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

Supplement 1

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 **Supplementary Table 3** and **Supplementary Figure 2**.

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 GxS 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.

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

Here, we focused on the interaction analysis. However, to characterize the quality of the suggestive GxS interaction signals ($p<1\times10^{-6}$), included in the tables with GxS interaction results (**Tables 1-2, Supplementary Tables 6-9**), we also report sex-specific association statistics. Miami plots show the genome-wide sex-specific associations (**Supplementary Figure 3**). None of these GxS SNPs showed a genome-wide significant sex-specific signal. Furthermore, a scatter plot of -log10(*p*-values) for sex-specific genome-wide associations indicated little overlap in the top signals across sexes (**Supplementary Figure 4**).

Linkage Disequilibrium Score Regression

Estimates of h^2_{SNP} 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^2_{SNP} increased minimally across a range of MAF cutoffs (MAF>1%, 2%, 5%), indicating rarer variants contributed little to the heritability estimates (**Supplementary Table 7**).

For traits with non-zero h^2_{SNP} estimates in both sexes (significantly greater than zero; $z=h^2_{SNP}/SE$), we tested whether the estimates were significantly different between the sexes by calculating Z-scores using the Equation above (replacing Beta with h^2_{SNP}), 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 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/SE) and significantly less than 1 (z=(1 – r_g)/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^2_{SNP} and r_g are based on the autosomal contributions only, as LDSC currently does not allow for estimation of h^2_{SNP} 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 (GxS) interaction analysis of each study cohort, followed by standard-error weighted (i.e., inverse variance) meta-analysis of the GxS interaction results using METAL (7). GxS 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 (PC) 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 three-degrees-of-freedom (df) 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 ($p < 5\times10^{-8}$) and suggestive GxS signals ($p < 1\times10^{-6}$) were used as index SNPs to obtain credible SNPs (i.e., potentially causal in disease risk). All SNPs associated with $p < 1\times10^{-6}$ 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 (**Supplementary Table 10**) 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 GxS 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 (PC), 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 $p < 2.6\times10^{-6}$, which accounts for 19,427 autosome and sex chromosome genes evaluated in the test (**Supplementary Table 11**).

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 Ca^{2+} channels. The number of genes in each (top) pathway are listed in **Supplementary Tables 12-13**.

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://hbatlas.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 GxS interaction results (variants with a GxS interaction *p*-value $< 1\times10^{-6}$**).**

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 GxS interaction *p*-value $< 1\times10^{-6}$ were analyzed further to test whether their genotype was associated with RNA(-Seq) expression. The most significant SNP from each locus having $p < 1\times10^{-6}$ in GxS 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 ($p < 1\times10^{-6}$) 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 GxS interaction for sex-dependent and cross-disorder SNPs from prior studies

To assess overlap of GxS signals between the current study and prior published studies, GxS interaction results were compared to previously reported sex-dependent or sex-specific effects on psychiatric illness risk ($p<5\times10^{-8}$) from sex-stratified analyses by the PGC (2, 39, 40), ASD collection (41), 23andMe (42), and UK Biobank (43) (see Supplementary Methods). Additionally, GxS 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 ($p < 5\times10^{-8}$) between the sexes only. The Z difference score was calculated as described above. Additionally, GxS interaction effects were evaluated for genome-wide significant SNPs (main additive effect across sexes) from the recent PGC cross-disorder group (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 GxS interactions ($p<1\times10^{-6}$; i.e. the SNPs listed in **Tables 1-2)**. As shown in **Supplementary Figures 11-13**, 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. TUSC1 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 TUSC1 in neuron (**Supplementary Figure 15**).

Evaluation of sex-specific expression detected different expression levels between males and females of several of the genes in some brain regions (**Supplementary Figure 21**).

Evaluation of GxS 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 GxS interactions in our analyses (**Supplementary Table 14)** of MDD (rs2042772; $p=0.037$) and BIP (rs4543289; $p=0.034$). SNPs with significant sex-dependent effects ($p<5\times10^{-8}$) in prior within-disorder studies of ADHD, OCD, PTSD, and ASD (2, 39-41) or UK Biobank psychiatric phenotypes (43) had non-significant ($p_{FDR} > 0.05$) GxS 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 GxS omnibus test of SCZ, BIP and rMDD ($p_{FDR} = 0.034$); rs11688767 had a *p*-value of 3.2×10^{-4} in our meta-analysis of rMDD ($p_{FDR} = 0.034$). Of note, *CSMD1*, identified in the PGC-CDG cross-disorder analysis (44), was among our top cross-disorder GxS results (regular meta-analysis). However, the most significant SNP in each analysis differed.

