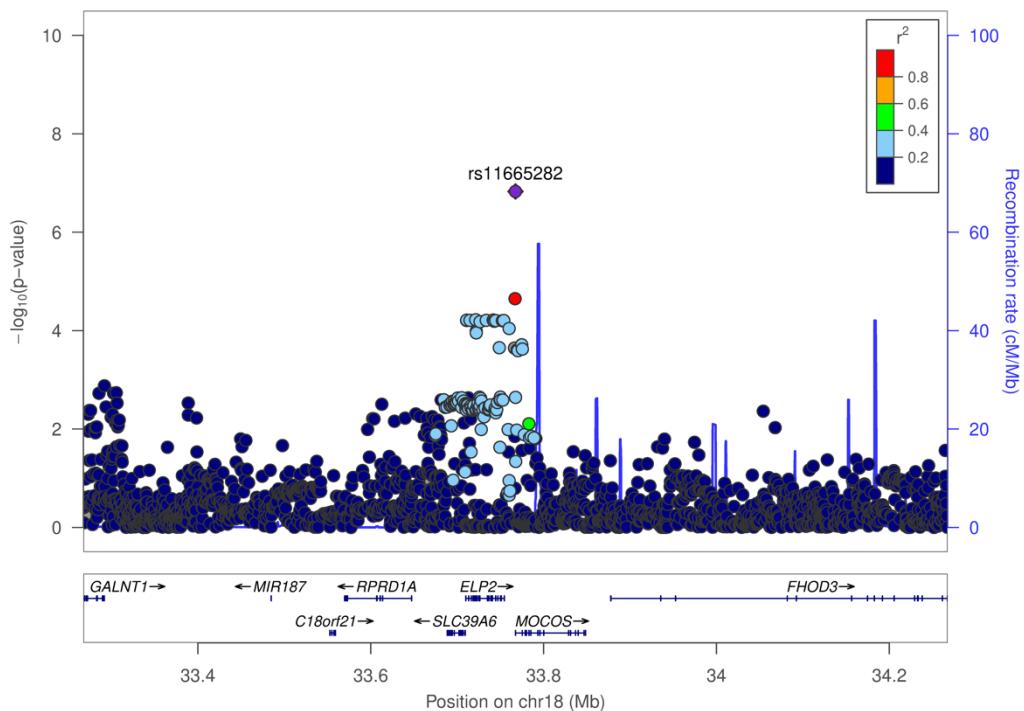
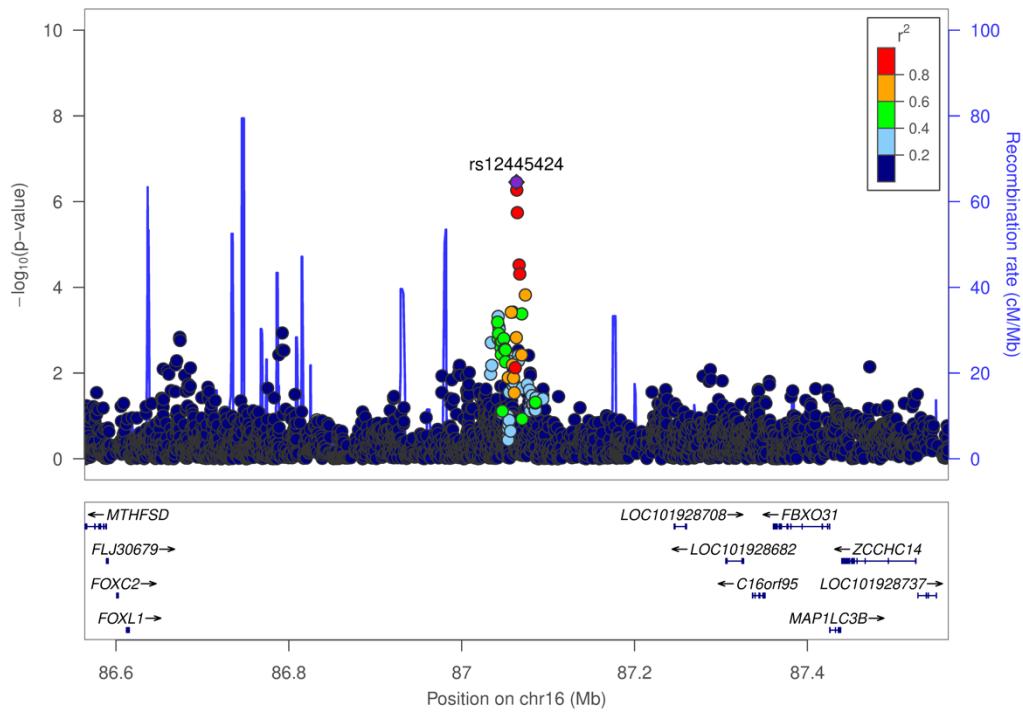
m) Omnibus Test SCZ-BIP-rMDD – European + East Asian ancestry

Figure S7. LocusZoom plots for loci with G×S interaction in PGC + iPSYCH

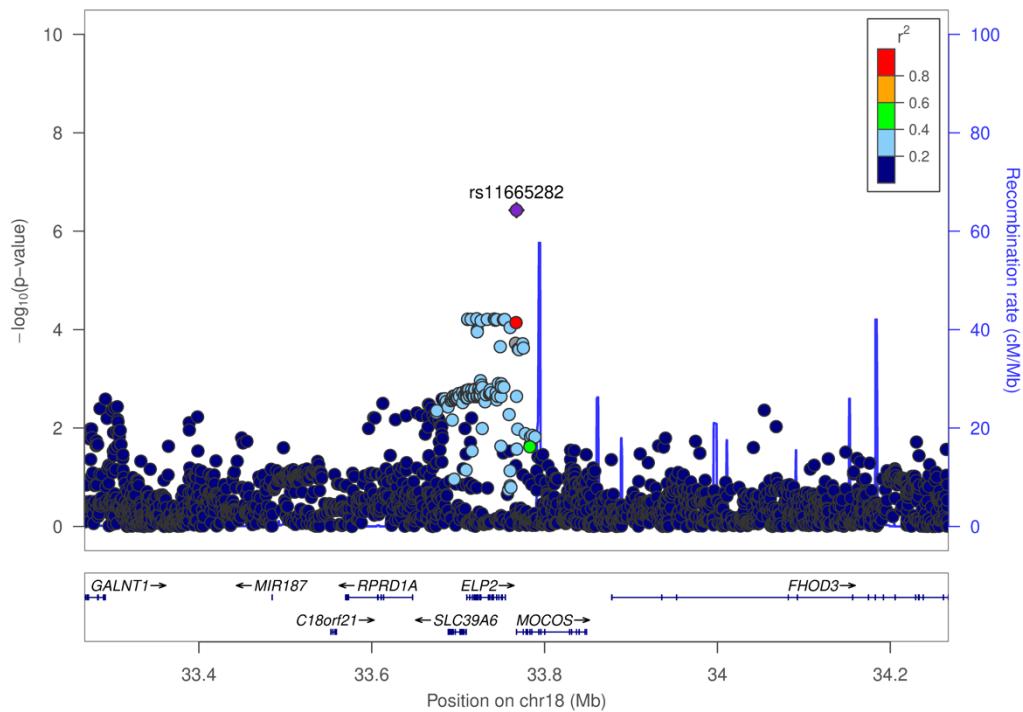
Plots were generated using the LocusZoom 1.4 Standalone application (49) for loci with G×S interaction $p < 1 \times 10^{-6}$.

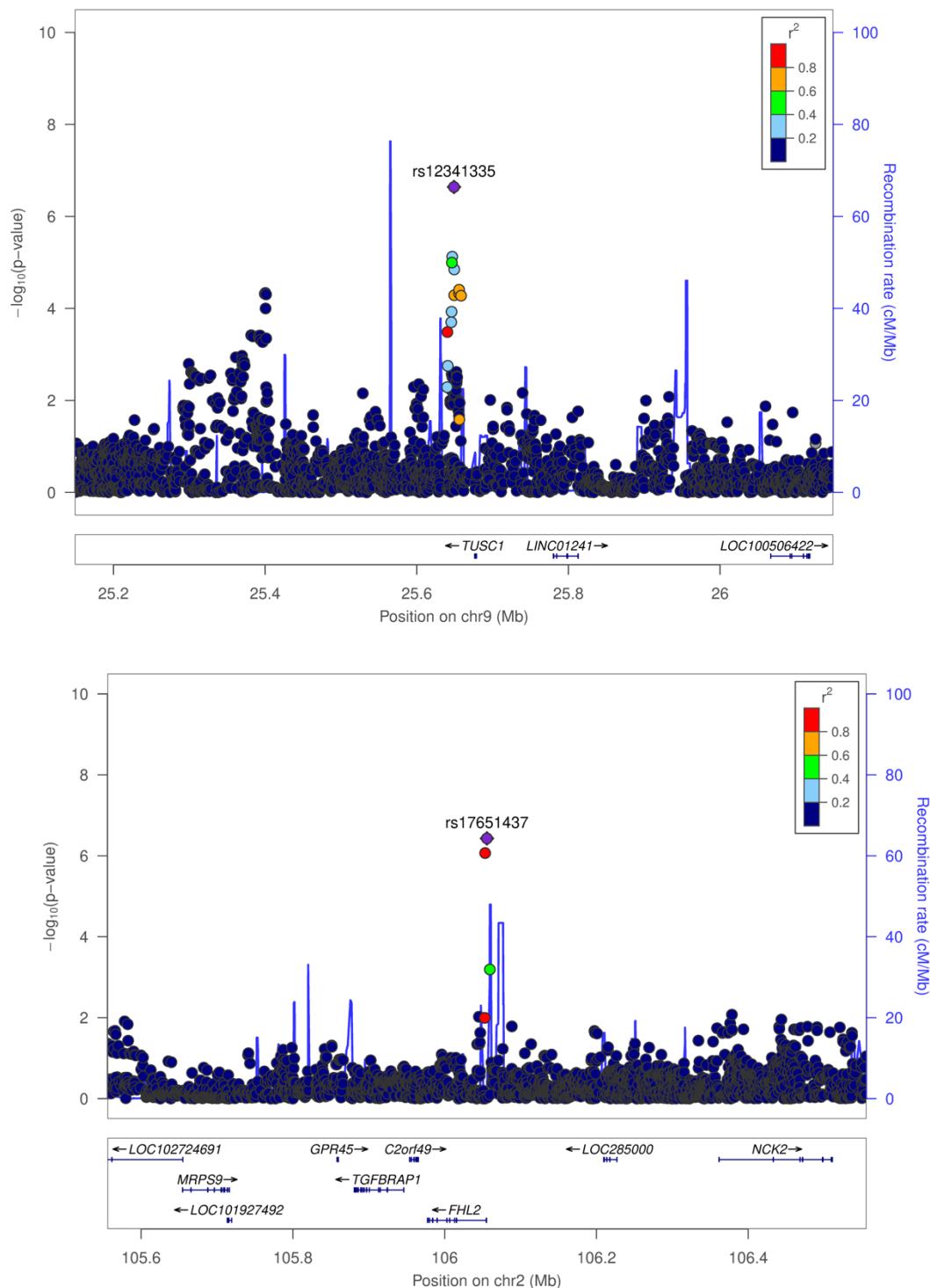
Abbreviations: chr = chromosome; cM = centimorgans; Mb = megabases; r^2 = linkage disequilibrium level; BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia

a) Schizophrenia – European ancestry only


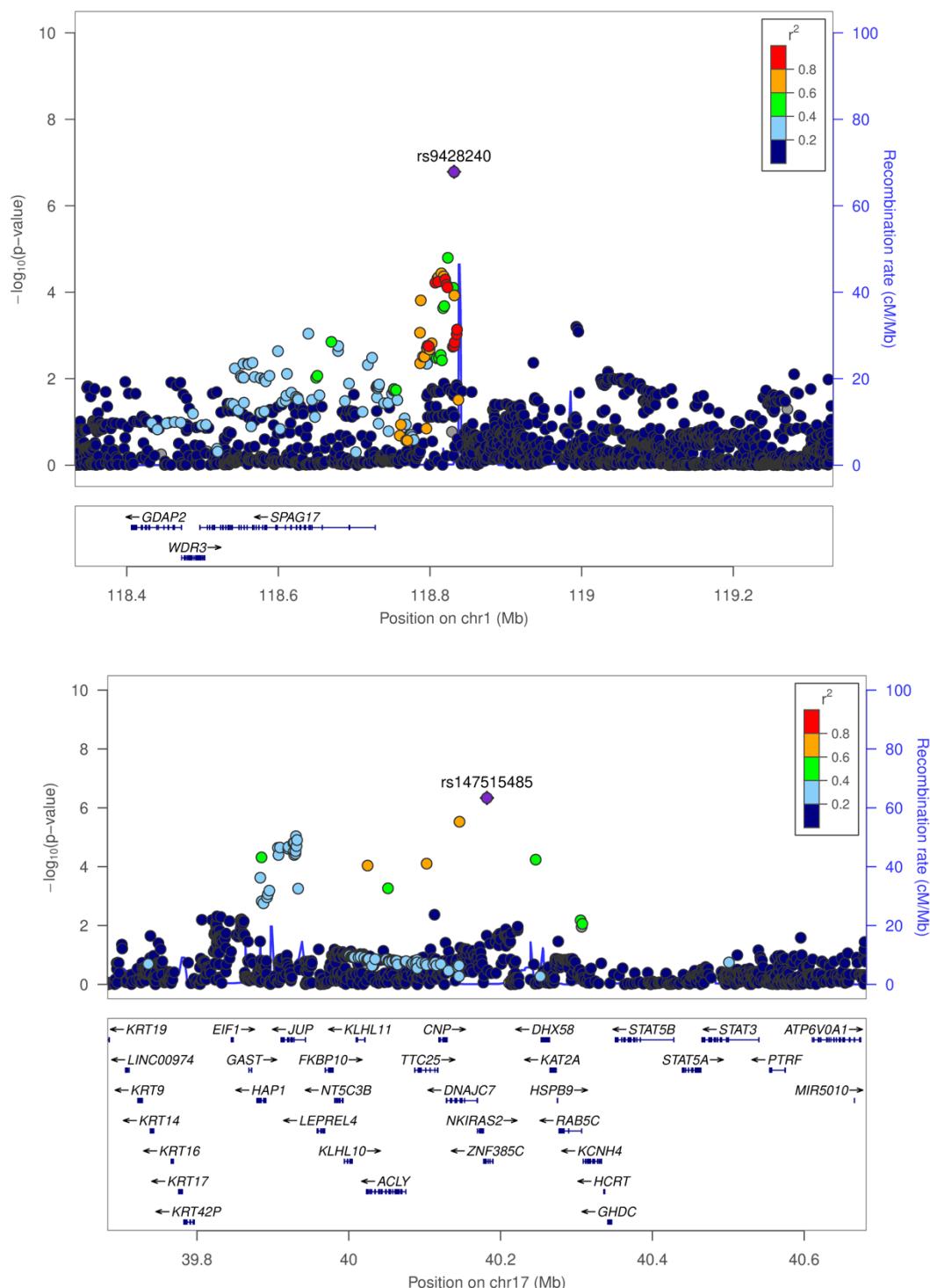


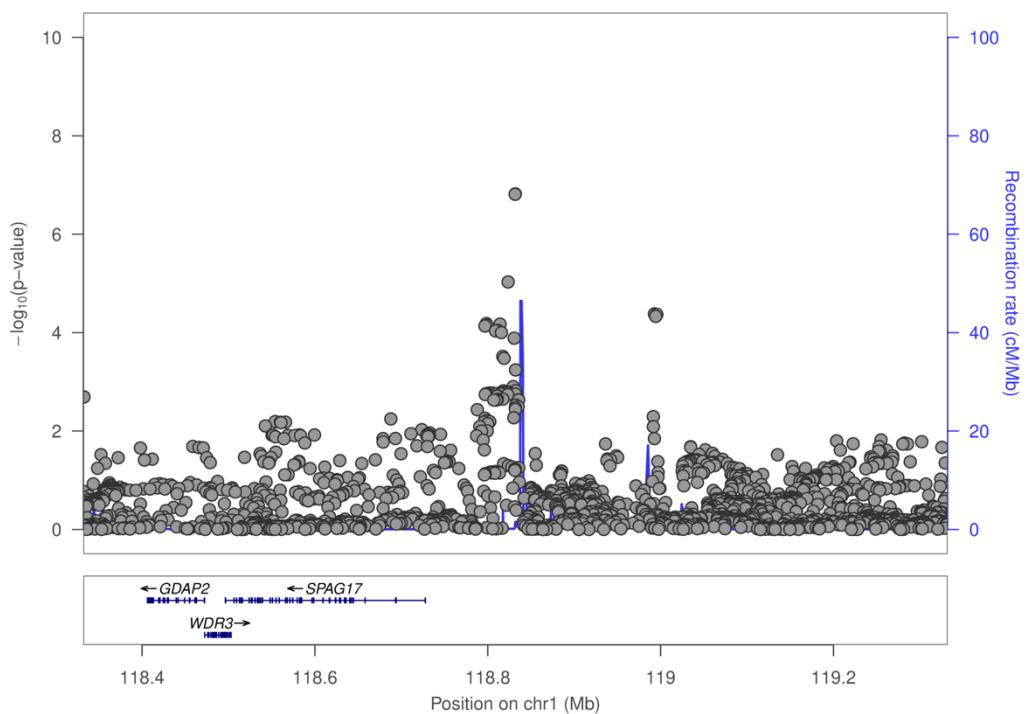
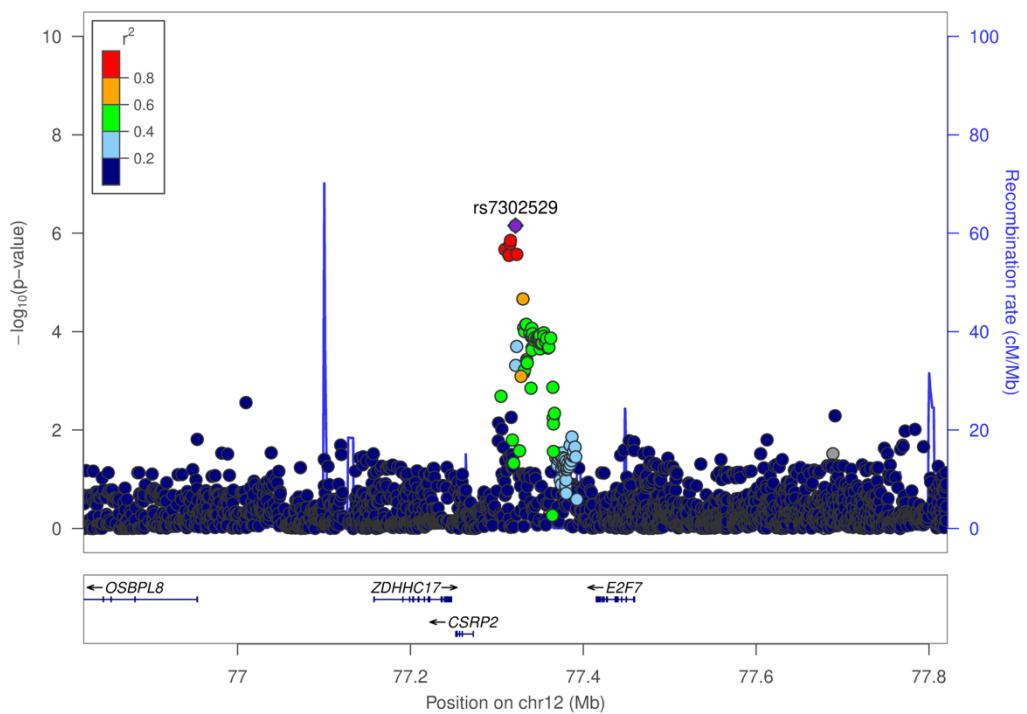
b) Schizophrenia – European + East Asian ancestry

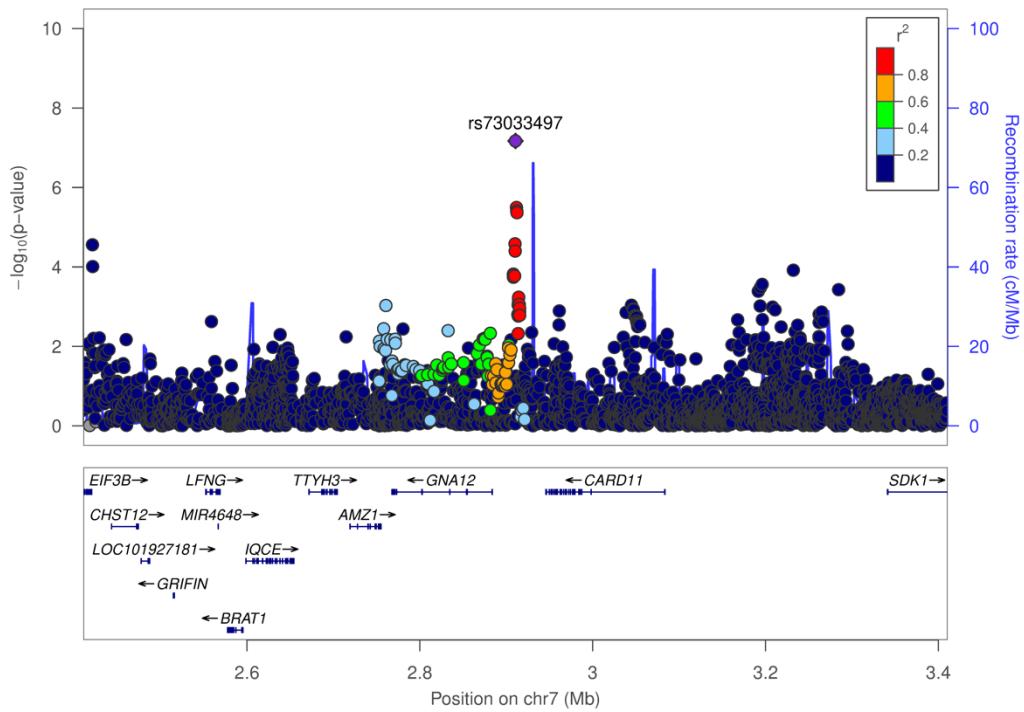


c) Bipolar Disorder

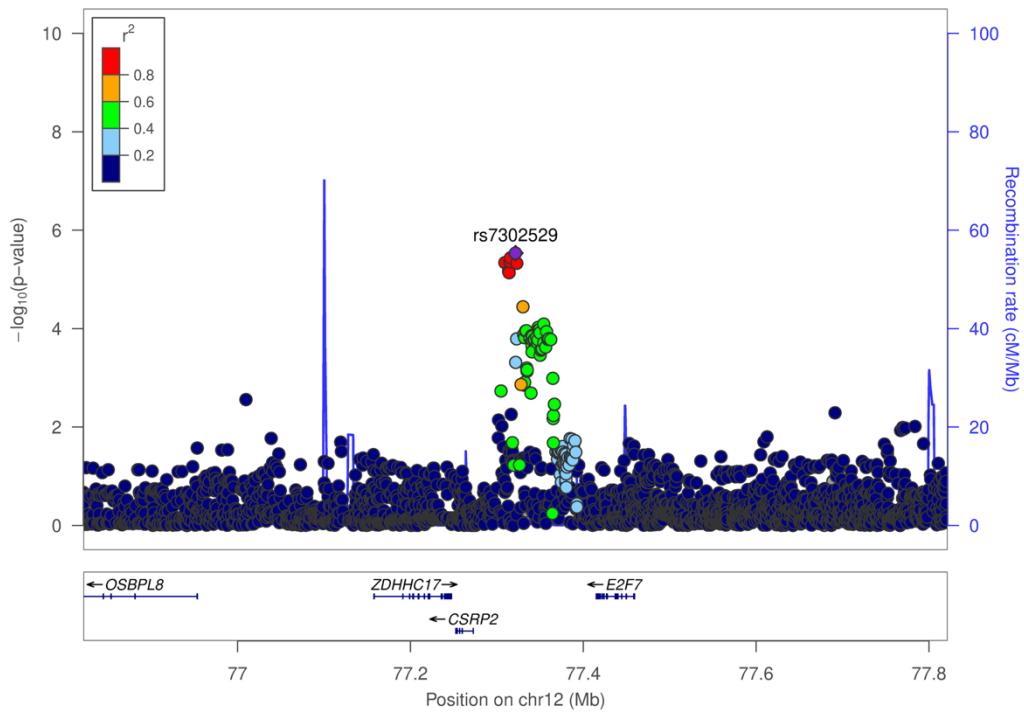
d) Major Depressive Disorder

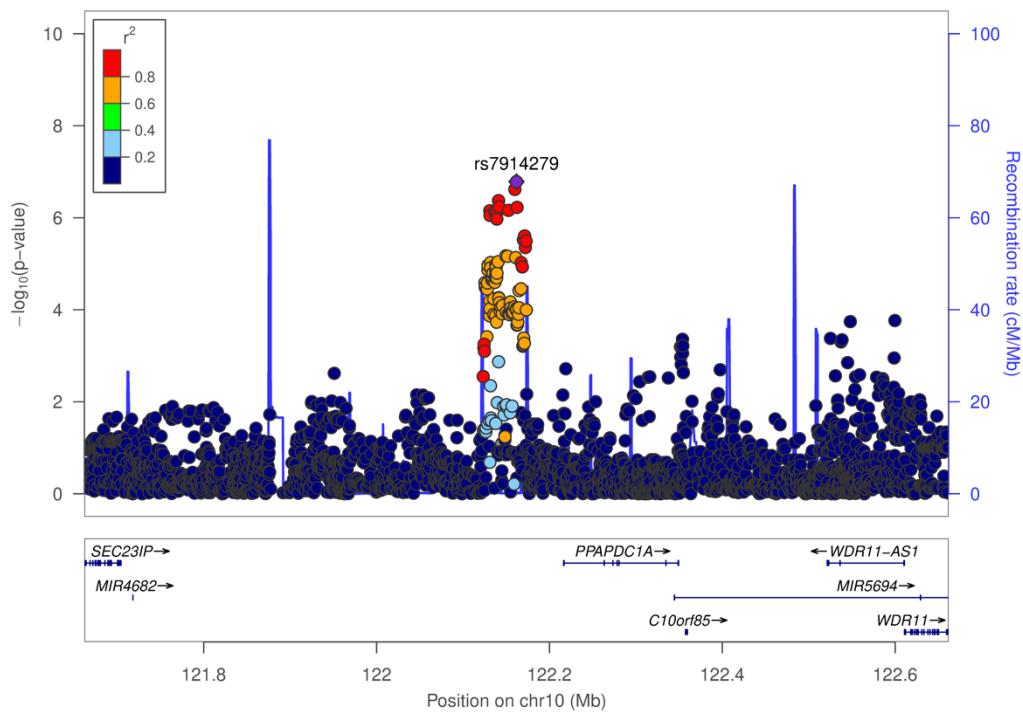


e) Recurrent Major Depressive Disorder**f) Cross-Disorder SCZ-BIP-MDD – European ancestry only**

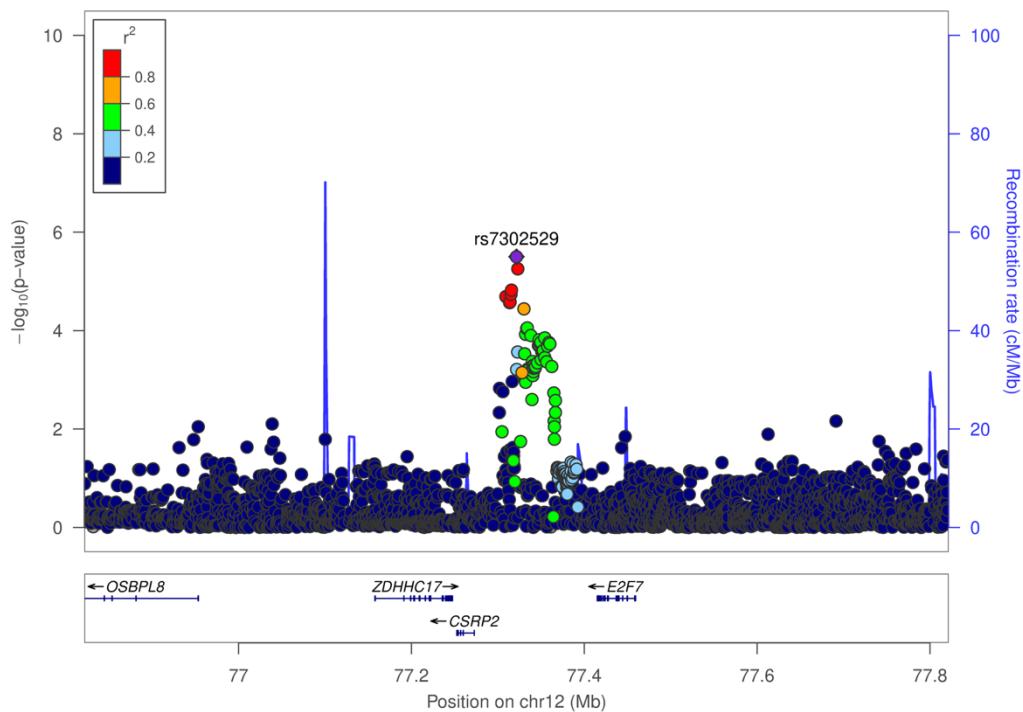


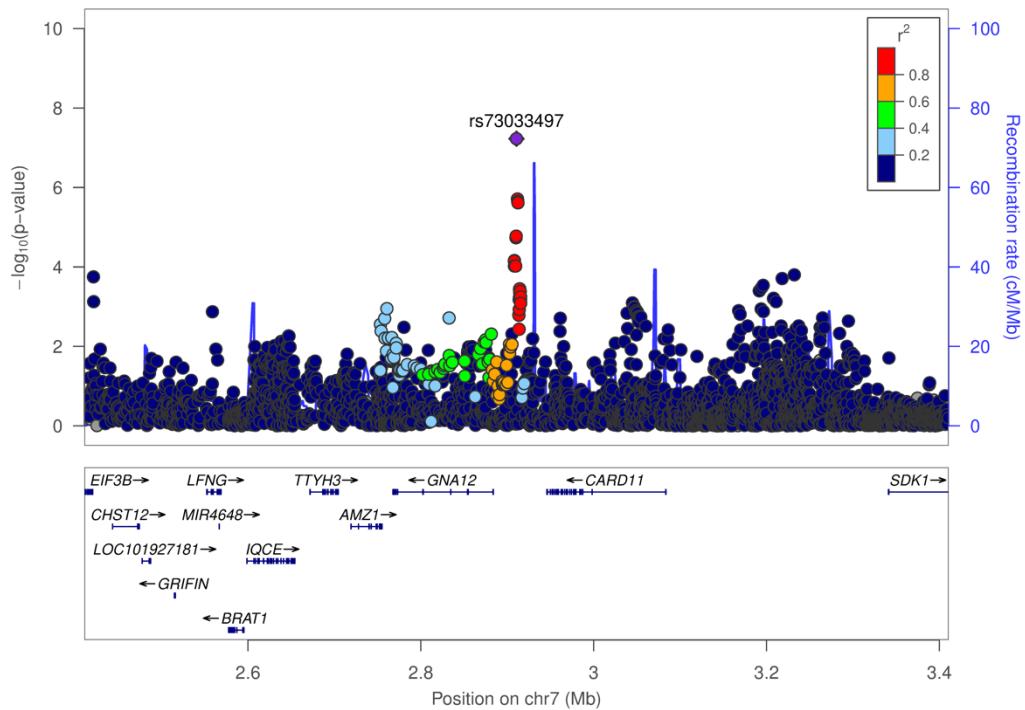
g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



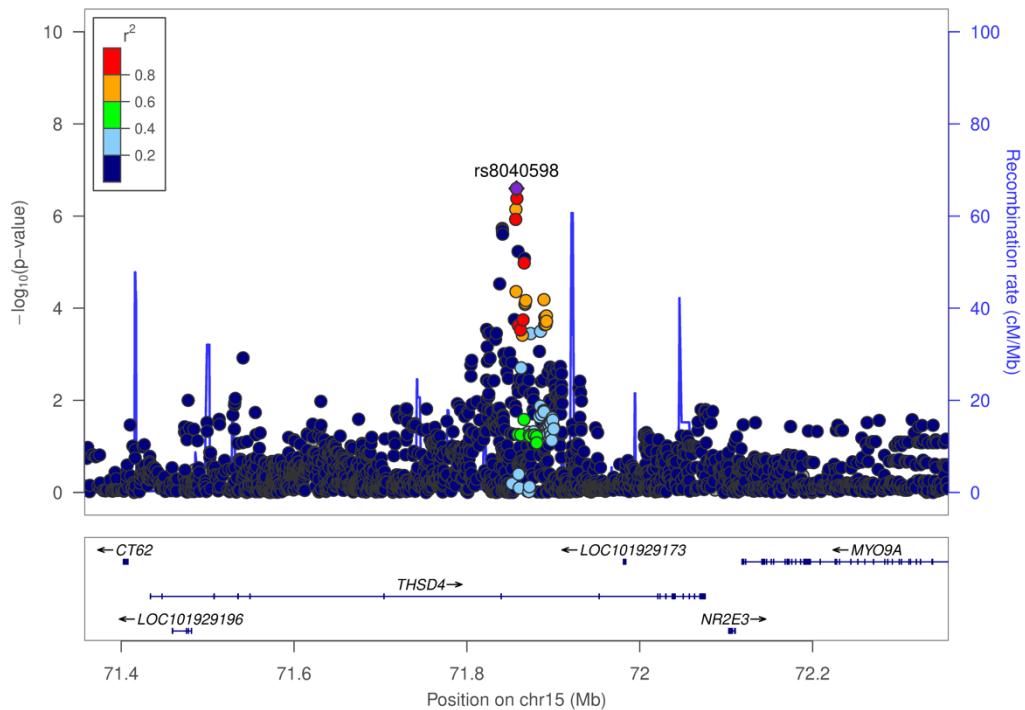


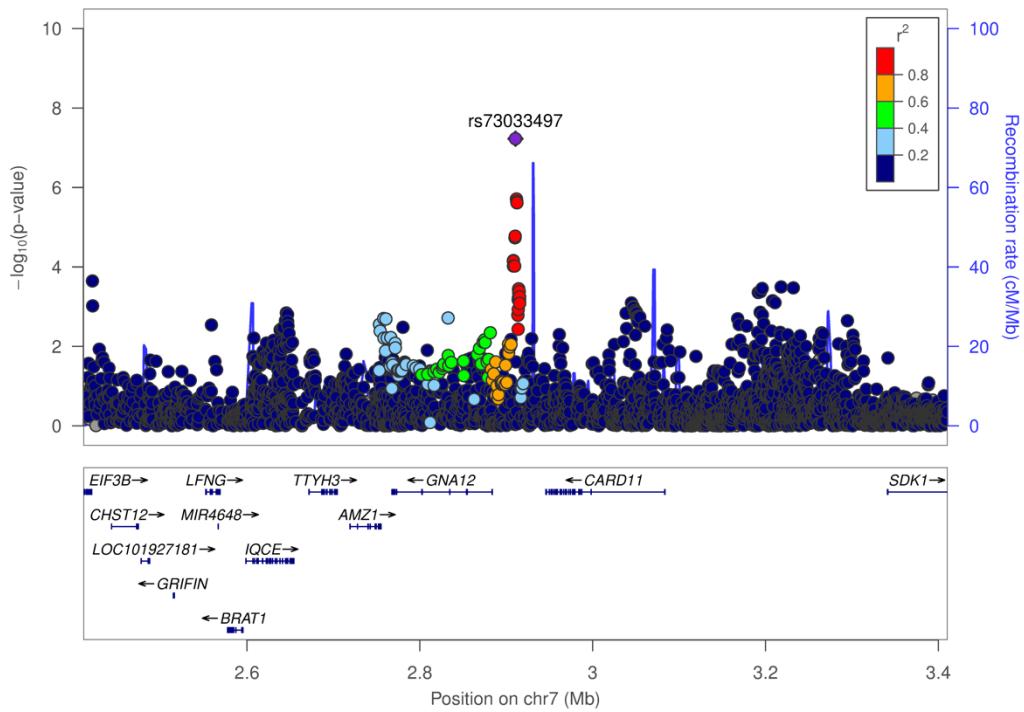
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



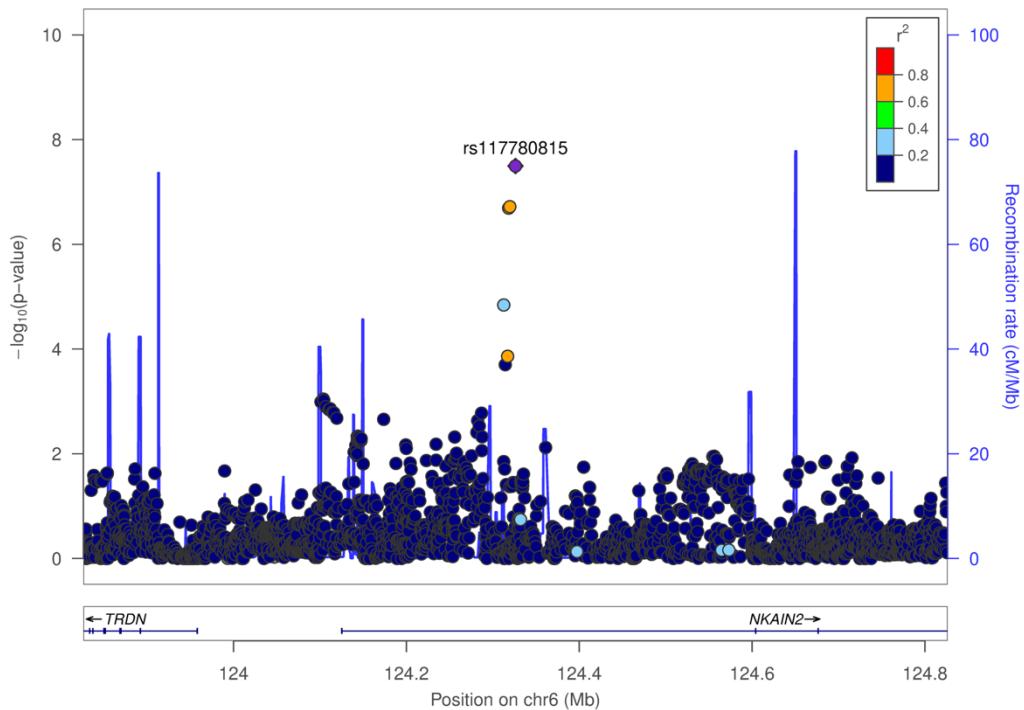


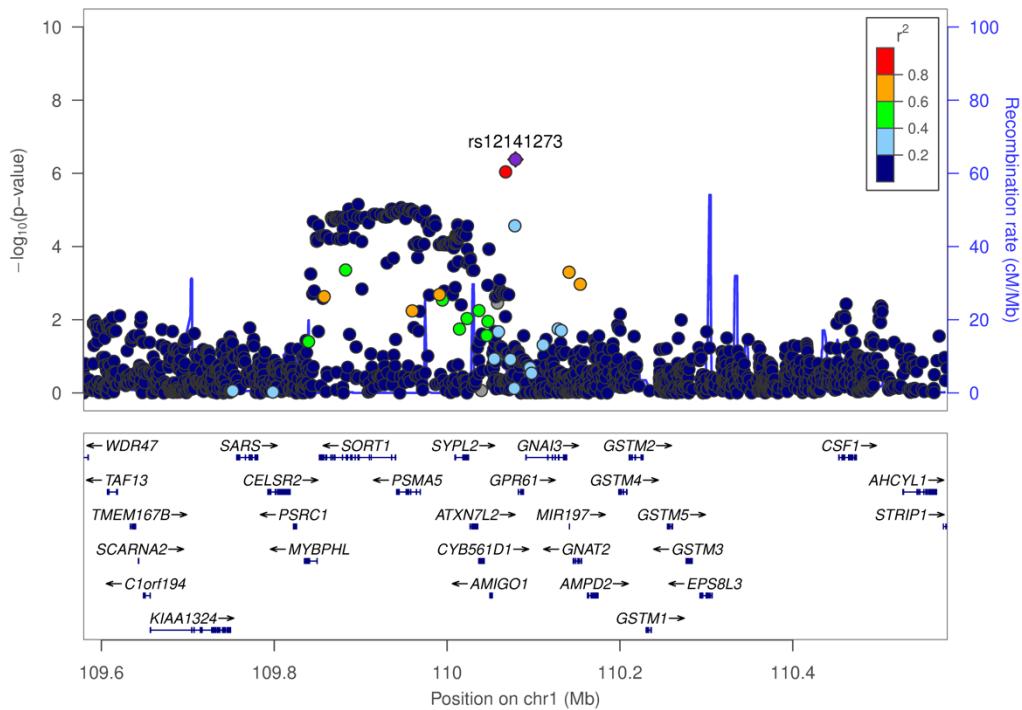
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry



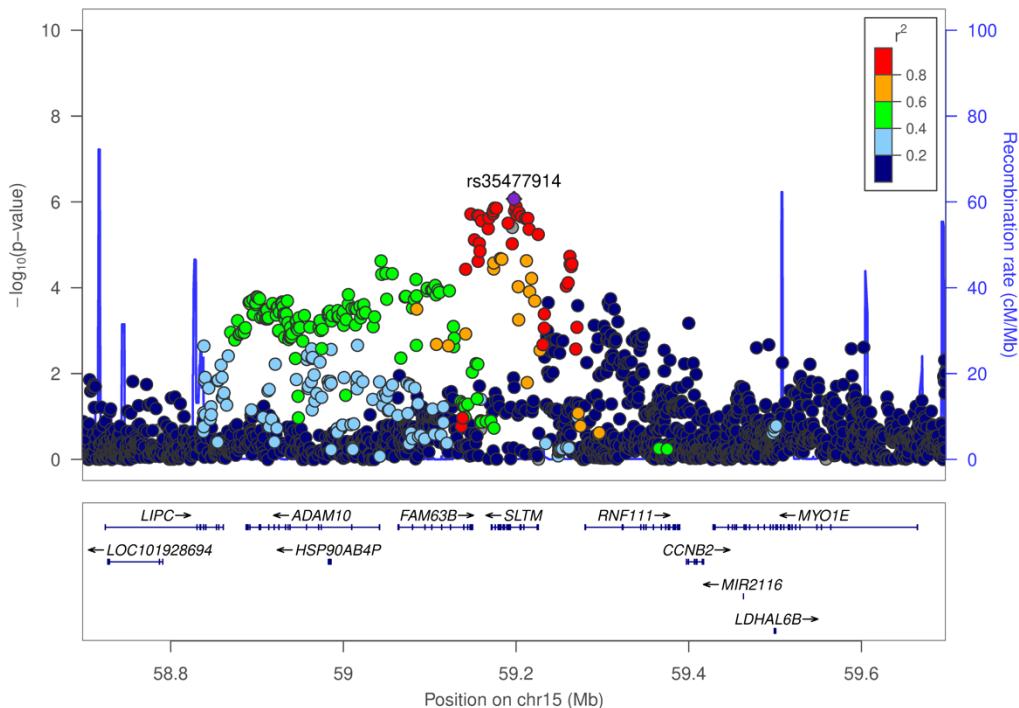


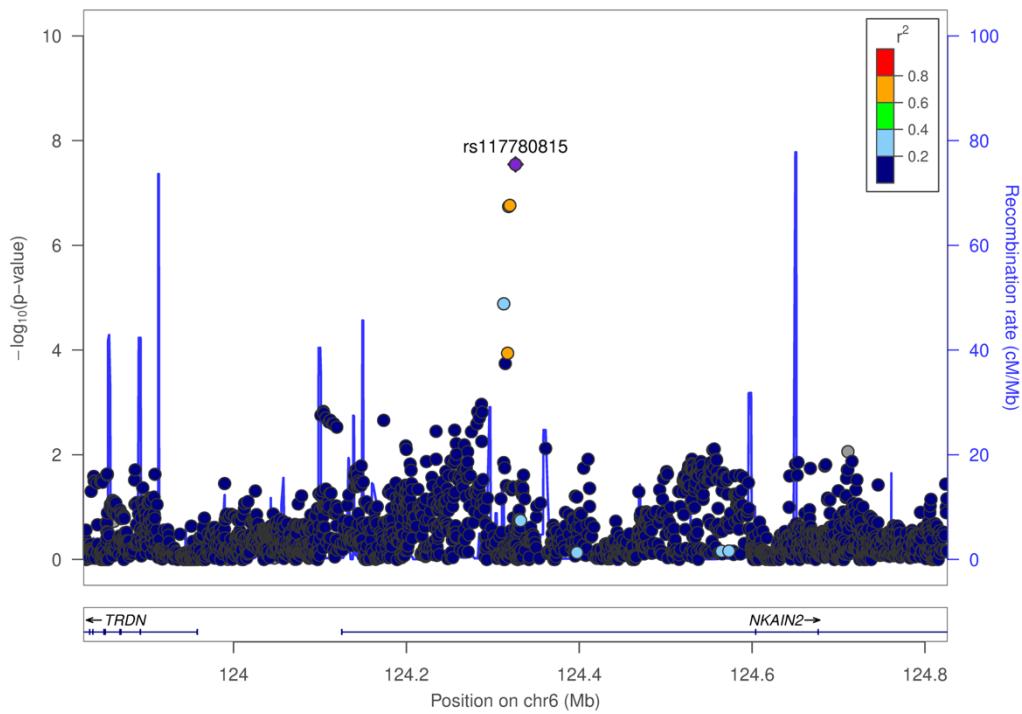
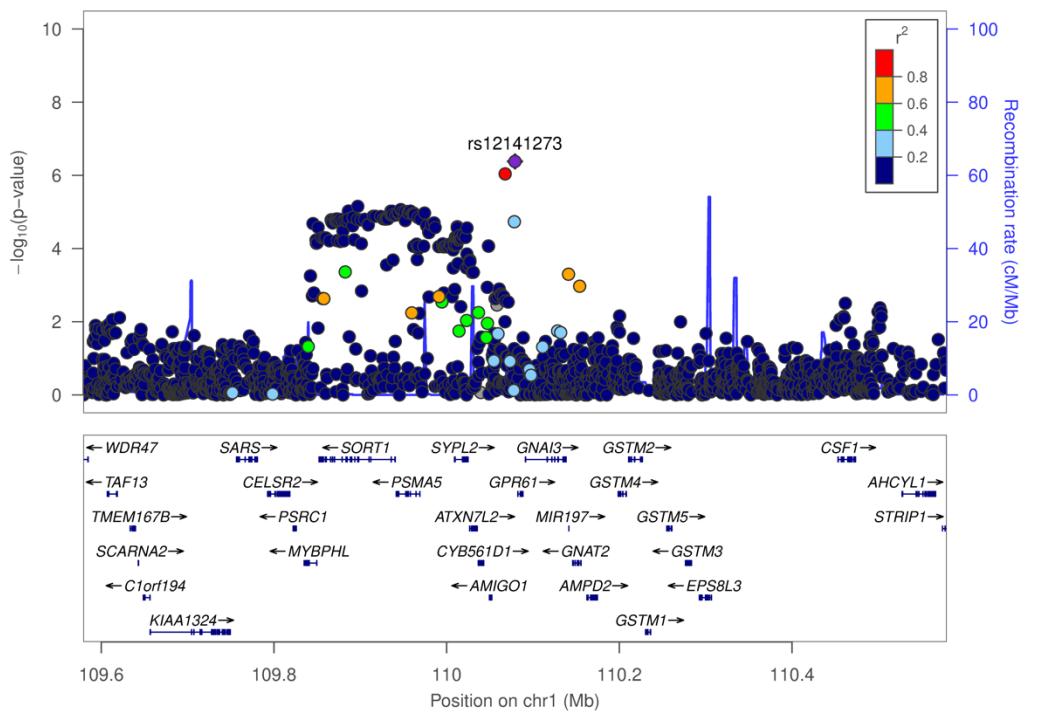
j) Omnibus Test SCZ-BIP-MDD – European ancestry



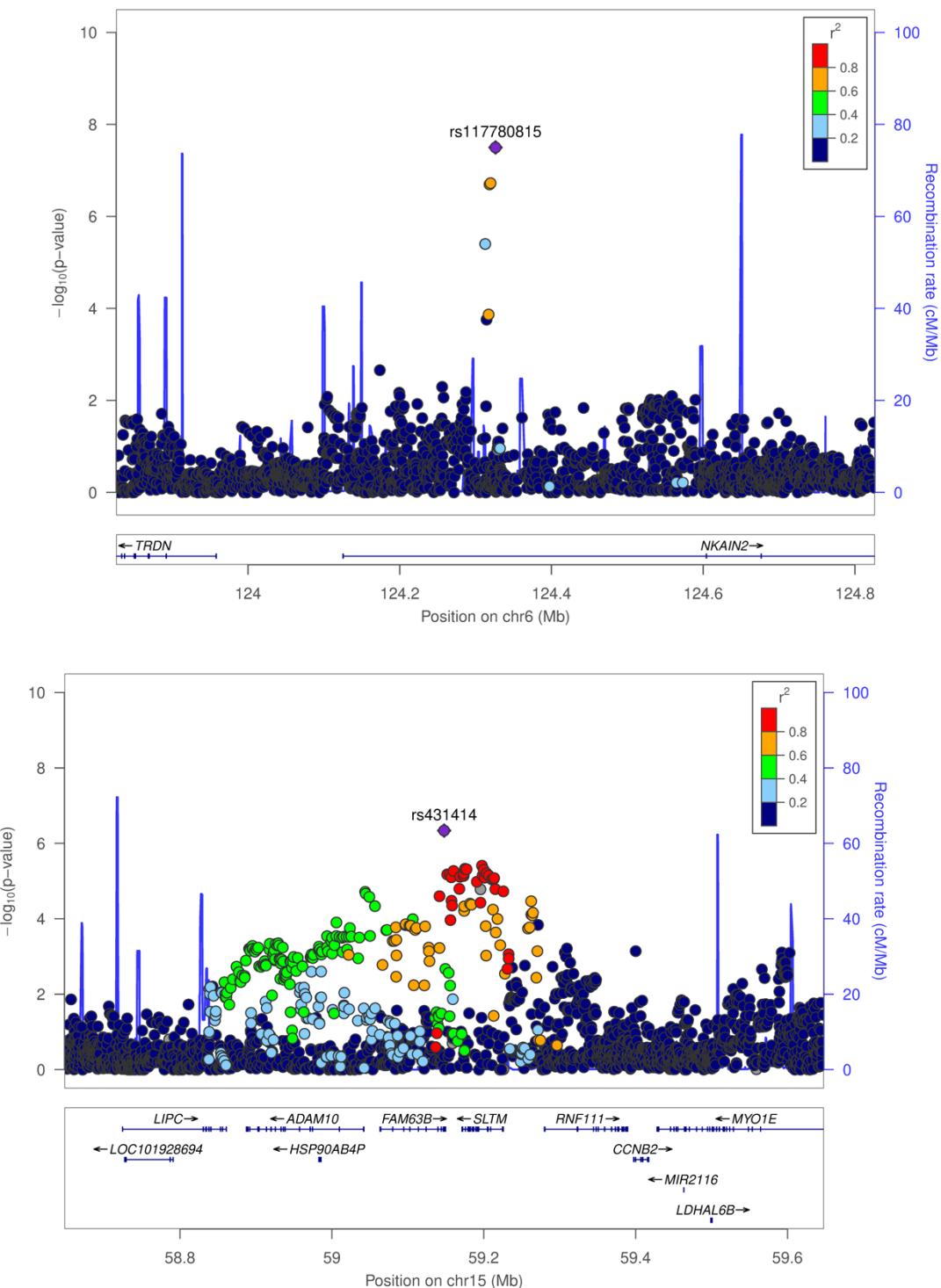


k) Omnibus Test SCZ-BIP-MDD – European + East Asian ancestry





I) Omnibus Test SCZ-BIP-rMDD – European ancestry



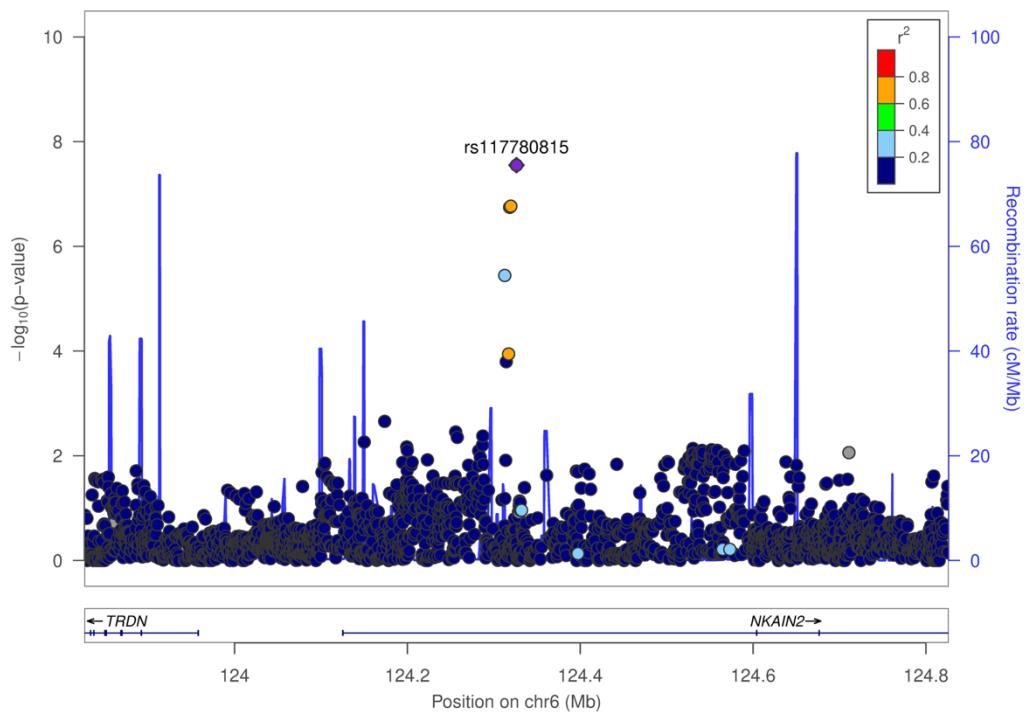
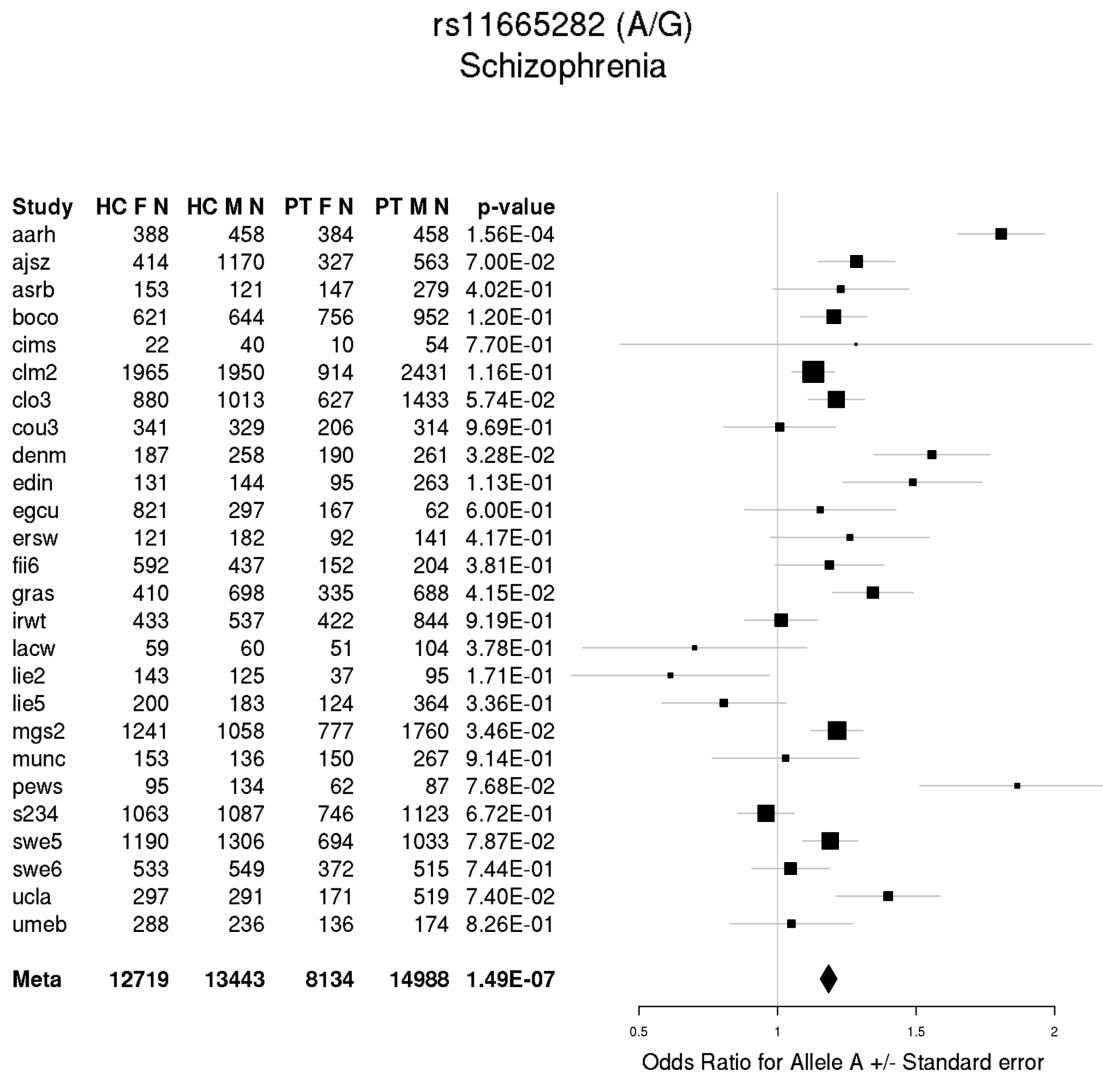
m) Omnibus Test SCZ-BIP-rMDD – European + East Asian ancestry

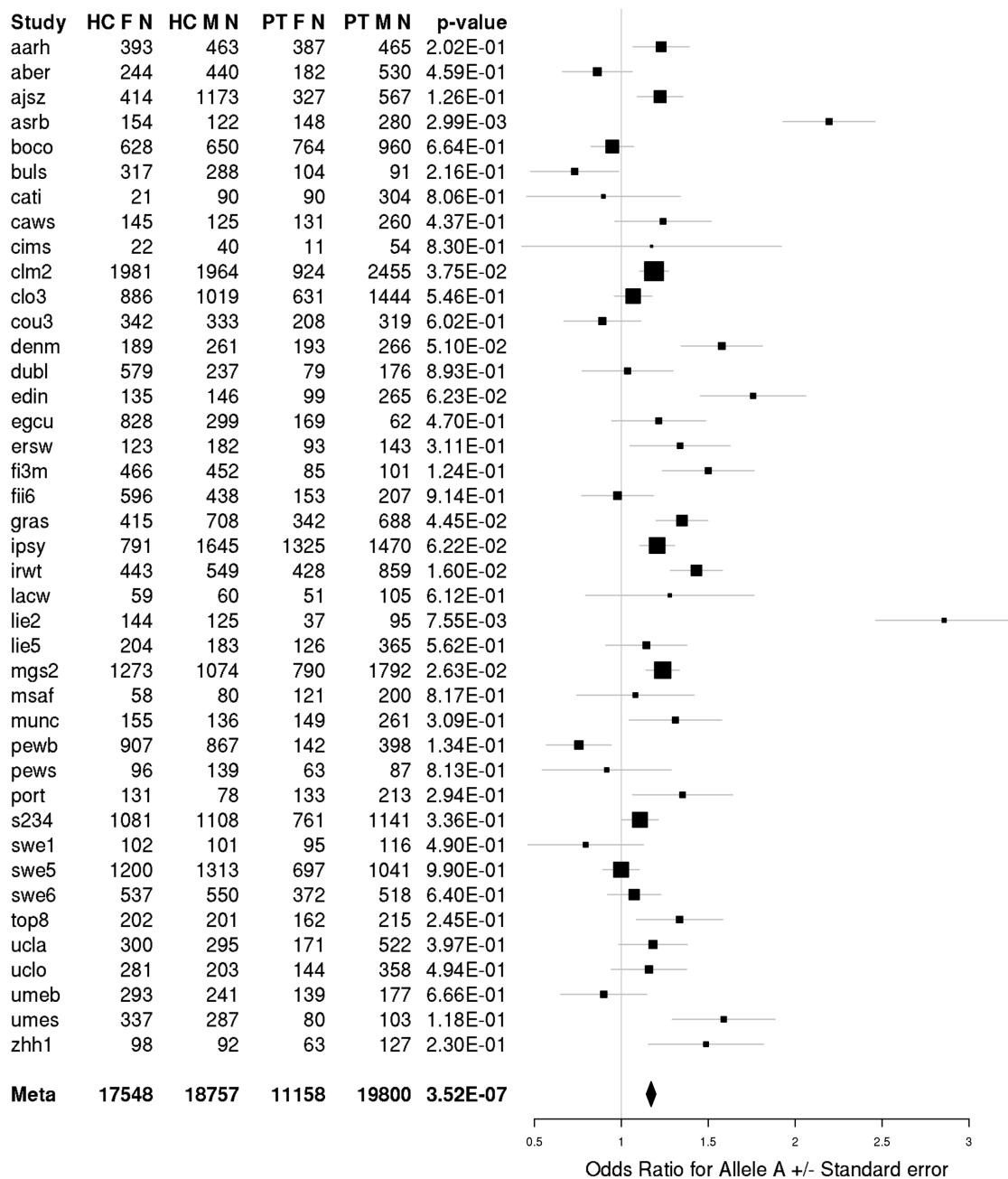
Figure S8. Forest plots for PGC + iPSYCH

Plots were generated using the ‘rmeta’ package in R for loci (index SNPs) with G×S interaction $p < 1 \times 10^{-6}$.

Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; HC F N = number of female healthy controls; HC M N = number of male healthy controls; PT F N = number of female patients; PT M N = number of male patients; Study = cohort abbreviation used by PGC; Meta = meta-analysis results

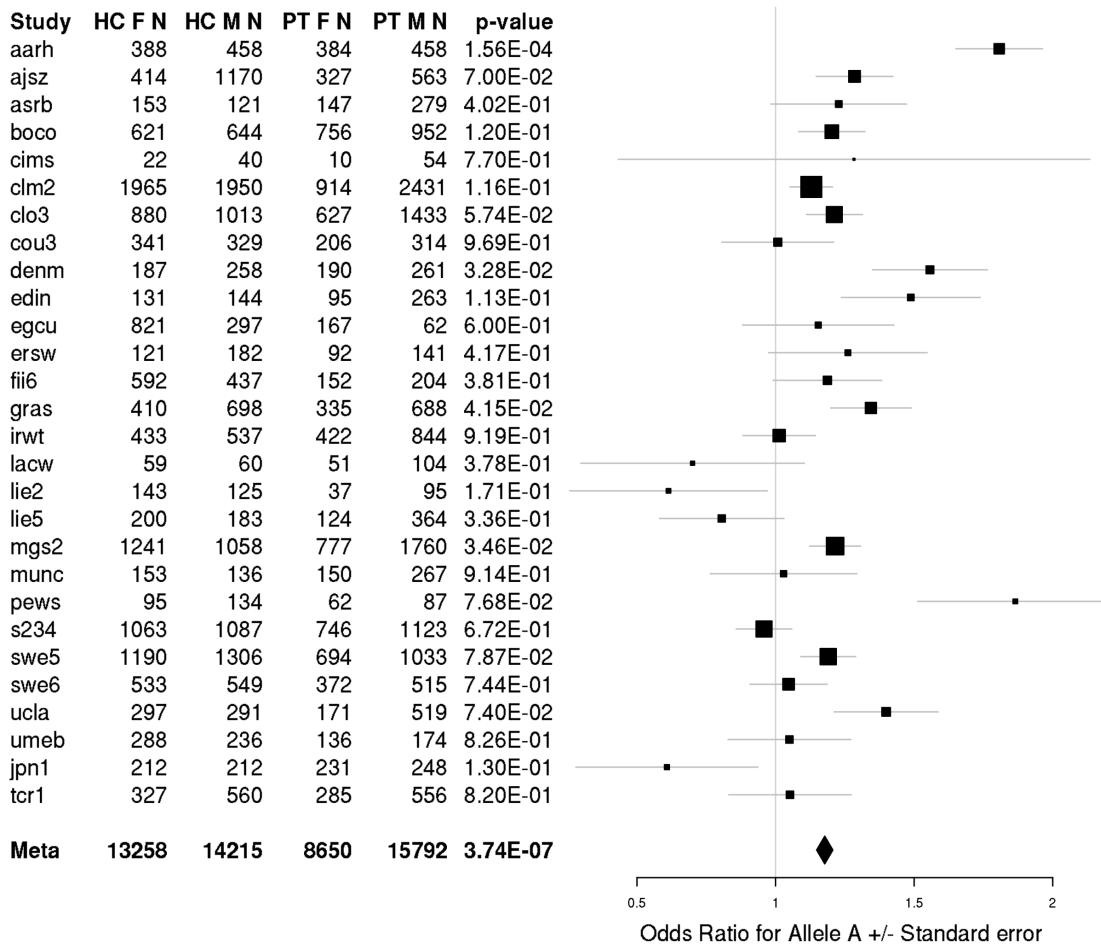
a) Schizophrenia – European ancestry only

rs12445424 (A/G)
Schizophrenia



b) Schizophrenia – European + East Asian ancestry

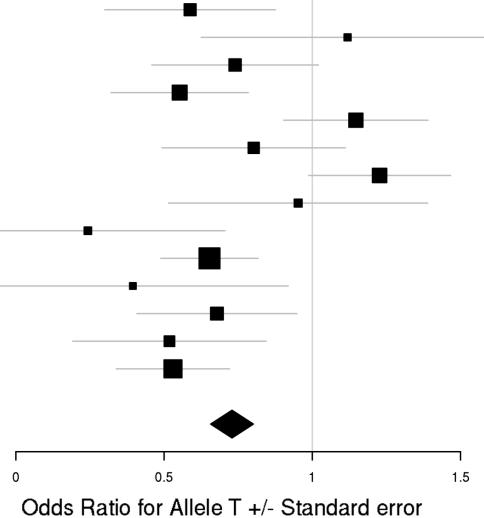
rs11665282 (A/G)
Schizophrenia



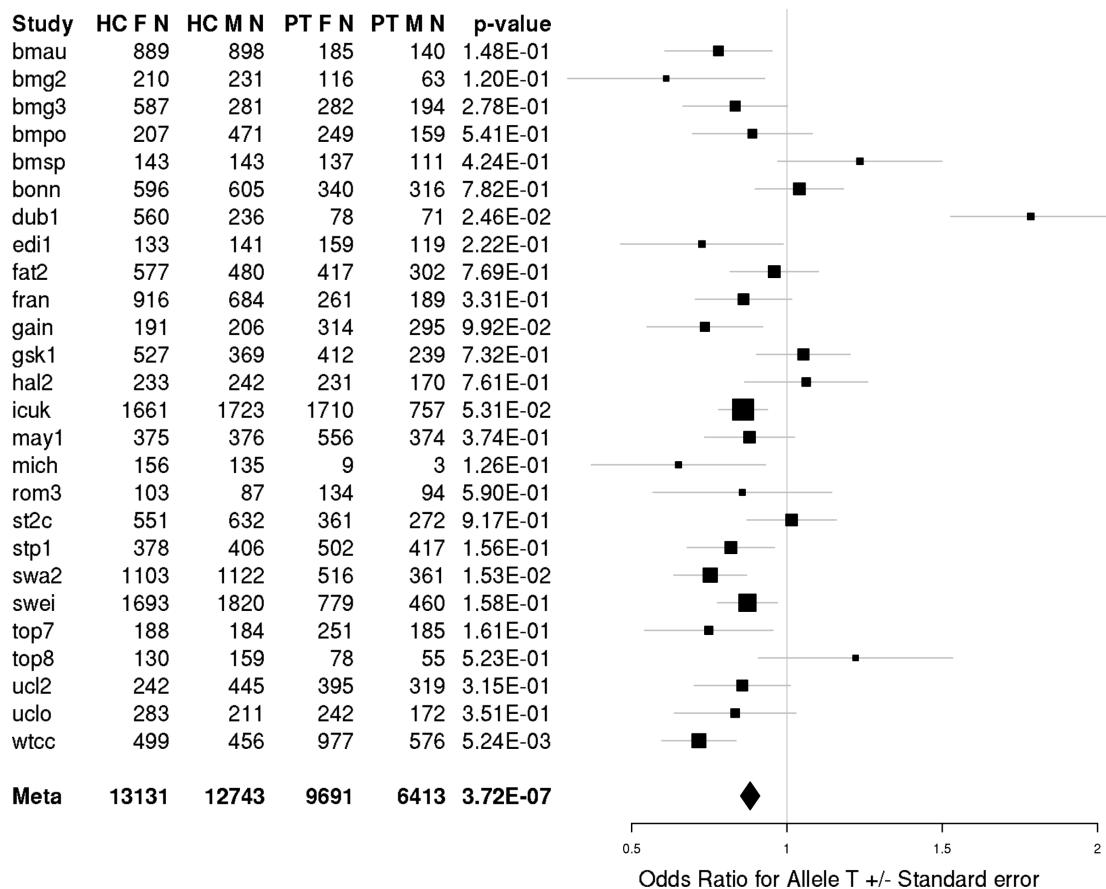
c) Bipolar Disorder

rs12341335 (T/C)
Bipolar Disorder

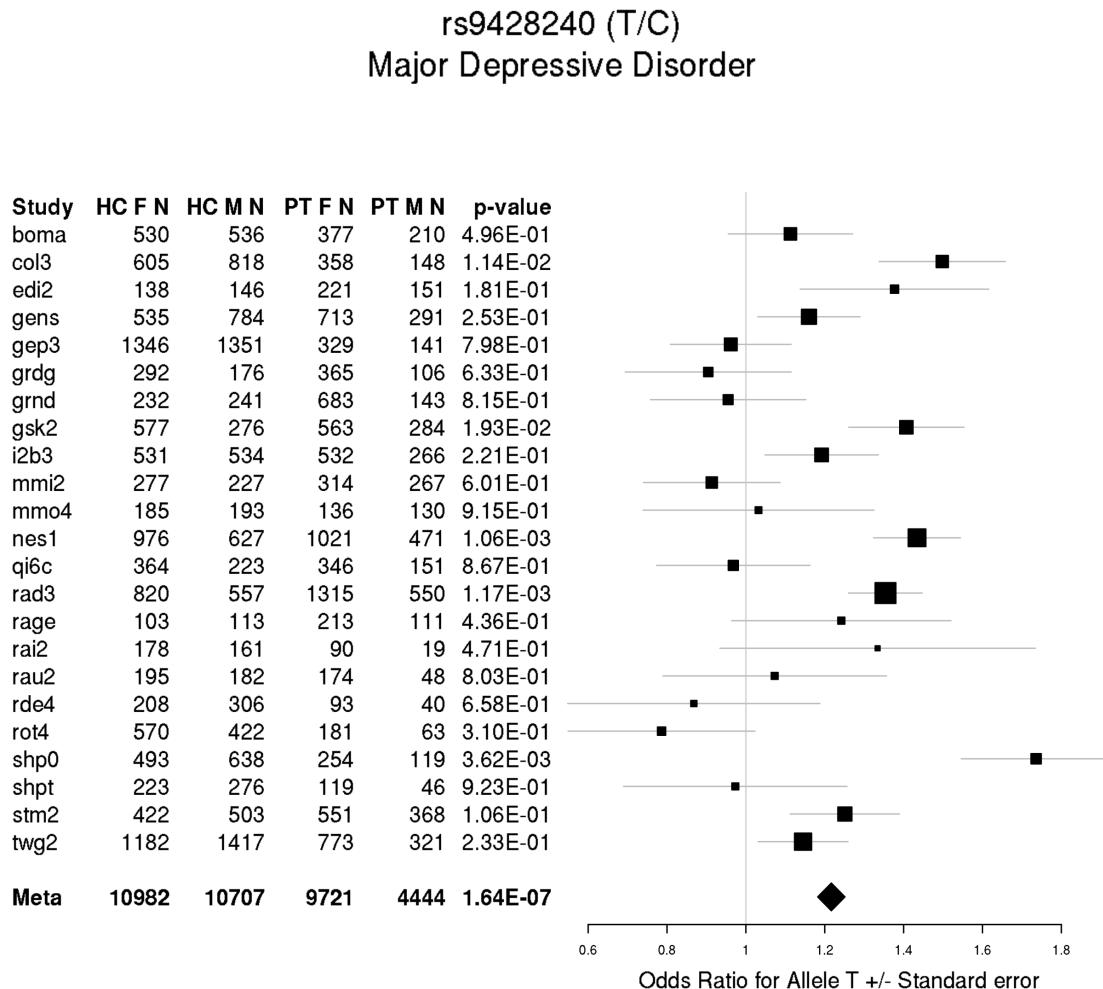
Study	HC F N	HC M N	PT F N	PT M N	p-value
bmau	891	901	189	140	6.52E-02
bmrg2	211	232	117	64	8.20E-01
bmrg3	584	279	286	193	2.83E-01
bonn	593	607	343	321	1.04E-02
gsk1	524	369	413	237	5.74E-01
hal2	234	243	234	170	4.76E-01
may1	377	377	560	374	3.92E-01
mich	153	135	9	3	9.11E-01
rom3	107	86	134	96	2.23E-03
swei	1726	1846	786	470	9.50E-03
top8	130	161	81	56	7.60E-02
ucl2	244	444	397	324	1.50E-01
ume4	291	257	350	211	4.39E-02
usc2	680	472	633	661	8.94E-04
Meta	6745	6409	4532	3320	2.29E-07



rs17651437 (T/C)
Bipolar Disorder

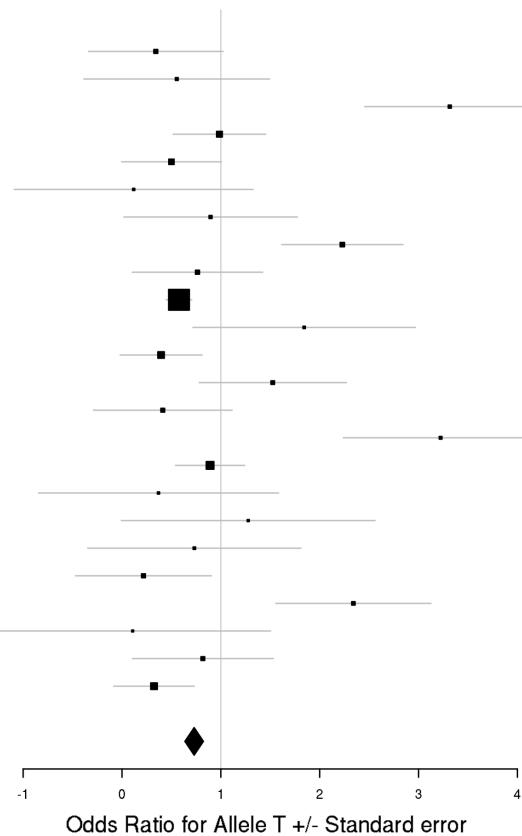


d) Major Depressive Disorder



rs147515485 (T/C)
Major Depressive Disorder

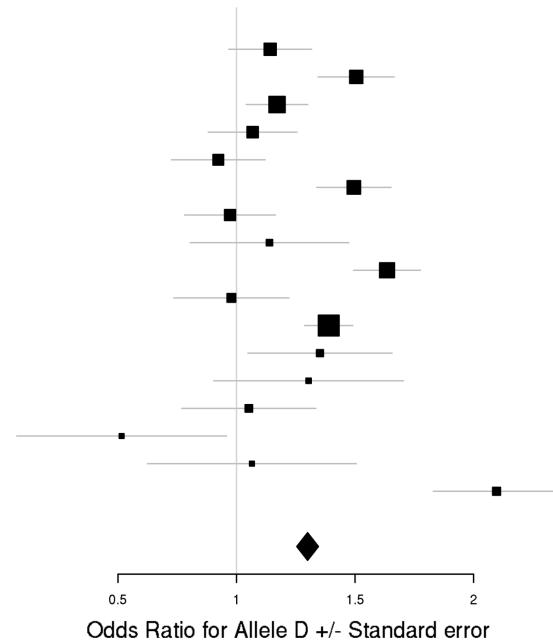
Study	HC F N	HC M N	PT F N	PT M N	p-value
boma	531	531	376	210	1.15E-01
col3	603	807	355	148	5.30E-01
edi2	137	146	220	151	1.63E-01
gens	530	777	706	291	9.76E-01
gep3	1337	1341	324	141	1.69E-01
grdg	292	173	361	104	7.74E-02
grnd	230	238	681	142	9.00E-01
gsk2	574	277	559	285	1.92E-01
i2b3	527	529	532	264	6.83E-01
ipsy	6512	6512	5048	5048	1.99E-05
mmo4	186	192	136	130	5.87E-01
nes1	964	619	1009	468	2.49E-02
qi3c	358	207	494	357	5.71E-01
qi6c	363	221	346	152	2.07E-01
qio2	303	222	399	160	2.35E-01
rad3	811	557	1306	546	7.41E-01
rage	102	114	213	110	4.12E-01
rau2	192	181	174	48	8.49E-01
rde4	204	305	90	40	7.72E-01
rot4	569	418	181	62	2.61E-02
shp0	486	632	253	118	2.78E-01
shpt	224	275	119	46	1.11E-01
stm2	421	496	543	363	7.78E-01
twg2	1179	1417	773	319	5.65E-03
Meta	17813	17187	15288	9703	4.61E-07



e) Recurrent Major Depressive Disorder

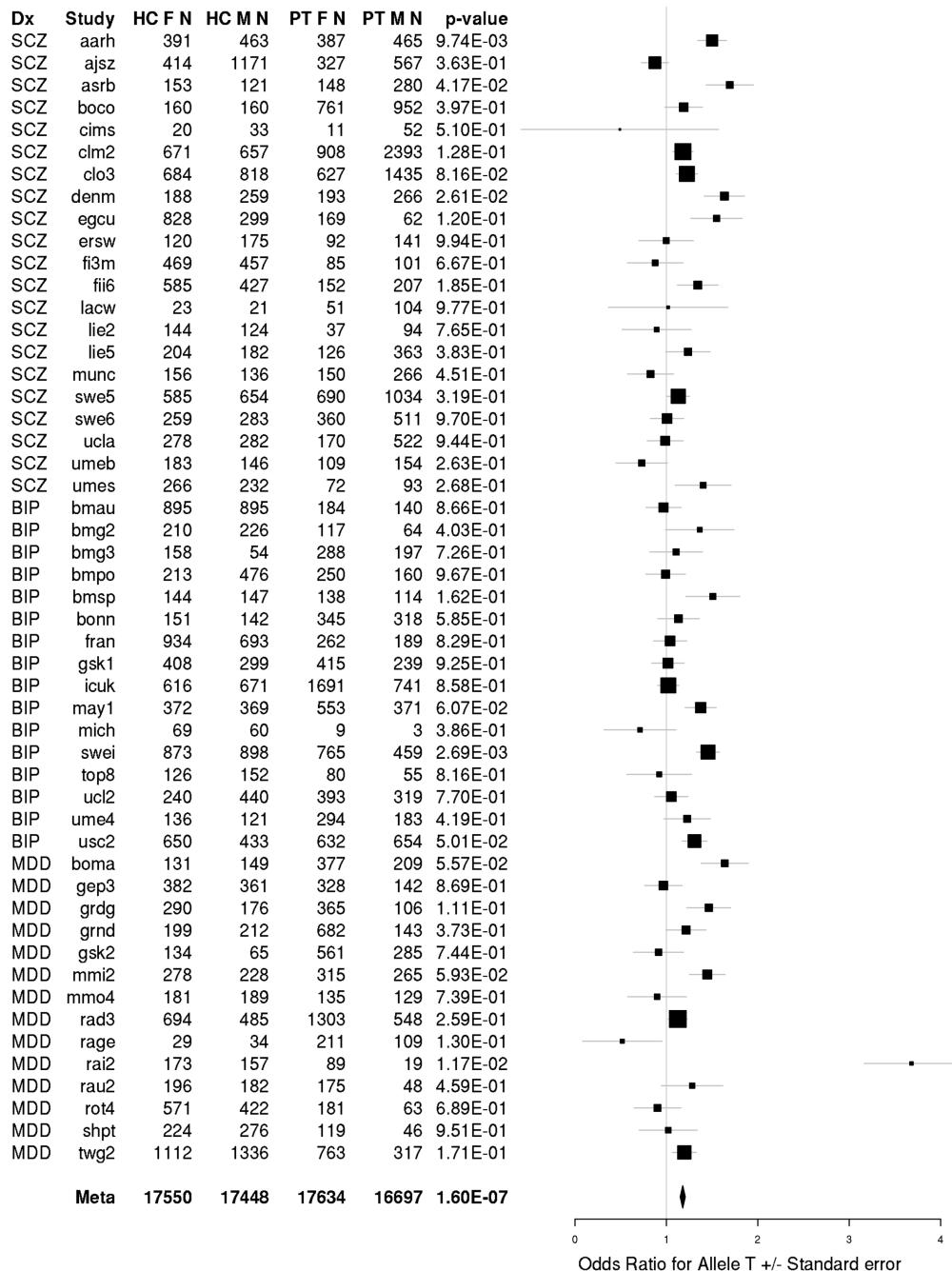
chr1_118832069_D (D/I2)
Recurrent Major Depressive Disorder

Study	HC F N	HC M N	PT F N	PT M N	p-value
boma	530	536	297	149	4.47E-01
col3	604	818	355	146	1.09E-02
gens	535	782	711	291	2.22E-01
gep3	1345	1349	260	85	7.27E-01
grnd	231	238	673	140	6.86E-01
gsk2	577	275	440	226	1.02E-02
mmi2	276	227	229	174	8.85E-01
mmo4	185	193	104	89	6.97E-01
nes1	976	627	482	220	4.93E-04
q16c	364	222	156	84	9.28E-01
rad3	817	556	1016	419	1.19E-03
rage	103	113	182	75	3.21E-01
rai2	178	161	89	19	5.07E-01
rau2	195	182	175	47	8.59E-01
rde4	208	306	41	18	1.34E-01
rot4	570	422	58	14	8.87E-01
shp0	493	638	128	52	5.52E-03
Meta	8187	7645	5396	2248	1.39E-07

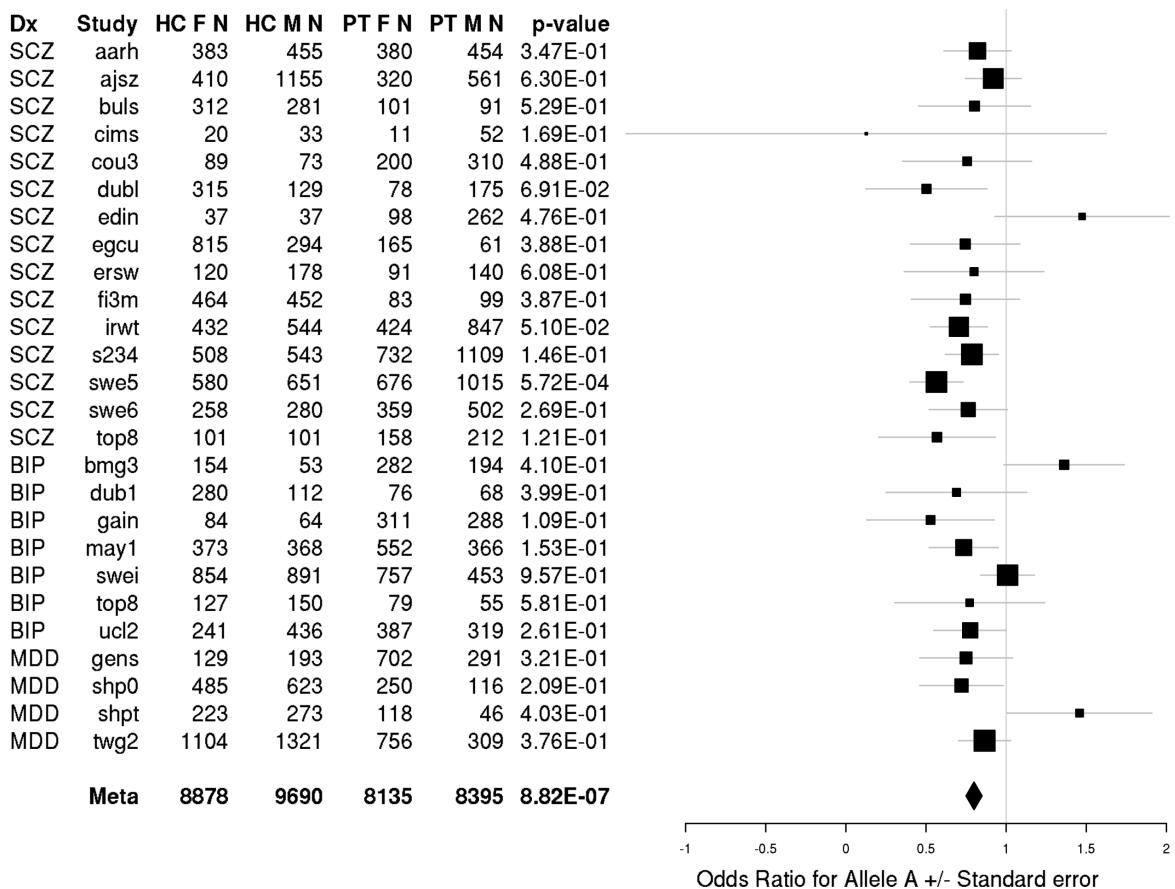


f) Cross-Disorder SCZ-BIP-MDD – European ancestry only

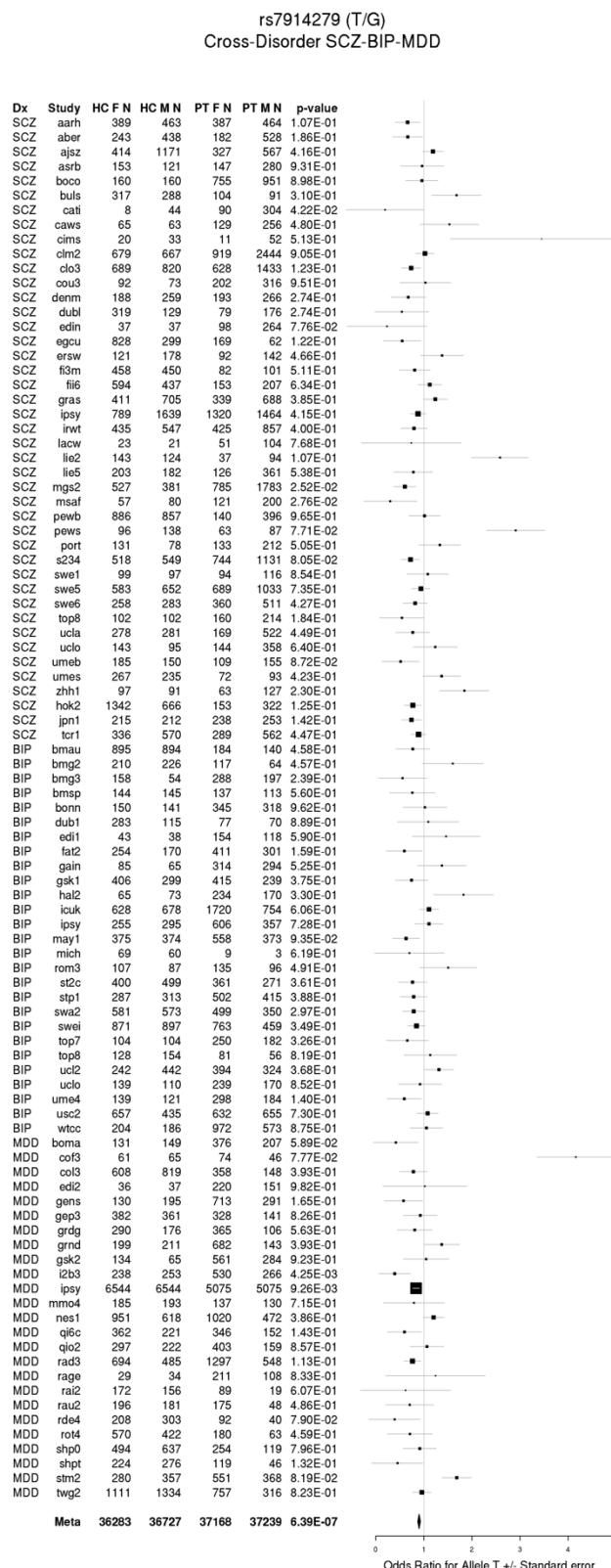
rs7302529 (T/C)
Cross-Disorder SCZ-BIP-MDD



rs73033497 (A/T)
Cross-Disorder SCZ-BIP-MDD

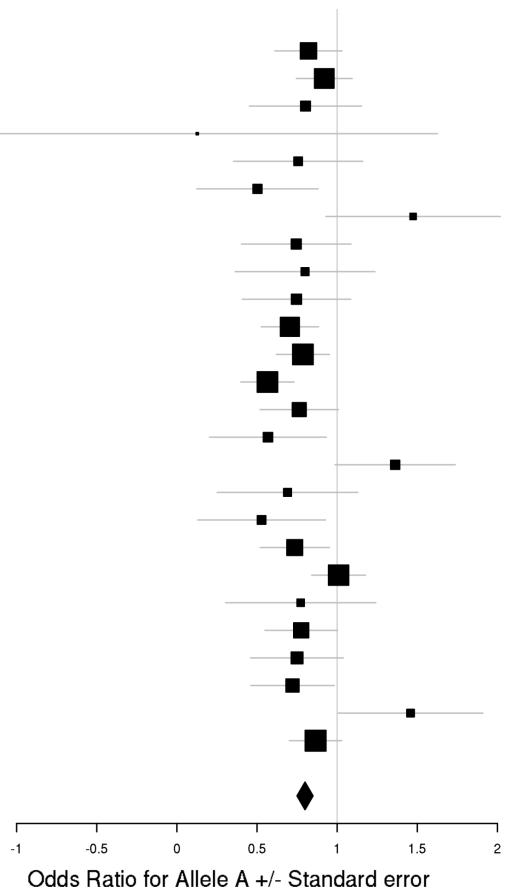


g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



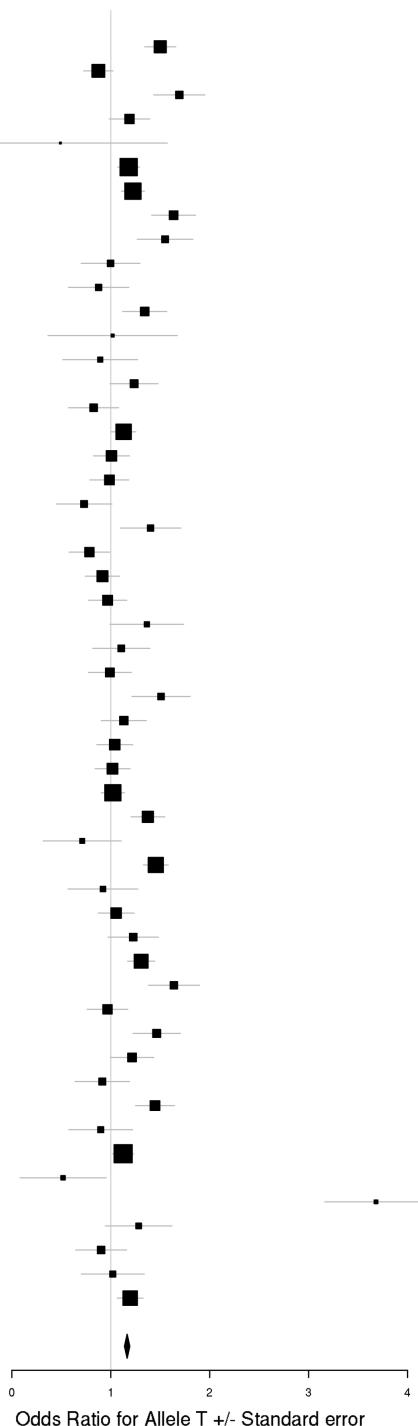
rs73033497 (A/T)
Cross-Disorder SCZ-BIP-MDD

Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	383	455	380	454	3.47E-01
SCZ	ajsz	410	1155	320	561	6.30E-01
SCZ	buls	312	281	101	91	5.29E-01
SCZ	cims	20	33	11	52	1.69E-01
SCZ	cou3	89	73	200	310	4.88E-01
SCZ	dubl	315	129	78	175	6.91E-02
SCZ	edin	37	37	98	262	4.76E-01
SCZ	egcu	815	294	165	61	3.88E-01
SCZ	ersw	120	178	91	140	6.08E-01
SCZ	fi3m	464	452	83	99	3.87E-01
SCZ	irwt	432	544	424	847	5.10E-02
SCZ	s234	508	543	732	1109	1.46E-01
SCZ	swe5	580	651	676	1015	5.72E-04
SCZ	swe6	258	280	359	502	2.69E-01
SCZ	top8	101	101	158	212	1.21E-01
BIP	bmg3	154	53	282	194	4.10E-01
BIP	dub1	280	112	76	68	3.99E-01
BIP	gain	84	64	311	288	1.09E-01
BIP	may1	373	368	552	366	1.53E-01
BIP	swei	854	891	757	453	9.57E-01
BIP	top8	127	150	79	55	5.81E-01
BIP	ucl2	241	436	387	319	2.61E-01
MDD	gens	129	193	702	291	3.21E-01
MDD	shp0	485	623	250	116	2.09E-01
MDD	shpt	223	273	118	46	4.03E-01
MDD	twg2	1104	1321	756	309	3.76E-01
Meta		8878	9690	8135	8395	8.82E-07



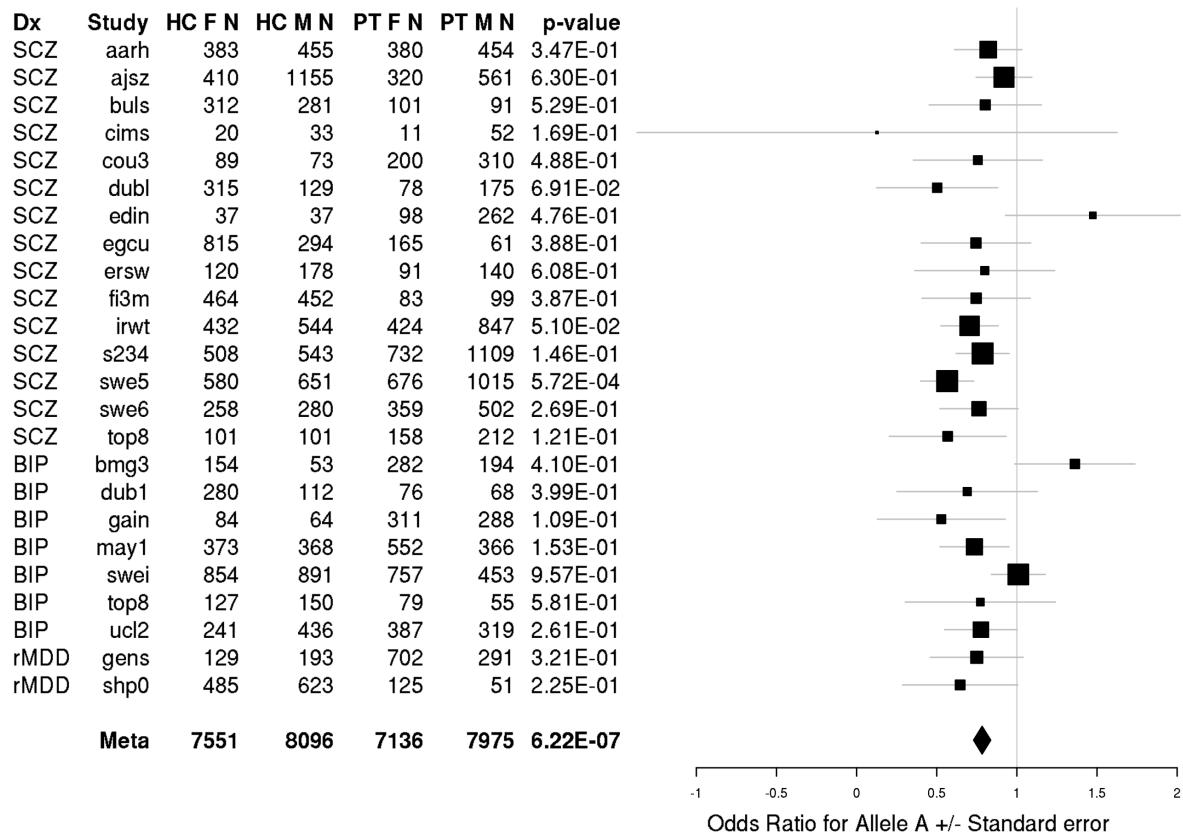
rs7302529 (T/C)
Cross-Disorder SCZ-BIP-MDD

Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	391	463	387	465	9.74E-03
SCZ	ajsz	414	1171	327	567	3.63E-01
SCZ	asrb	153	121	148	280	4.17E-02
SCZ	boco	160	160	761	952	3.97E-01
SCZ	cims	20	33	11	52	5.10E-01
SCZ	clm2	671	657	908	2393	1.28E-01
SCZ	clo3	684	818	627	1435	8.16E-02
SCZ	denm	188	259	193	266	2.61E-02
SCZ	egcu	828	299	169	62	1.20E-01
SCZ	ersw	120	175	92	141	9.94E-01
SCZ	fi3m	469	457	85	101	6.67E-01
SCZ	fi6	585	427	152	207	1.85E-01
SCZ	lacw	23	21	51	104	9.77E-01
SCZ	lie2	144	124	37	94	7.65E-01
SCZ	lie5	204	182	126	363	3.83E-01
SCZ	munc	156	136	150	266	4.51E-01
SCZ	swe5	585	654	690	1034	3.19E-01
SCZ	swe6	259	283	360	511	9.70E-01
SCZ	ucla	278	282	170	522	9.44E-01
SCZ	umeb	183	146	109	154	2.63E-01
SCZ	umes	266	232	72	93	2.68E-01
SCZ	hok2	1344	668	154	322	2.33E-01
SCZ	tcr1	336	570	289	563	6.13E-01
BIP	bmau	895	895	184	140	8.66E-01
BIP	bmrg2	210	226	117	64	4.03E-01
BIP	bmrg3	158	54	288	197	7.26E-01
BIP	bmpo	213	476	250	160	9.67E-01
BIP	bmsp	144	147	138	114	1.62E-01
BIP	bonn	151	142	345	318	5.85E-01
BIP	fran	934	693	262	189	8.29E-01
BIP	gsk1	408	299	415	239	9.25E-01
BIP	icuk	616	671	1691	741	8.58E-01
BIP	may1	372	369	553	371	6.07E-02
BIP	mich	69	60	9	3	3.86E-01
BIP	sweti	873	898	765	459	2.69E-03
BIP	top8	126	152	80	55	8.16E-01
BIP	ucl2	240	440	393	319	7.70E-01
BIP	ume4	136	121	294	183	4.19E-01
BIP	usc2	650	433	632	654	5.01E-02
MDD	boma	131	149	377	209	5.57E-02
MDD	gep3	382	361	328	142	8.69E-01
MDD	grdg	290	176	365	106	1.11E-01
MDD	grnd	199	212	682	143	3.73E-01
MDD	gsk2	134	65	561	285	7.44E-01
MDD	mmi2	278	228	315	265	5.93E-02
MDD	mmo4	181	189	135	129	7.39E-01
MDD	rad3	694	485	1303	548	2.59E-01
MDD	rage	29	34	211	109	1.30E-01
MDD	rai2	173	157	89	19	1.17E-02
MDD	rau2	196	182	175	48	4.59E-01
MDD	rot4	571	422	181	63	6.89E-01
MDD	shpt	224	276	119	46	9.51E-01
MDD	twg2	1112	1336	763	317	1.71E-01
Meta		19230	18686	18077	17582	9.37E-07