Supplementary Tables

Supplementary Table 1. PGC cohort characteristics

See SupplTable1_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.

Supplementary Table 2. iPSYCH cohort characteristics

See SupplTable2_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.

Supplementary Table 3. Power analyses

See SupplTable3_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.

Supplementary Table 4. SNP-based heritability

See SupplTable4_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 LD 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.

Supplementary Table 5. SNP-based genetic correlations

See SupplTable5_SNP-based_rg_LDSC.xlsx

Estimates of SNP-based genetic correlations, r_g (standard error, SE), were obtained using LD 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.

Supplementary Table 6. Meta-analysis Autosomal GxS interaction loci in PGC+iPSYCH

See SupplTable6_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 < 1×10^{-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.

Supplementary Table 7. Omnibus test Autosomal GxS interaction loci in PGC+iPSYCH

See SupplTable7_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 < 1×10^{-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.

Supplementary Table 8. Meta-analysis chrX GxS interaction loci in PGC+iPSYCH

See SupplTable8_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 < 1×10^{-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.

Supplementary Table 9. Omnibus test chrX GxS interaction loci in PGC+iPSYCH

See SupplTable9_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 < 1×10^{-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 < 1×10^{-6}.

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

Supplementary Table 10. Credible SNPs for GxS loci in PGC+iPSYCH

See SupplTable10_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 $p < 1\times10^{-6}$ 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.

Supplementary Table 11. Gene-based test in PGC+iPSYCH

See SupplTable11_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 < 1×10^{-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; MDD = major depressive disorder; rMDD = recurrent major depressive disorder; SCZ = schizophrenia.

Supplementary Table 12. MSigDB pathway gene set enrichment analyses in PGC+iPSYCH

See SupplTable12_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; MDD = major depressive disorder; P_{BONF} = Bonferroni-corrected *p*-value; P_{FDR} = False Discovery Rate-corrected *p*-value; rMDD = recurrent major depressive disorder; SCZ = schizophrenia; SE = Standard Error.

Supplementary Table 13. Selected pathway gene set enrichment analyses in PGC+iPSYCH

See SupplTable13_ 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; MDD = major depressive disorder; MP = Mouse Phenome; P_{FDR} = False Discovery Rate-corrected *p*-value; PGC-NPA = Psychiatric Genomics Consortium – Network and Pathway Analysis Working Group; rMDD = recurrent major depressive disorder; SCZ = schizophrenia; SE = Standard Error.

Supplementary Table 14. Lookup of interaction for SNPs showing sex-stratification or GxS interaction in 23andme, PGC, and UK Biobank