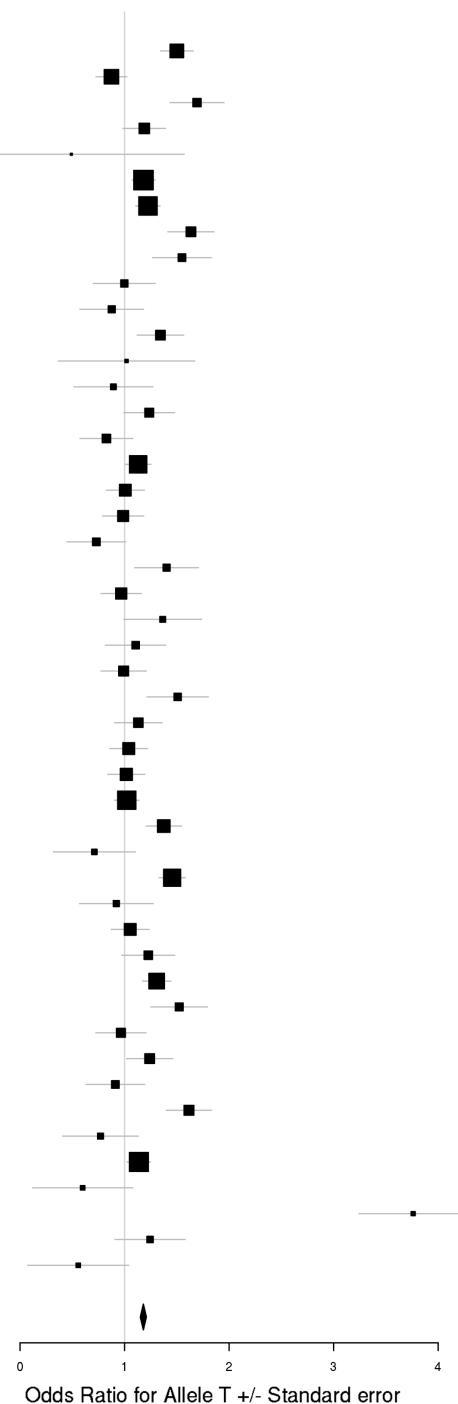
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only

rs73033497 (A/T)
Cross-Disorder SCZ-BIP-RMDD

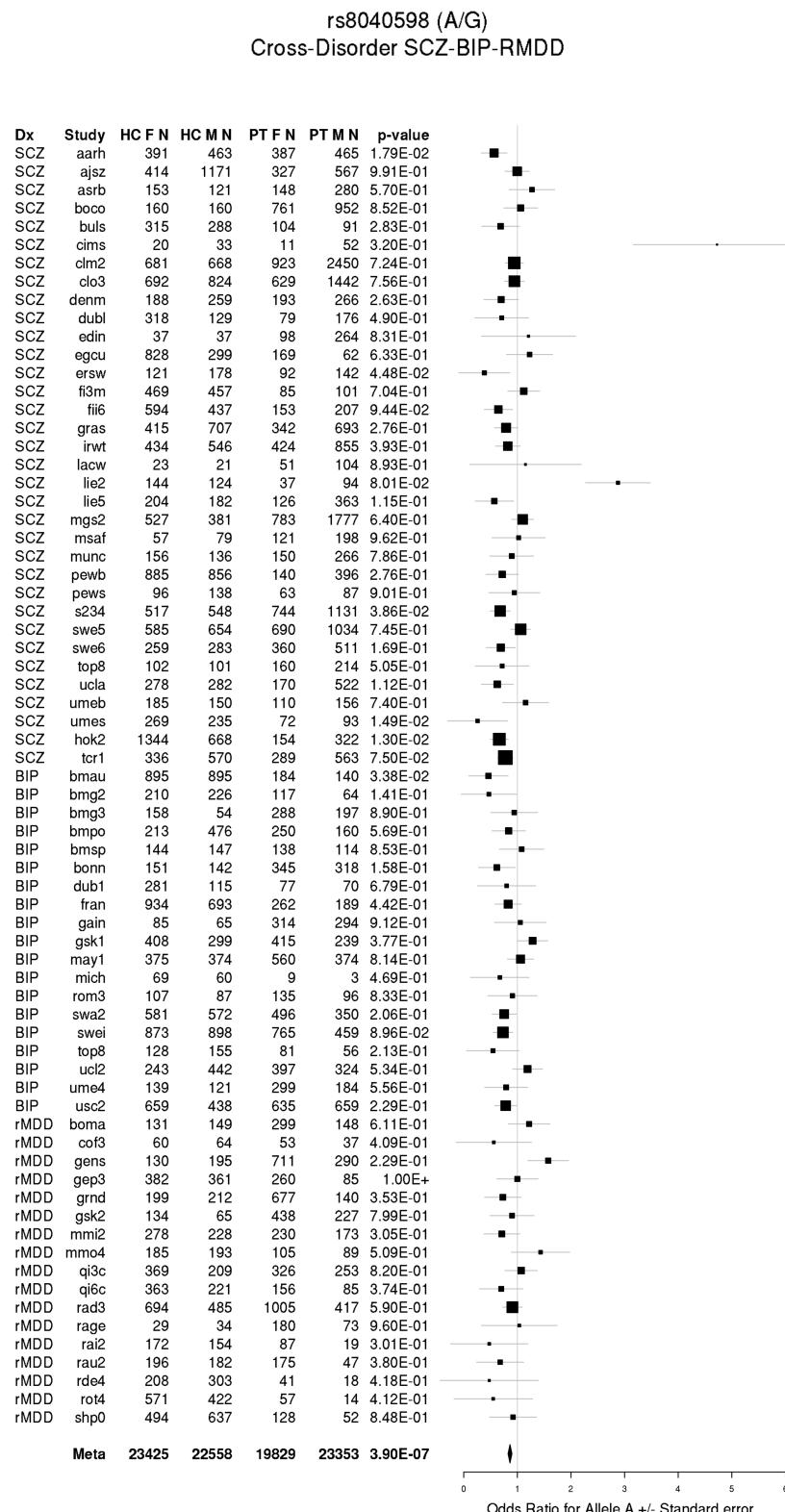


rs7302529 (T/C)
Cross-Disorder SCZ-BIP-RMDD

Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	391	463	387	465	9.74E-03
SCZ	ajsz	414	1171	327	567	3.63E-01
SCZ	asrb	153	121	148	280	4.17E-02
SCZ	boco	160	160	761	952	3.97E-01
SCZ	cims	20	33	11	52	5.10E-01
SCZ	clm2	671	657	908	2393	1.28E-01
SCZ	clo3	684	818	627	1435	8.16E-02
SCZ	denm	188	259	193	266	2.61E-02
SCZ	egcu	828	299	169	62	1.20E-01
SCZ	ersw	120	175	92	141	9.94E-01
SCZ	fi3m	469	457	85	101	6.67E-01
SCZ	fii6	585	427	152	207	1.85E-01
SCZ	lacw	23	21	51	104	9.77E-01
SCZ	lie2	144	124	37	94	7.65E-01
SCZ	lie5	204	182	126	363	3.83E-01
SCZ	munc	156	136	150	266	4.51E-01
SCZ	swe5	585	654	690	1034	3.19E-01
SCZ	swe6	259	283	360	511	9.70E-01
SCZ	ucla	278	282	170	522	9.44E-01
SCZ	umeb	183	146	109	154	2.63E-01
SCZ	umes	266	232	72	93	2.68E-01
BIP	bmau	895	895	184	140	8.66E-01
BIP	bmrg2	210	226	117	64	4.03E-01
BIP	bmrg3	158	54	288	197	7.26E-01
BIP	bmopo	213	476	250	160	9.67E-01
BIP	bmsp	144	147	138	114	1.62E-01
BIP	bonn	151	142	345	318	5.85E-01
BIP	fran	934	693	262	189	8.29E-01
BIP	gsk1	408	299	415	239	9.25E-01
BIP	icuk	616	671	1691	741	8.58E-01
BIP	may1	372	369	553	371	6.07E-02
BIP	mich	69	60	9	3	3.86E-01
BIP	sweti	873	898	765	459	2.69E-03
BIP	top8	126	152	80	55	8.16E-01
BIP	ucl2	240	440	393	319	7.70E-01
BIP	ume4	136	121	294	183	4.19E-01
BIP	usc2	650	433	632	654	5.01E-02
rMDD	boma	131	149	299	148	1.20E-01
rMDD	gep3	382	361	260	85	8.82E-01
rMDD	grnd	199	212	677	140	3.29E-01
rMDD	gsk2	134	65	438	227	7.43E-01
rMDD	mmi2	278	228	230	173	2.70E-02
rMDD	mmo4	181	189	104	89	4.70E-01
rMDD	rad3	694	485	1005	417	2.52E-01
rMDD	rage	29	34	180	73	2.86E-01
rMDD	rai2	173	157	88	19	1.05E-02
rMDD	rau2	196	182	175	47	5.17E-01
rMDD	rot4	571	422	57	14	2.25E-01
Meta		15924	15660	15543	15700	7.43E-07



i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry



rs73033497 (A/T)
Cross-Disorder SCZ-BIP-RMDD

Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	383	455	380	454	3.47E-01
SCZ	aksz	410	1155	320	561	6.30E-01
SCZ	buls	312	281	101	91	5.29E-01
SCZ	cims	20	33	11	52	1.69E-01
SCZ	cou3	89	73	200	310	4.88E-01
SCZ	dubl	315	129	78	175	6.91E-02
SCZ	edin	37	37	98	262	4.76E-01
SCZ	egcu	815	294	165	61	3.88E-01
SCZ	ersw	120	178	91	140	6.08E-01
SCZ	fi3m	464	452	83	99	3.87E-01
SCZ	irwt	432	544	424	847	5.10E-02
SCZ	s234	508	543	732	1109	1.46E-01
SCZ	swe5	580	651	676	1015	5.72E-04
SCZ	swe6	258	280	359	502	2.69E-01
SCZ	top8	101	101	158	212	1.21E-01
BIP	bmg3	154	53	282	194	4.10E-01
BIP	dub1	280	112	76	68	3.99E-01
BIP	gain	84	64	311	288	1.09E-01
BIP	may1	373	368	552	366	1.53E-01
BIP	swei	854	891	757	453	9.57E-01
BIP	top8	127	150	79	55	5.81E-01
BIP	ucl2	241	436	387	319	2.61E-01
rMDD	gens	129	193	702	291	3.21E-01
rMDD	shp0	485	623	125	51	2.25E-01
Meta		7551	8096	7136	7975	6.22E-07

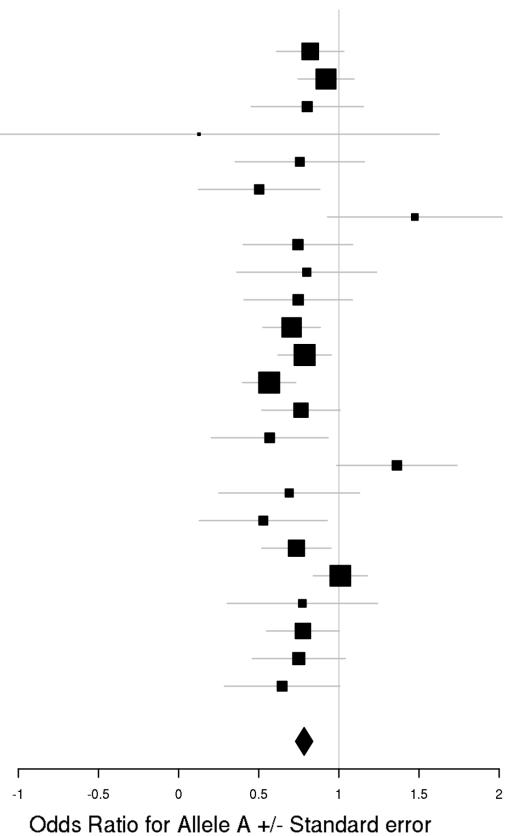


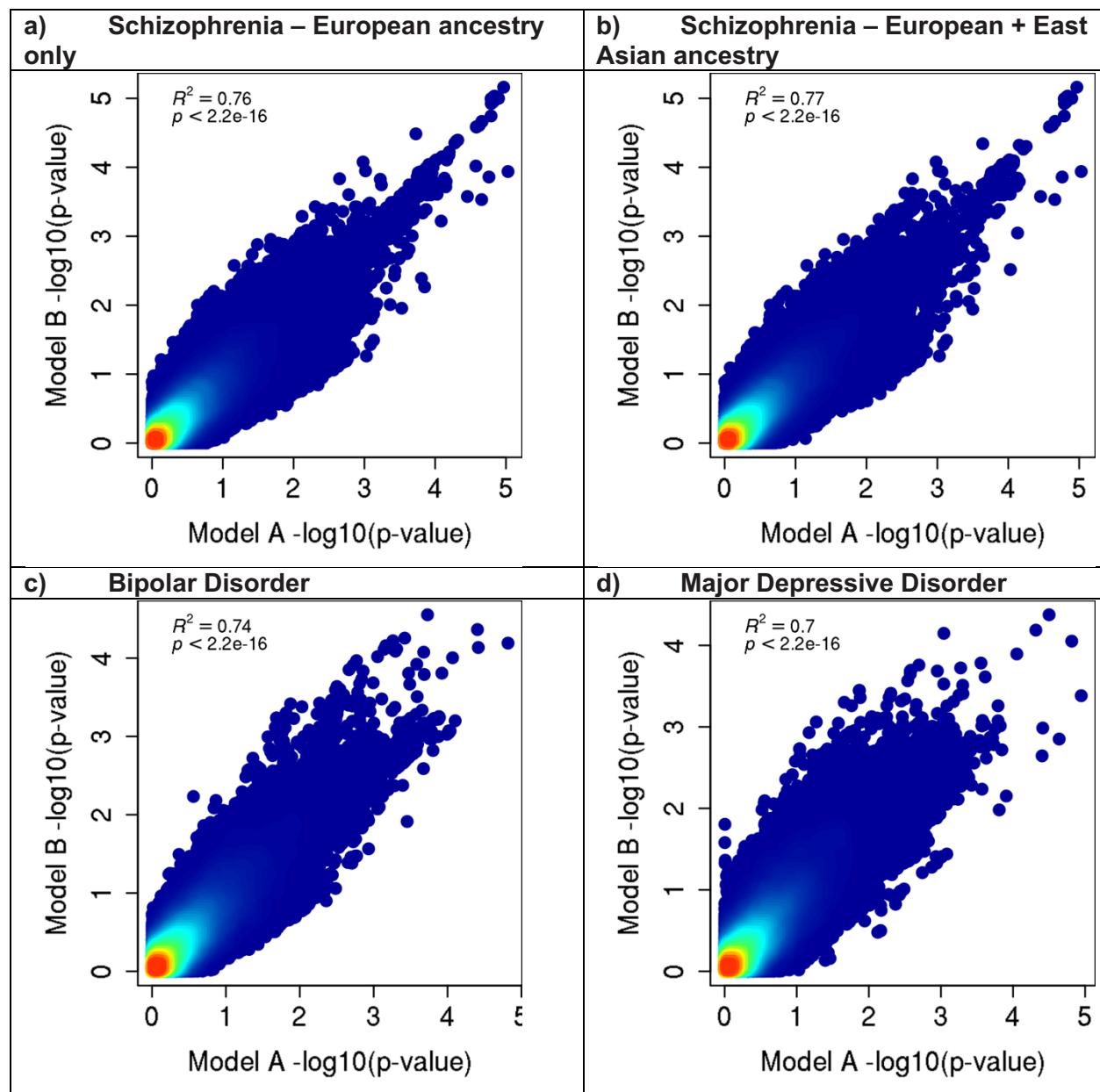
Figure S9. X chromosome model comparisons in PGC + iPSYCH

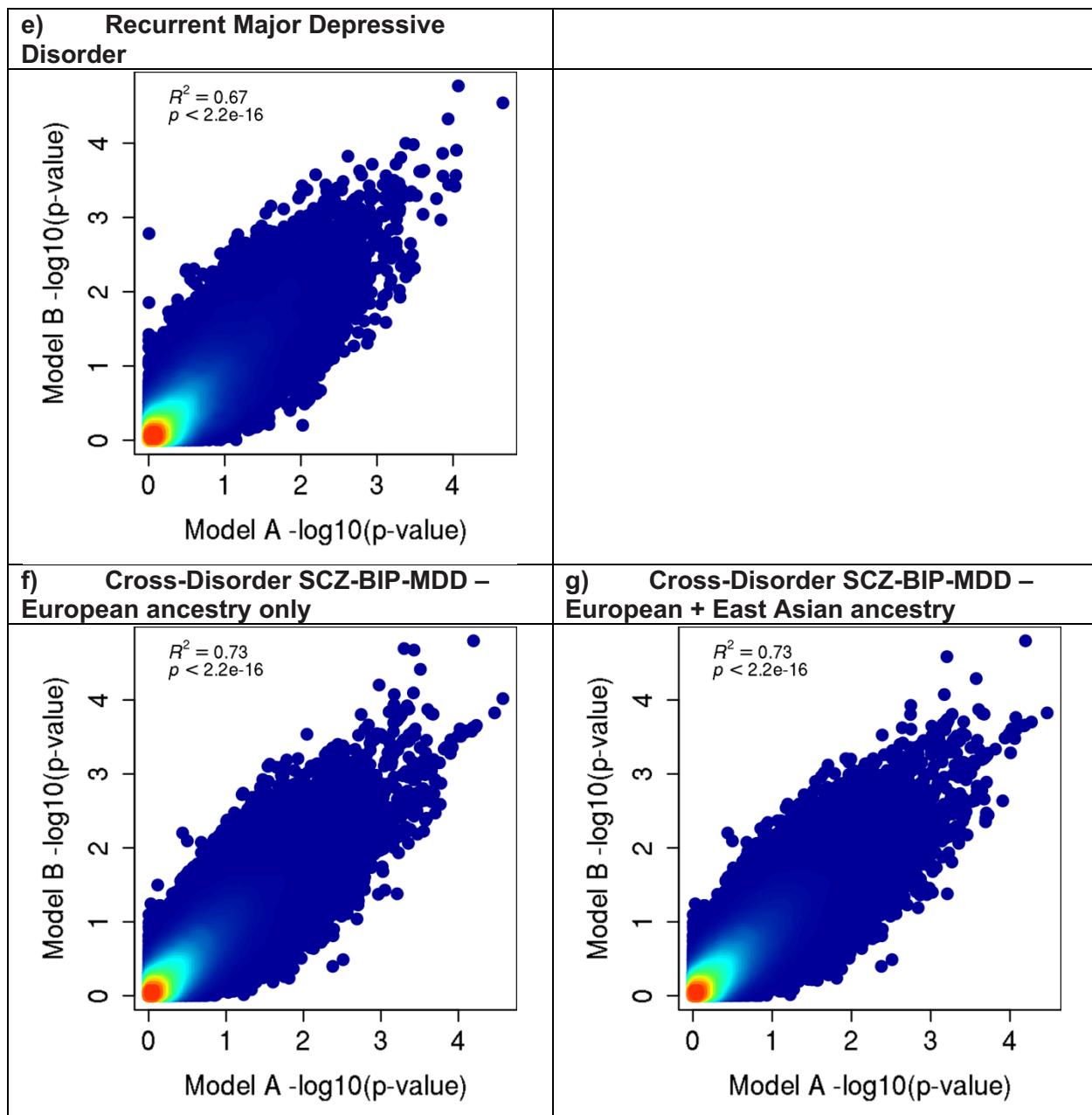
$G \times S$ interactions with X-linked SNPs were tested using two different models. Model A assumed complete and uniform X-inactivation in females and similar effect size between males and females by assigning 0, 1, or 2 copies of an allele to females and 0 or 2 copies to males. As these assumptions often do not hold, Model B assigned 0 or 1 copy to males.

The scatter plots show substantial correlation (R) between p -values from the two X chromosome models, indicating the results from the two models did not differ substantially.

Plots were generated using the ‘plot’ package in R.

Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; R^2 = proportion variance explained.





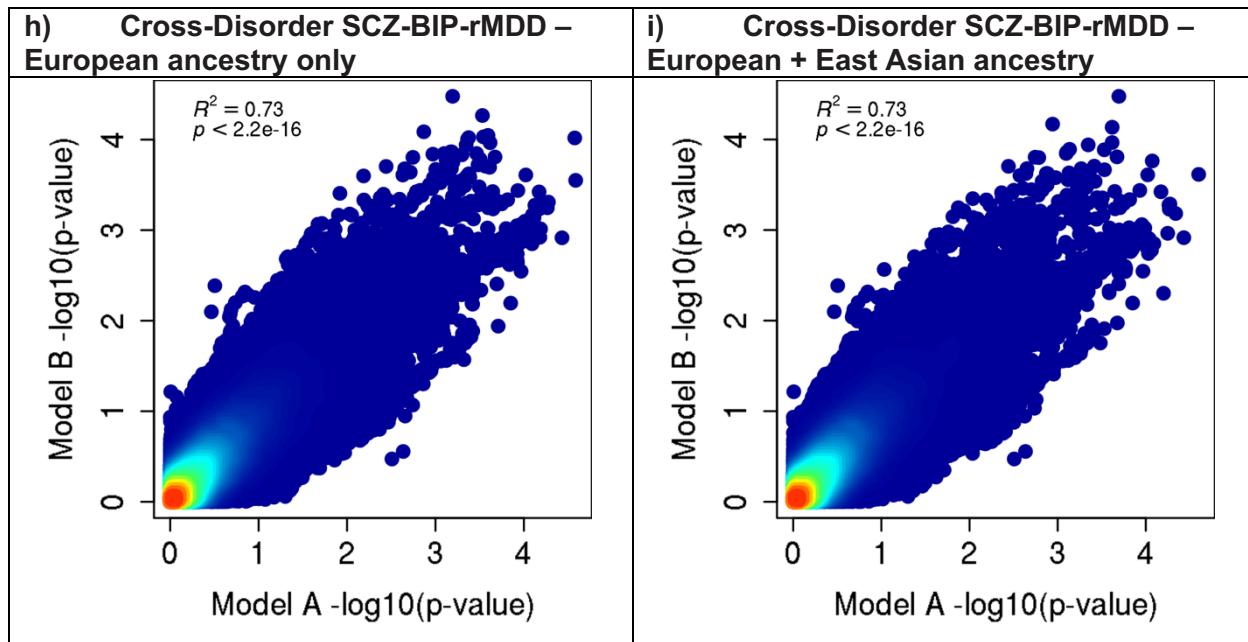


Figure S10. Manhattan plots for gene-based G×S tests in PGC + iPSYCH

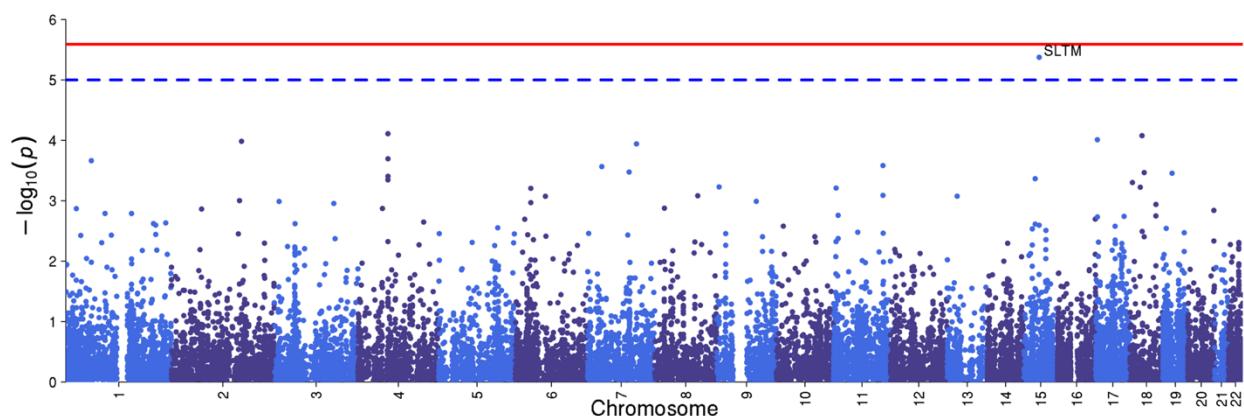
These analyses were carried out in MAGMA on the genomic control output with INFO score > 0.6 , *European ancestry only*, and autosomal SNPs only, with the MHC region included.

Negative log₁₀-transformed *p*-values for each gene (y-axis) are plotted by chromosomal position (x-axis). Each dot represents a gene, and the solid red and dotted blue horizontal lines represent the thresholds for genome-wide significant association ($p = 2.57 \times 10^{-6}$) and suggestive association ($p = 1 \times 10^{-5}$), respectively.

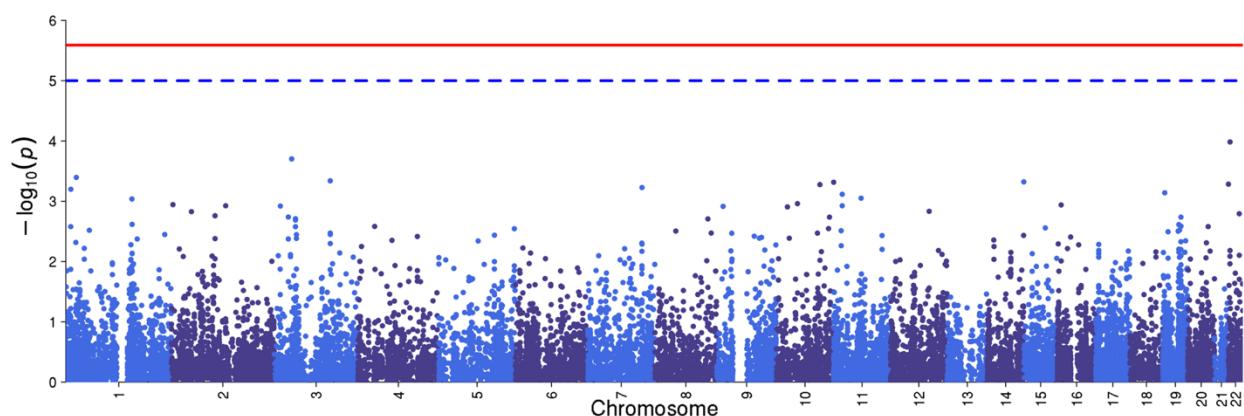
Plots were generated using the ‘plot’ package in R.

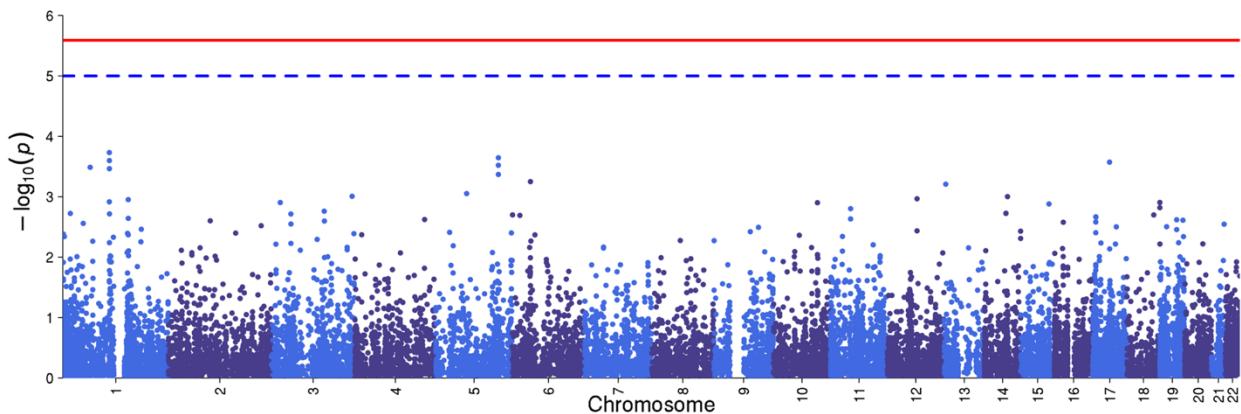
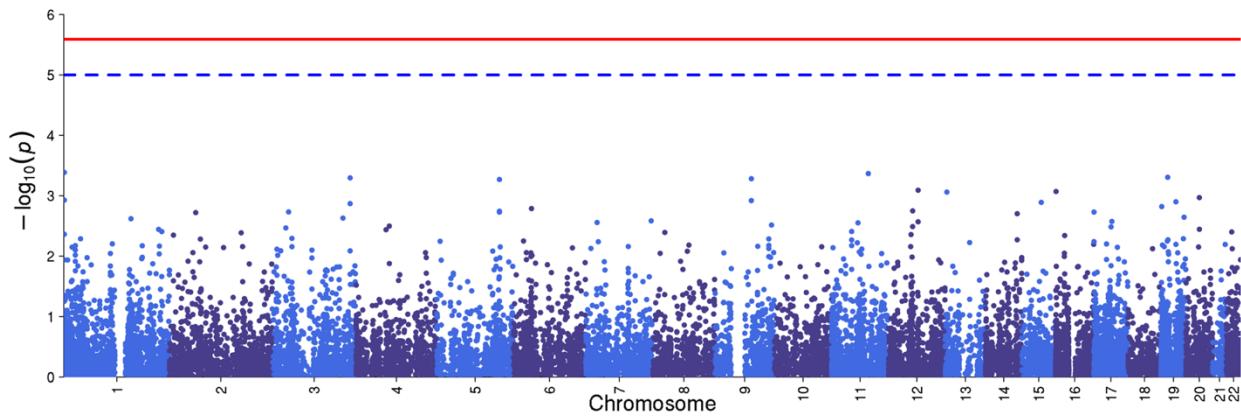
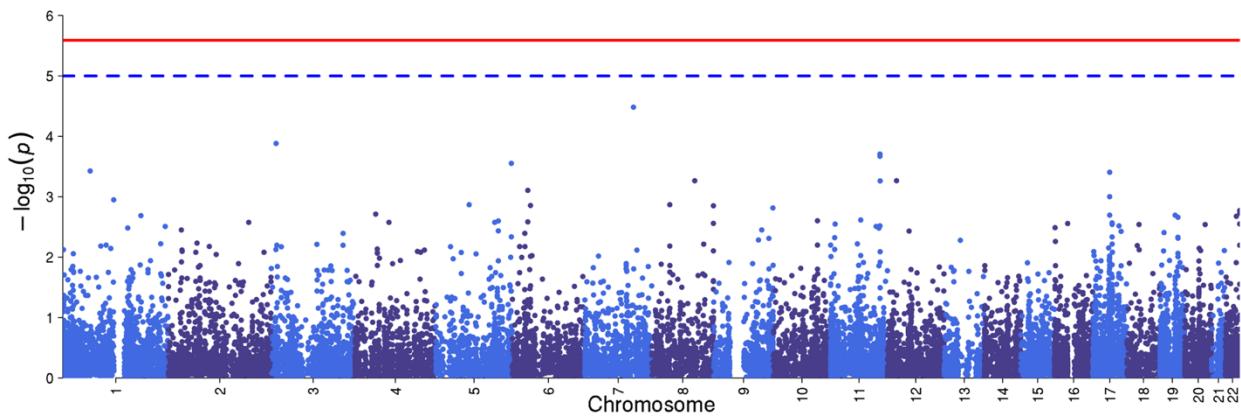
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; SLTM = SAFB Like Transcription Modulator

a) Schizophrenia



b) Bipolar Disorder



c) Major Depressive Disorder**d) Recurrent Major Depressive Disorder****e) Cross-Disorder SCZ-BIP-MDD**

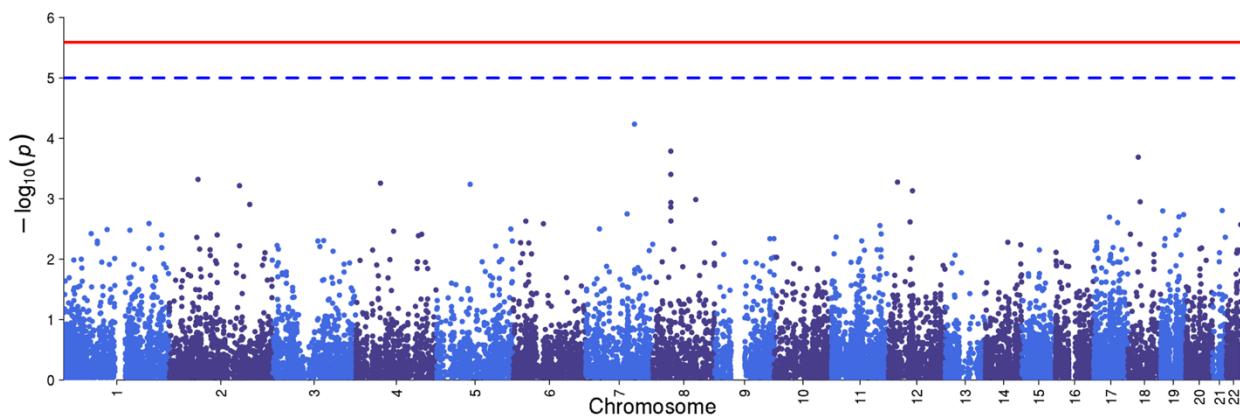
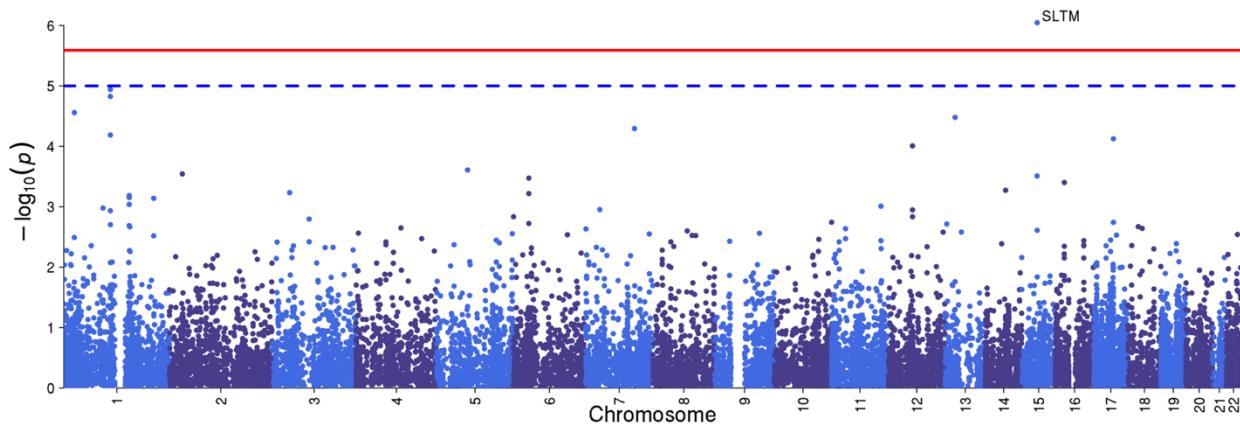
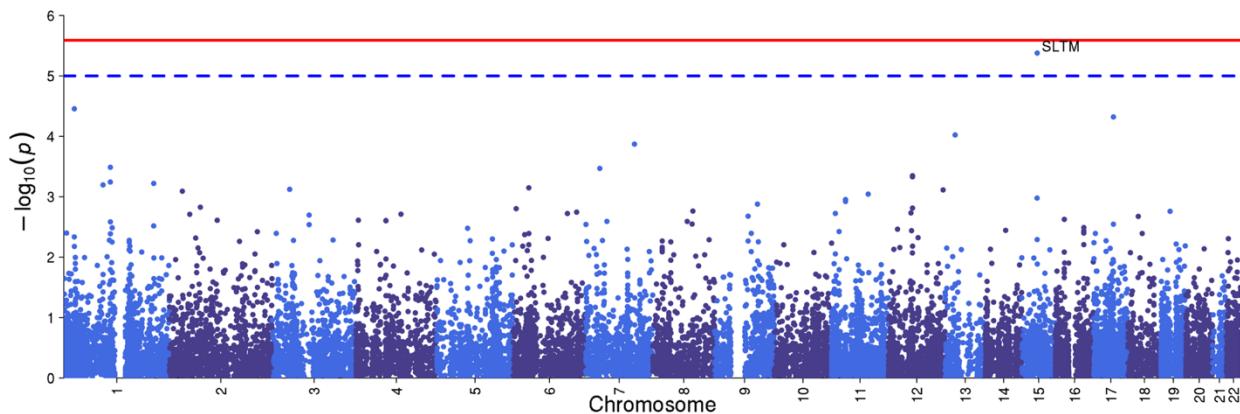
f) Cross-Disorder SCZ-BIP-rMDD**g) Omnibus Test SCZ-BIP-MDD****h) Omnibus Test SCZ-BIP-rMDD**

Figure S11. GTEx multi-tissue expression for G×S loci

This plot was generated via website gtexportal.org. Genes were included based on the following thresholds: SNP-based G×S interaction $p < 1 \times 10^{-6}$ and genes with gene-based test p -values $< 2.7 \times 10^{-6}$.

The “Brain - Frontal Cortex” and “Brain – Cortex”, and the “Brain – Cerebellum” and “Brain - Cerebellar Hemisphere” samples should be considered as sample duplicates. One set of each pair (the “Brain – Cortex” and “Brain - Cerebellum”) were sampled at the same time as the remaining donor non-brain tissue samples, and were preserved in PAXgene tissue fixative solution. The remaining whole brain was then shipped to the University of Miami Brain Endowment Bank, where 8-11 brain sub-regions were sampled. The “Brain - Frontal Cortex” and “Brain - Cerebellar Hemisphere” were re-sampled at this time, as close as possible to the original sampling sites. All brain sub-regions sampled at the Miami Brain bank were preserved by snap freezing. Hence the paired brain regions differ in the time of sampling (those re-sampled at the Brain Bank, have a longer ischemic time) and in the manner in which the sample was preserved.

Abbreviations: ACC = Anterior Cingulate Cortex; BA = Brodmann Area; BG = basal ganglia; C1 = cervical-1; NAcc = Nucleus Accumbens; PFC = prefrontal cortex; TPM = Transcripts Per Kilobase Million mapped reads.

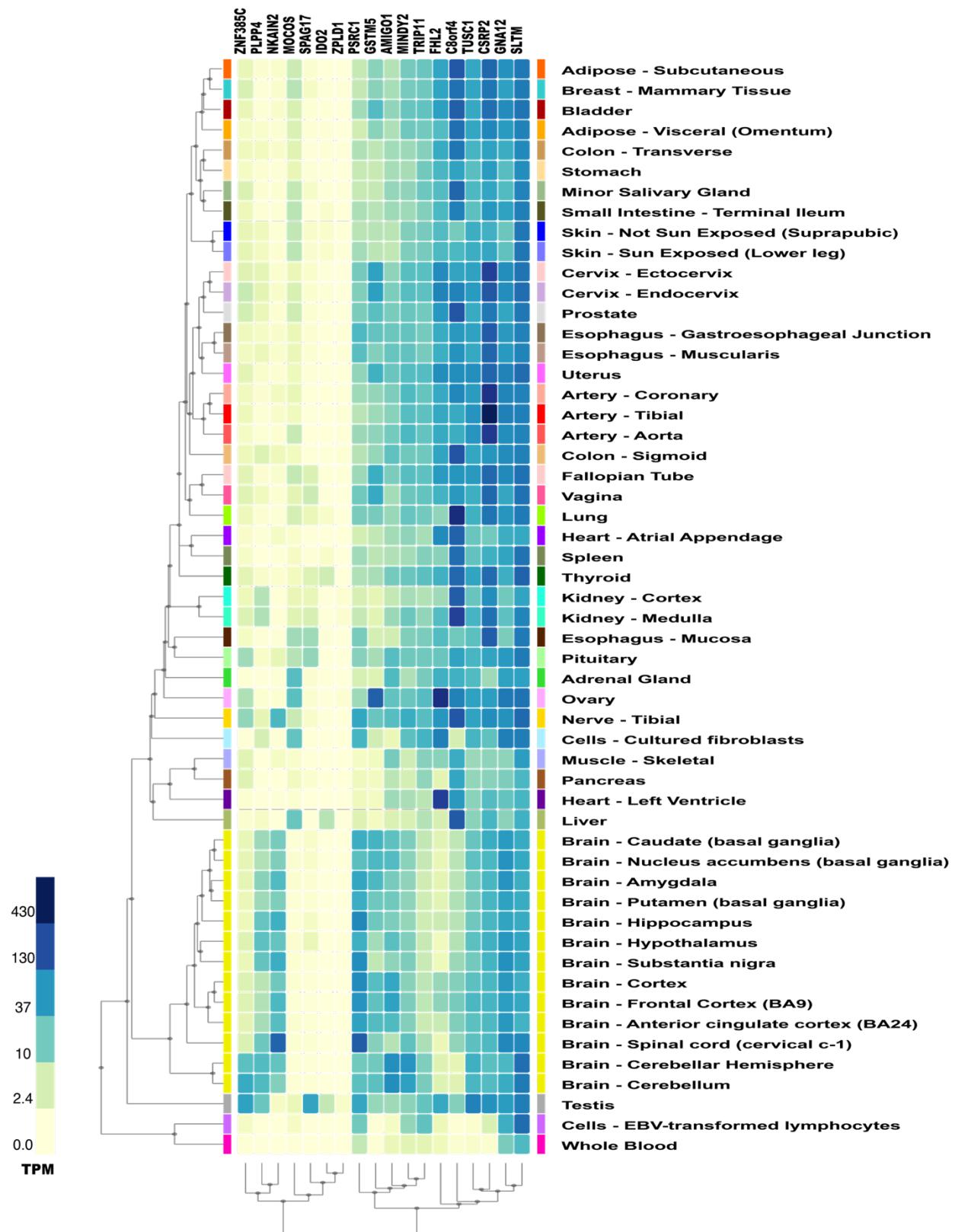
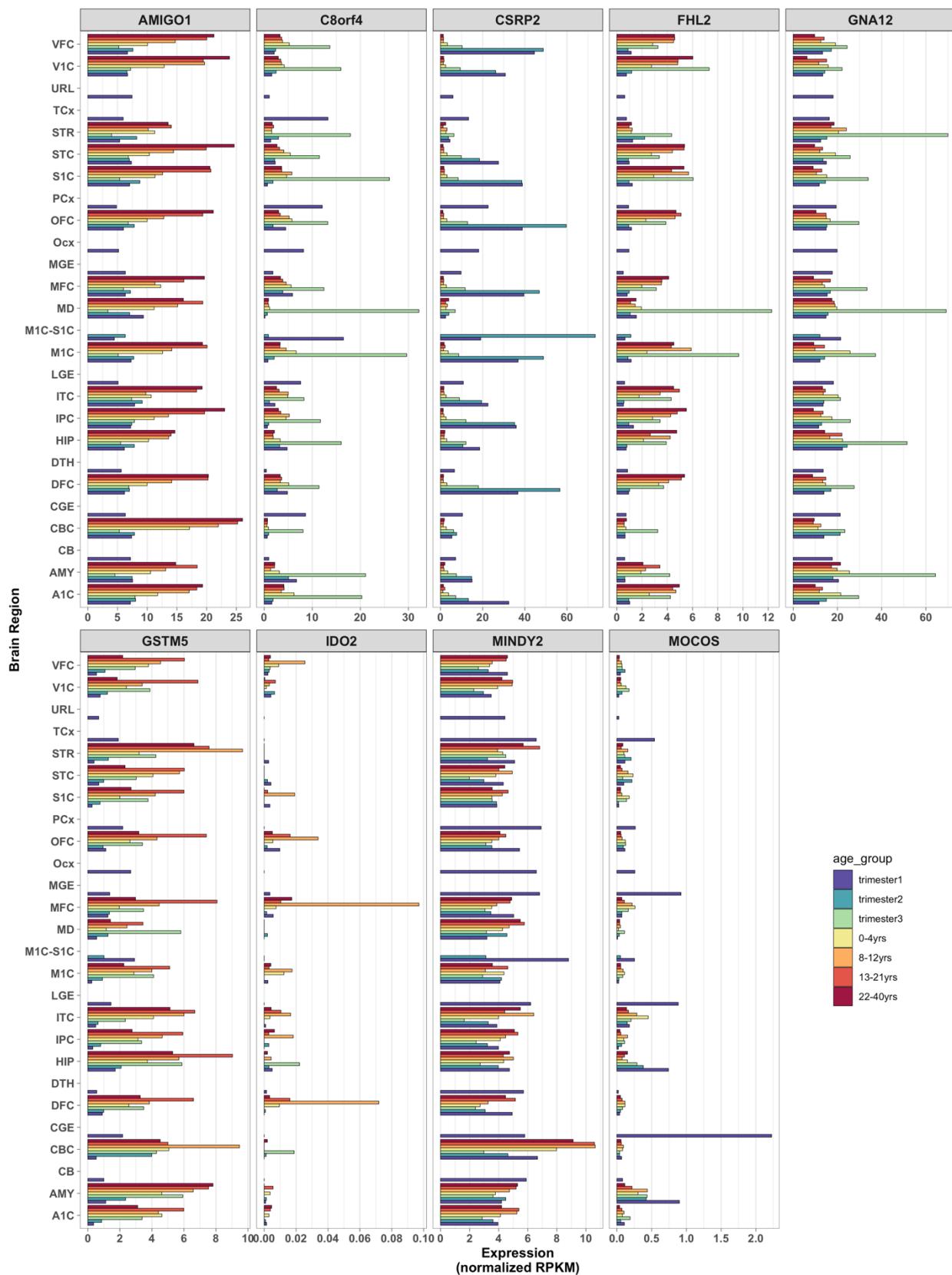


Figure S12. Allen Brain Atlas expression across development for G×S loci

Plots were generated using the ‘ggplot2’ package in R. Data were downloaded from <https://human.brain-map.org/>. Genes were included, in alphabetical order, based on the following thresholds: SNP-based G×S interaction $p < 1 \times 10^{-6}$ and genes with gene-based test p -values $< 2.7 \times 10^{-6}$.

Most of the genes examined were expressed in multiple brain regions at several stages from prenatal neurodevelopment through adulthood. However, some of the genes are predominantly expressed prenatally in one or more regions (*CRSP2*, *MOCOS*, *C8orf4* [= *TCIM*], *SPAG17*) or, in the case of *IDO2*, at the beginning of puberty (8–12 years) in prefrontal and orbitofrontal cortex.

Abbreviations: RPKM = Reads Per Kilobase of transcript per Million mapped reads; A1C = primary auditory cortex (core); AMY = amygdaloid complex; CB = cerebellum; CBC = cerebellar cortex; CGE = caudal ganglionic eminence; DFC = dorsolateral prefrontal cortex; DTH = dorsal thalamus; HIP = hippocampus (hippocampal formation); IPC = posteroventral (inferior) parietal cortex; ITC = inferolateral temporal cortex (area TEv, area 20); LGE = lateral ganglionic eminence; M1C = primary motor cortex (area M1, area 4); M1C-S1C = primary motor-sensory cortex (samples); MD = mediodorsal nucleus of thalamus; MFC = anterior (rostral) cingulate (medial prefrontal) cortex; MGE = medial ganglionic eminence; Ocx = occipital neocortex; OFC = orbital frontal cortex; PCx = parietal neocortex; S1C = primary somatosensory cortex (area S1, areas 3,1,2); STC = posterior (caudal) superior temporal cortex (area 22c); STR = striatum; TCx = temporal neocortex; URL = upper (rostral) rhombic lip; V1C = primary visual cortex (striate cortex, area V1/17); VFC = ventrolateral prefrontal cortex



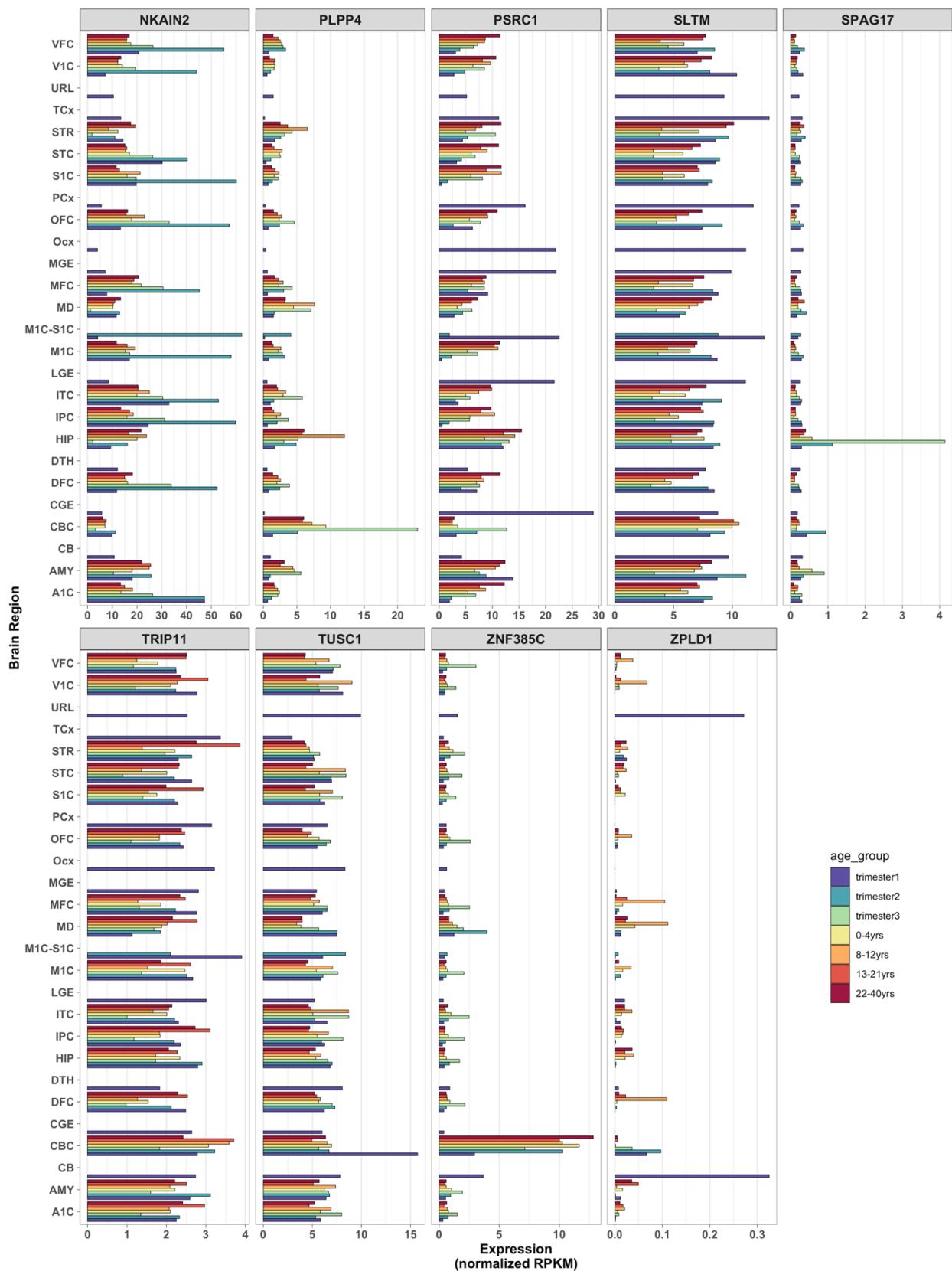
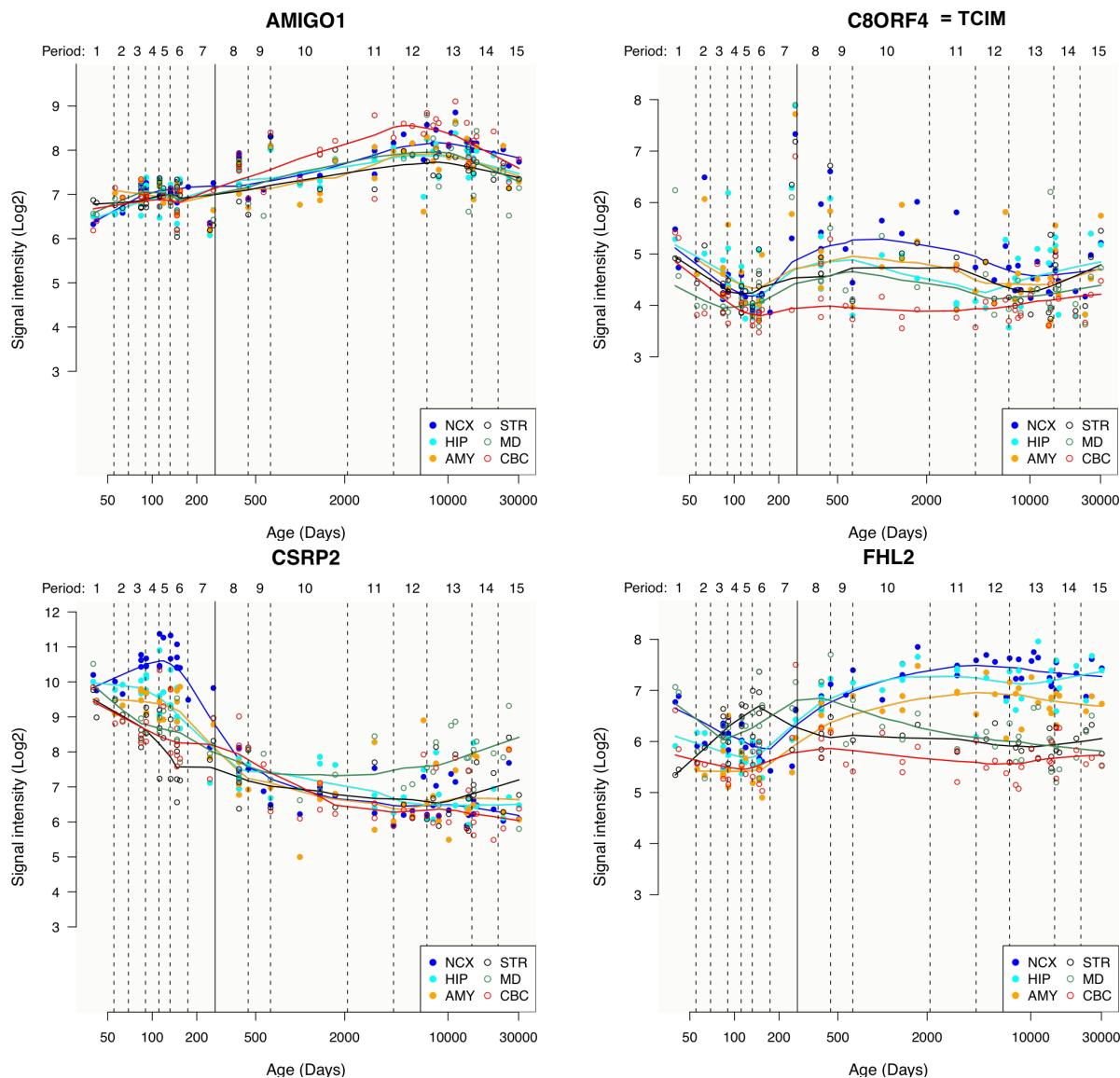
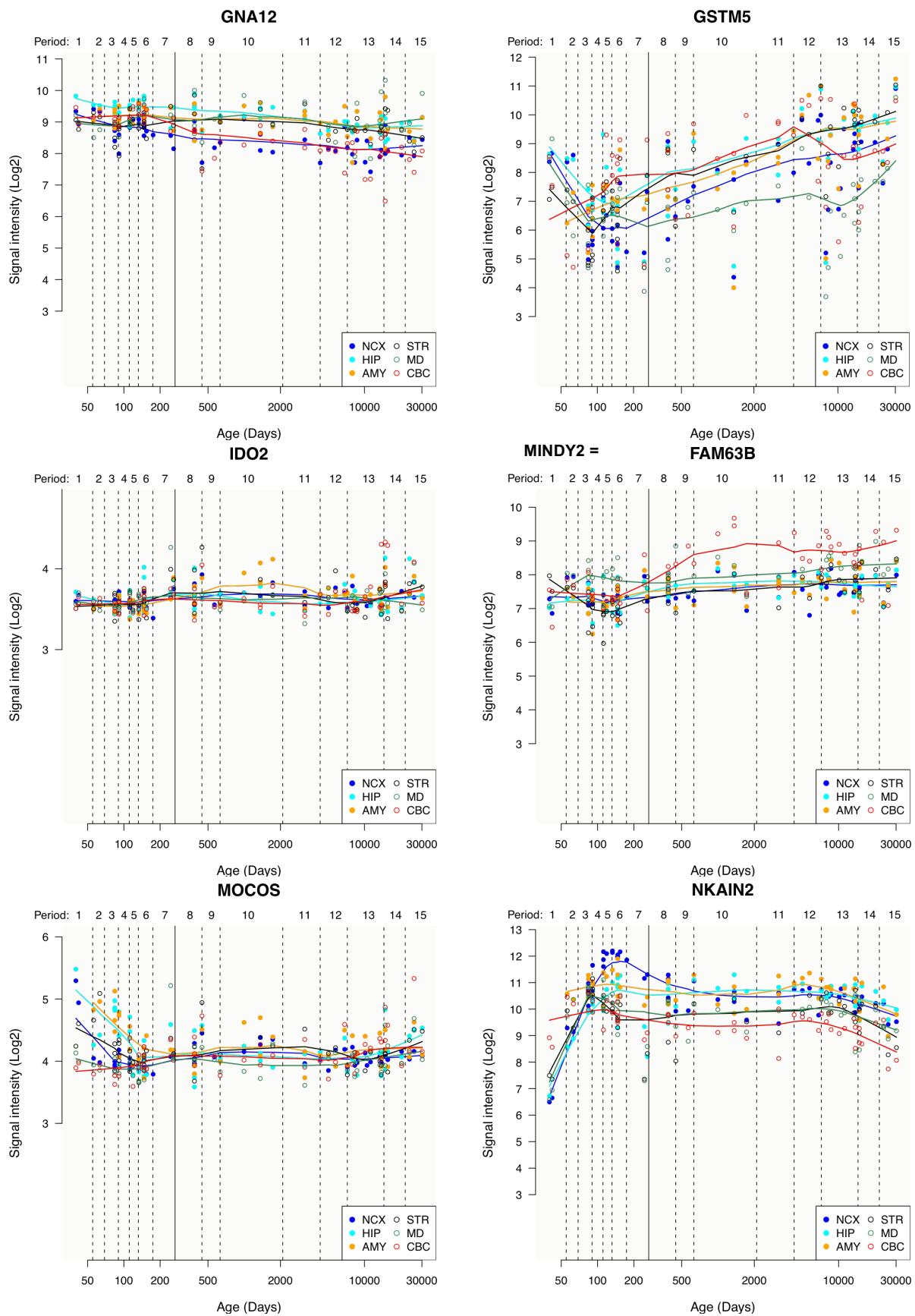


Figure S13. Life brain expression course derived from the Human Brain Transcriptome Project for G×S loci

Plots were generated via website hbatlas.org. Genes were included, in alphabetical order, based on the following thresholds: SNP-based G×S interaction $p < 1 \times 10^{-6}$ and genes with gene-based test p -values $< 2.7 \times 10^{-6}$. Periods 1 through 7 are prenatal; Periods 8 and 9 are infant and toddler, respectively; Periods 10 and 11 are childhood; Periods 12 and 13 correspond to age ranges 12-20 years and 20-40 years, respectively; Periods 14 and 15 are middle age and 65+, respectively. Most of the genes examined were expressed in multiple brain regions at several stages from prenatal neurodevelopment through adulthood. However, some of the genes are predominantly expressed prenatally in one or more regions (*CRSP2*, *MOCOS*, *C8orf4* [= *TCIM*], *SPAG17*) or, in the case of *IDO2*, at the beginning of puberty (8-12 years) in prefrontal and orbitofrontal cortex.

Abbreviations: CBC = cerebellar cortex; MD = mediodorsal nucleus of the thalamus; STR = striatum; AMY = amygdala; HIP = hippocampus; NCX = 11 areas of neocortex.





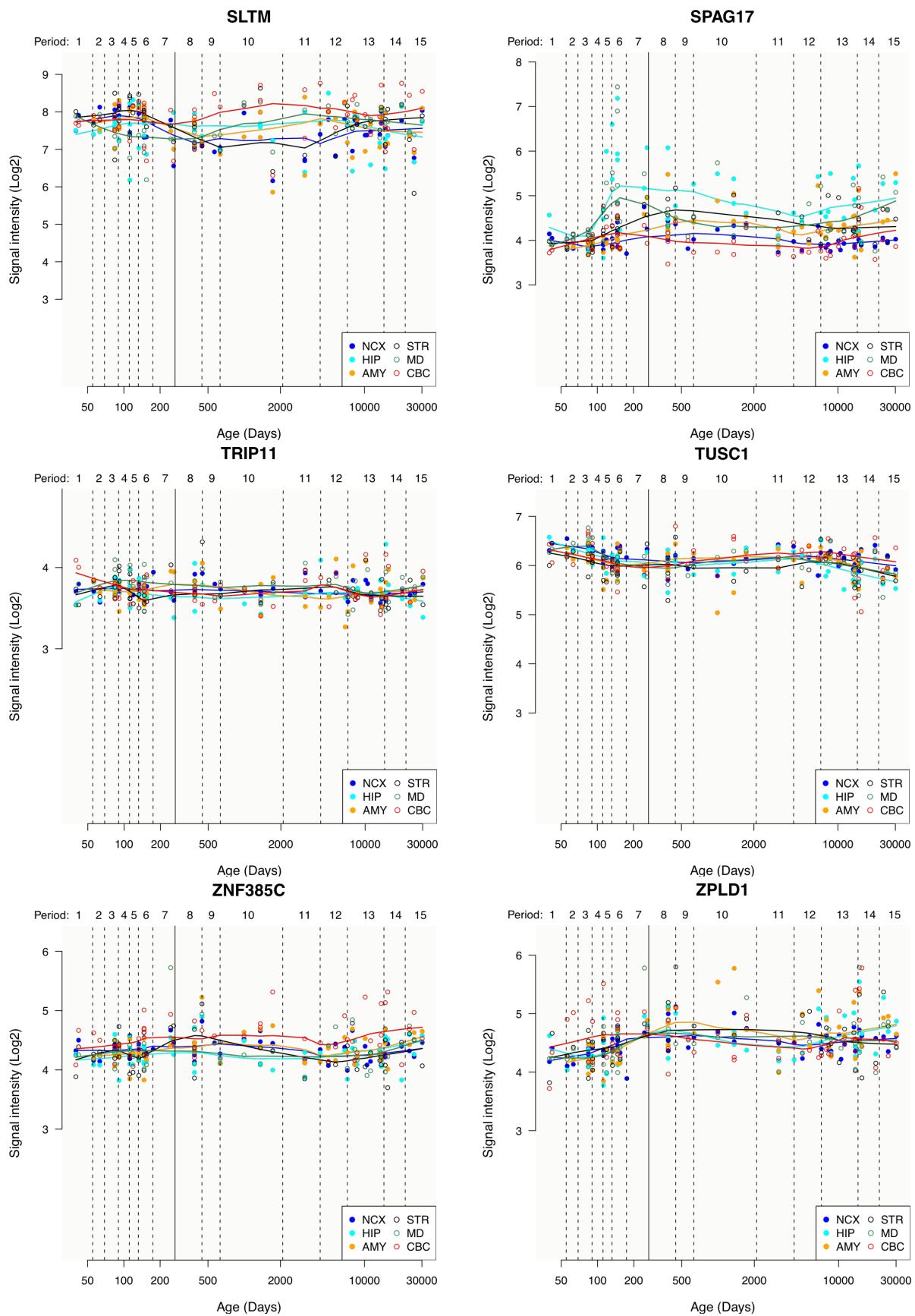
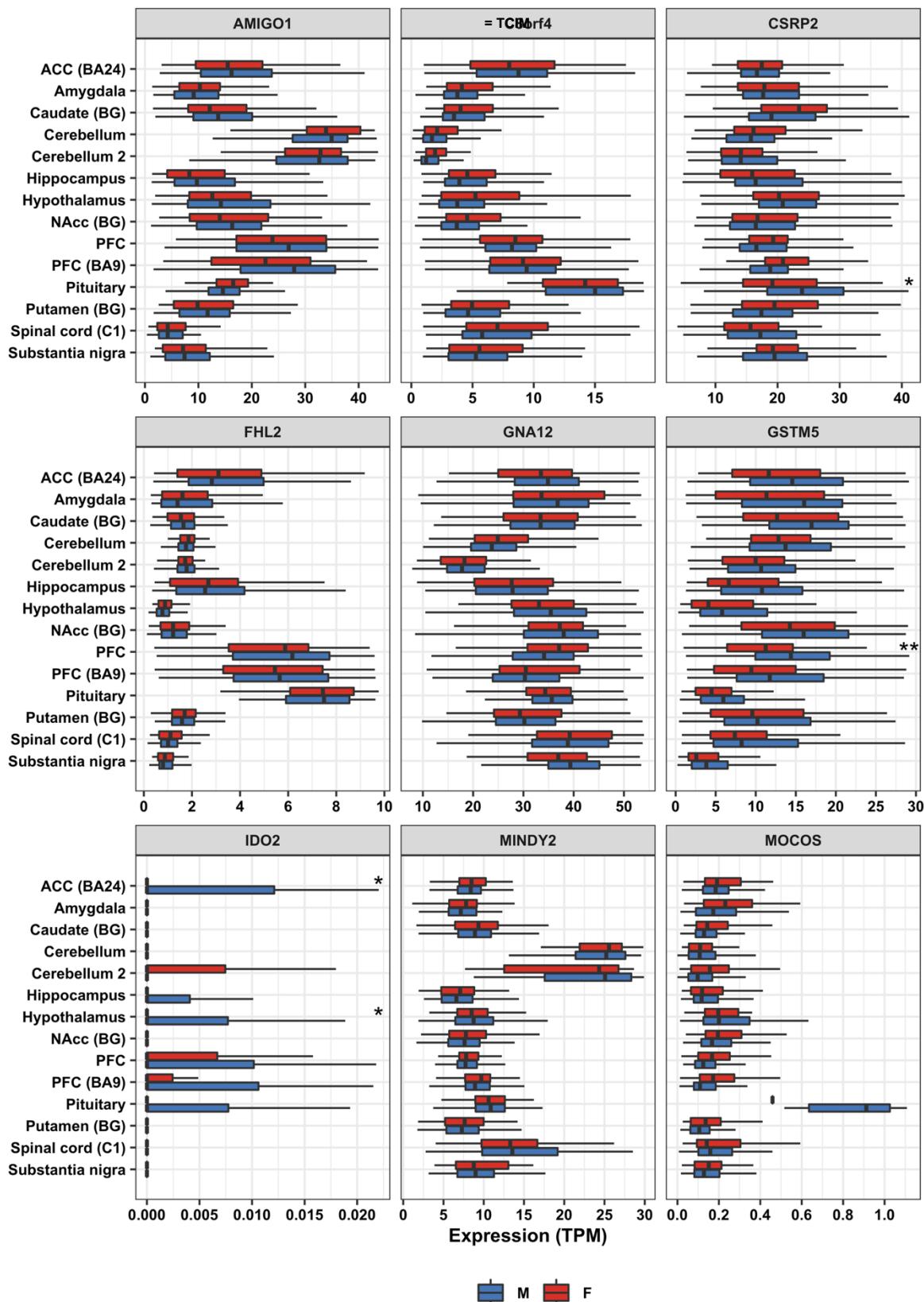


Figure S14. GTEx sex-specific multi-tissue expression for G×S loci

Expression data (v.8) were obtained from the Genotype-Tissue Expression (GTEx) project and downloaded from gtexportal.org. Tissue expression per gene was filtered for outliers with values > 9th decile prior to t-test comparisons. Plots were generated using the ‘ggplot2’ package in R. Genes were included, in alphabetical order, based on the following thresholds: SNP-based G×S interaction $p < 1 \times 10^{-6}$ and genes with gene-based test p -values $< 2.7 \times 10^{-6}$. Evaluation of sex-specific expression detected significantly different expression levels between males and females of several of the genes, particularly in PFC, ACC, pituitary, and hypothalamus. * $p < 0.05$; ** $p < 0.01$ (Bonferroni-corrected for 14 tissues compared). The “Brain - Frontal Cortex” and “Brain – Cortex”, and the “Brain – Cerebellum” and “Brain - Cerebellar Hemisphere” samples should be considered as sample duplicates. One set of each pair (the “Brain – Cortex” and “Brain – Cerebellum”) were sampled at the same time as the remaining donor non-brain tissue samples, and were preserved in PAXgene tissue fixative solution. The remaining whole brain was then shipped to the University of Miami Brain Endowment Bank, where 8-11 brain sub-regions were sampled. The “Brain - Frontal Cortex” and “Brain - Cerebellar Hemisphere” were re-sampled at this time, as close as possible to the original sampling sites. All brain sub-regions sampled at the Miami Brain bank were preserved by snap freezing. Hence the paired brain regions differ in the time of sampling (those re-sampled at the Brain Bank, have a longer ischemic time) and in the manner in which the sample was preserved.

Abbreviations: ACC = Anterior Cingulate Cortex; BA = Brodmann Area; BG = basal ganglia; C1 = cervical-1; F = Females; M = Males; NAcc = Nucleus Accumbens; PFC = prefrontal cortex; TPM = Transcripts Per Kilobase Million mapped reads.



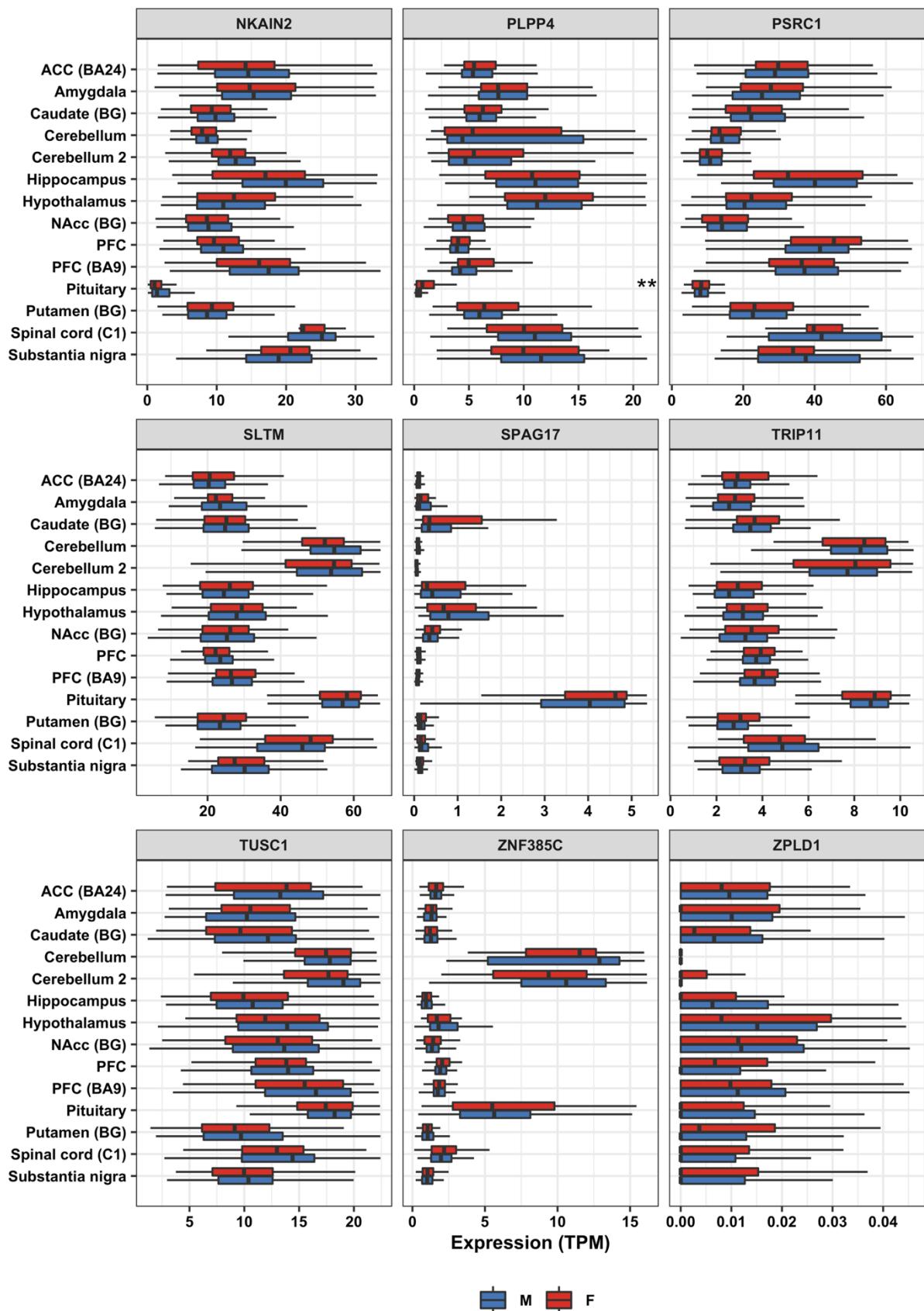
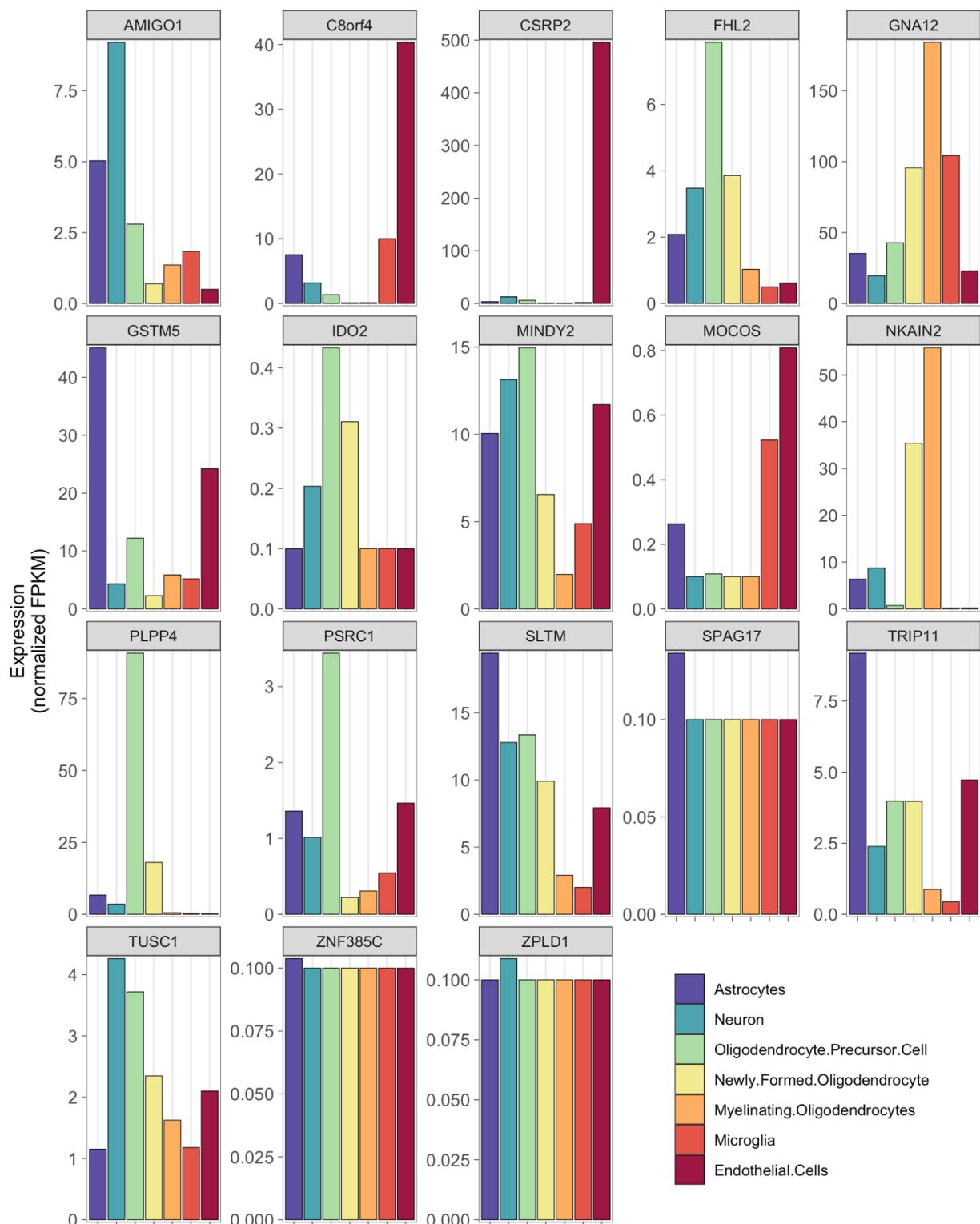


Figure S15. Cell type-specific brain expression derived from the Stanford RNA-Seq database for G×S loci

Mouse brain expression data were downloaded from <https://www.brainrnaseq.org/>. Genes were mapped to human orthologous genes using Ensembl. Genes were included, in alphabetical order, based on the following thresholds: SNP-based G×S interaction $p < 1 \times 10^{-6}$ and genes with gene-based test p -values $< 2.7 \times 10^{-6}$. Plots were generated using the ‘ggplot2’ package in R. Among seven brain cell types, the genes examined are expressed in various cell types, with no preponderance of expression in a particular type.

Abbreviations: FPKM = Fragments Per Kilobase of transcript per Million mapped reads.



Supplementary Tables PGC only

Table S15. Meta-analysis Autosomal G×S interaction loci in PGC

See TableS15_MetaAnalysisSTDERR_auto_PGC.xlsx

Cross-disorder and within-disorder meta-analyses were carried out using METAL, incorporating cohort-level summary statistics from PLINK. Listed are LD-independent SNPs with interaction p -values $< 1 \times 10^{-6}$ in SCZ, BIP, (r)MDD, and cross-disorder. Loci were clumped using ‘*plink --bfile 1kgp_ref_file --clump metal_output --clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.6 --clump-kb 3000*’

Abbreviations: BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S16. Omnibus test Autosomal G×S interaction loci in PGC

See TableS16_OmnibusTestASSET_auto_PGC.xlsx

Omnibus tests were carried out using ASSET, incorporating the within-disorder meta-analysis summary statistics from METAL. Listed are LD-independent SNPs with cross-disorder interaction p -values $< 1 \times 10^{-6}$. Loci were clumped using ‘*plink --bfile 1kgp_ref_file --clump asset_output --clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.6 --clump-kb 3000*’

Abbreviations: BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S17. Meta-analysis chrX G×S interaction loci in PGC

See TableS17_MetaAnalysisSTDERR_xchr_PGC.xlsx

Cross-disorder and within-disorder meta-analyses were carried out using METAL, incorporating cohort-level summary statistics from PLINK. Listed are LD-independent SNPs with interaction p -values $< 1 \times 10^{-6}$ in SCZ, BIP, (r)MDD, and cross-disorder. Model A (**a**) effectively assumes complete and uniform X-inactivation in females and a similar effect size between males and females. Females are considered to have 0, 1, or 2 copies of an allele; males are considered to have 0 or 2 copies of the same allele. Model B (**b**) considers the allelic dosages for females to be 0, 1, or 2 copies, and males to be 0 or 1 copy as in an autosomal analysis. Loci were clumped using ‘*plink --bfile 1kgp_ref_file --clump metal_output --clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.6 --clump-kb 3000*’

Abbreviations: BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S18. Omnibus test chrX G×S interaction loci in PGC

See TableS18_OmnibusTestASSET_xchr_PGC.xlsx

Omnibus tests were carried out using ASSET, incorporating the within-disorder meta-analysis summary statistics from METAL. Listed are LD-independent SNPs with cross-disorder interaction p -values $< 1 \times 10^{-6}$. Loci were clumped using ‘*plink --bfile 1kgp_ref_file --clump asset_output --clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.6 --clump-kb 3000*’

Abbreviations: BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S19. Credible SNPs for G×S loci in PGC

See TableS19_CredibleSNPs_FineMapping_PGC.xlsx

Fine mapping was carried out using both FINEMAP and CAVIAR. Fine mapping using FINEMAP was carried out with settings: `--sss --corr-config 0.95 --n-causal-snps 5 --n-configs-top 50000 --prior-k0 0 --prior-std 0.05`. If there were less than 5 SNPs in the locus, `--n-causal-snps` was set to the number of SNPs in the locus according to LD. The most likely causal SNPs per locus are highlighted in bold font. The shotgun stochastic search (`--sss`) conducts a pre-defined number of iterations within the space of causal configurations. In each iteration, the neighborhood of the current causal configuration is defined by configurations that result from deleting, changing or adding a causal SNP from the current configuration. The next iteration starts by sampling a new causal configuration from the neighborhood based on the scores normalized within the neighborhood. Fine mapping using CAVIAR was carried out with settings: `-r 0.95 -c 5 -f 1`. If there were less than 5 SNPs in the locus, `-c` was set to the number of SNPs in the locus according to LD. Analyses used European ancestry only summary statistics. Loci with $p < 1 \times 10^{-6}$ were analyzed (index SNPs determined based on clumping using LD threshold 0.1). The most likely causal SNPs per locus are highlighted in bold font.

Abbreviations: PP_group = posterior probability that there is at least one causal signal among SNPs in the same group with this SNP; PP_causal = posterior probability that the SNP is causal; BP = base pair position; BIP = bipolar disorder; CHR = chromosome; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia; SNP = Single Nucleotide Polymorphism rs ID.

Table S20. Gene-based test in PGC

See TableS20_Gene-BasedTest_PGC.xlsx

Gene-based analyses were carried out in MAGMA on the genomic control output with INFO score > 0.6 , European ancestry only, and autosomal SNPs only, with the MHC region included. Genes with p -values $< 1 \times 10^{-4}$ are shown. There was no difference in the p -values when the MHC region was excluded. There were minor differences in p -values when using INFO score > 0.8 , but with the same top 10 genes. *Significant at genome-wide threshold for gene-based test of 0.05 / 19,427 genes = 2.6×10^{-6} .

Abbreviations: BP = base pair position; Chr = chromosome; N SNPs = number of SNPs in gene; N Param = number of parameters; N = sample size; Z = Z-statistic; BIP = bipolar disorder; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia.

Table S21. MSigDB pathway gene set enrichment analyses in PGC

See TableS21_MSigDB_pathway_GSEA_PGC.xlsx

Enrichment analyses were carried out in MAGMA on the genomic control output with INFO score > 0.6 , European ancestry only, and autosomal SNPs only. Analyses were run both with (top subtable) and without (bottom subtable) inclusion of the Chromosome 6 MHC region. Each (sub)table displays the top 10 gene sets based on the uncorrected p -value. Hyperlinks link to the GSEA/MSigDB website with a description of the pathway.

Abbreviations: BIP = bipolar disorder; P_{BONF} = Bonferroni-corrected p -value; P_{FDR} = False Discovery Rate-corrected p -value; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia; SE = Standard Error.

Table S22. Selected pathway gene set enrichment analyses in PGC

See TableS22_Selected_pathway_GSEA_PGC.xlsx

Analyses were run with (top) and without (bottom) inclusion of the Chromosome 6 MHC region in MAGMA. These analyses were carried out on the genomic control output with INFO score > 0.6, European ancestry only, and autosomal SNPs only. * Significant after adjusting *p*-values for multiple testing.

Abbreviations: BIP = bipolar disorder; CNS = central nervous system; MP = Mouse Phenome; PFDR = False Discovery Rate-corrected *p*-value; PGC-NPA = Psychiatric Genomics Consortium – Network and Pathway Analysis Working Group; (r)MDD = (recurrent) major depressive disorder; SCZ = schizophrenia; SE = Standard Error.

Supplementary Figures PGC only

Figure S16. Linkage Disequilibrium Score Regression estimates of SNP-based heritability and genetic correlations in PGC

This graph shows h^2 and r_g estimates for MAF > 0.01.

- a) Heritability estimates were substantially different between the sexes for SCZ ($p_{FDR} = 0.019$) and MDD ($p_{FDR} = 0.005$), but not BIP ($p_{FDR} = 0.381$).
- b) SNP-based genetic correlations (r_g / SE) between males and females within each disorder ranged between 0.86 and 1 and were significantly different from 1 for SCZ ($p_{FDR} = 0.039$) and BIP ($p_{FDR} = 0.039$), but not MDD ($p_{FDR} = 0.397$). No significant differences in the cross-disorder genetic correlations between males and females, with the exception of r_g between BIP and MDD ($r_{gF} = 0.42$; $r_{gM} = 0.04$; $p_{FDR} = 0.044$).

Abbreviations: BIP = Bipolar Disorder; MDD = Major Depressive Disorder; SCZ = Schizophrenia; F = Females; M = Males; SE = standard error.

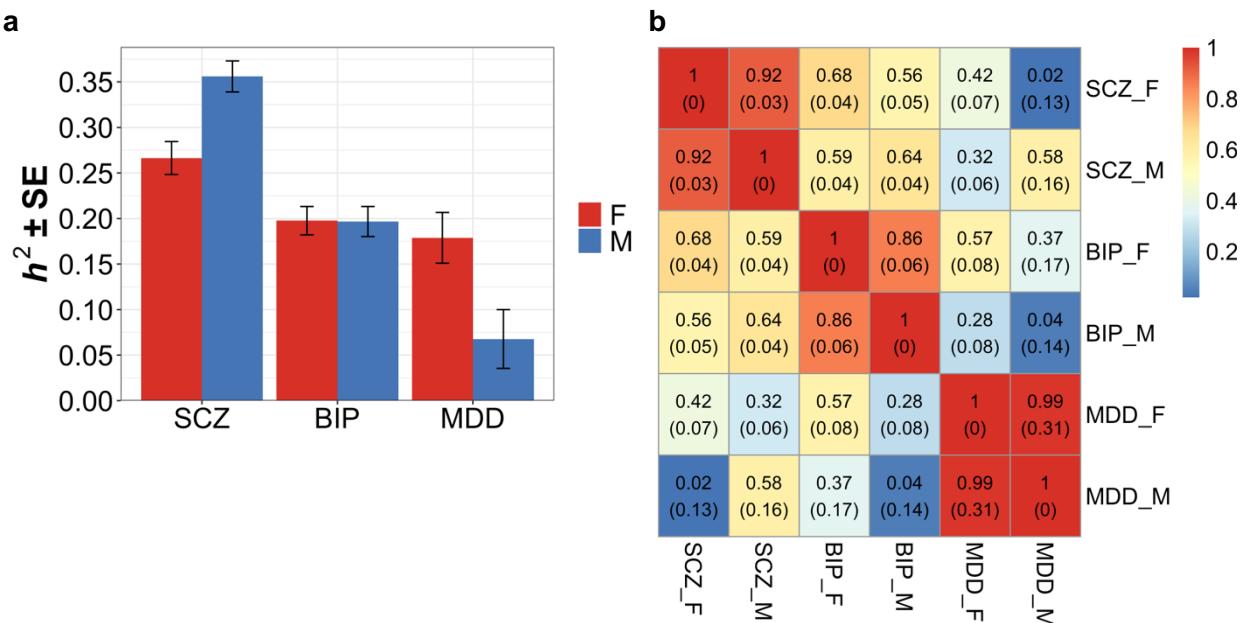


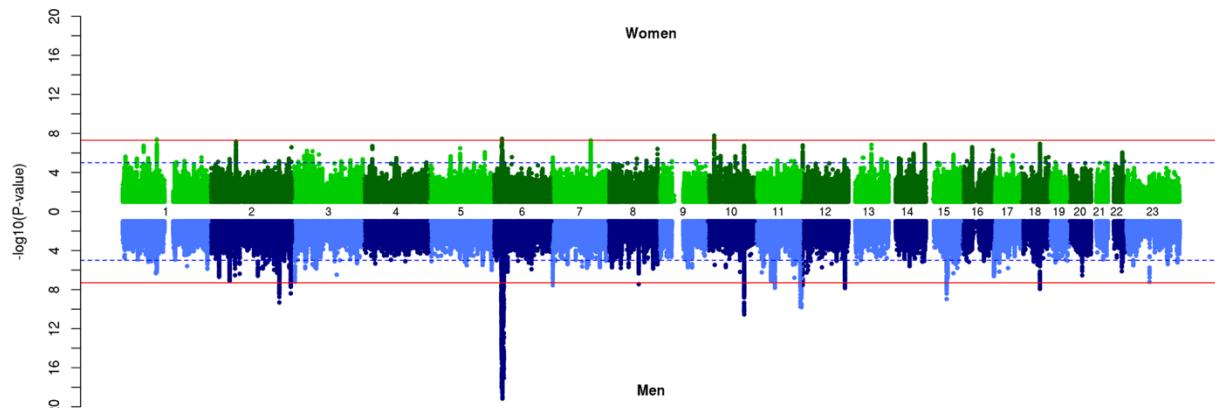
Figure S17. Miami plots for sex-stratified analyses in PGC

GWAS SNP main effects for men (blue) are plotted downward, and are plotted upward for women (green). Negative log₁₀-transformed *p*-values for each variant (each dot) (y-axis) are plotted by chromosomal position (x-axis). The solid red and dotted blue horizontal lines represent the thresholds for genome-wide significant association ($p = 5 \times 10^{-8}$) and suggestive association ($p = 1 \times 10^{-5}$), respectively. Plotted are the regular meta-analysis results within and across disorders only; omnibus tests were not carried out for sex-stratified analyses.

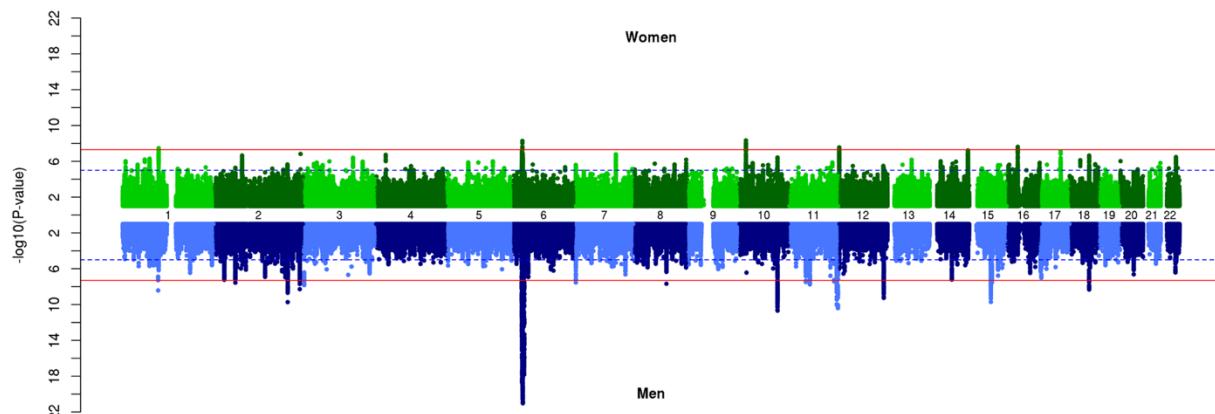
Plots were generated using the ‘plot’ package in R.

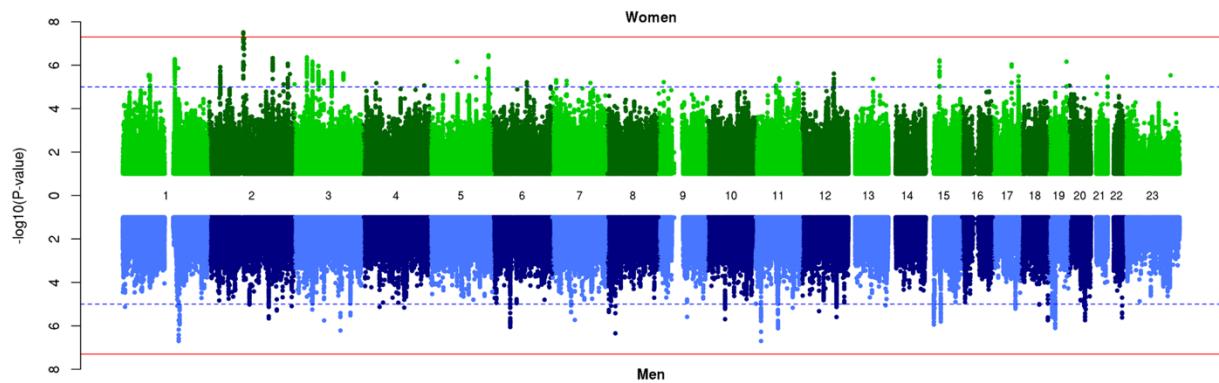
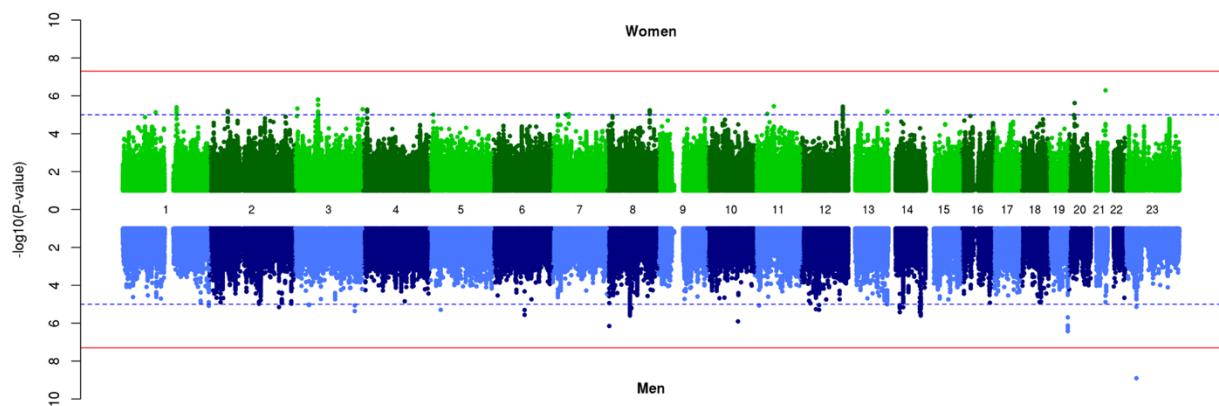
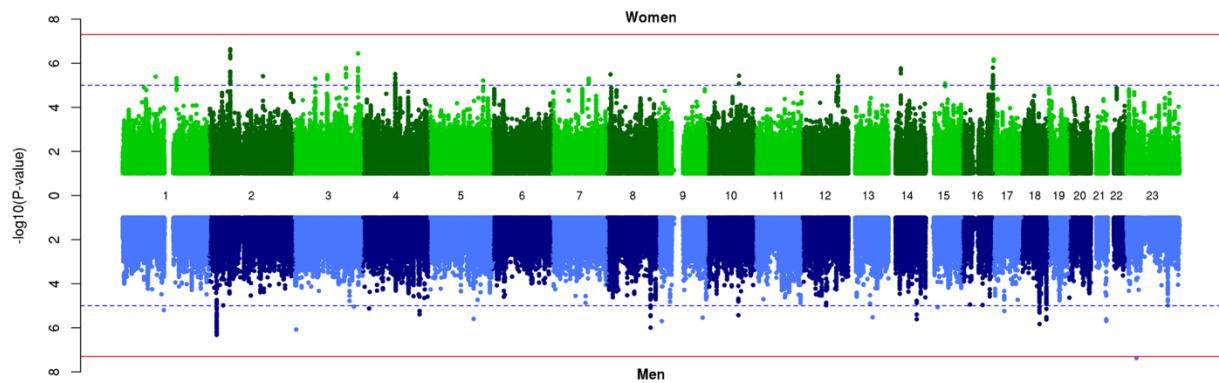
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia

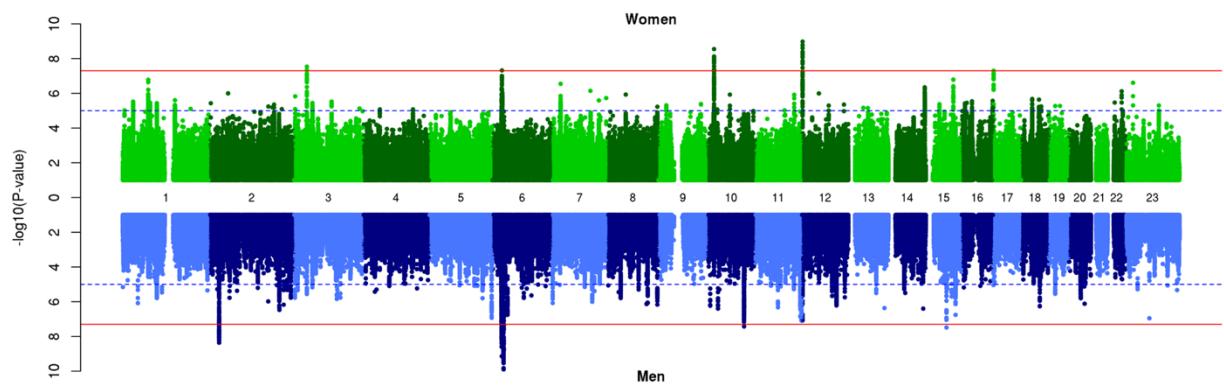
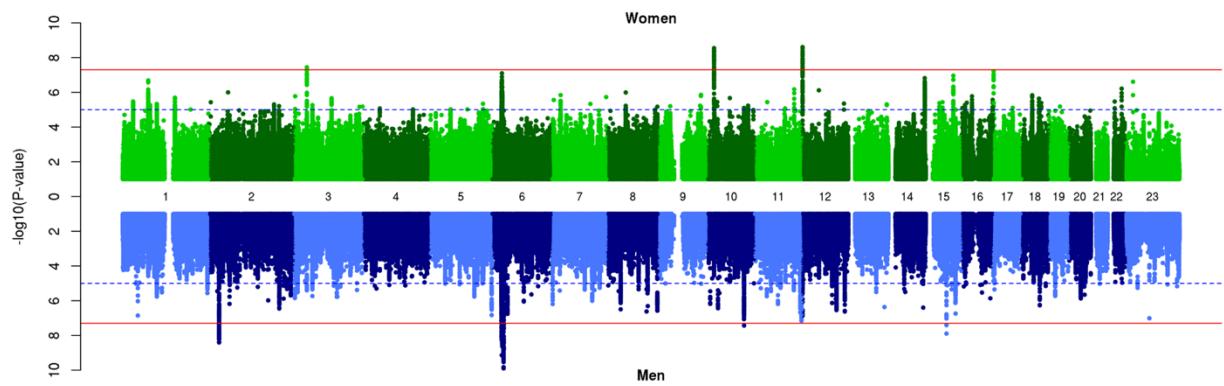
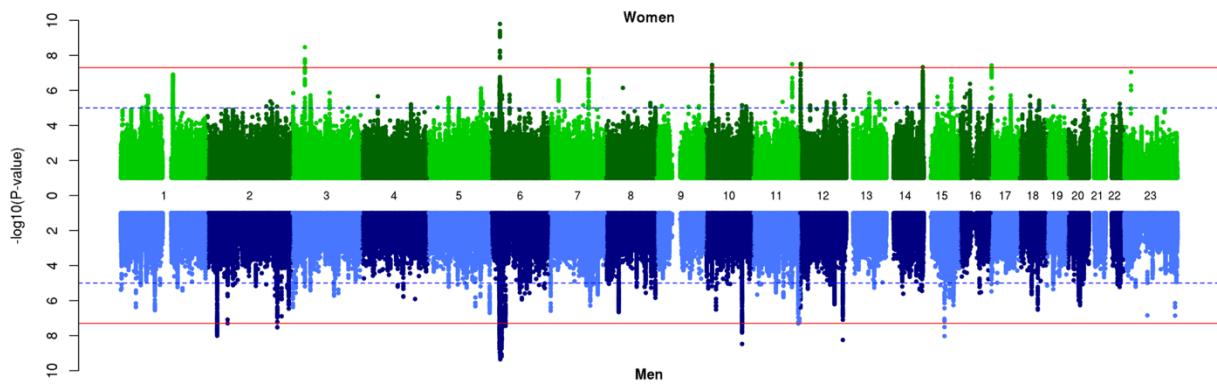
a) Schizophrenia – European ancestry only



b) Schizophrenia – European + East Asian ancestry



c) Bipolar Disorder**d) Major Depressive Disorder****e) Recurrent Major Depressive Disorder**

f) Cross-Disorder SCZ-BIP-MDD – European ancestry only**g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry****h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only**