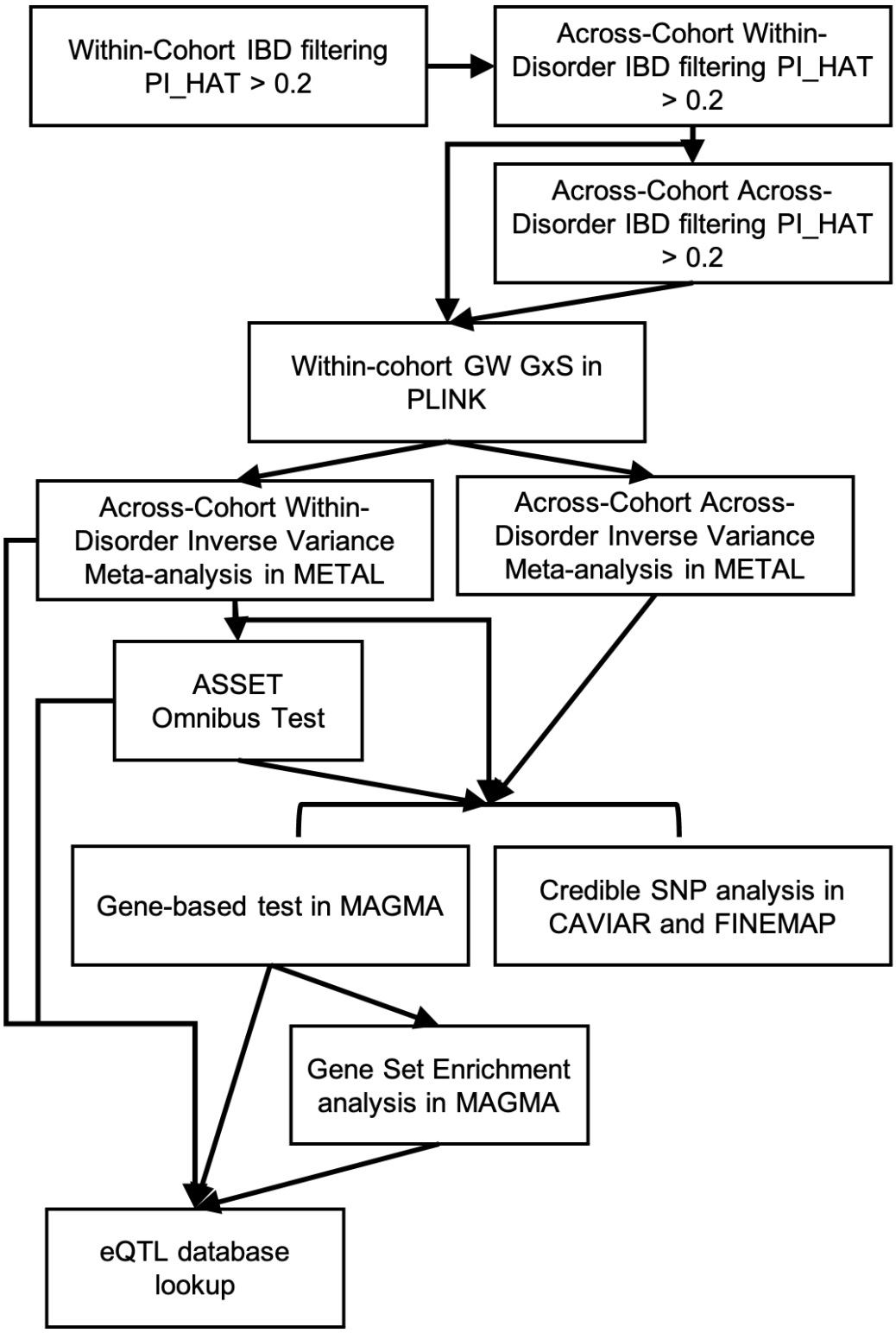
See SupplTable14_Prior_GWAS_SNP_Lookups.xlsx