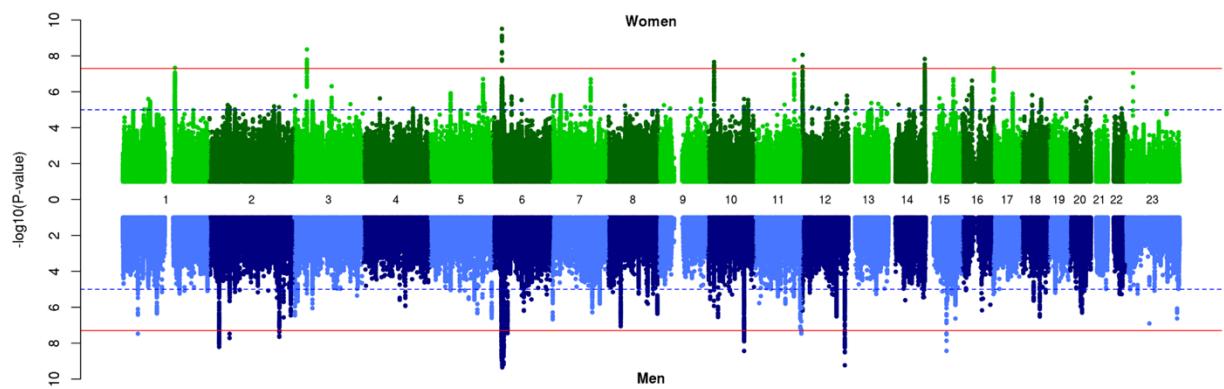
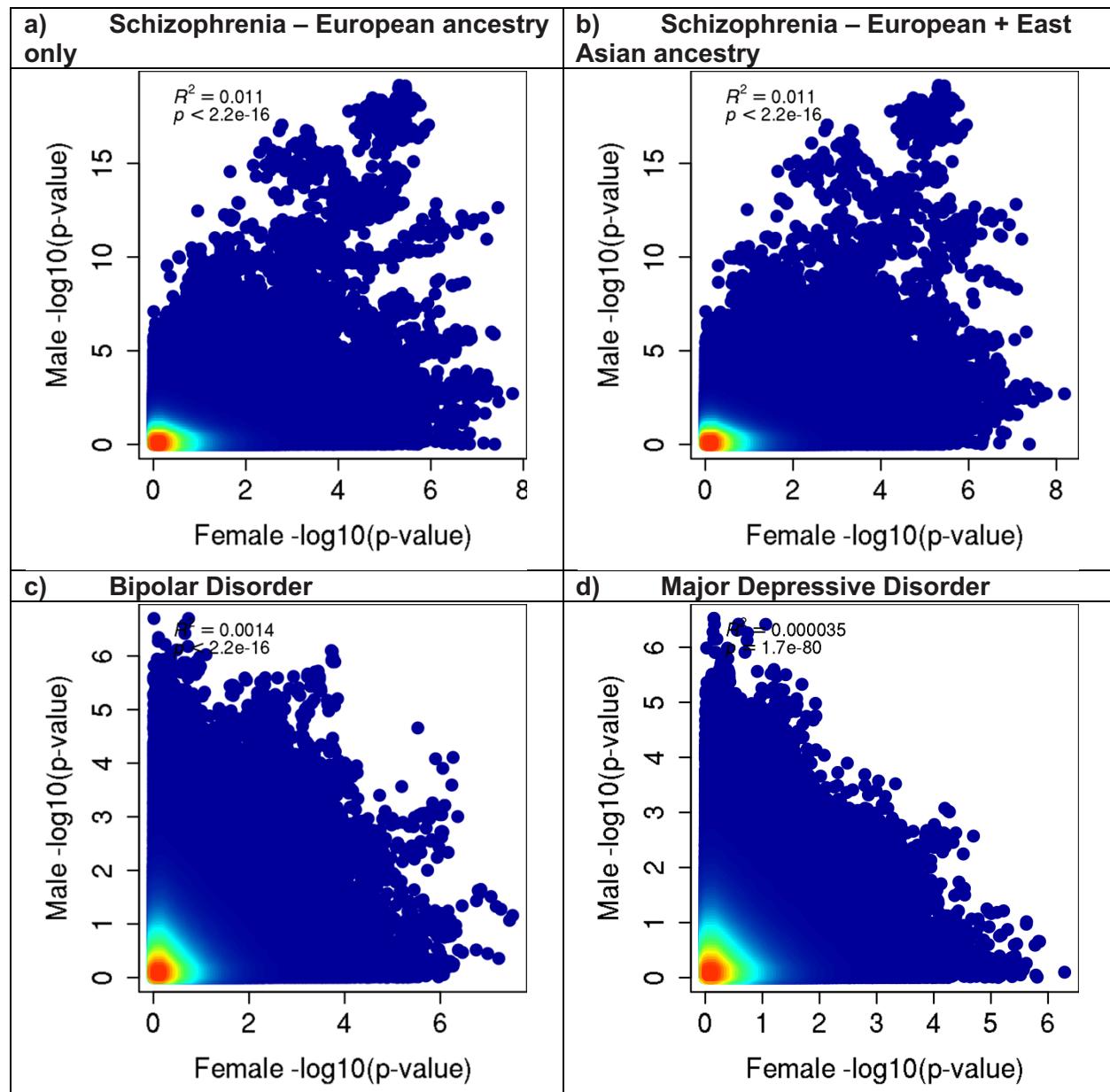
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry

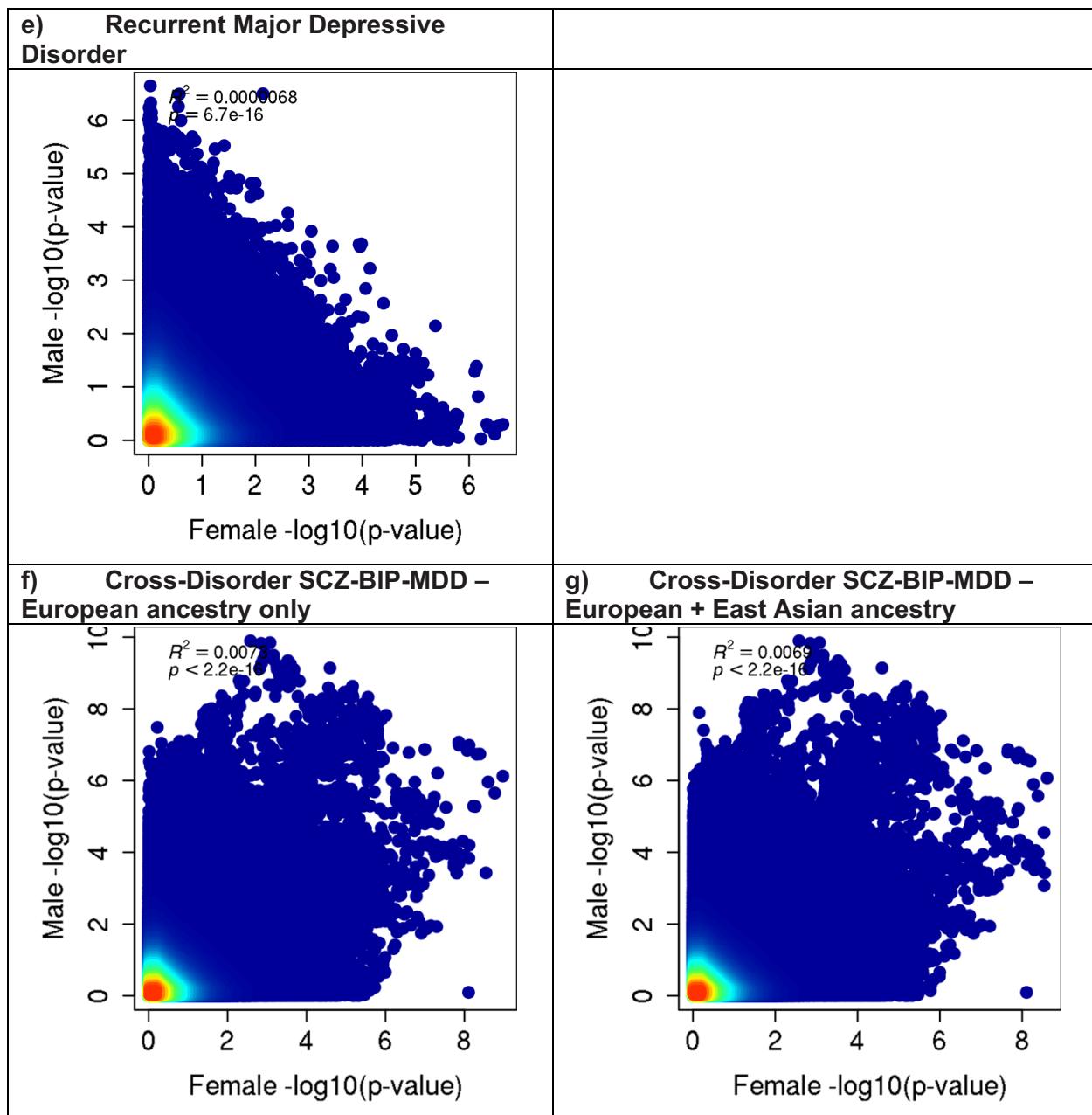
Figure S18. Scatter plots of female vs male associations in PGC

The scatter plots show little correlation (R) between GWAS SNP main effect p -values from the two sexes, indicating the strength of association differed substantially between the two sexes.

Plots were generated using the ‘plot’ package in R.

Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; R^2 = proportion variance explained.





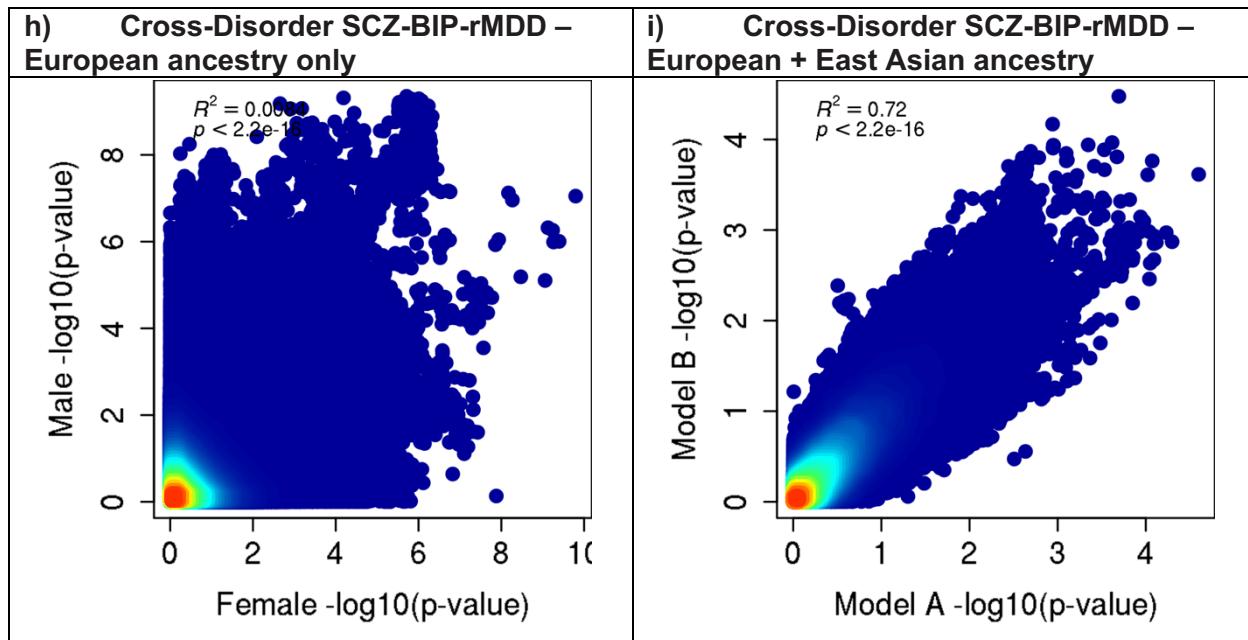
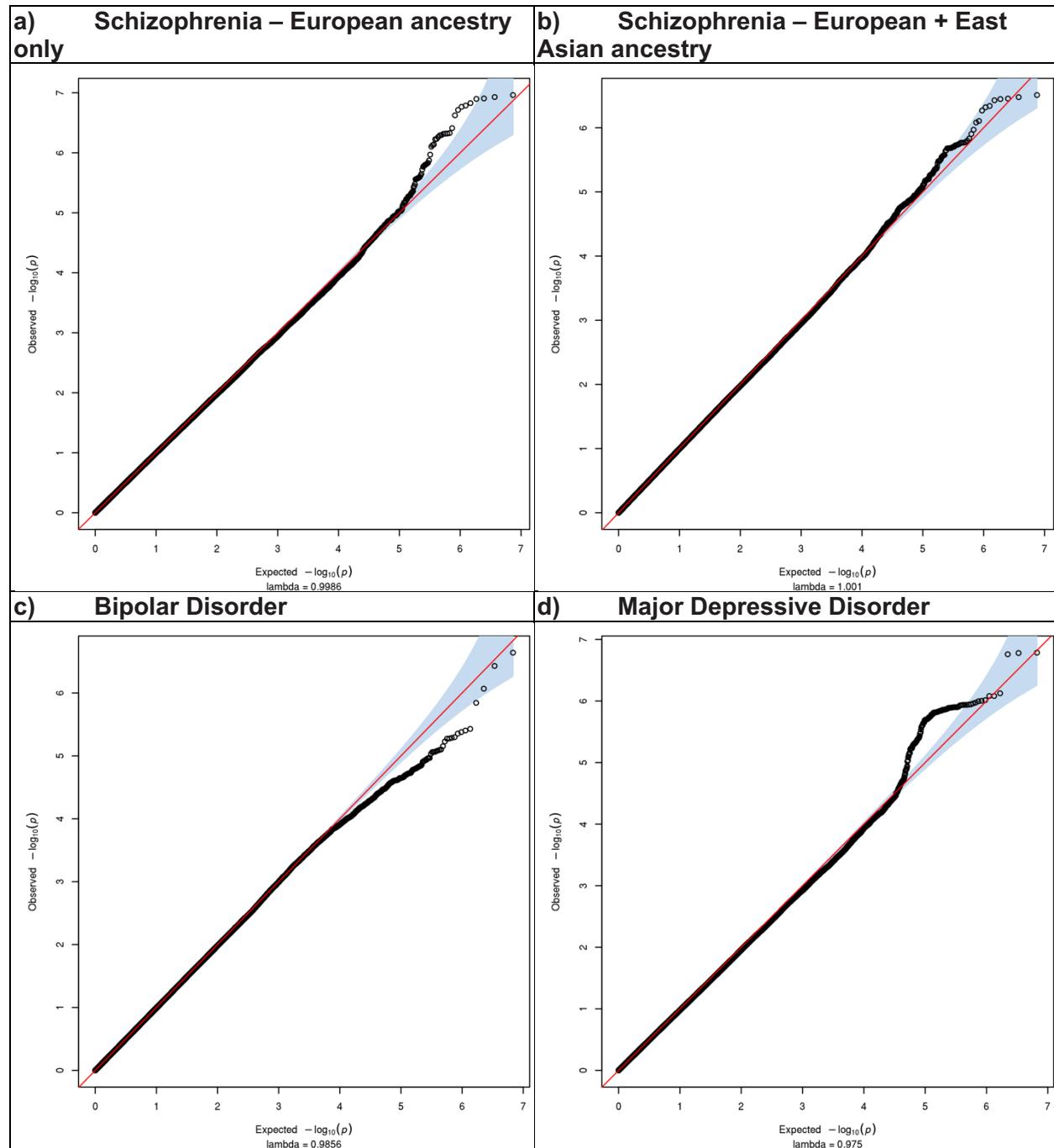
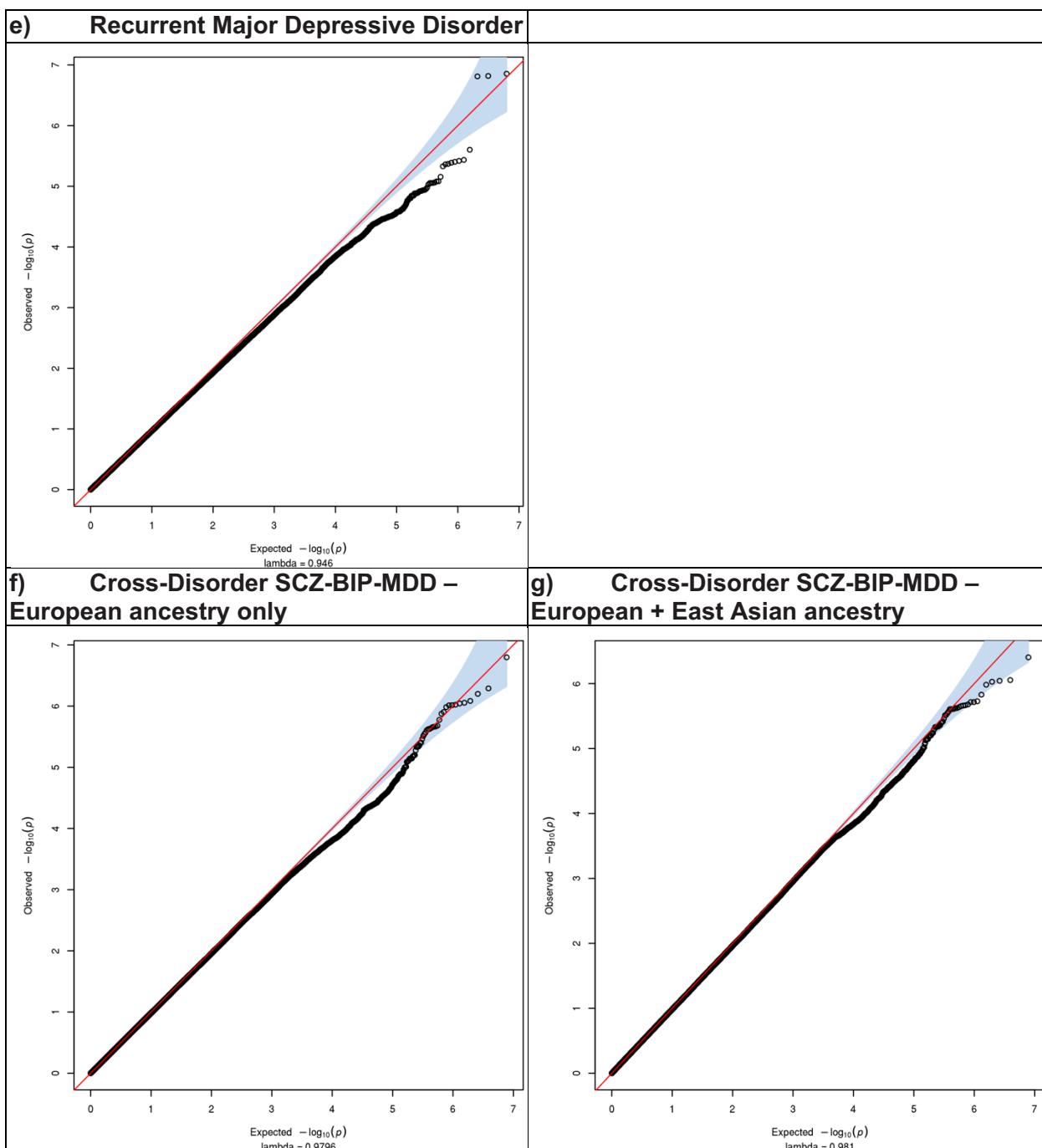


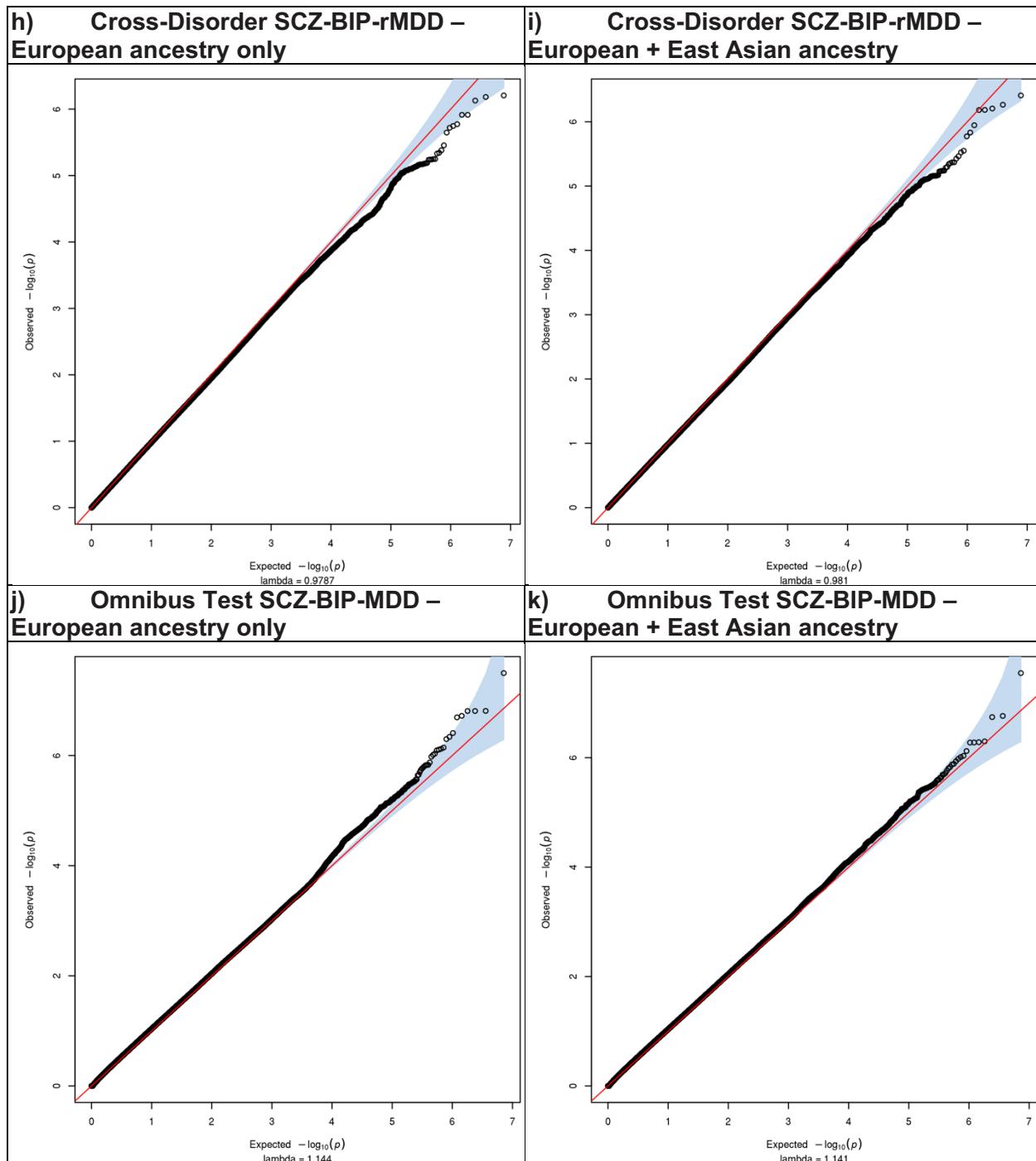
Figure S19. Quantile-Quantile plots for G×S interaction in PGC

The Quantile-Quantile (Q-Q) plot is used to assess the number and magnitude of observed associations compared with the expectations under no association. The nature of deviations from the identity line provide clues whether the observed associations are true associations or may be due to for example population stratification or cryptic relatedness.

Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia







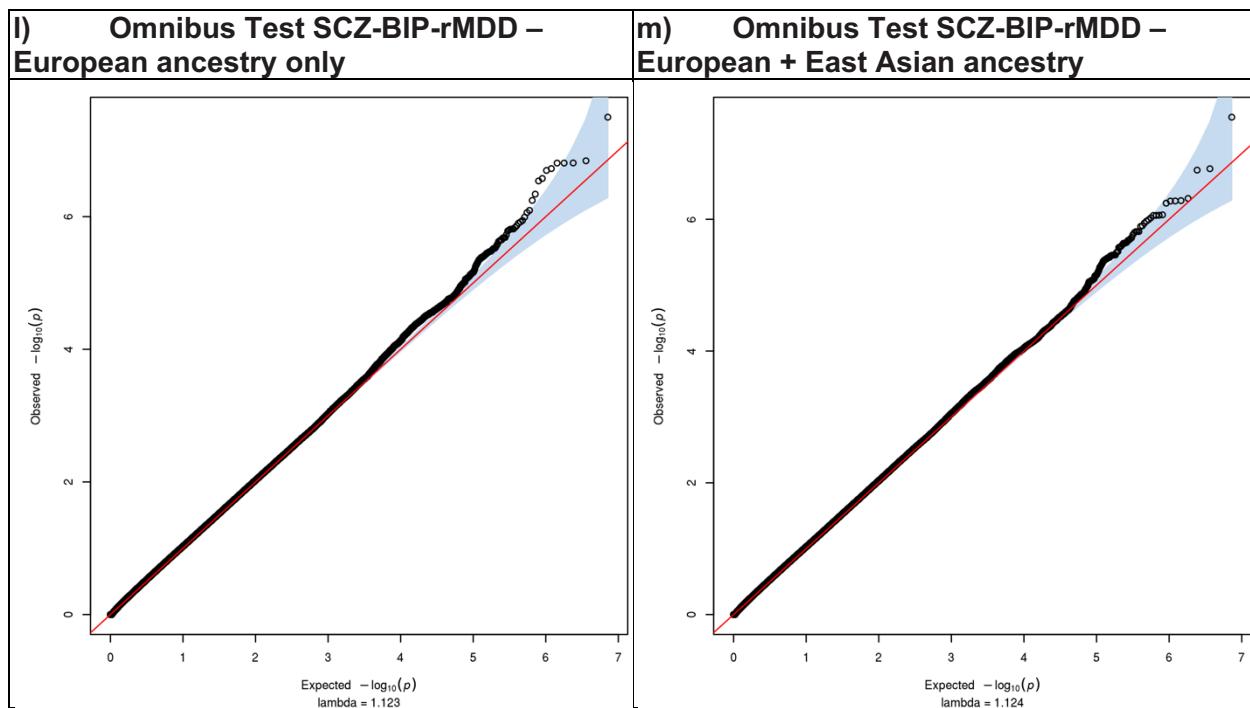
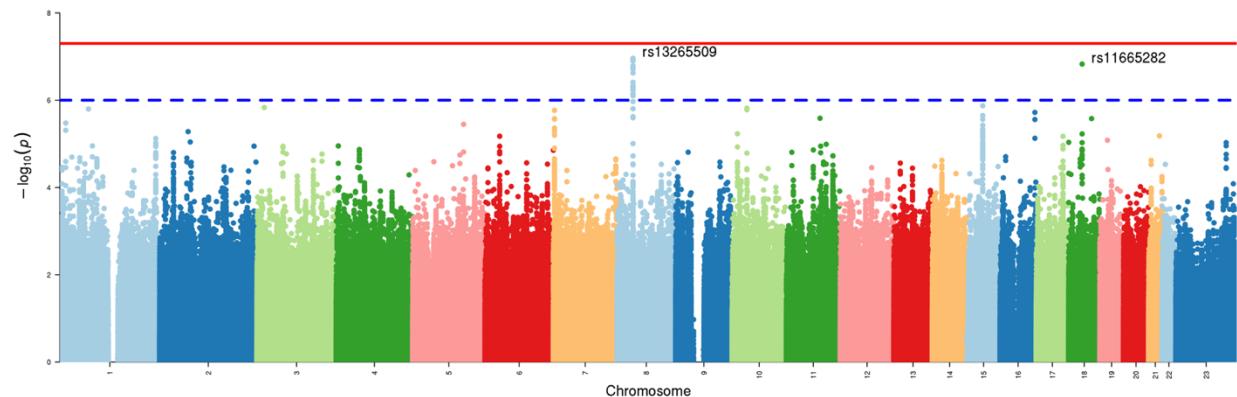
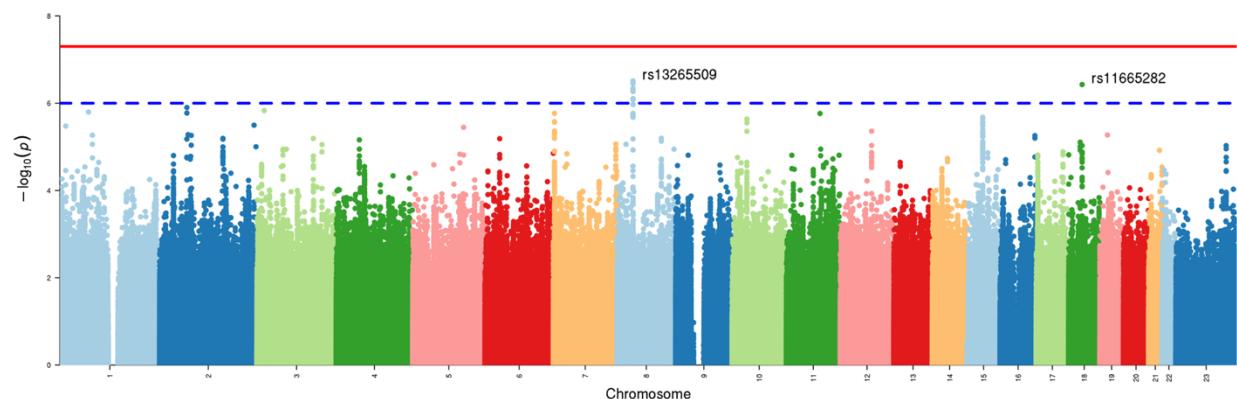
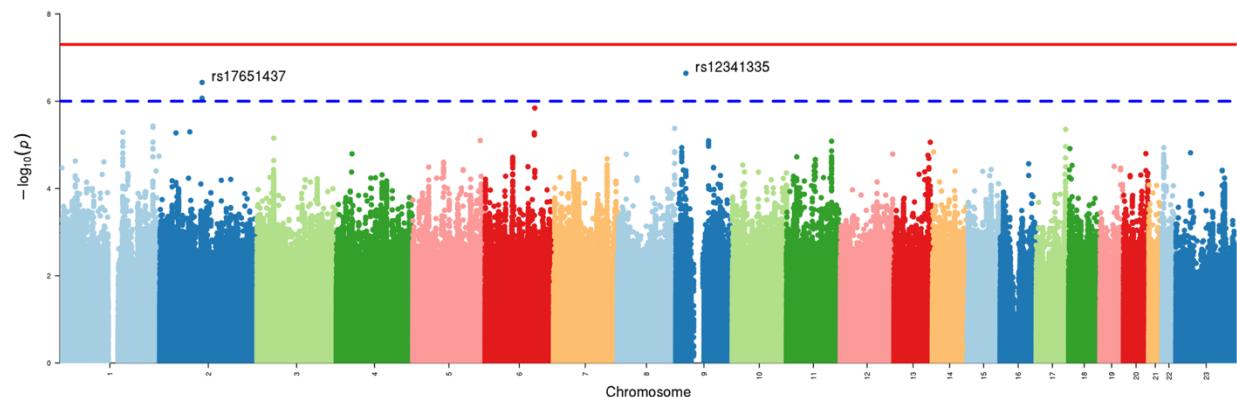
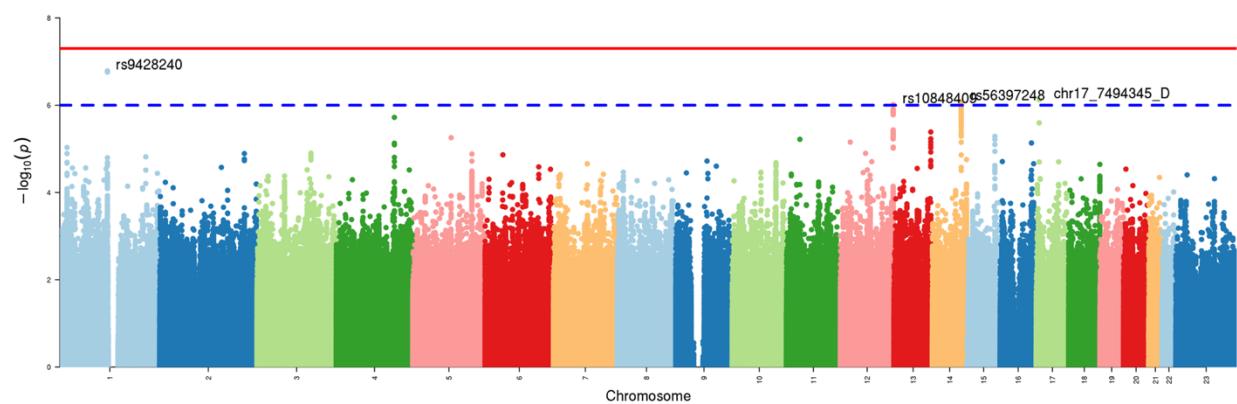
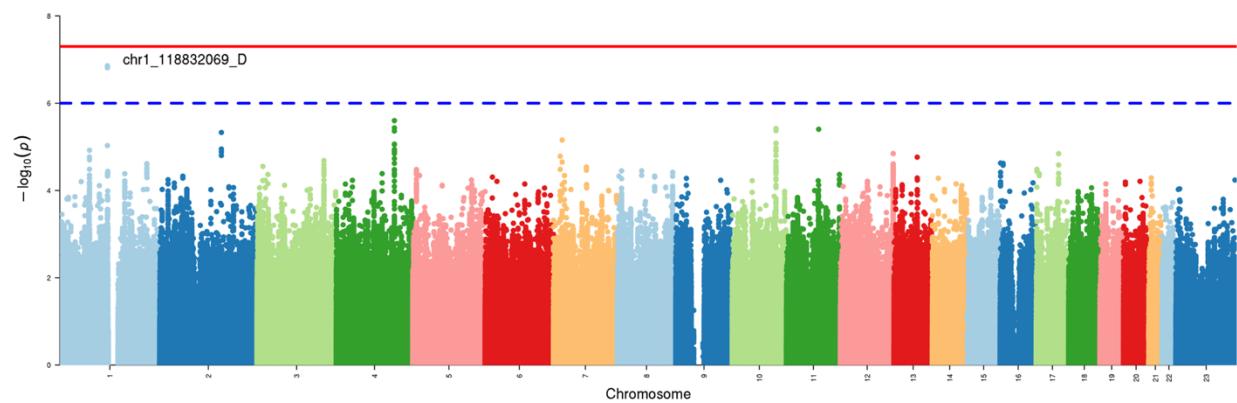


Figure S20. Manhattan plots of the G×S interaction GWAS in PGC

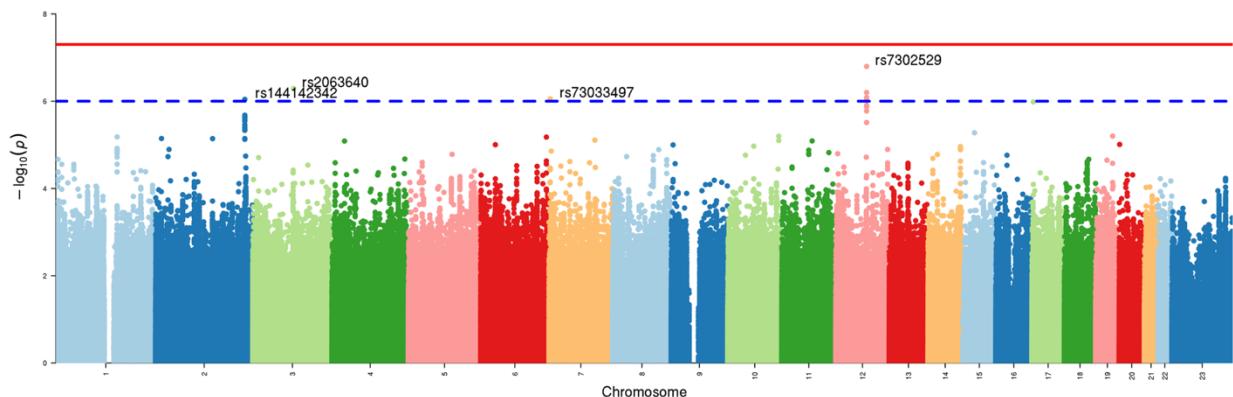
Negative log₁₀-transformed *p*-values for each variant (each dot) (y-axis) are plotted by chromosomal position (x-axis). The red and blue lines represent the thresholds for genome-wide significant association ($p = 5 \times 10^{-8}$) and suggestive association ($p = 1 \times 10^{-5}$), respectively. *P*-values for X chromosome (23) model B (alleles: females 0, 1, or 2; males 0 or 1) are included.

Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia

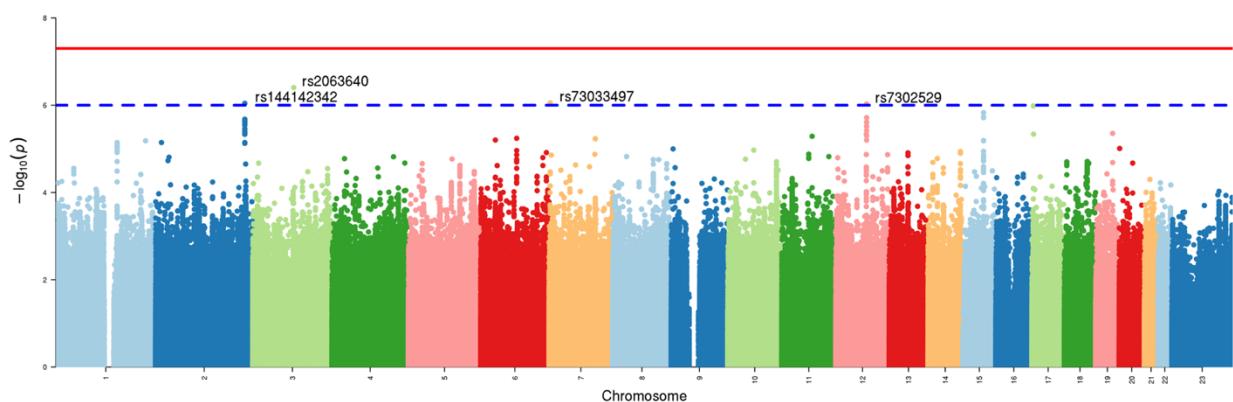
a) Schizophrenia – European ancestry only**b) Schizophrenia – European + East Asian ancestry**

c) Bipolar Disorder**d) Major Depressive Disorder****e) Recurrent Major Depressive Disorder**

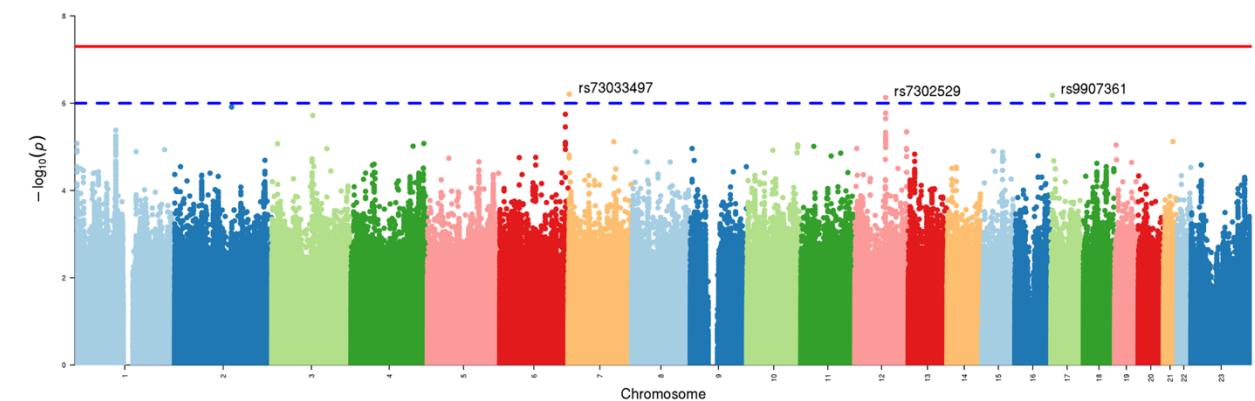
f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



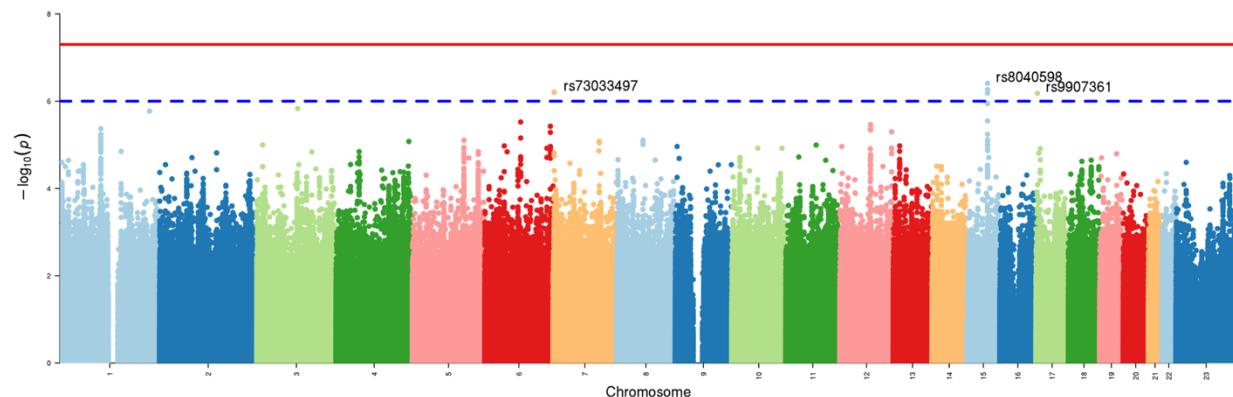
g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



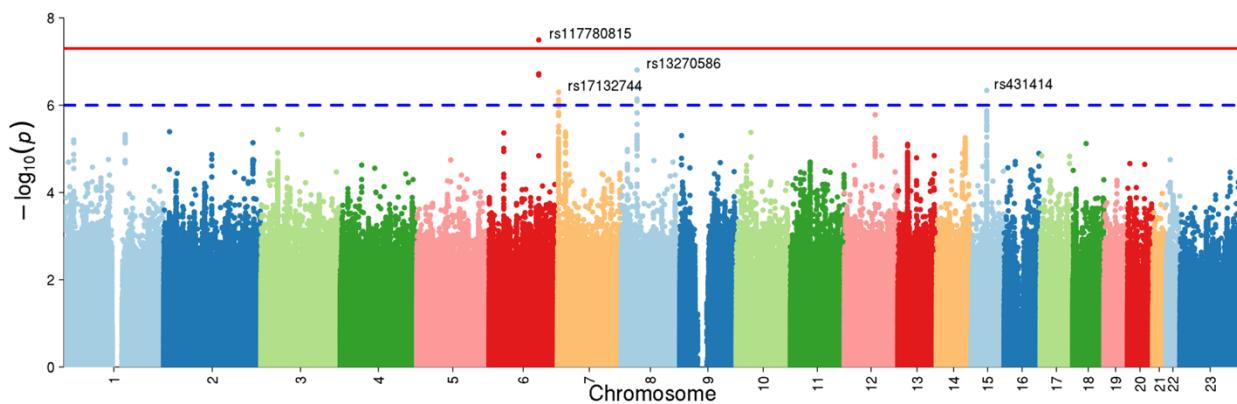
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



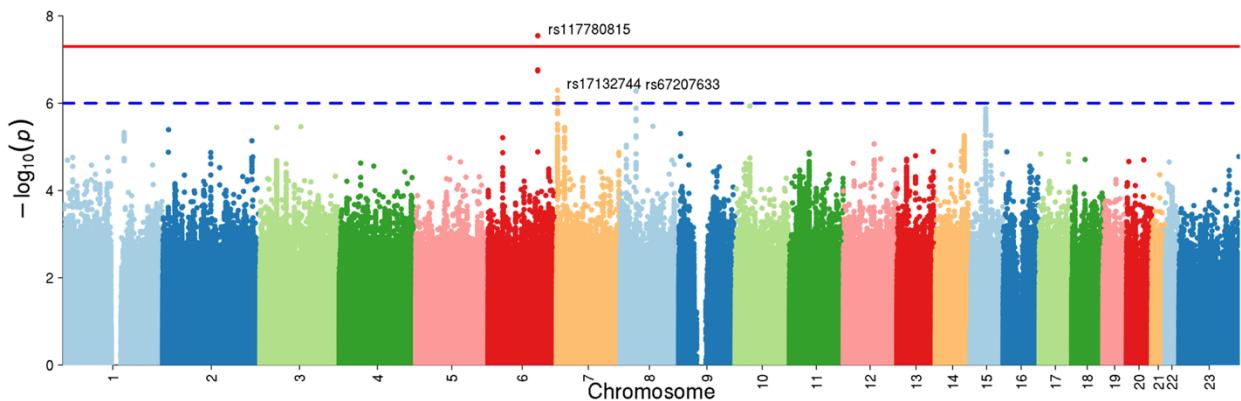
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry



j) Omnibus Test SCZ-BIP-MDD – European ancestry only



k) Omnibus Test SCZ-BIP-MDD – European + East Asian ancestry



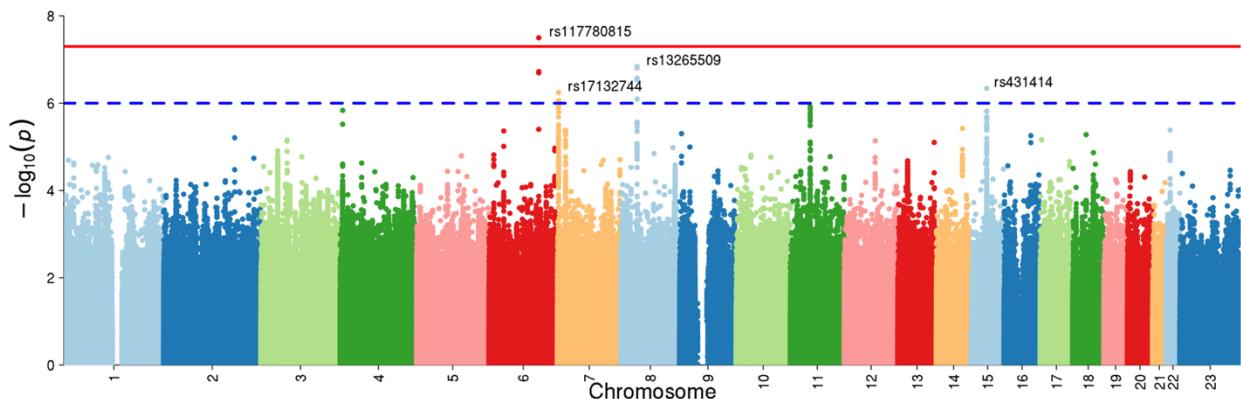
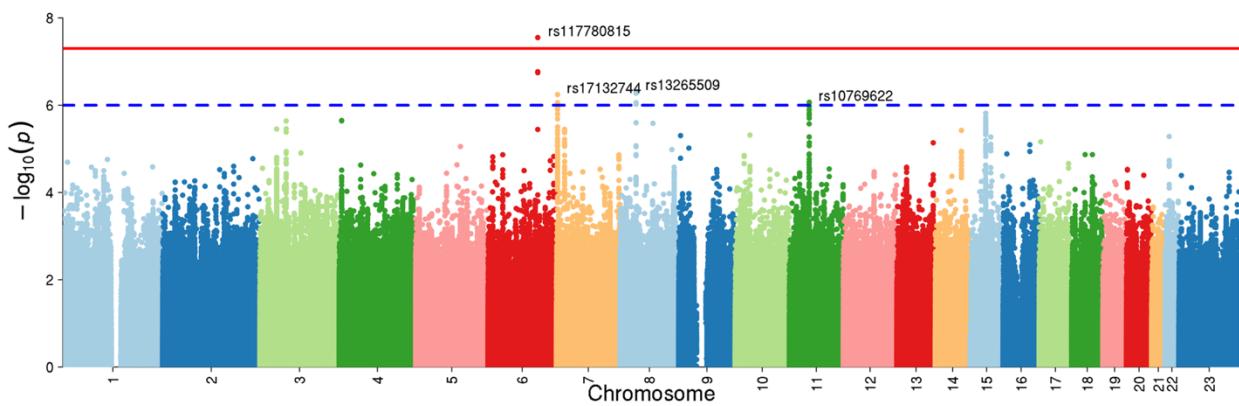
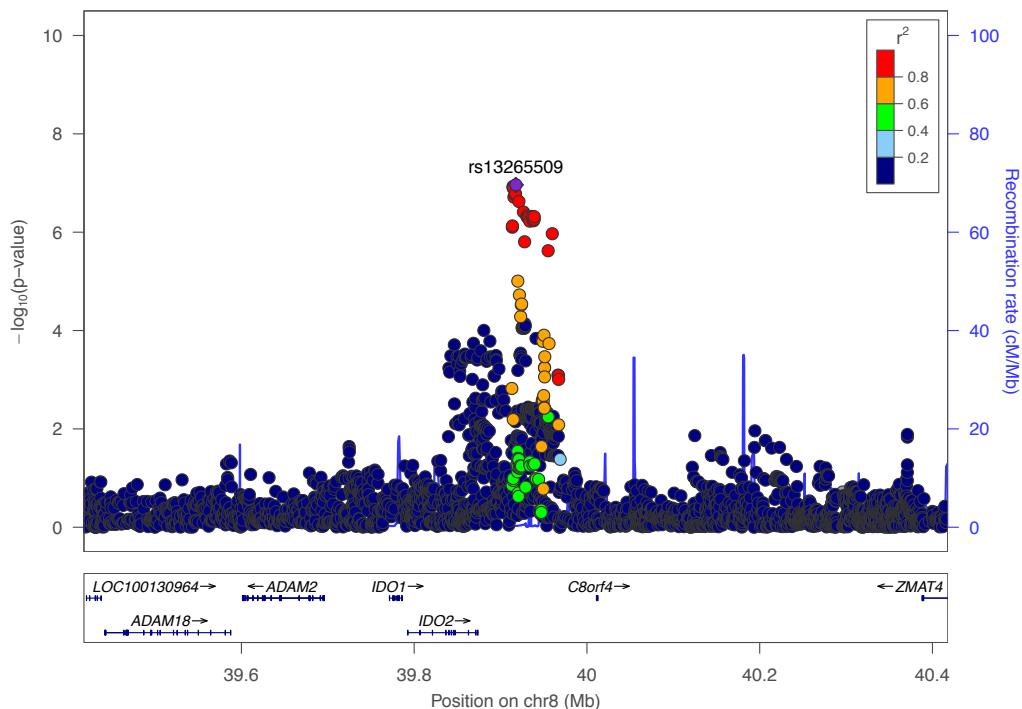
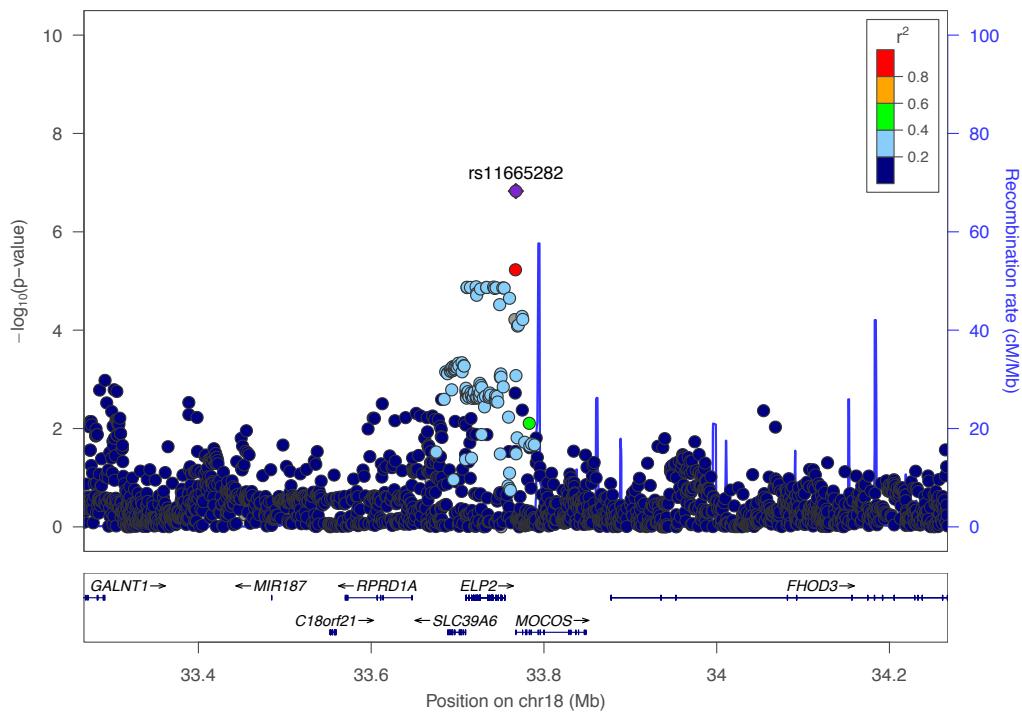
I) Omnibus Test SCZ-BIP-rMDD – European ancestry only**m) Omnibus Test SCZ-BIP-rMDD – European + East Asian ancestry**

Figure S21. LocusZoom plots for loci with G×S interaction in PGC

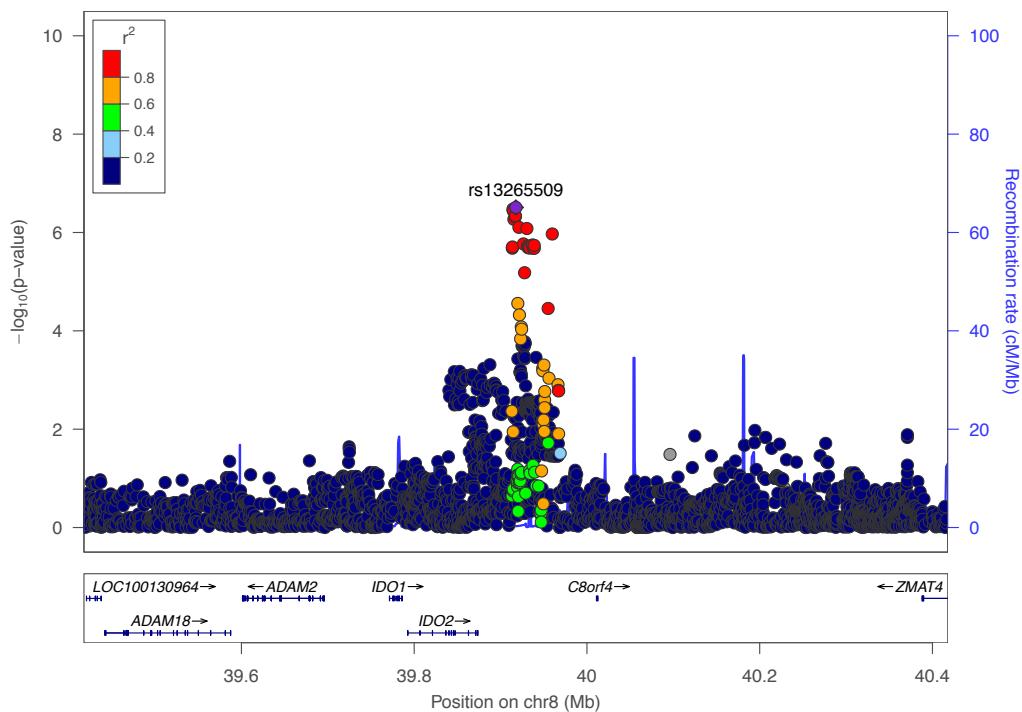
Plots were generated using the LocusZoom 1.4 Standalone application (49) for loci with G×S interaction $p < 1 \times 10^{-6}$.