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

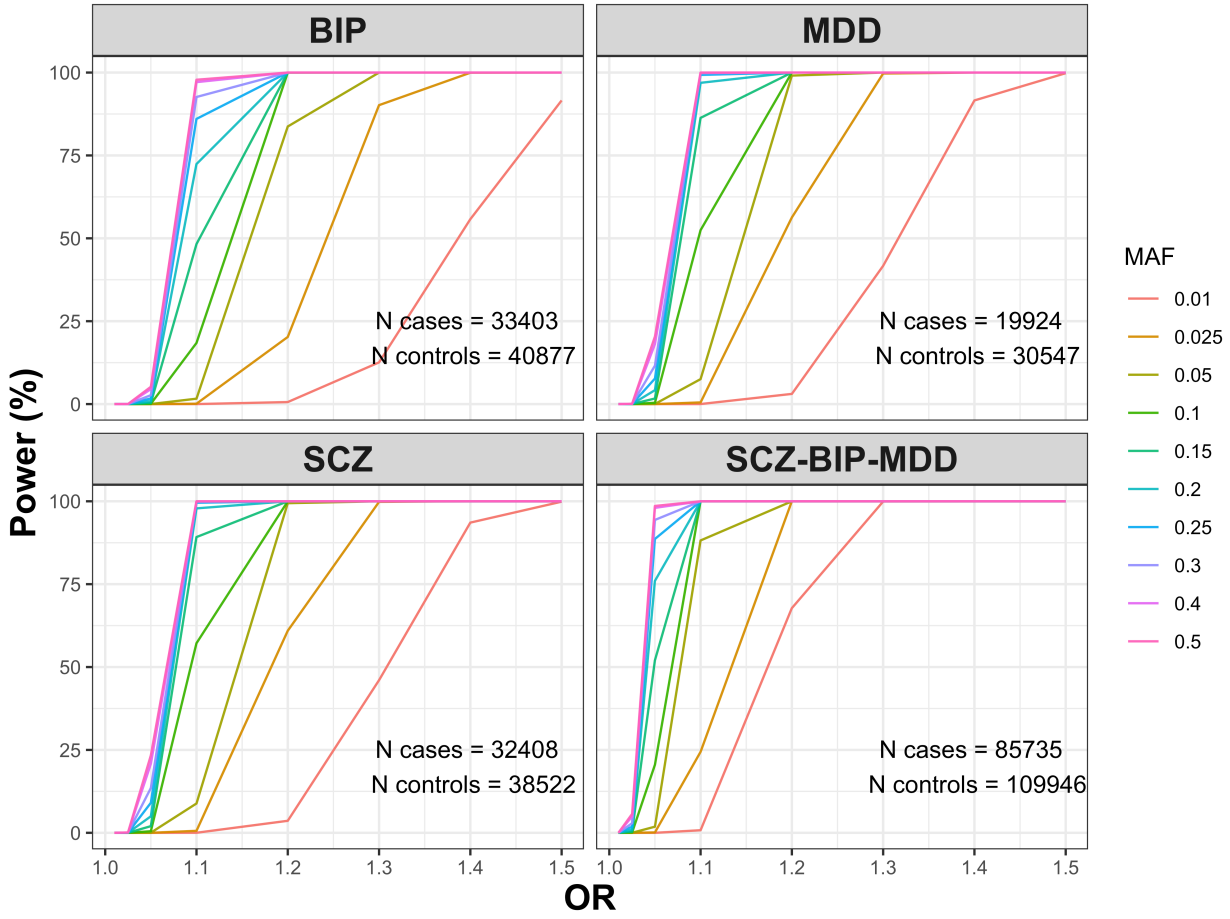
Abbreviations: BP = base pair position; CHR = Chromosome; SE = Standard Error; SNP = Single Nucleotide Polymorphism rs ID.

Supplementary Figures

Supplementary Figure 1. Experimental Design.



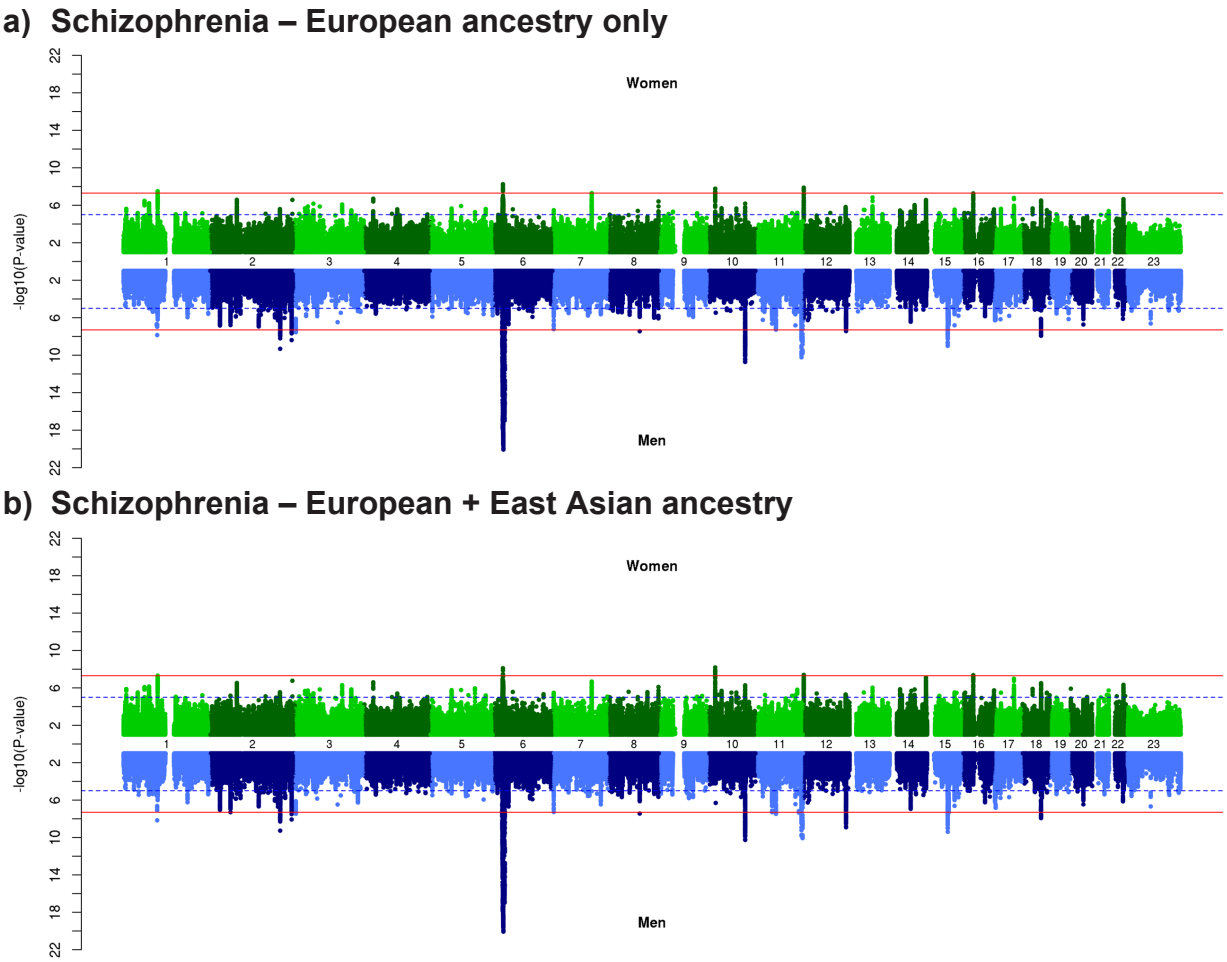
Supplementary Figure 2. Power analyses.
Abbreviations: MAF = Minor Allele Frequency; OR = Odds Ratio.