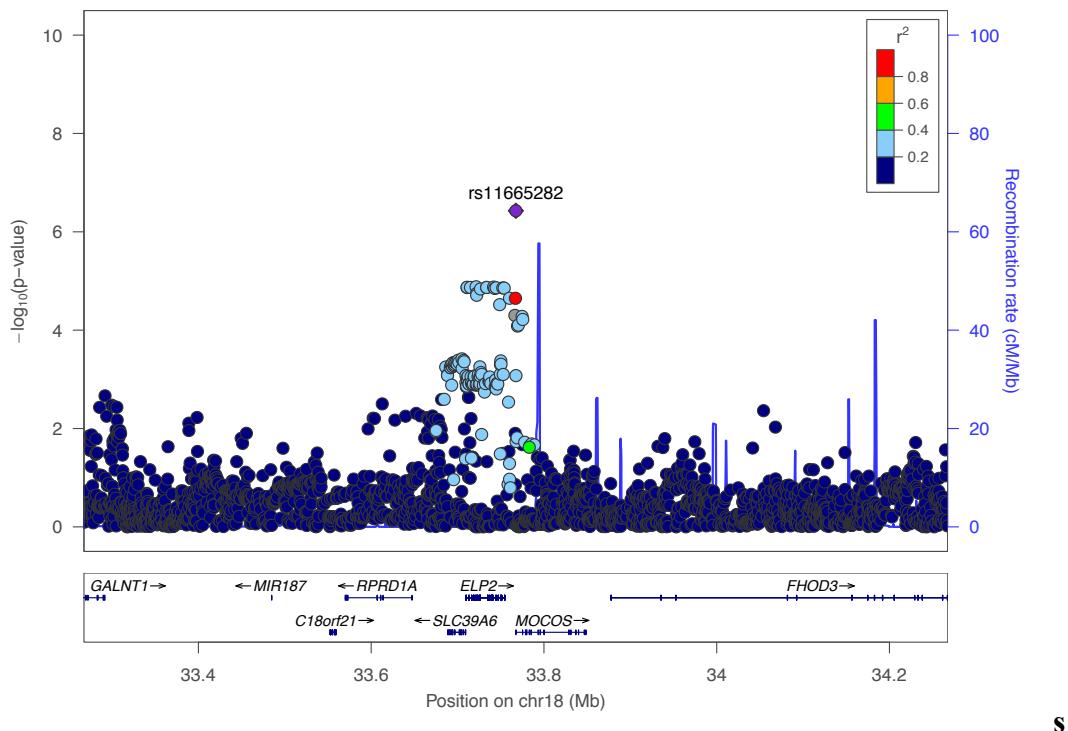
Abbreviations: chr = chromosome; cM = centimorgans; Mb = megabases; r^2 = linkage disequilibrium level; BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia

a) Schizophrenia – European ancestry only


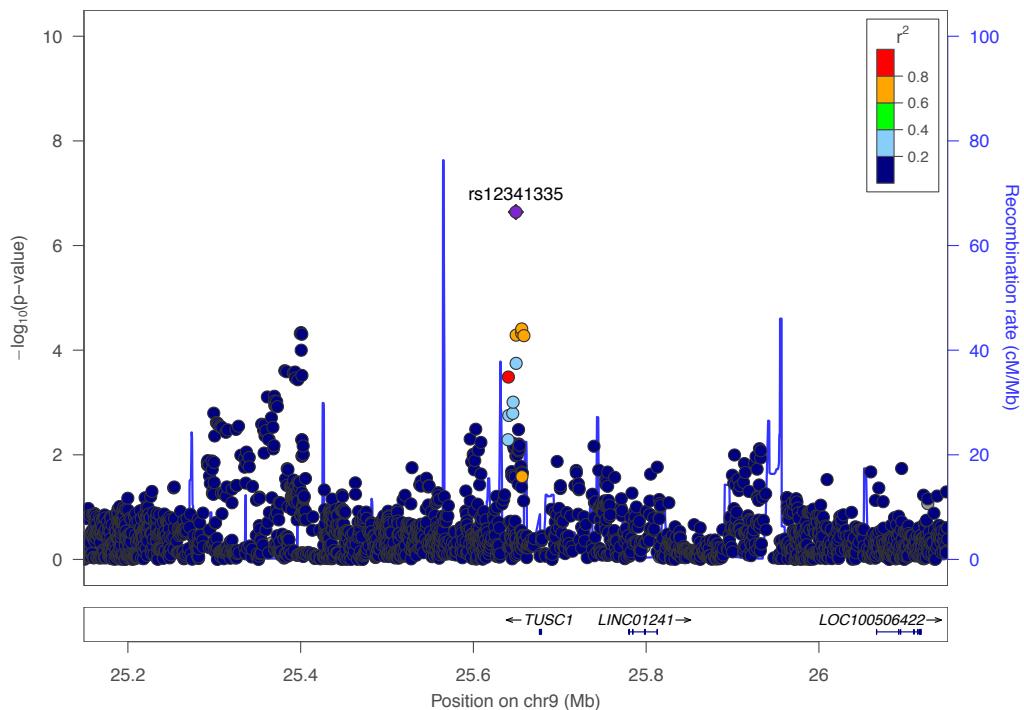


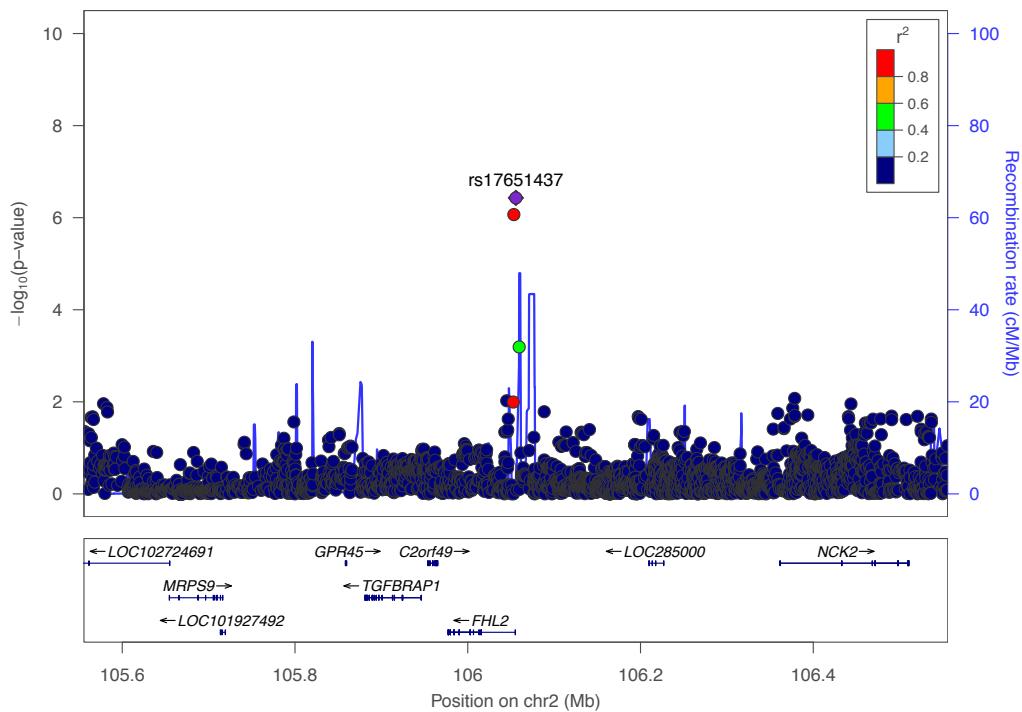
b) Schizophrenia – European + East Asian ancestry



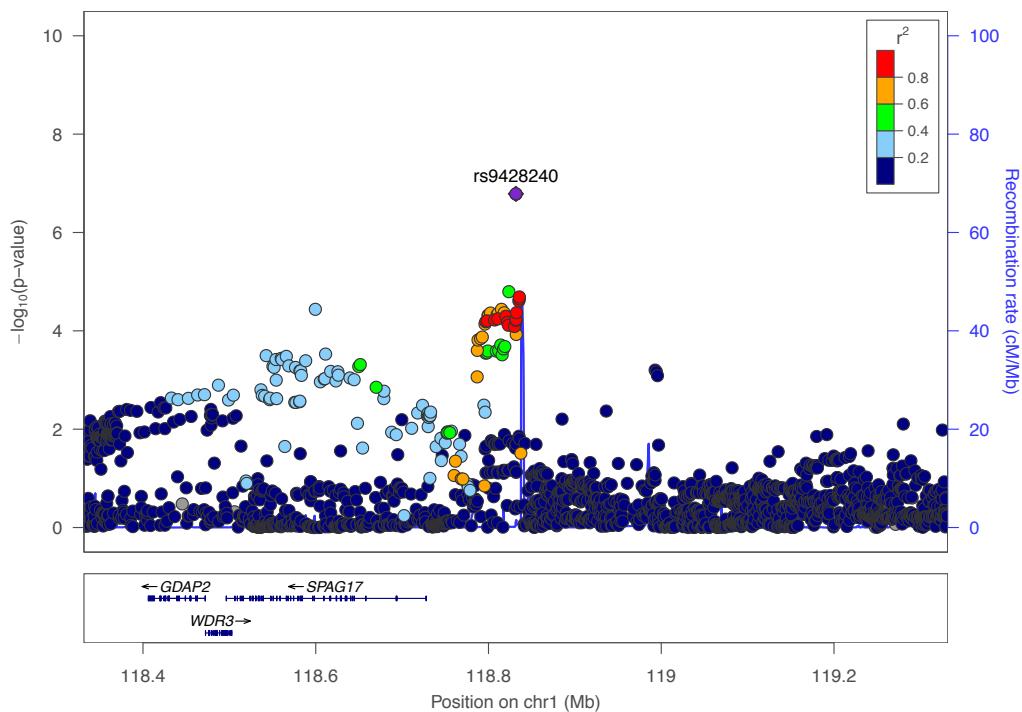


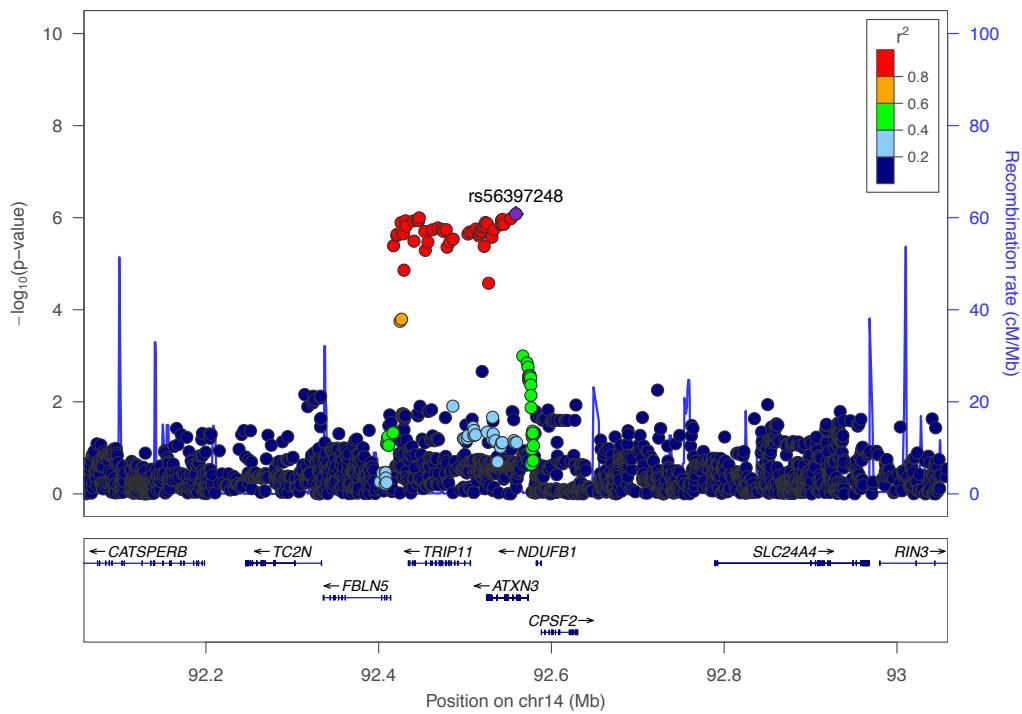
c) Bipolar Disorder



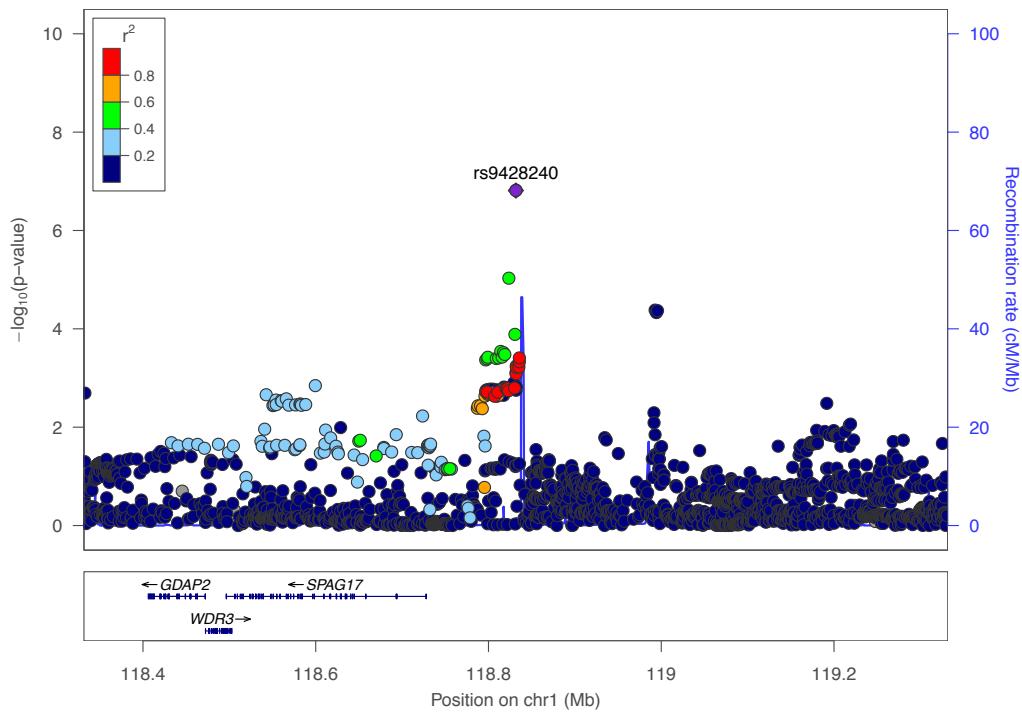


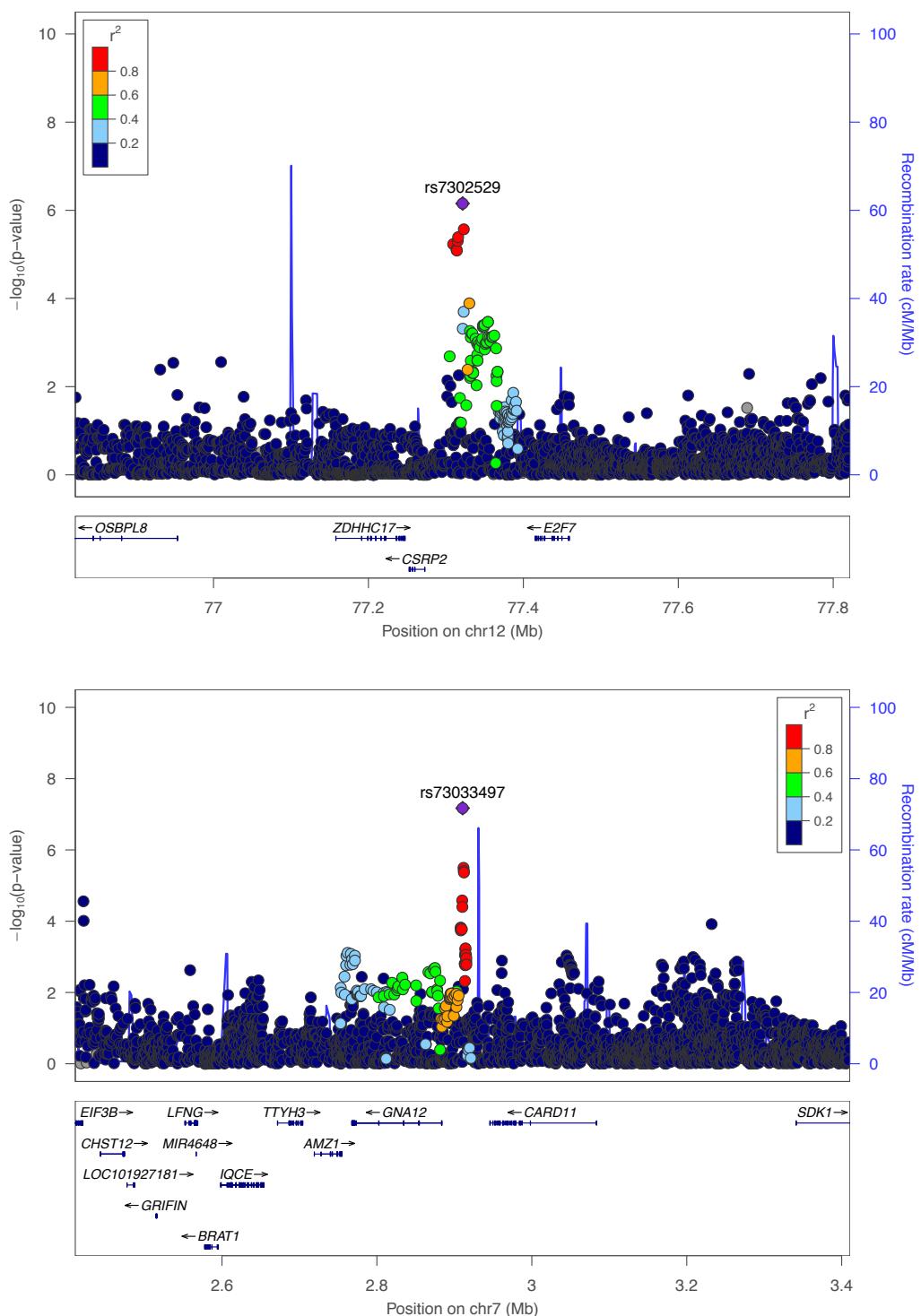
d) Major Depressive Disorder

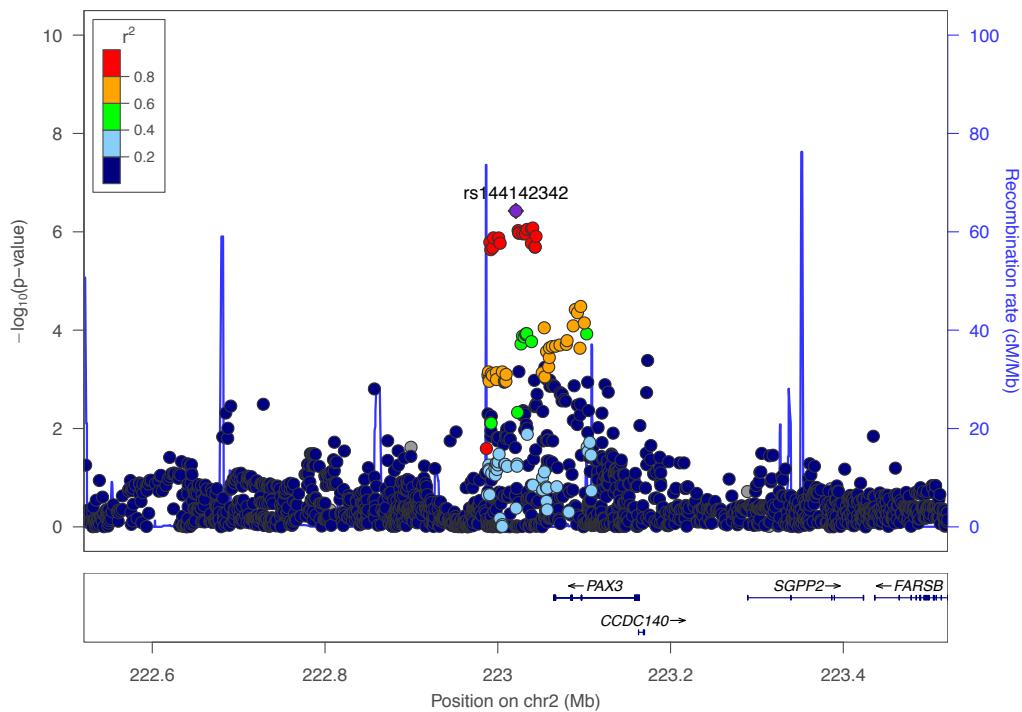




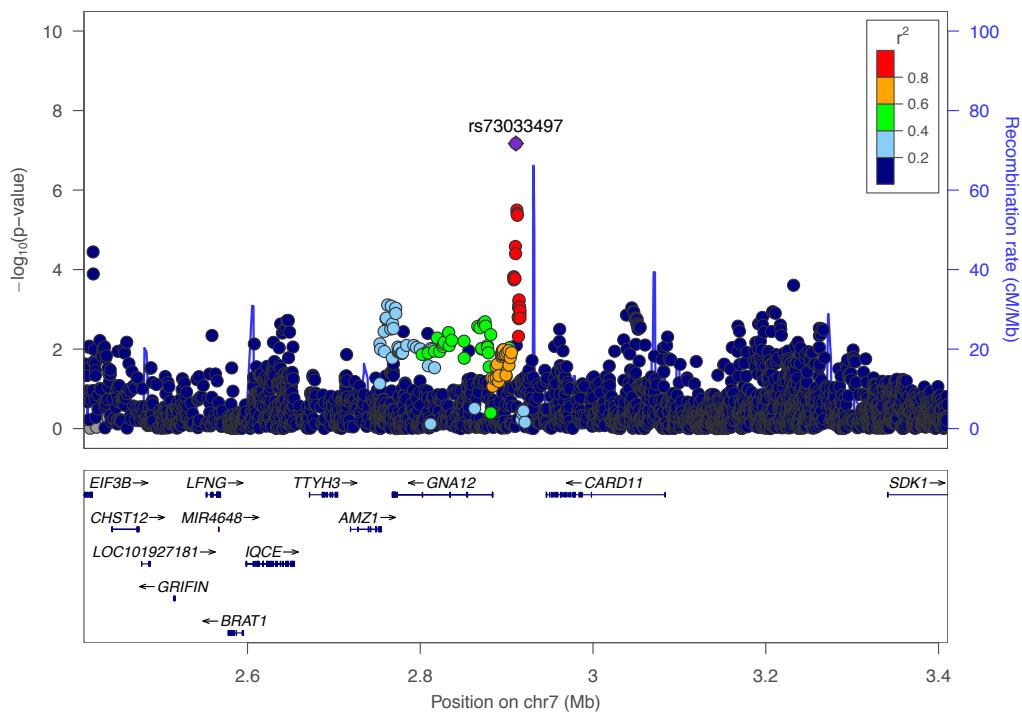
e) Recurrent Major Depressive Disorder

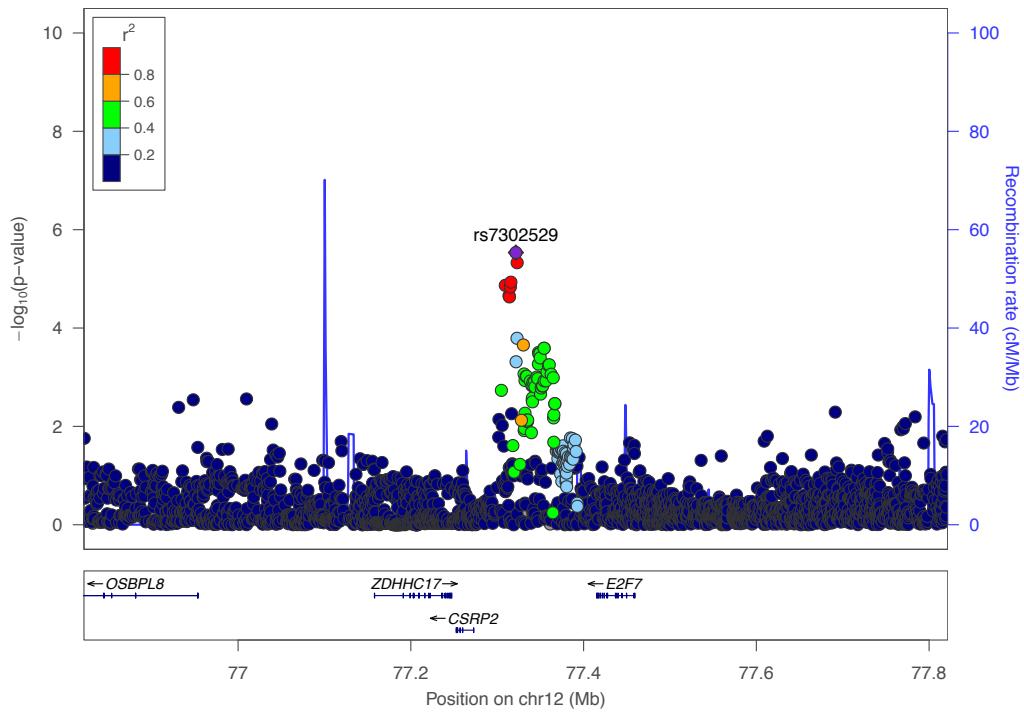
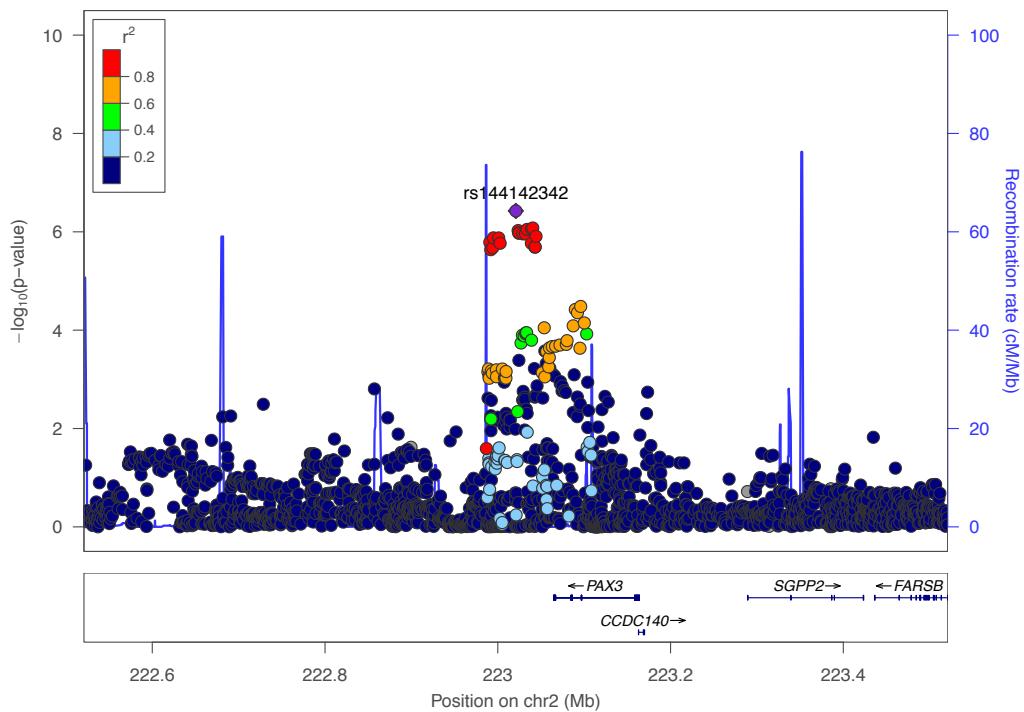


f) Cross-Disorder SCZ-BIP-MDD – European ancestry only

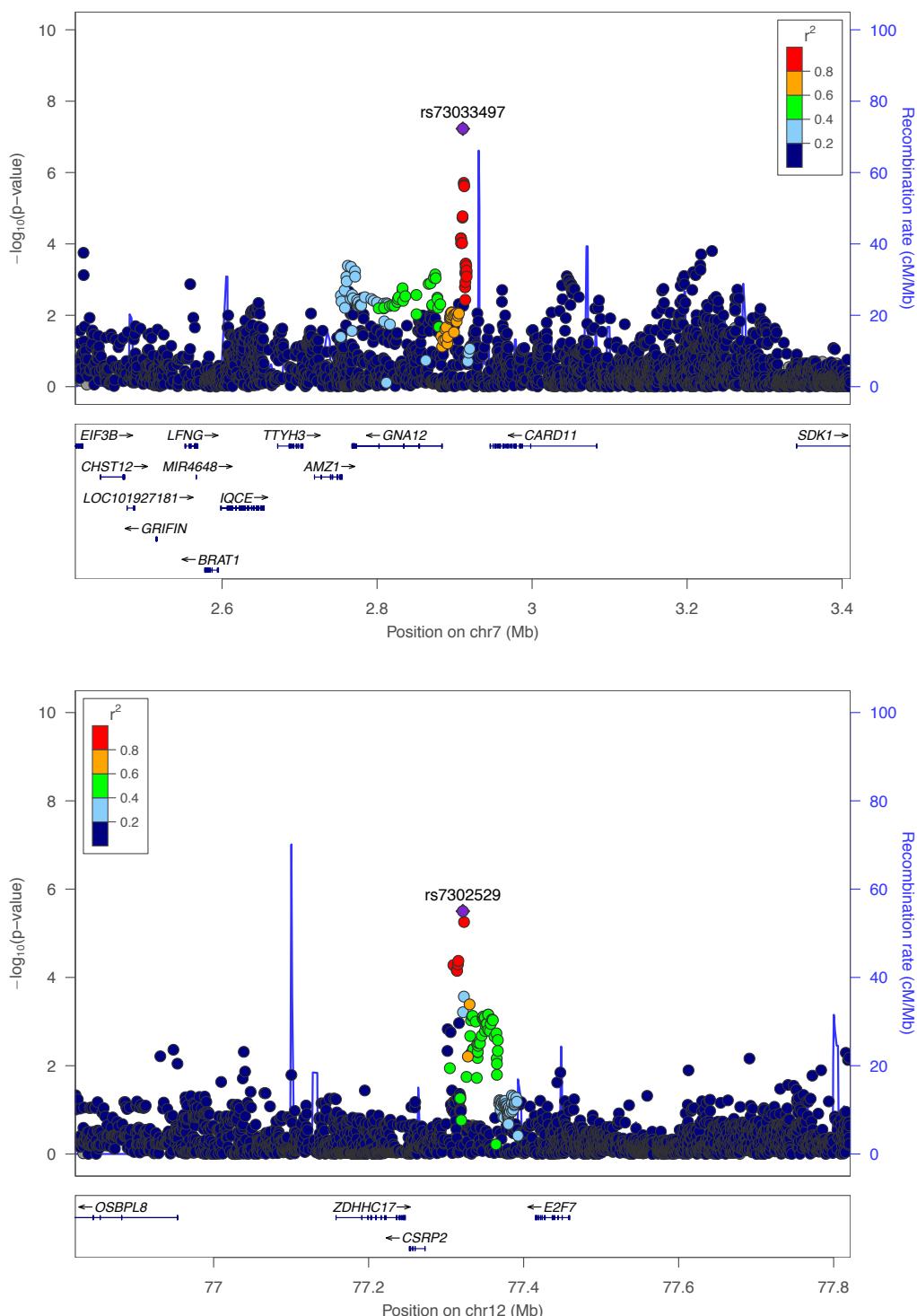


g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry

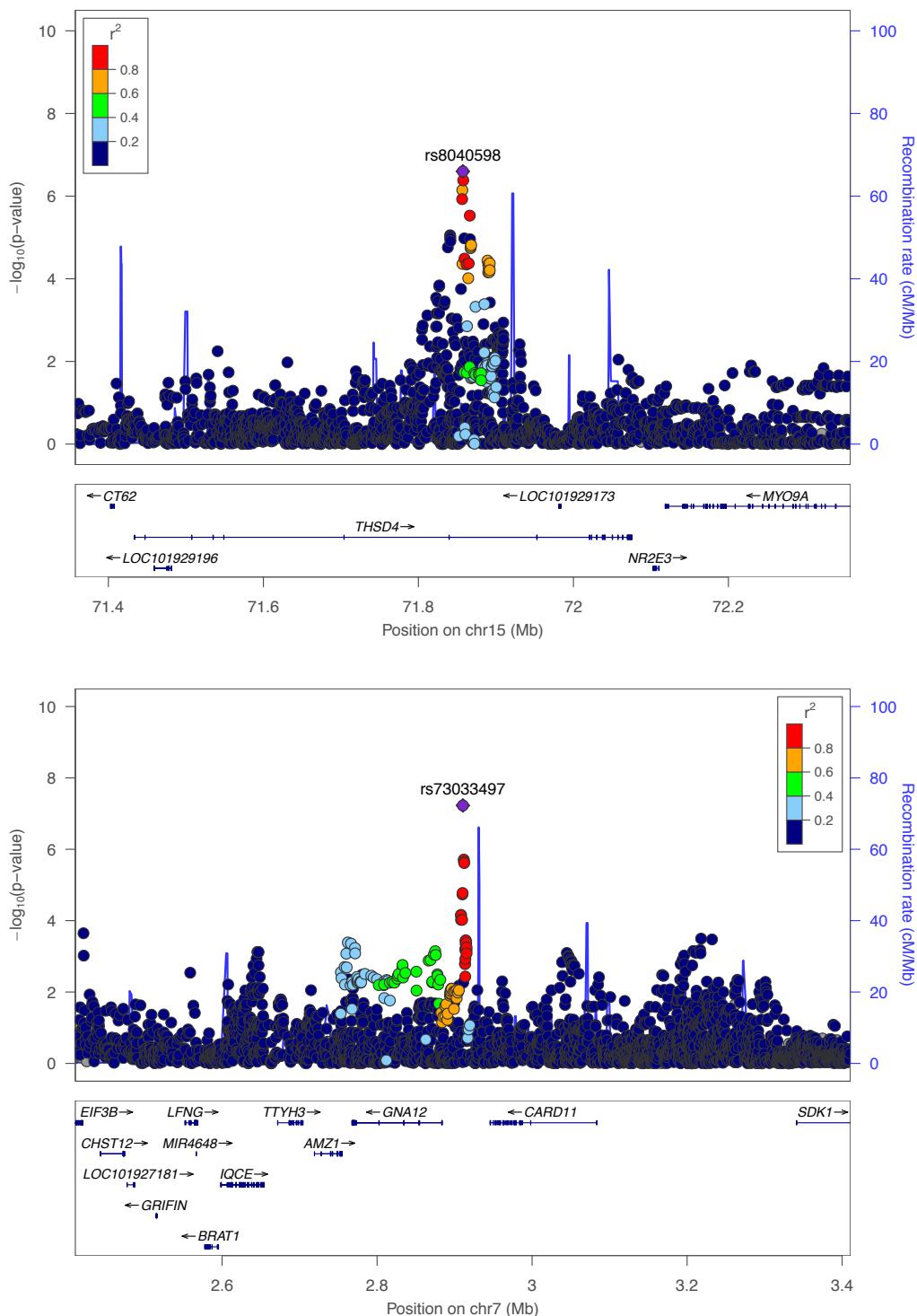


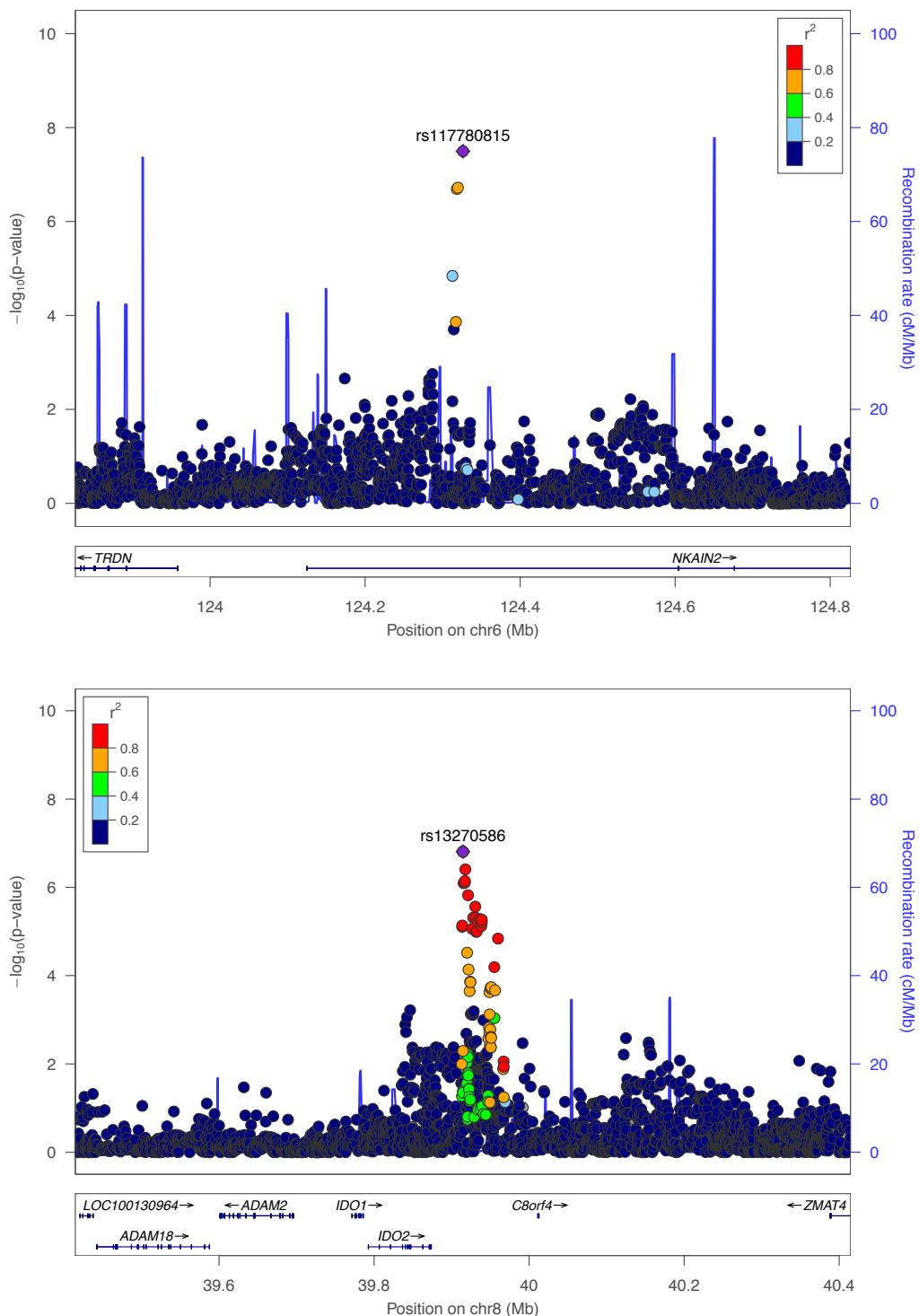


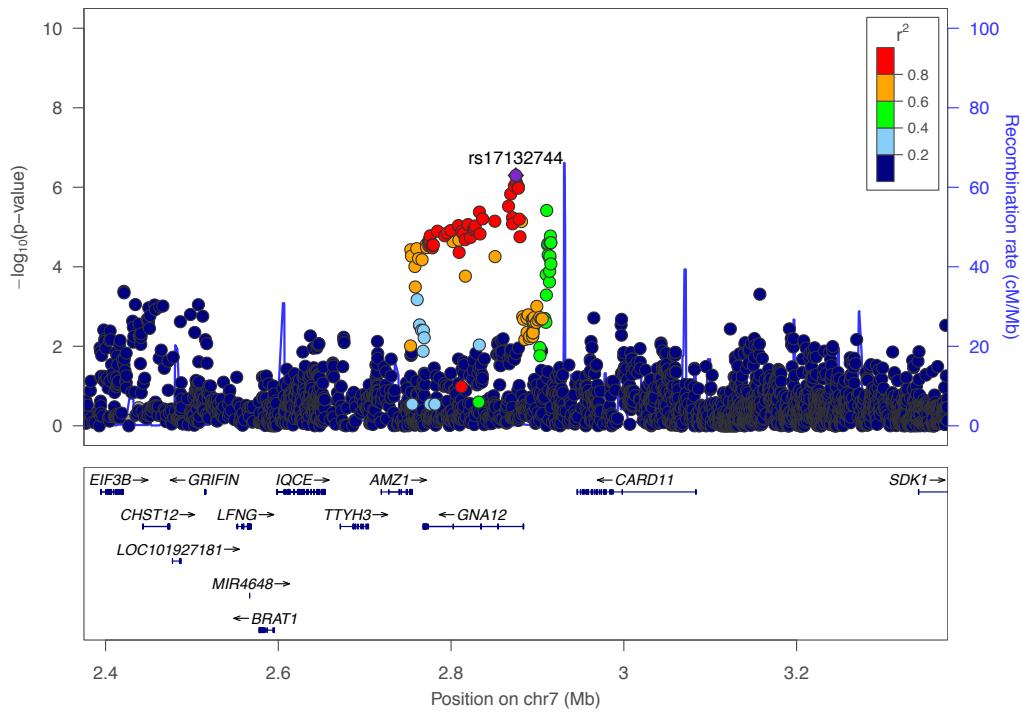
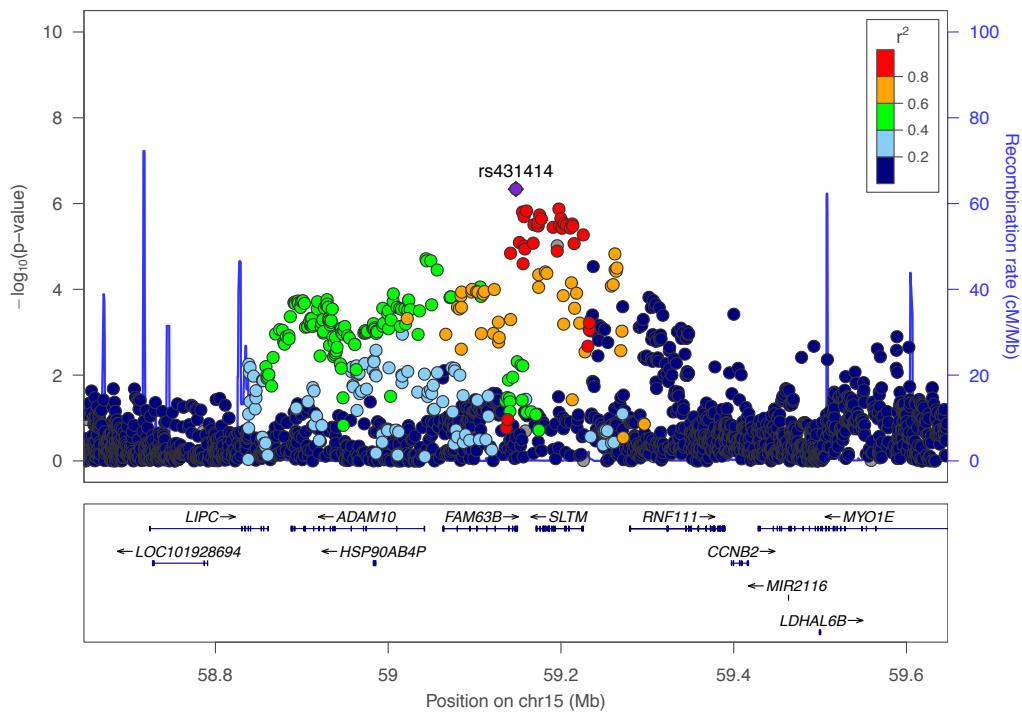
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



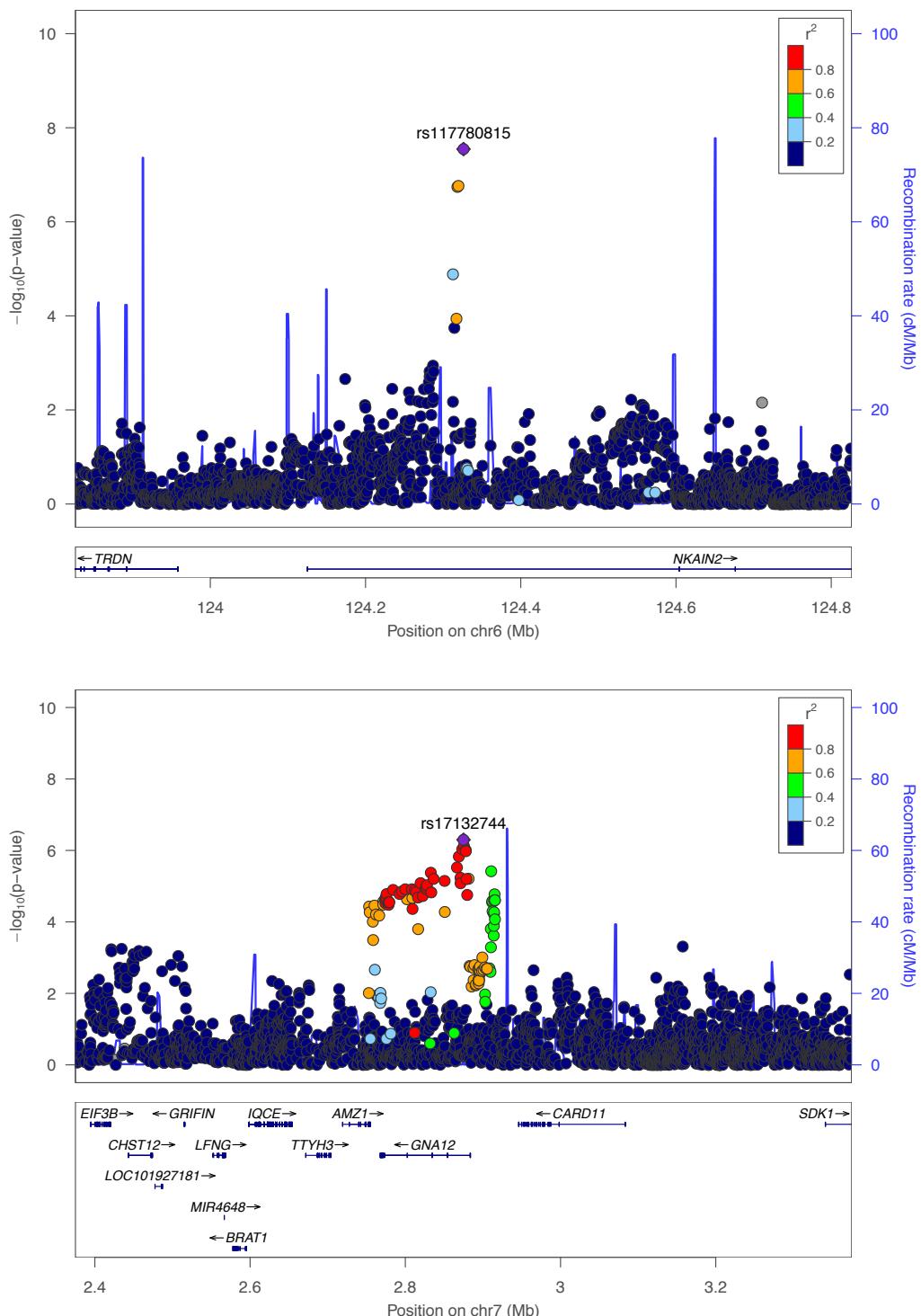
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry

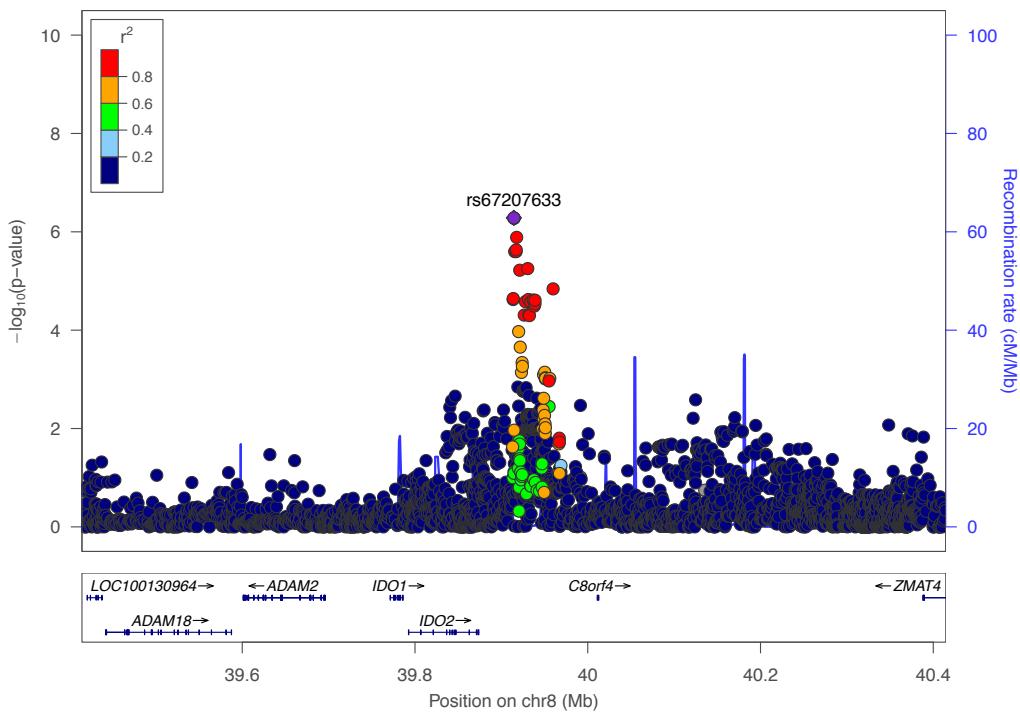


j) Omnibus Test SCZ-BIP-MDD – European ancestry

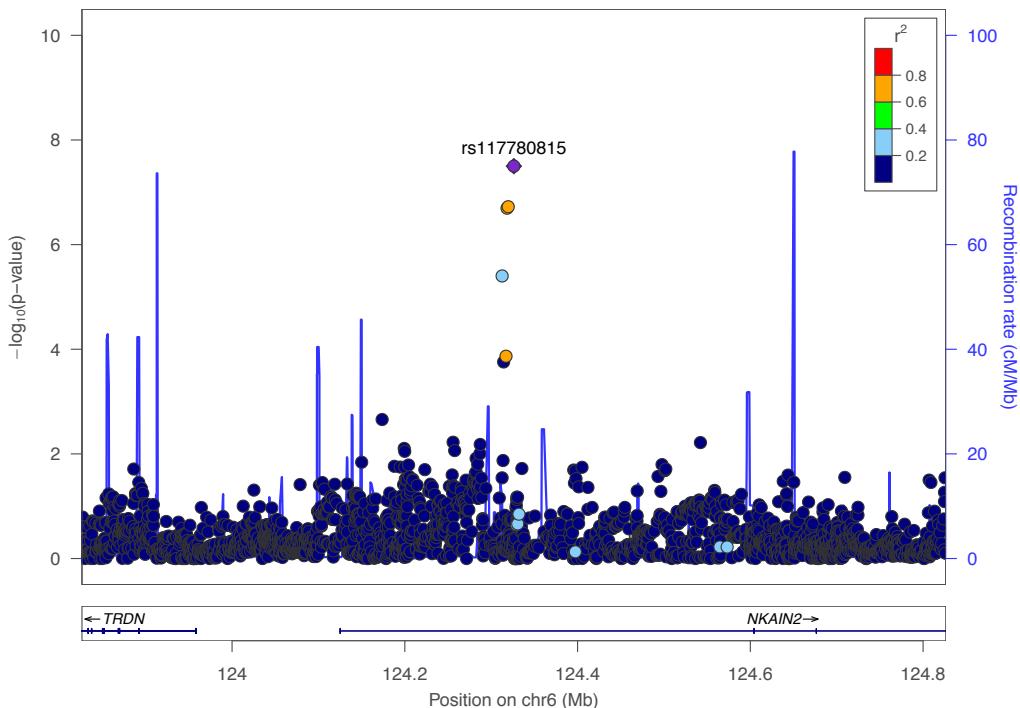


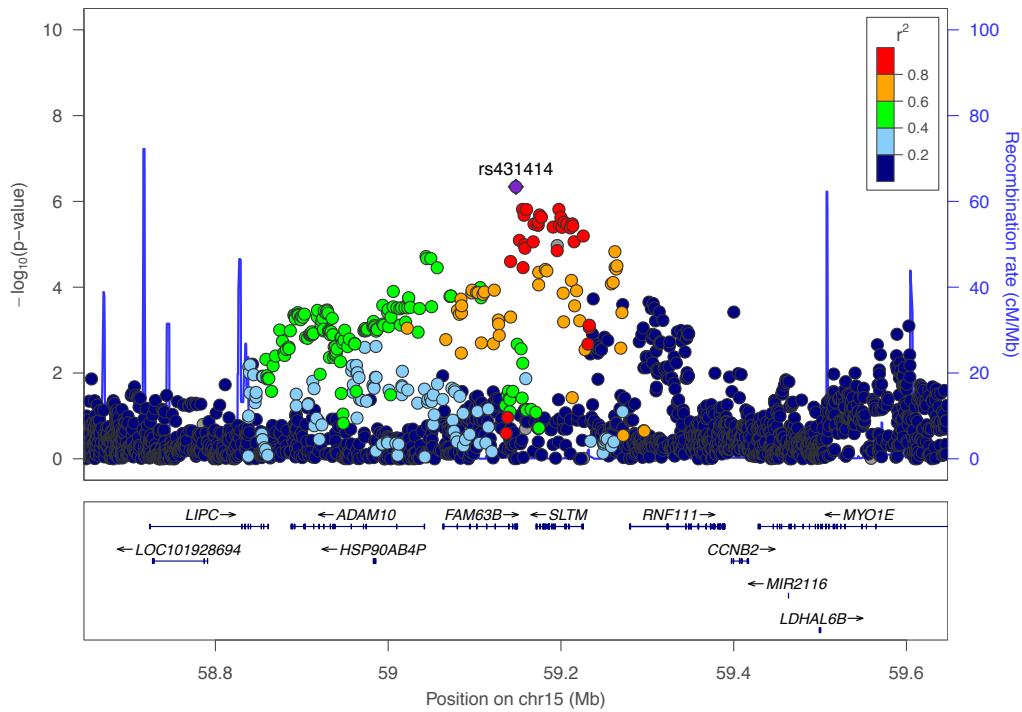
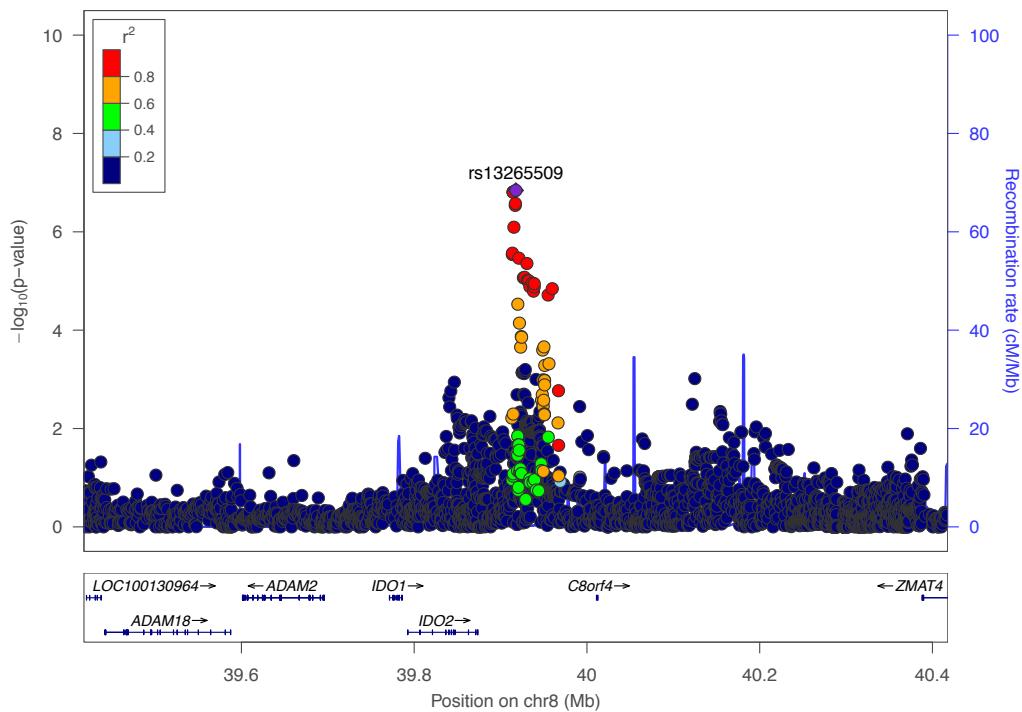
k) Omnibus Test SCZ-BIP-MDD – European + East Asian ancestry

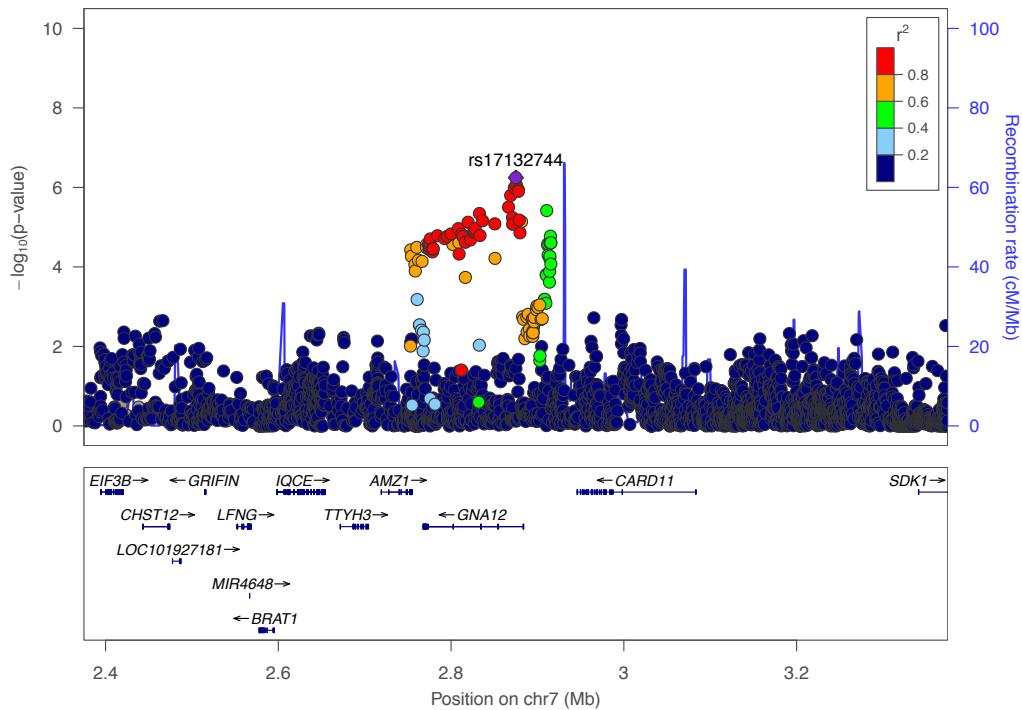




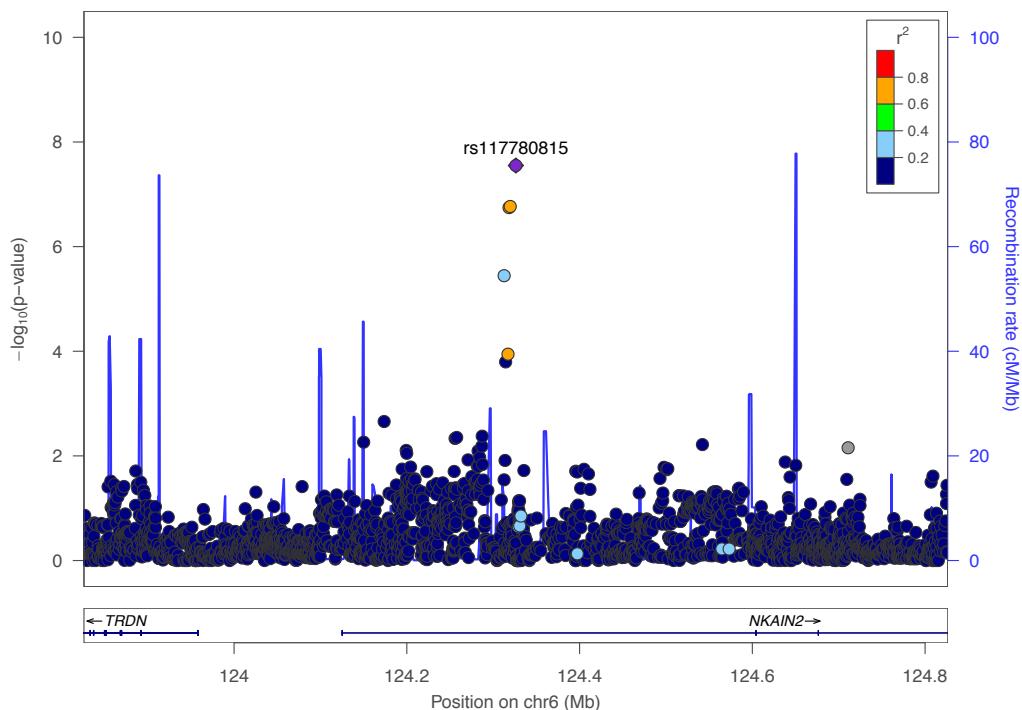
I) Omnibus Test SCZ-BIP-rMDD – European ancestry

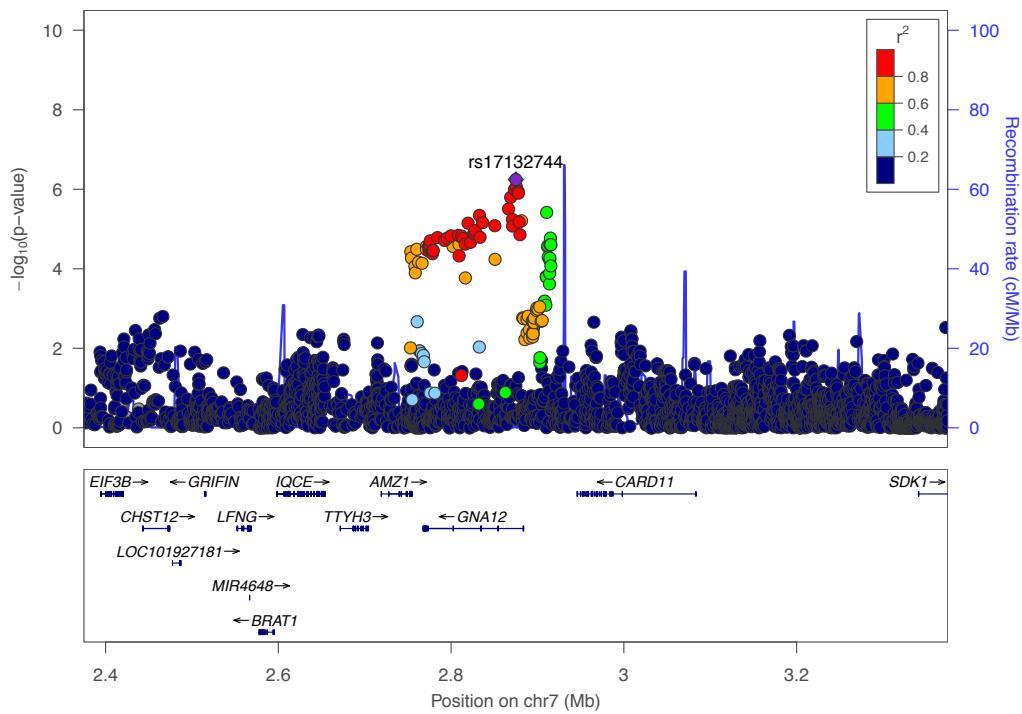
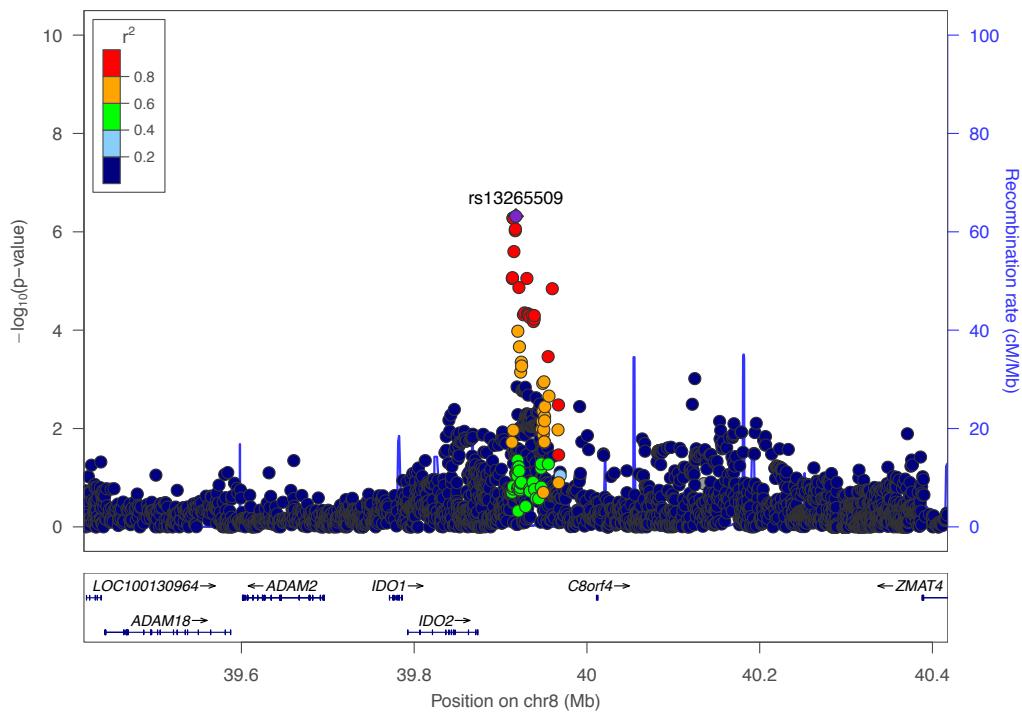






m) Omnibus Test SCZ-BIP-rMDD – European + East Asian ancestry





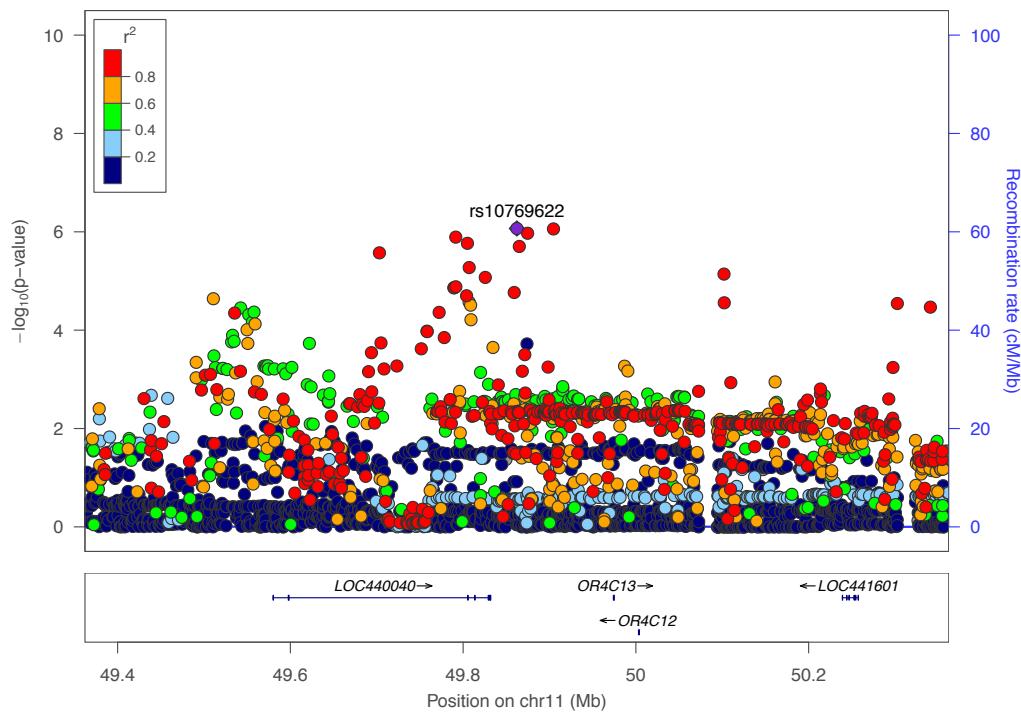


Figure S22. Forest plots for PGC

Plots were generated using the ‘rmeta’ package in R for loci (index SNPs) with G×S interaction $p < 1 \times 10^{-6}$.

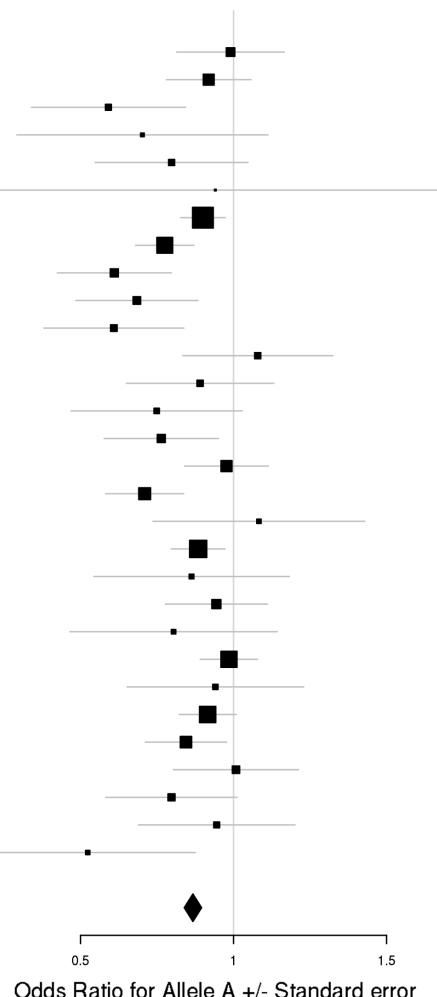
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; HC F N = number of female healthy controls; HC M N = number of male healthy controls; PT F N = number of female patients; PT M N = number of male patients; Study = cohort abbreviation used by PGC; Meta = meta-analysis results

a) Schizophrenia – European ancestry only

rs13265509 (A/G)

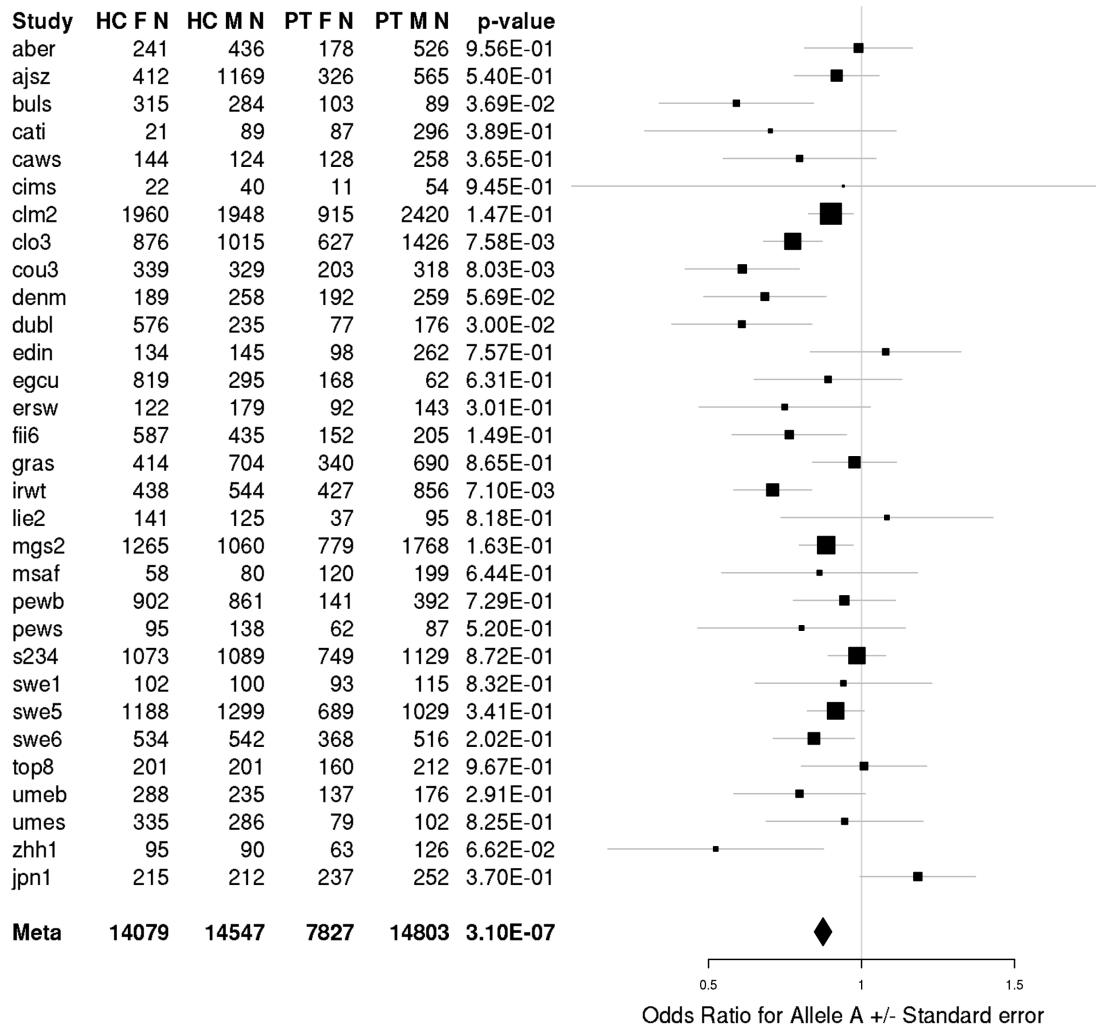
Schizophrenia

Study	HC F N	HC M N	PT F N	PT M N	p-value
aber	241	436	178	526	9.56E-01
ajsz	412	1169	326	565	5.40E-01
buls	315	284	103	89	3.69E-02
cati	21	89	87	296	3.89E-01
caws	144	124	128	258	3.65E-01
cims	22	40	11	54	9.45E-01
clm2	1960	1948	915	2420	1.47E-01
clo3	876	1015	627	1426	7.58E-03
cou3	339	329	203	318	8.03E-03
denm	189	258	192	259	5.69E-02
dubl	576	235	77	176	3.00E-02
edin	134	145	98	262	7.57E-01
egcu	819	295	168	62	6.31E-01
ersw	122	179	92	143	3.01E-01
fii6	587	435	152	205	1.49E-01
gras	414	704	340	690	8.65E-01
irwt	438	544	427	856	7.10E-03
lie2	141	125	37	95	8.18E-01
mgs2	1265	1060	779	1768	1.63E-01
msaf	58	80	120	199	6.44E-01
pewb	902	861	141	392	7.29E-01
pews	95	138	62	87	5.20E-01
s234	1073	1089	749	1129	8.72E-01
swe1	102	100	93	115	8.32E-01
swe5	1188	1299	689	1029	3.41E-01
swe6	534	542	368	516	2.02E-01
top8	201	201	160	212	9.67E-01
umeb	288	235	137	176	2.91E-01
umes	335	286	79	102	8.25E-01
zhh1	95	90	63	126	6.62E-02
Meta	13864	14335	7590	14551	1.09E-07



b) Schizophrenia – European + East Asian ancestry

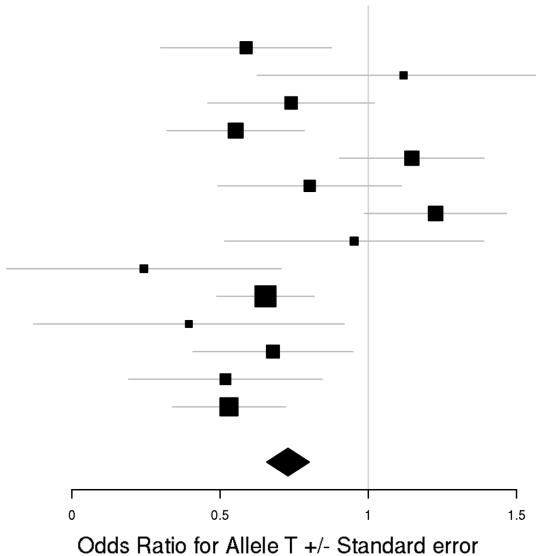
rs13265509 (A/G)
Schizophrenia



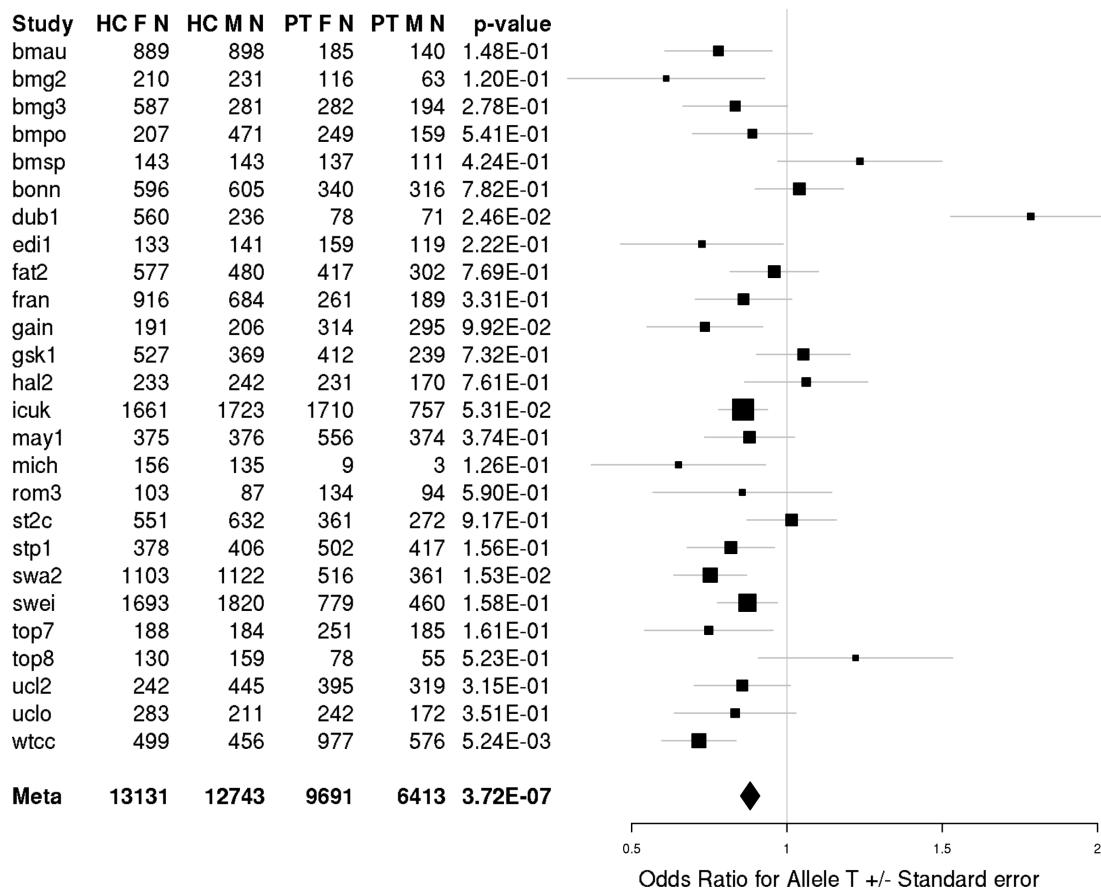
c) Bipolar Disorder

rs12341335 (T/C)
Bipolar Disorder

Study	HC F N	HC M N	PT F N	PT M N	p-value
bmau	891	901	189	140	6.52E-02
bmrg2	211	232	117	64	8.20E-01
bmrg3	584	279	286	193	2.83E-01
bonn	593	607	343	321	1.04E-02
gsk1	524	369	413	237	5.74E-01
hal2	234	243	234	170	4.76E-01
may1	377	377	560	374	3.92E-01
mich	153	135	9	3	9.11E-01
rom3	107	86	134	96	2.23E-03
swei	1726	1846	786	470	9.50E-03
top8	130	161	81	56	7.60E-02
ucl2	244	444	397	324	1.50E-01
ume4	291	257	350	211	4.39E-02
usc2	680	472	633	661	8.94E-04
Meta	6745	6409	4532	3320	2.29E-07

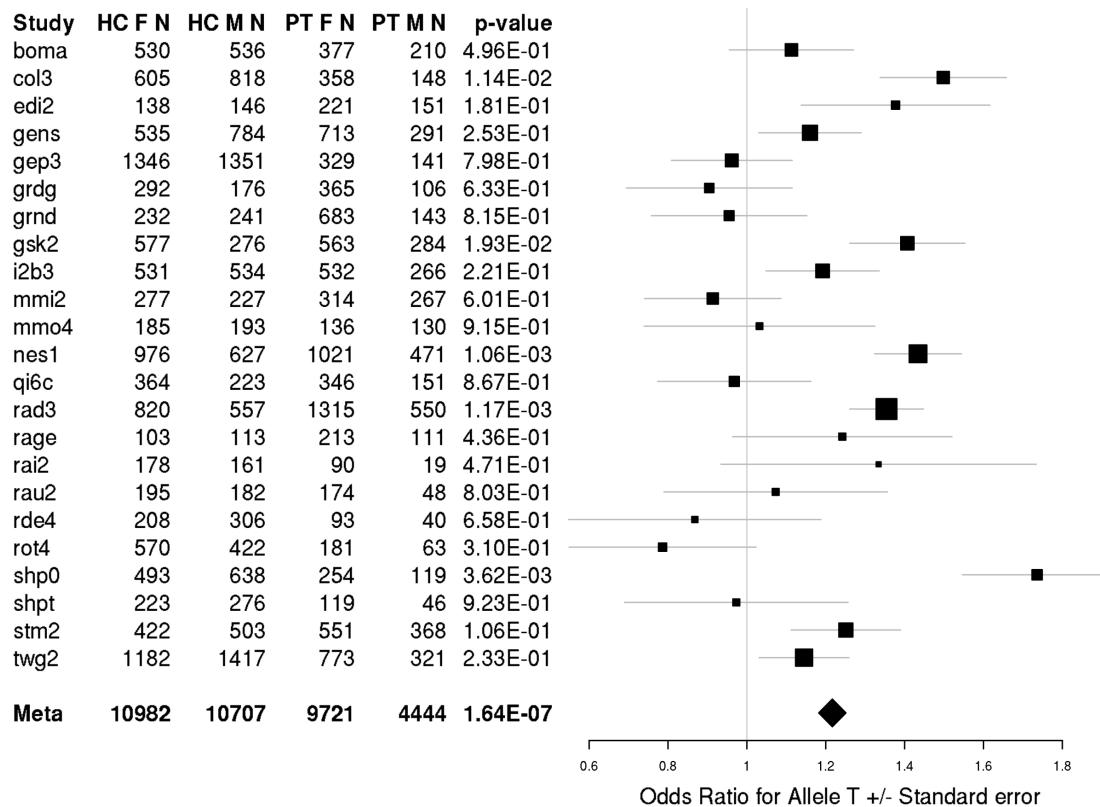


rs17651437 (T/C)
Bipolar Disorder



d) Major Depressive Disorder

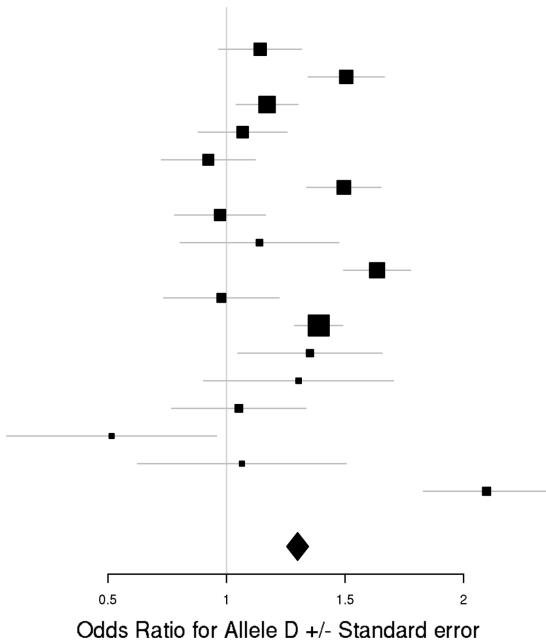
rs9428240 (T/C)
Major Depressive Disorder



e) Recurrent Major Depressive Disorder

chr1_118832069_D (D/I2)
Recurrent Major Depressive Disorder

Study	HC F N	HC M N	PT F N	PT M N	p-value
boma	530	536	297	149	4.47E-01
col3	604	818	355	146	1.09E-02
gens	535	782	711	291	2.22E-01
gep3	1345	1349	260	85	7.27E-01
grnd	231	238	673	140	6.86E-01
gsk2	577	275	440	226	1.02E-02
mmi2	276	227	229	174	8.85E-01
mmo4	185	193	104	89	6.97E-01
nes1	976	627	482	220	4.93E-04
qi6c	364	222	156	84	9.28E-01
rad3	817	556	1016	419	1.19E-03
rage	103	113	182	75	3.21E-01
rai2	178	161	89	19	5.07E-01
rau2	195	182	175	47	8.59E-01
rde4	208	306	41	18	1.34E-01
rot4	570	422	58	14	8.87E-01
shp0	493	638	128	52	5.52E-03
Meta	8187	7645	5396	2248	1.39E-07

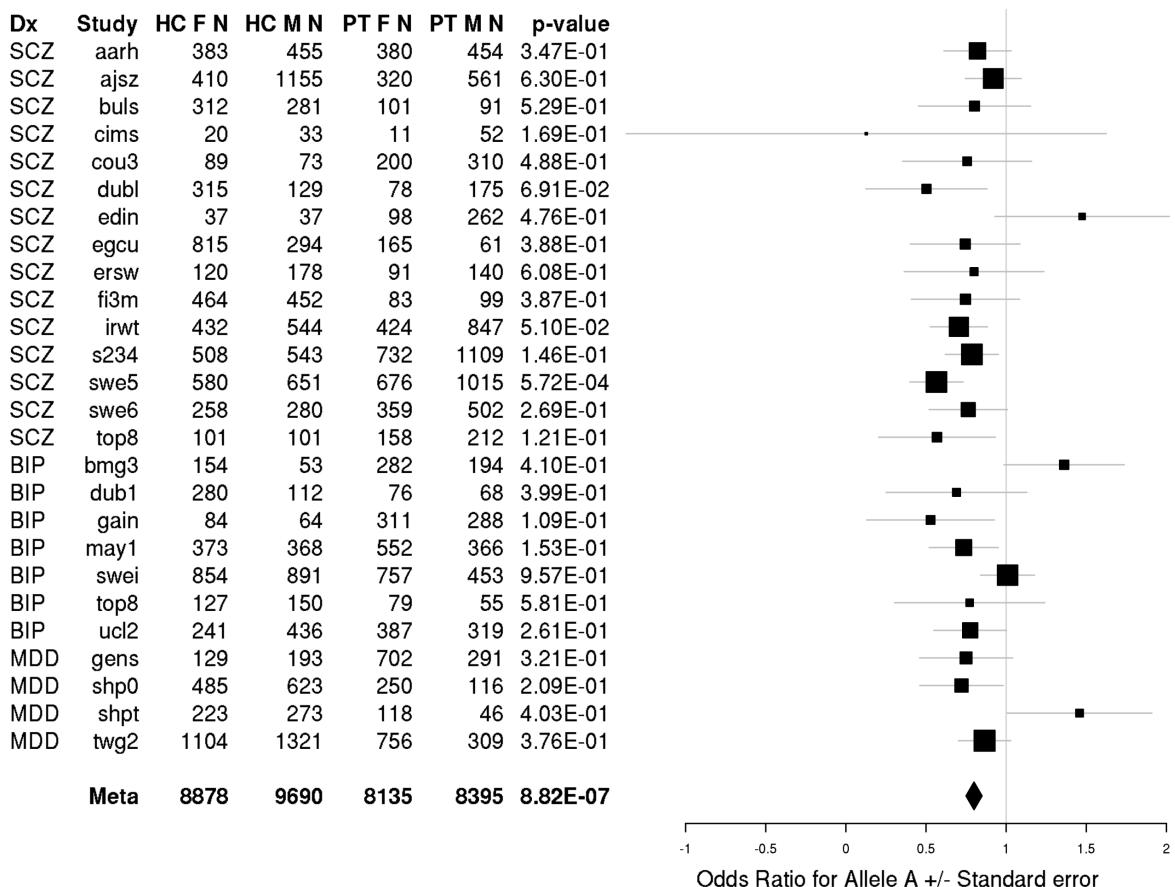


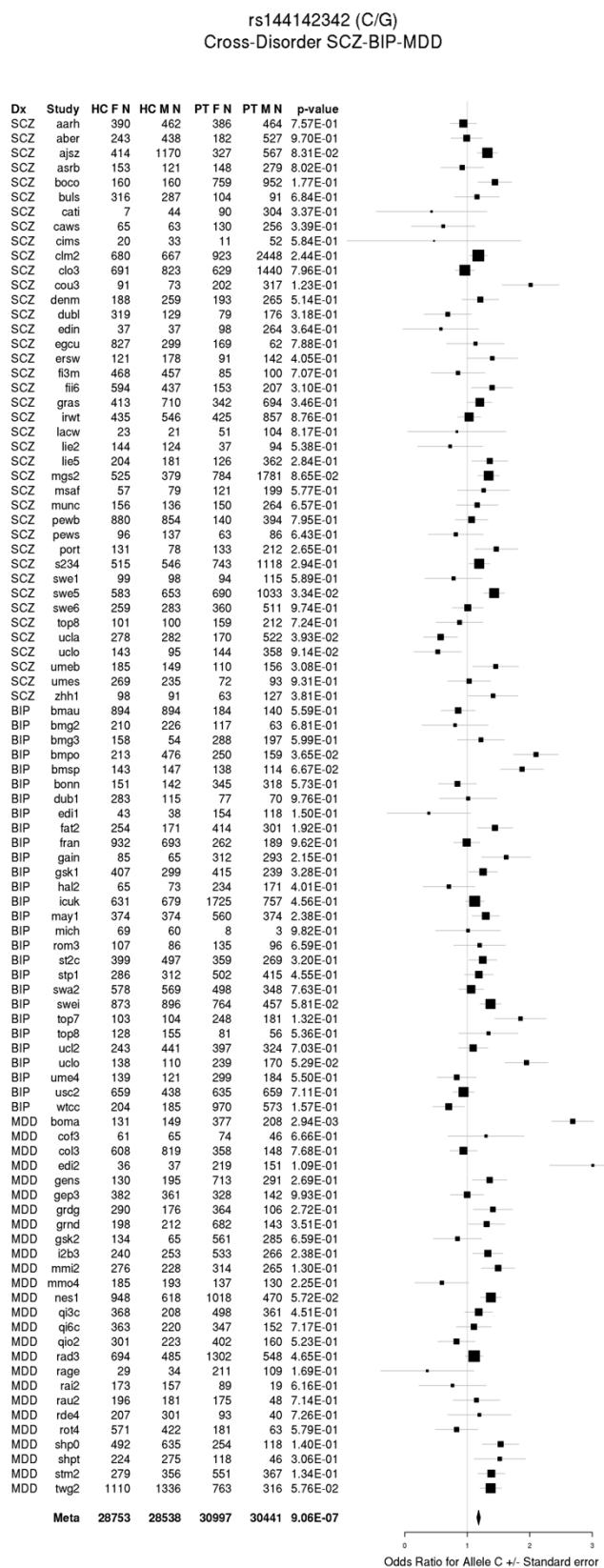
f) Cross-Disorder SCZ-BIP-MDD – European ancestry only
 rs7302529 (T/C)
 Cross-Disorder SCZ-BIP-MDD

Dx	Study	HC F	N	HC M	N	PT F	N	PT M	N	p-value
SCZ	aarh	391		463		387		465		9.74E-03
SCZ	ajsz	414		1171		327		567		3.63E-01
SCZ	asrb	153		121		148		280		4.17E-02
SCZ	boco	160		160		761		952		3.97E-01
SCZ	cims	20		33		11		52		5.10E-01
SCZ	clm2	671		657		908		2393		1.28E-01
SCZ	clo3	684		818		627		1435		8.16E-02
SCZ	denm	188		259		193		266		2.61E-02
SCZ	egcu	828		299		169		62		1.20E-01
SCZ	ersw	120		175		92		141		9.94E-01
SCZ	fi3m	469		457		85		101		6.67E-01
SCZ	fi6	585		427		152		207		1.85E-01
SCZ	lacw	23		21		51		104		9.77E-01
SCZ	lie2	144		124		37		94		7.65E-01
SCZ	lie5	204		182		126		363		3.83E-01
SCZ	munc	156		136		150		266		4.51E-01
SCZ	swe5	585		654		690		1034		3.19E-01
SCZ	swe6	259		283		360		511		9.70E-01
SCZ	ucla	278		282		170		522		9.44E-01
SCZ	umeb	183		146		109		154		2.63E-01
SCZ	umes	266		232		72		93		2.68E-01
BIP	bmau	895		895		184		140		8.66E-01
BIP	bm2	210		226		117		64		4.03E-01
BIP	bm3	158		54		288		197		7.26E-01
BIP	bmpo	213		476		250		160		9.67E-01
BIP	bmsp	144		147		138		114		1.62E-01
BIP	bonn	151		142		345		318		5.85E-01
BIP	fran	934		693		262		189		8.29E-01
BIP	gsk1	408		299		415		239		9.25E-01
BIP	icuk	616		671		1691		741		8.58E-01
BIP	may1	372		369		553		371		6.07E-02
BIP	mich	69		60		9		3		3.86E-01
BIP	sweti	873		898		765		459		2.69E-03
BIP	top8	126		152		80		55		8.16E-01
BIP	ucl2	240		440		393		319		7.70E-01
BIP	ume4	136		121		294		183		4.19E-01
BIP	usc2	650		433		632		654		5.01E-02
MDD	boma	131		149		377		209		5.57E-02
MDD	gep3	382		361		328		142		8.69E-01
MDD	grdg	290		176		365		106		1.11E-01
MDD	grnd	199		212		682		143		3.73E-01
MDD	gsk2	134		65		561		285		7.44E-01
MDD	mmi2	278		228		315		265		5.93E-02
MDD	mmo4	181		189		135		129		7.39E-01
MDD	rad3	694		485		1303		548		2.59E-01
MDD	rage	29		34		211		109		1.30E-01
MDD	rai2	173		157		89		19		1.17E-02
MDD	rau2	196		182		175		48		4.59E-01
MDD	rot4	571		422		181		63		6.89E-01
MDD	shpt	224		276		119		46		9.51E-01
MDD	twg2	1112		1336		763		317		1.71E-01
Meta		17550		17448		17634		16697		1.60E-07