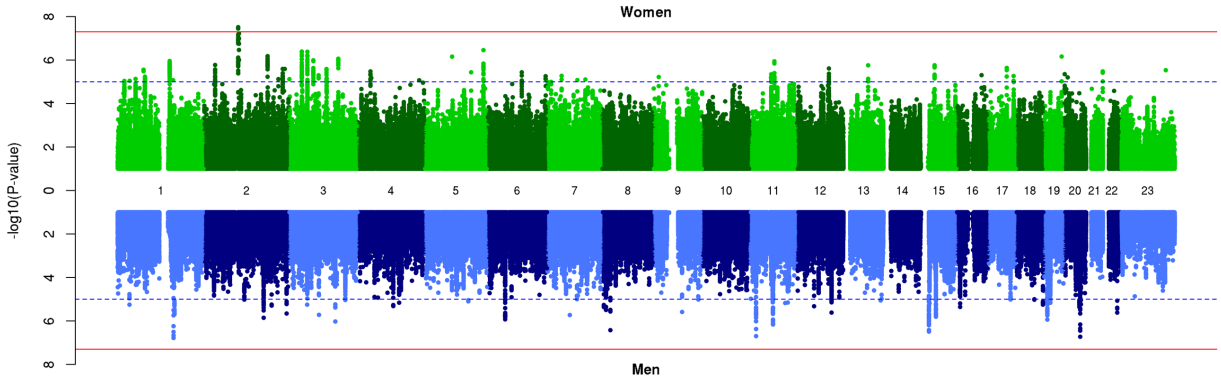
Supplementary Figure 3. Miami plots for sex-stratified analyses in PGC + iPSYCH

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 ($p = 5\times10^{-8}$) and suggestive association ($p = 1\times10^{-5}$), 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.