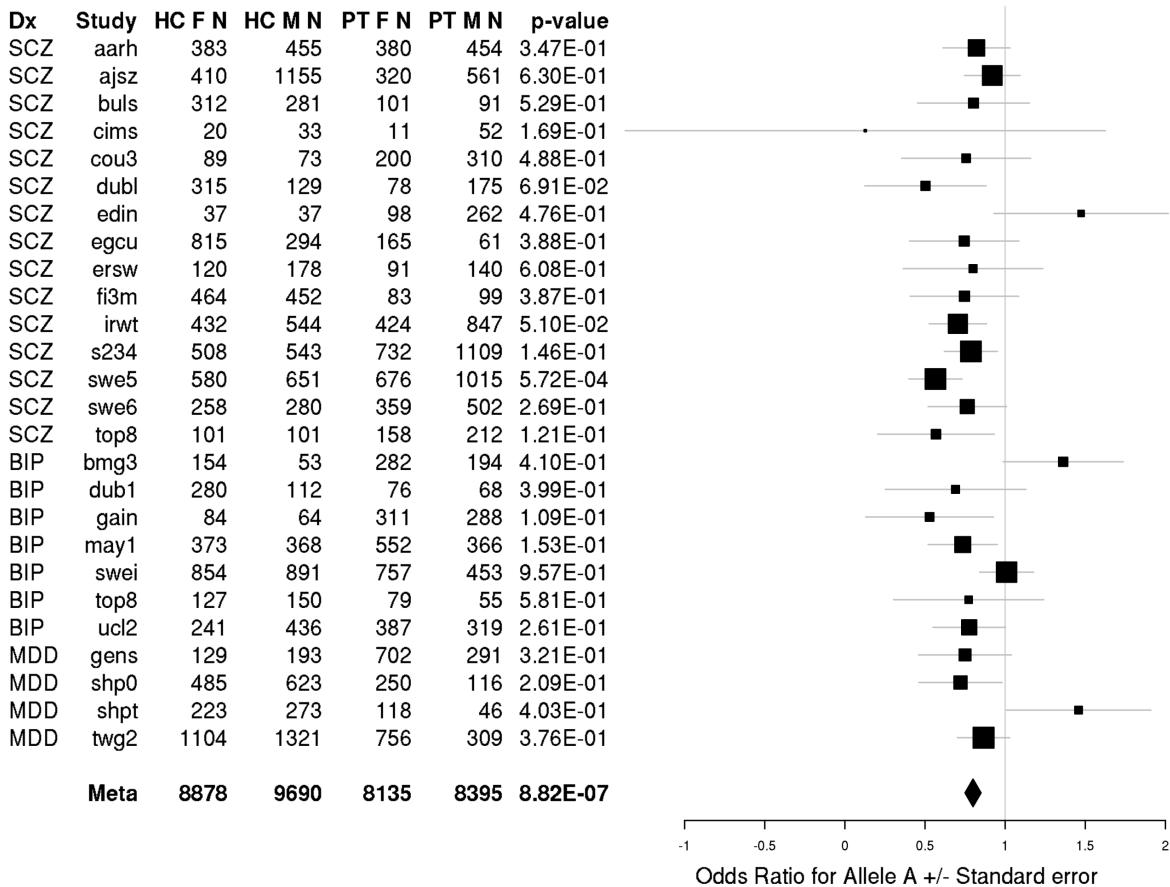
rs73033497 (A/T)
Cross-Disorder SCZ-BIP-MDD

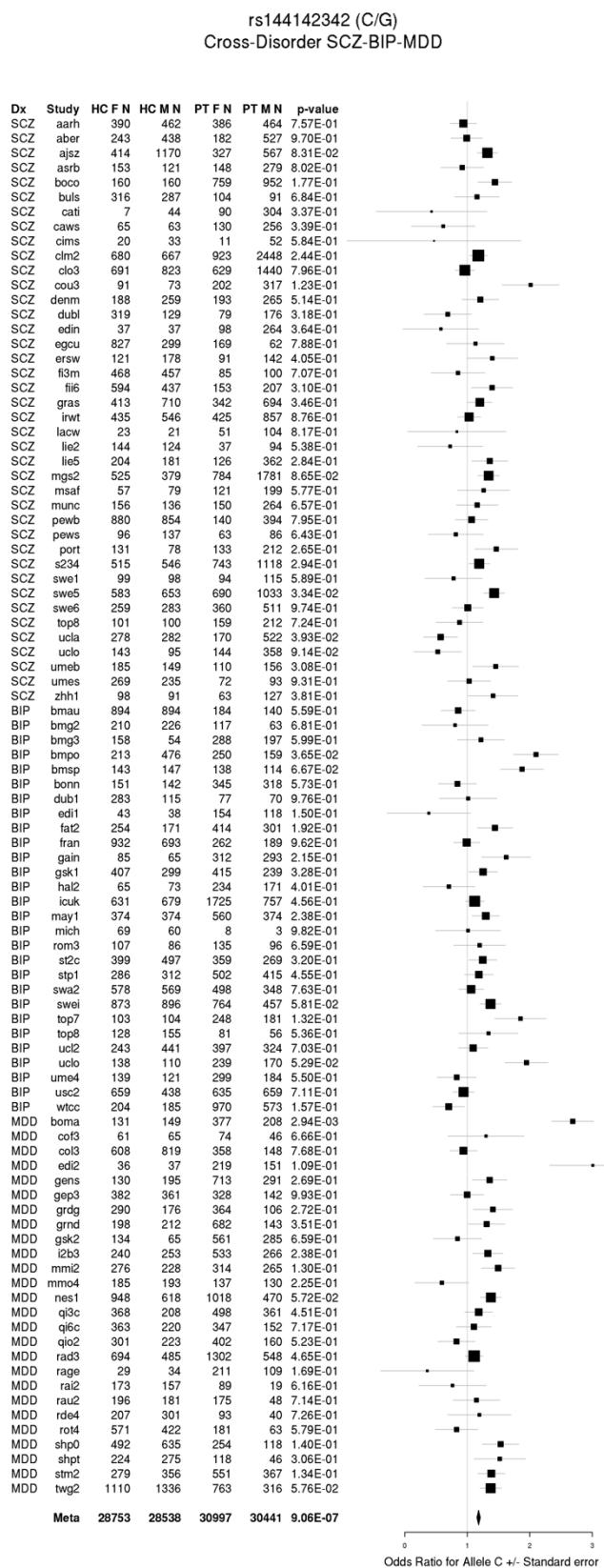




g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry

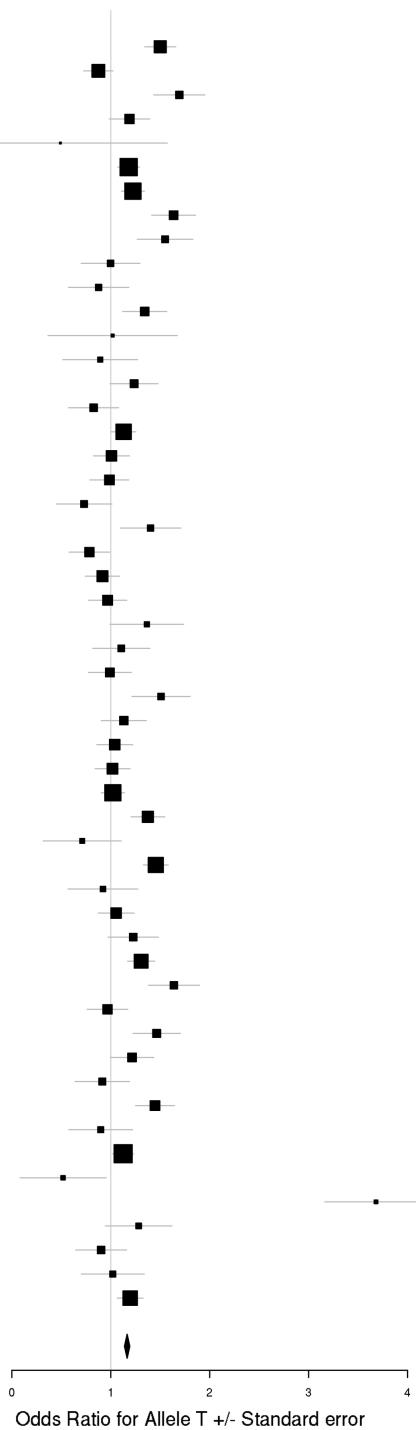
rs73033497 (A/T)
Cross-Disorder SCZ-BIP-MDD





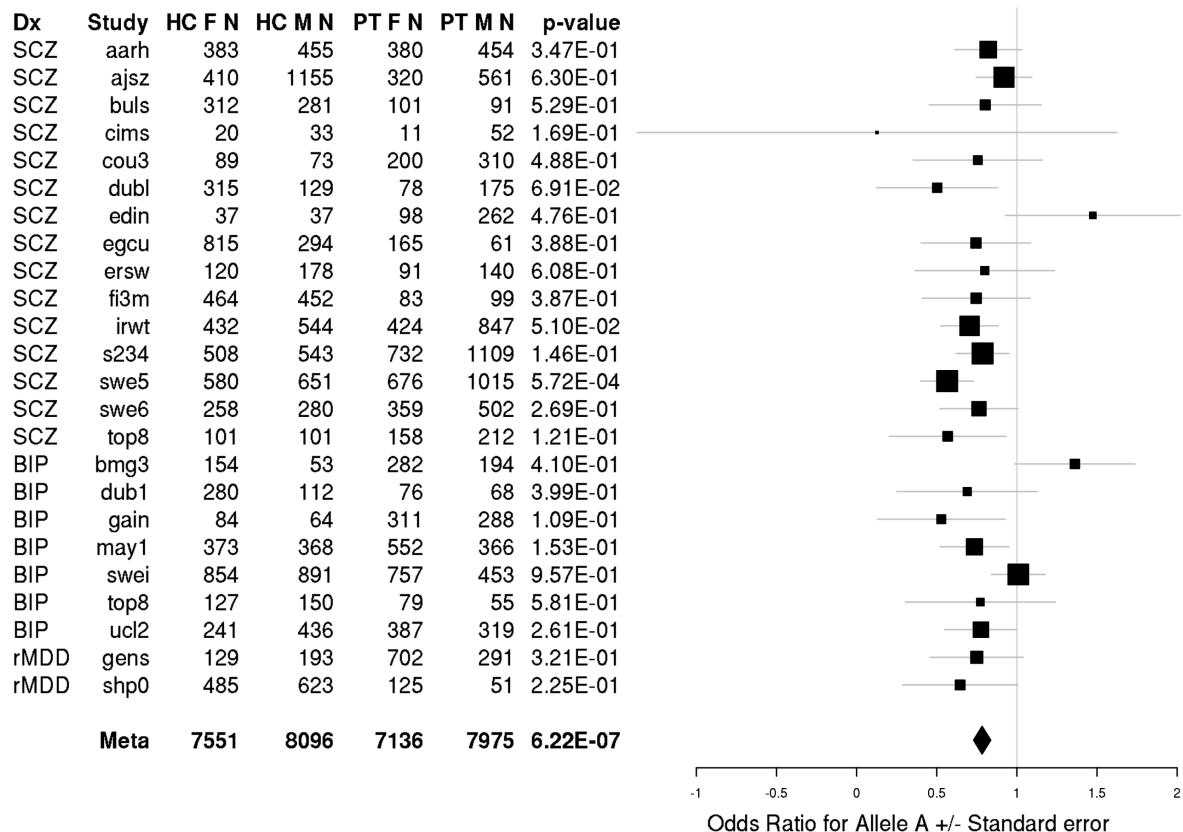
rs7302529 (T/C)
Cross-Disorder SCZ-BIP-MDD

Dx	Study	HC F	N	HC M	N	PT F	N	PT M	N	p-value
SCZ	aarh	391	463	387	465	9.74E-03				
SCZ	ajsz	414	1171	327	567	3.63E-01				
SCZ	asrb	153	121	148	280	4.17E-02				
SCZ	boco	160	160	761	952	3.97E-01				
SCZ	cims	20	33	11	52	5.10E-01				
SCZ	clm2	671	657	908	2393	1.28E-01				
SCZ	clo3	684	818	627	1435	8.16E-02				
SCZ	denm	188	259	193	266	2.61E-02				
SCZ	egcu	828	299	169	62	1.20E-01				
SCZ	ersw	120	175	92	141	9.94E-01				
SCZ	fi3m	469	457	85	101	6.67E-01				
SCZ	fi6	585	427	152	207	1.85E-01				
SCZ	lacw	23	21	51	104	9.77E-01				
SCZ	lie2	144	124	37	94	7.65E-01				
SCZ	lie5	204	182	126	363	3.83E-01				
SCZ	munc	156	136	150	266	4.51E-01				
SCZ	swe5	585	654	690	1034	3.19E-01				
SCZ	swe6	259	283	360	511	9.70E-01				
SCZ	ucla	278	282	170	522	9.44E-01				
SCZ	umeb	183	146	109	154	2.63E-01				
SCZ	umes	266	232	72	93	2.68E-01				
SCZ	hok2	1344	668	154	322	2.33E-01				
SCZ	tcr1	336	570	289	563	6.13E-01				
BIP	bmau	895	895	184	140	8.66E-01				
BIP	bmrg2	210	226	117	64	4.03E-01				
BIP	bmrg3	158	54	288	197	7.26E-01				
BIP	bmpo	213	476	250	160	9.67E-01				
BIP	bmsp	144	147	138	114	1.62E-01				
BIP	bonn	151	142	345	318	5.85E-01				
BIP	fran	934	693	262	189	8.29E-01				
BIP	gsk1	408	299	415	239	9.25E-01				
BIP	icuk	616	671	1691	741	8.58E-01				
BIP	may1	372	369	553	371	6.07E-02				
BIP	mich	69	60	9	3	3.86E-01				
BIP	swei	873	898	765	459	2.69E-03				
BIP	top8	126	152	80	55	8.16E-01				
BIP	ucl2	240	440	393	319	7.70E-01				
BIP	ume4	136	121	294	183	4.19E-01				
BIP	usc2	650	433	632	654	5.01E-02				
MDD	boma	131	149	377	209	5.57E-02				
MDD	gep3	382	361	328	142	8.69E-01				
MDD	grdg	290	176	365	106	1.11E-01				
MDD	grnd	199	212	682	143	3.73E-01				
MDD	gsk2	134	65	561	285	7.44E-01				
MDD	mmi2	278	228	315	265	5.93E-02				
MDD	mmo4	181	189	135	129	7.39E-01				
MDD	rad3	694	485	1303	548	2.59E-01				
MDD	rage	29	34	211	109	1.30E-01				
MDD	rai2	173	157	89	19	1.17E-02				
MDD	rau2	196	182	175	48	4.59E-01				
MDD	rot4	571	422	181	63	6.89E-01				
MDD	shpt	224	276	119	46	9.51E-01				
MDD	twg2	1112	1336	763	317	1.71E-01				
Meta		19230	18686	18077	17582	9.37E-07				



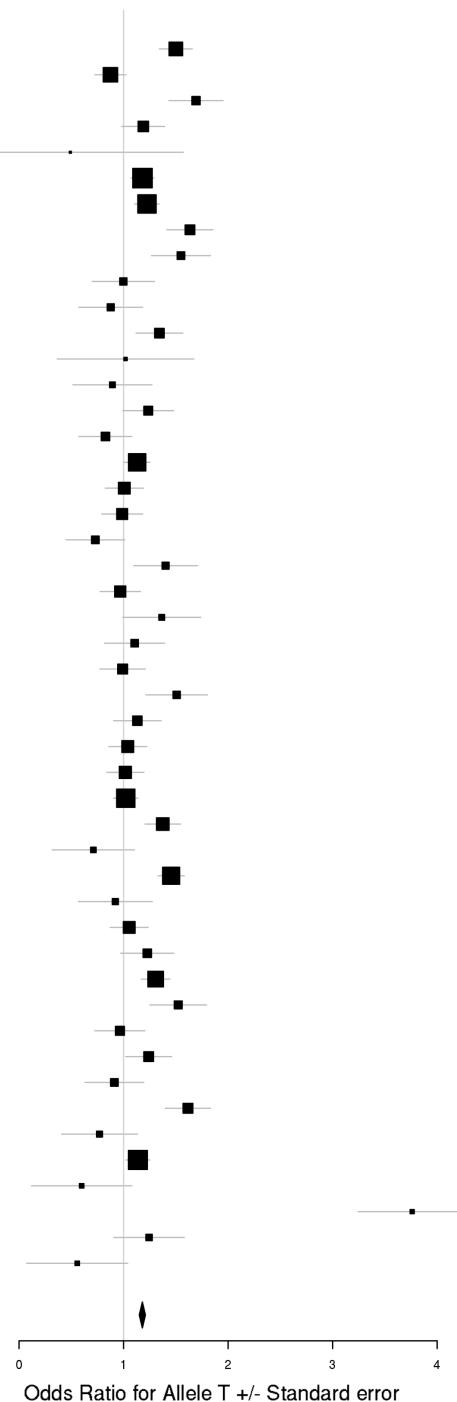
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only

rs73033497 (A/T)
Cross-Disorder SCZ-BIP-RMDD



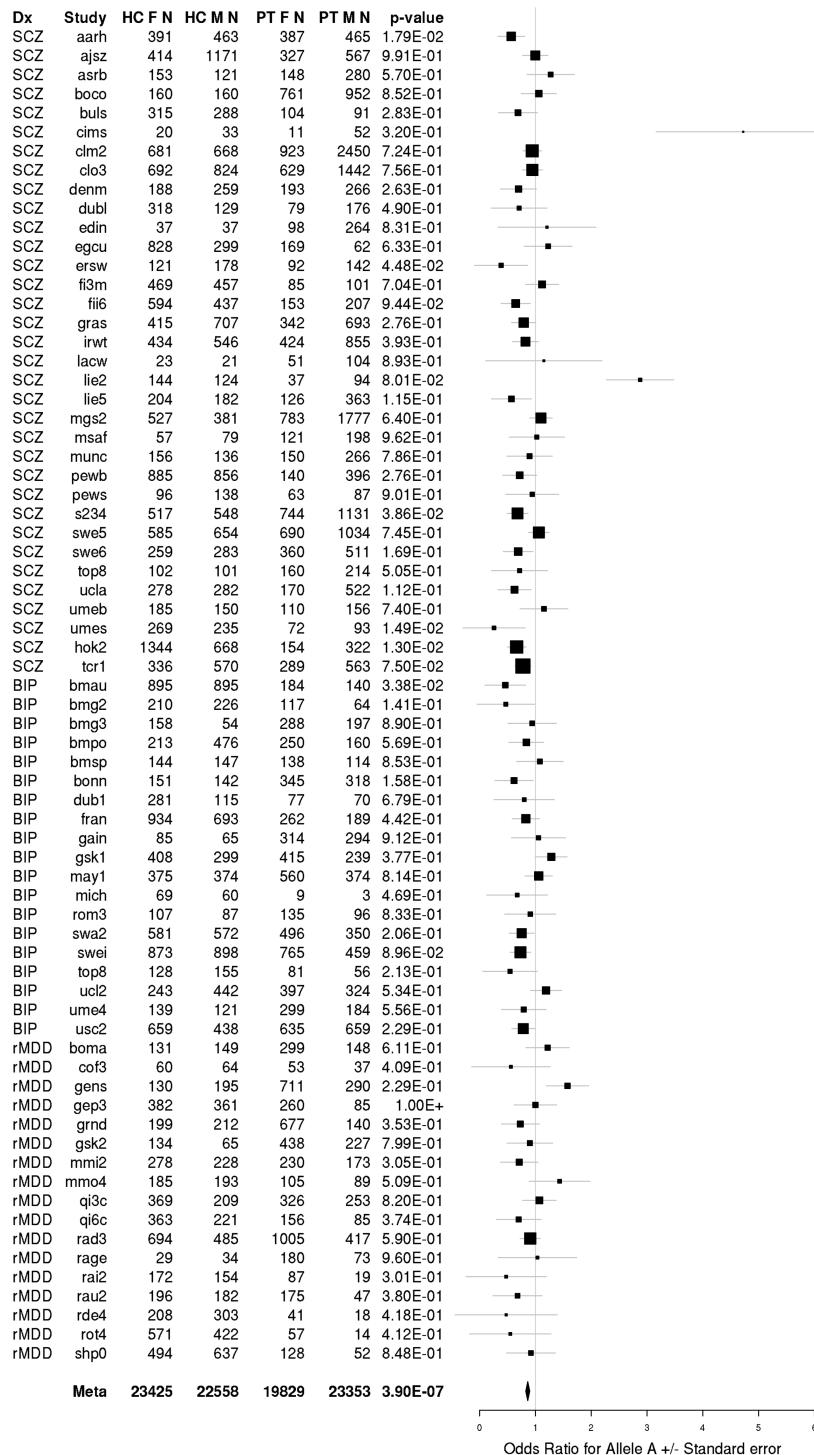
rs7302529 (T/C)
Cross-Disorder SCZ-BIP-RMDD

Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	391	463	387	465	9.74E-03
SCZ	ajsz	414	1171	327	567	3.63E-01
SCZ	asrb	153	121	148	280	4.17E-02
SCZ	boco	160	160	761	952	3.97E-01
SCZ	cims	20	33	11	52	5.10E-01
SCZ	clm2	671	657	908	2393	1.28E-01
SCZ	clo3	684	818	627	1435	8.16E-02
SCZ	denm	188	259	193	266	2.61E-02
SCZ	egcu	828	299	169	62	1.20E-01
SCZ	ersw	120	175	92	141	9.94E-01
SCZ	fi3m	469	457	85	101	6.67E-01
SCZ	fii6	585	427	152	207	1.85E-01
SCZ	lacw	23	21	51	104	9.77E-01
SCZ	lie2	144	124	37	94	7.65E-01
SCZ	lie5	204	182	126	363	3.83E-01
SCZ	munc	156	136	150	266	4.51E-01
SCZ	swe5	585	654	690	1034	3.19E-01
SCZ	swe6	259	283	360	511	9.70E-01
SCZ	ucla	278	282	170	522	9.44E-01
SCZ	umeb	183	146	109	154	2.63E-01
SCZ	umes	266	232	72	93	2.68E-01
BIP	bmau	895	895	184	140	8.66E-01
BIP	bmrg2	210	226	117	64	4.03E-01
BIP	bmrg3	158	54	288	197	7.26E-01
BIP	bmro	213	476	250	160	9.67E-01
BIP	bmrs	144	147	138	114	1.62E-01
BIP	bonn	151	142	345	318	5.85E-01
BIP	fran	934	693	262	189	8.29E-01
BIP	gsk1	408	299	415	239	9.25E-01
BIP	icuk	616	671	1691	741	8.58E-01
BIP	may1	372	369	553	371	6.07E-02
BIP	micb	69	60	9	3	3.86E-01
BIP	swei	873	898	765	459	2.69E-03
BIP	top8	126	152	80	55	8.16E-01
BIP	ucl2	240	440	393	319	7.70E-01
BIP	ume4	136	121	294	183	4.19E-01
BIP	usc2	650	433	632	654	5.01E-02
rMDD	boma	131	149	299	148	1.20E-01
rMDD	gep3	382	361	260	85	8.82E-01
rMDD	grnd	199	212	677	140	3.29E-01
rMDD	gsk2	134	65	438	227	7.43E-01
rMDD	mmi2	278	228	230	173	2.70E-02
rMDD	mmo4	181	189	104	89	4.70E-01
rMDD	rad3	694	485	1005	417	2.52E-01
rMDD	rage	29	34	180	73	2.86E-01
rMDD	rai2	173	157	88	19	1.05E-02
rMDD	rau2	196	182	175	47	5.17E-01
rMDD	rot4	571	422	57	14	2.25E-01
Meta		15924	15660	15543	15700	7.43E-07



i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry

rs8040598 (A/G)
Cross-Disorder SCZ-BIP-RMDD



rs73033497 (A/T)
Cross-Disorder SCZ-BIP-RMDD

Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	383	455	380	454	3.47E-01
SCZ	aksz	410	1155	320	561	6.30E-01
SCZ	buls	312	281	101	91	5.29E-01
SCZ	cims	20	33	11	52	1.69E-01
SCZ	cou3	89	73	200	310	4.88E-01
SCZ	dubl	315	129	78	175	6.91E-02
SCZ	edin	37	37	98	262	4.76E-01
SCZ	egcu	815	294	165	61	3.88E-01
SCZ	ersw	120	178	91	140	6.08E-01
SCZ	fi3m	464	452	83	99	3.87E-01
SCZ	irwt	432	544	424	847	5.10E-02
SCZ	s234	508	543	732	1109	1.46E-01
SCZ	swe5	580	651	676	1015	5.72E-04
SCZ	swe6	258	280	359	502	2.69E-01
SCZ	top8	101	101	158	212	1.21E-01
BIP	bmg3	154	53	282	194	4.10E-01
BIP	dub1	280	112	76	68	3.99E-01
BIP	gain	84	64	311	288	1.09E-01
BIP	may1	373	368	552	366	1.53E-01
BIP	swei	854	891	757	453	9.57E-01
BIP	top8	127	150	79	55	5.81E-01
BIP	ucl2	241	436	387	319	2.61E-01
rMDD	gens	129	193	702	291	3.21E-01
rMDD	shp0	485	623	125	51	2.25E-01
Meta		7551	8096	7136	7975	6.22E-07

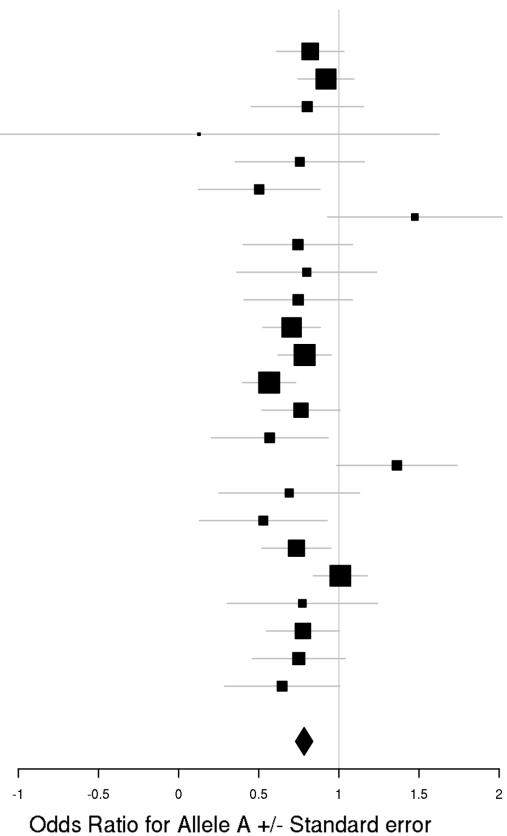
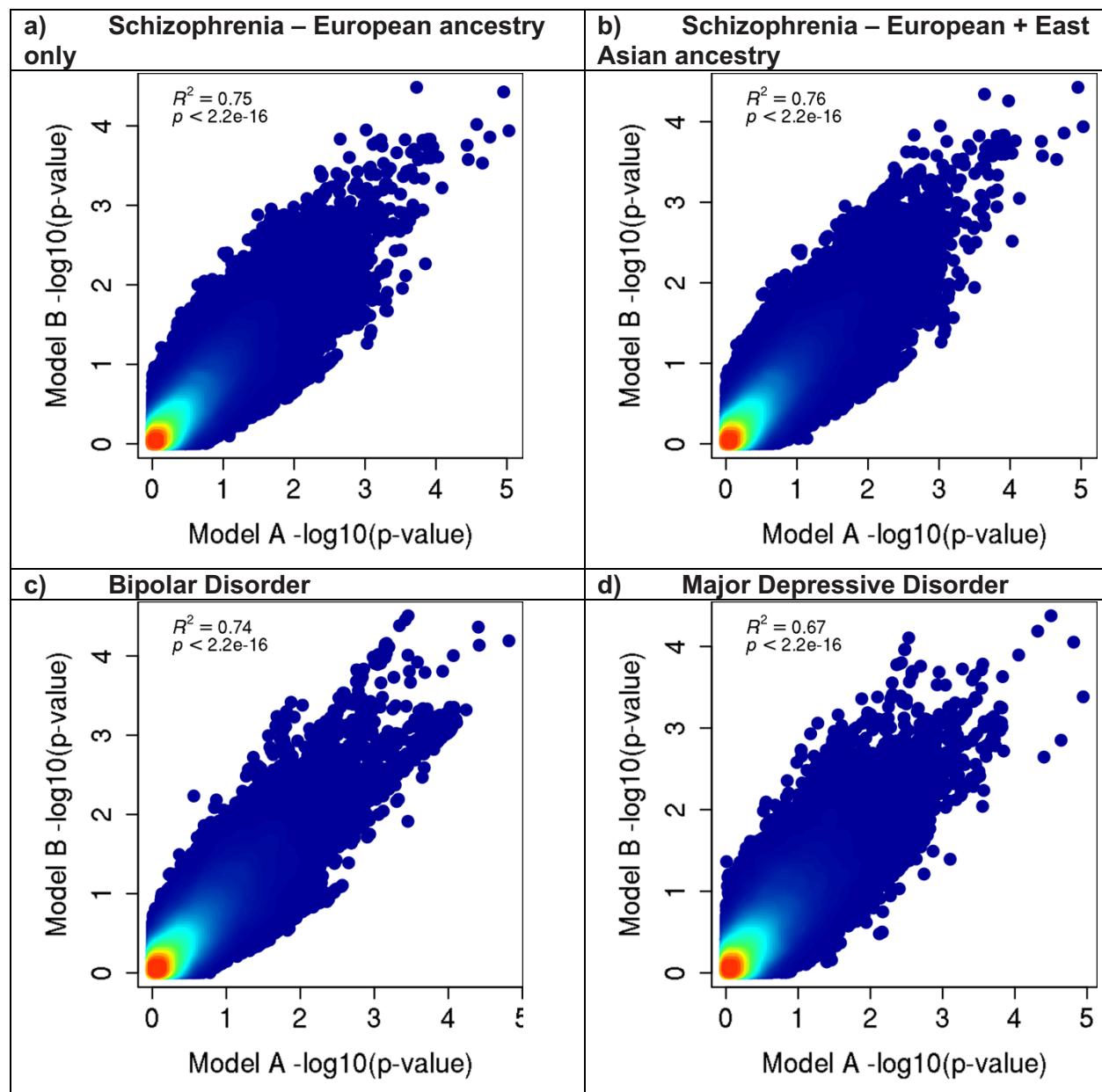
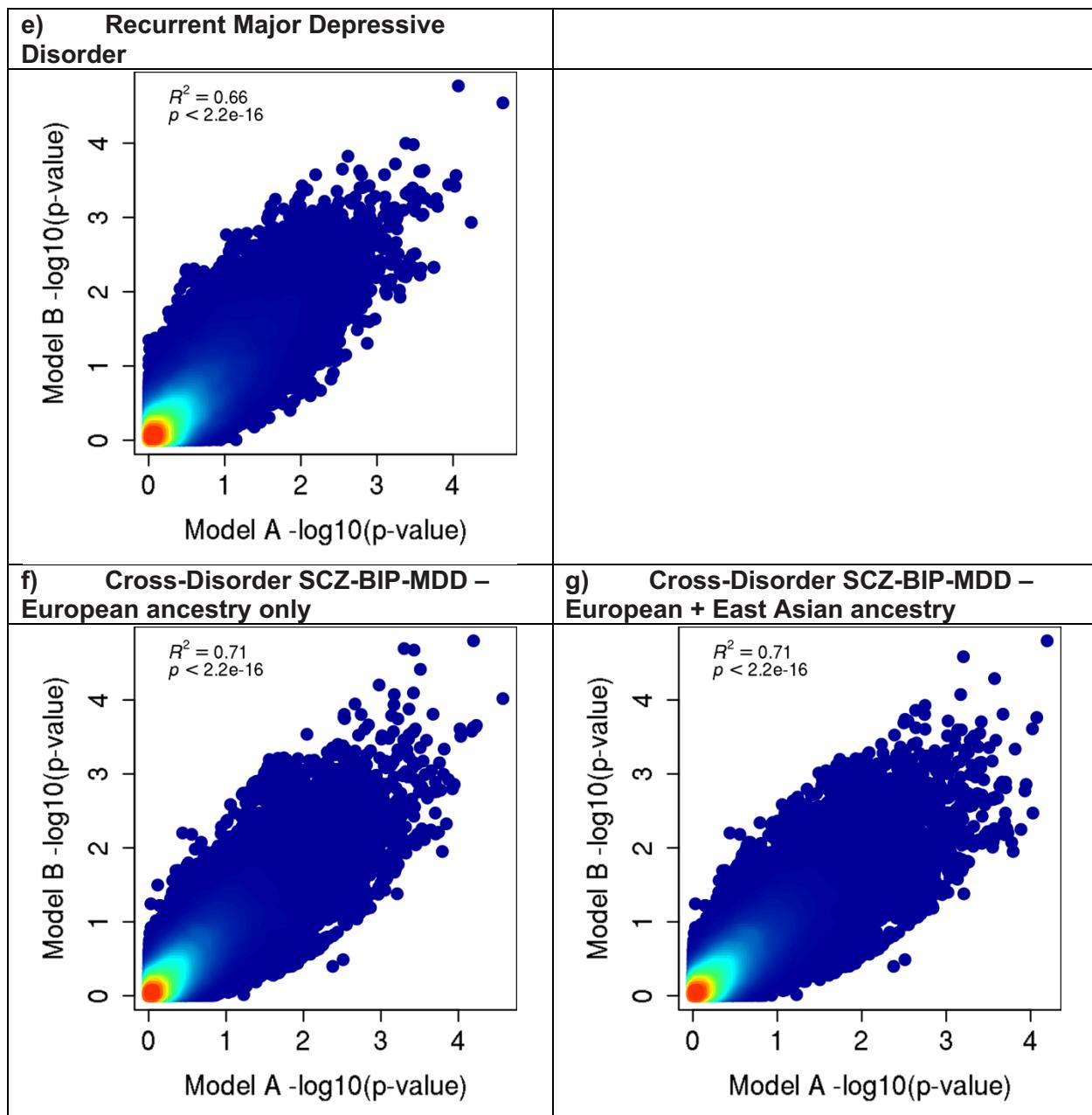


Figure S23. X chromosome model comparisons in PGC

Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; HC F N = number of female healthy controls; HC M N = number of male healthy controls; PT F N = number of female patients; PT M N = number of male patients; Study = cohort abbreviation used by PGC; Meta = meta-analysis results





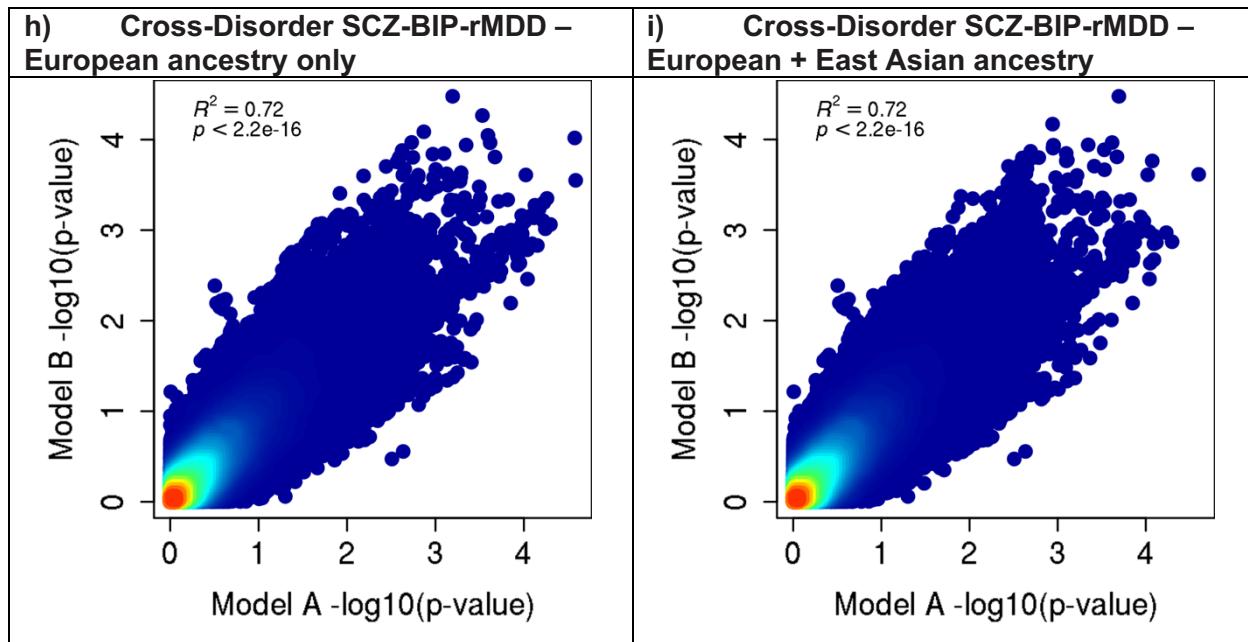


Figure S24. Manhattan plots for gene-based G×S tests in PGC

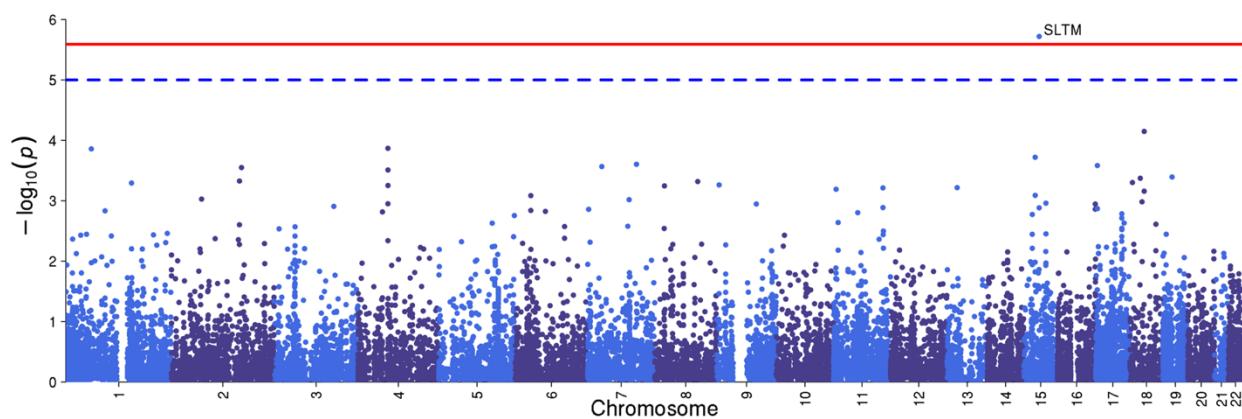
These analyses were carried out in MAGMA on the genomic control output with INFO score > 0.6 , *European ancestry only*, and autosomal SNPs only, with the MHC region included.

Negative log₁₀-transformed p-values for each gene (y-axis) are plotted by chromosomal position (x-axis). Each dot represents a gene, and the solid red and dotted blue horizontal lines represent the thresholds for genome-wide significant association ($p = 2.57 \times 10^{-6}$) and suggestive association ($p = 1 \times 10^{-5}$), respectively.

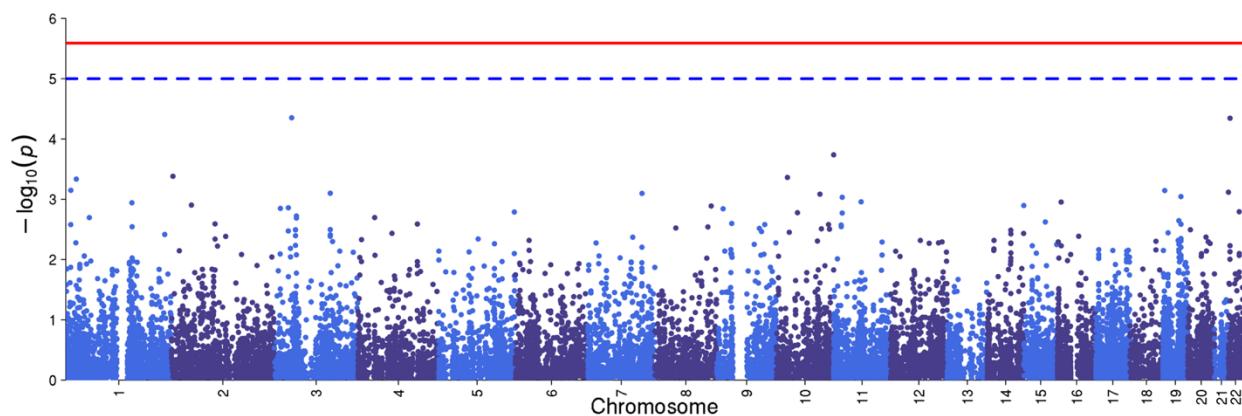
Plots were generated using the ‘plot’ package in R.

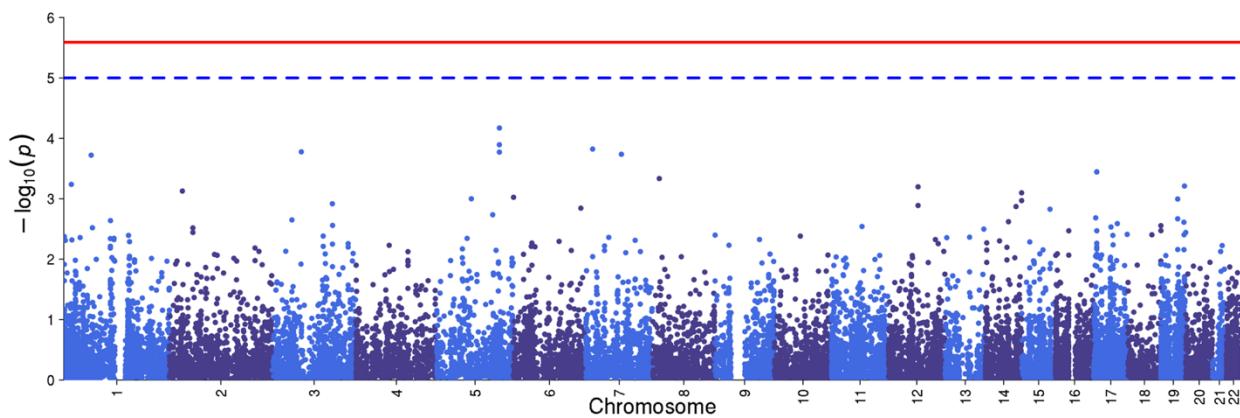
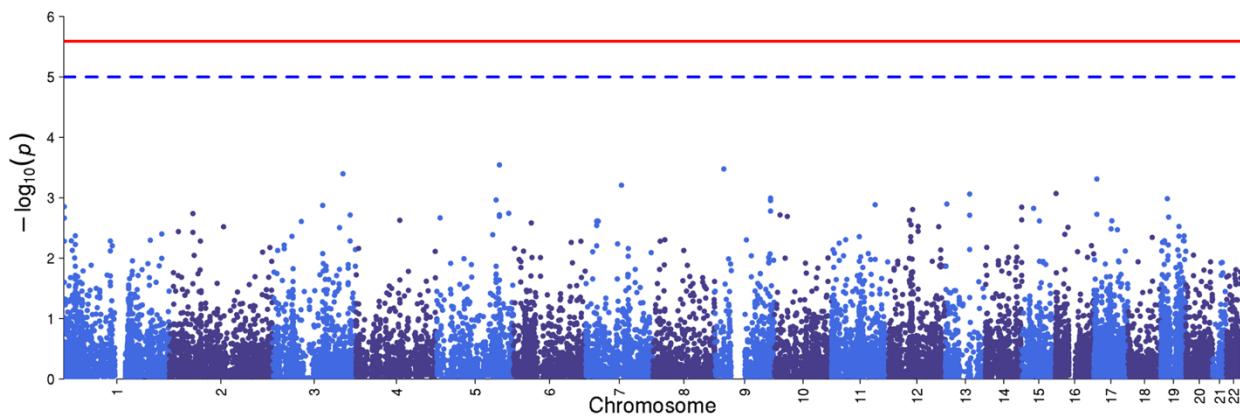
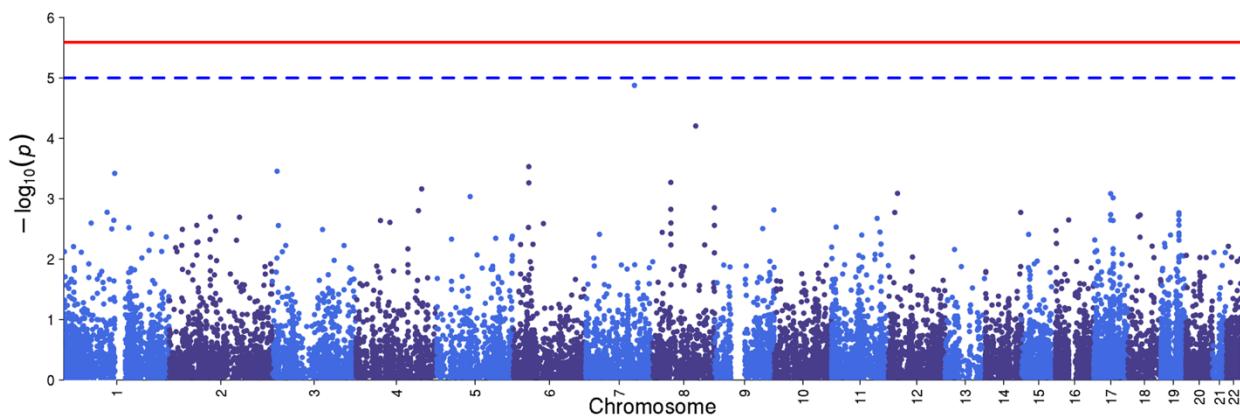
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; SLTM = SAFB Like Transcription Modulator

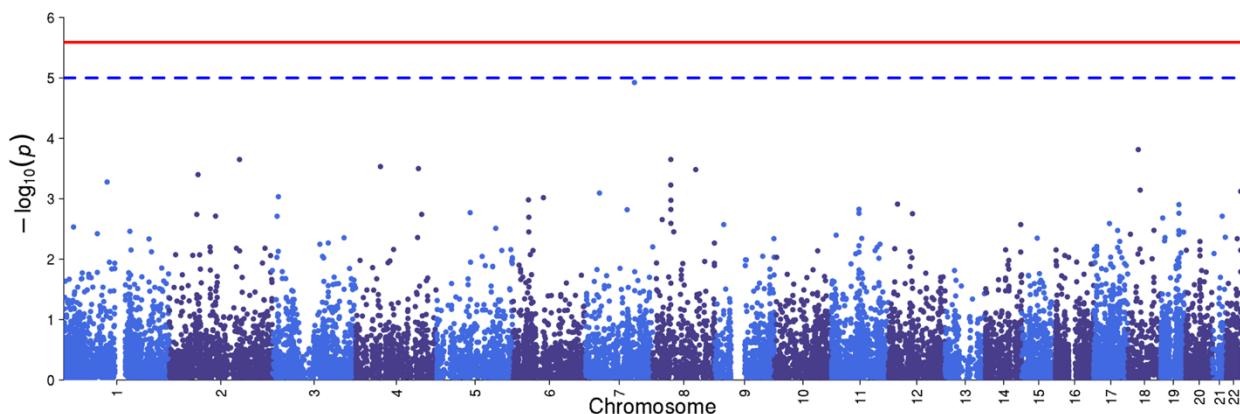
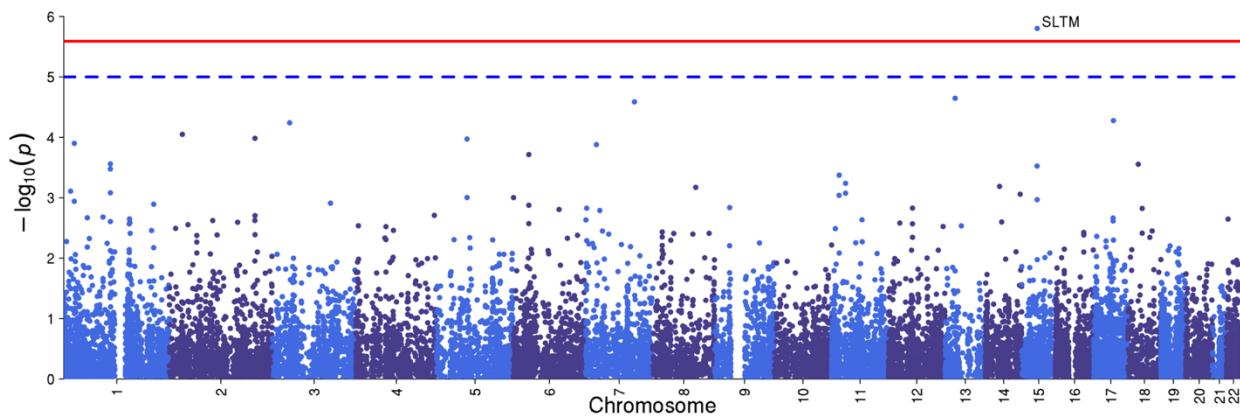
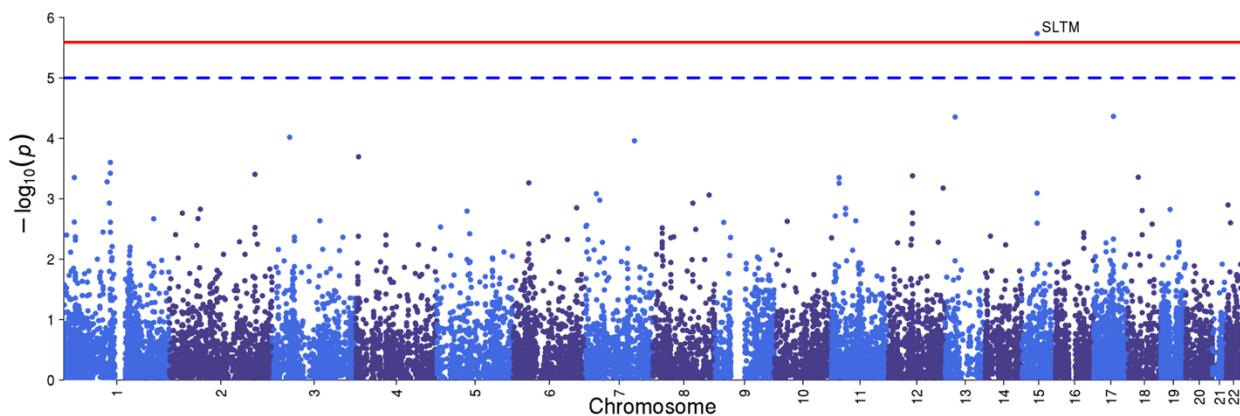
a) Schizophrenia



b) Bipolar Disorder



c) Major Depressive Disorder**d) Recurrent Major Depressive Disorder****e) Cross-Disorder SCZ-BIP-MDD**

f) Cross-Disorder SCZ-BIP-rMDD**g) Omnibus Test SCZ-BIP-MDD****h) Omnibus Test SCZ-BIP-rMDD**

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This study makes use of data generated by the Wellcome Trust Case-Control Consortium.(50-52) Data from (53) were excluded. A full list of the investigators who contributed to the generation of the data is available from www.wtccc.org.uk. Funding for the project was provided by the Wellcome Trust under award 076113, 085475 and 090355.

The Finnish schizophrenia data used for the research were obtained from the THL Biobank. We thank all study participants for their generous participation in the THL Psychiatric Family Collections, the National FINRISK Study, Health 2000, and Northern Finland Birth Cohorts studies.

Data have also been provided by the Study of Health in Pomerania (SHIP) from the Community Medicine Research Alliance of the Medical Faculty at the Ernst Moritz Arndt University of Greifswald. Funding for SHIP was provided by BMBF – Federal Ministry for Education and Research under subsidy identification codes 01ZZ9603, 01ZZ0103, and 01ZZ0701.

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