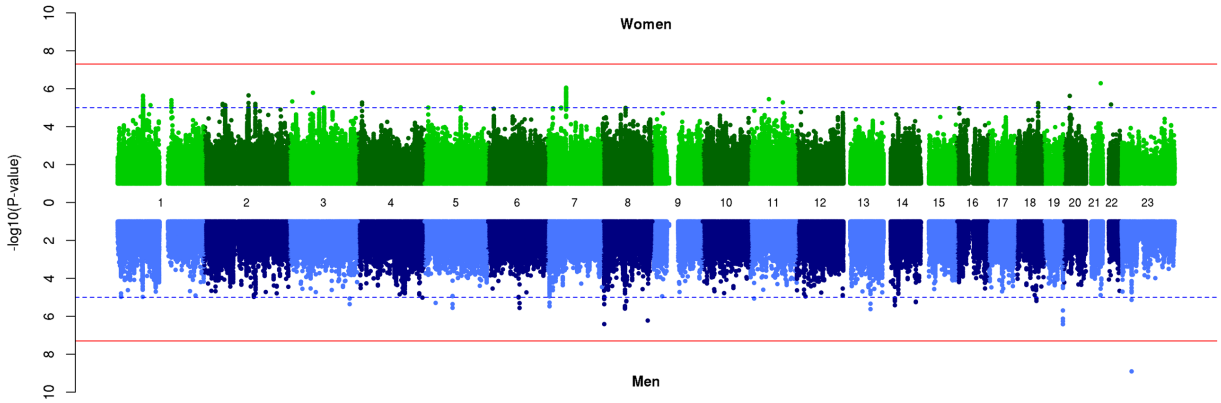
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia



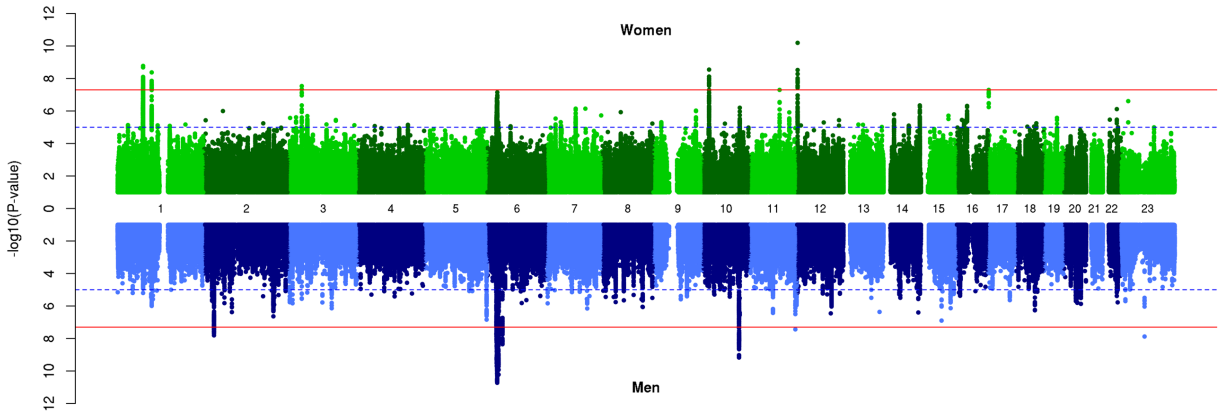
c) Bipolar Disorder



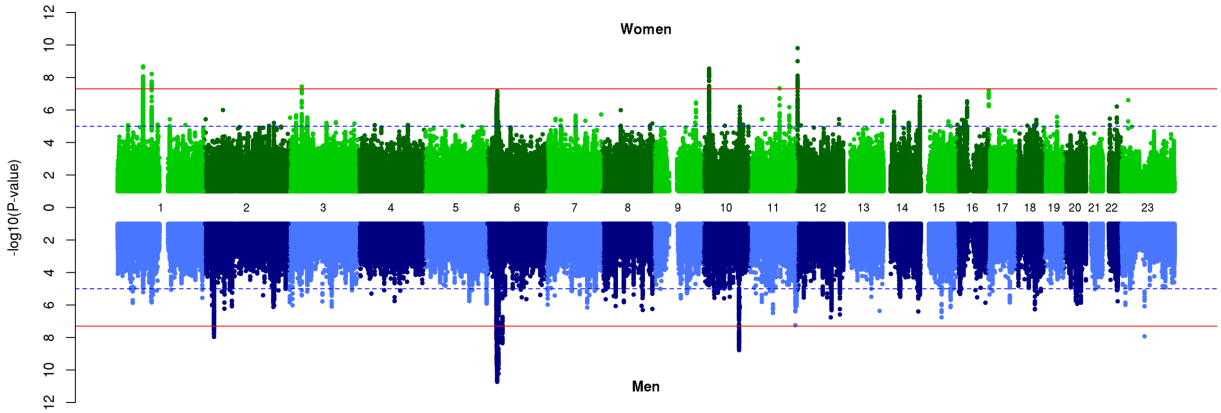
d) Major Depressive Disorder



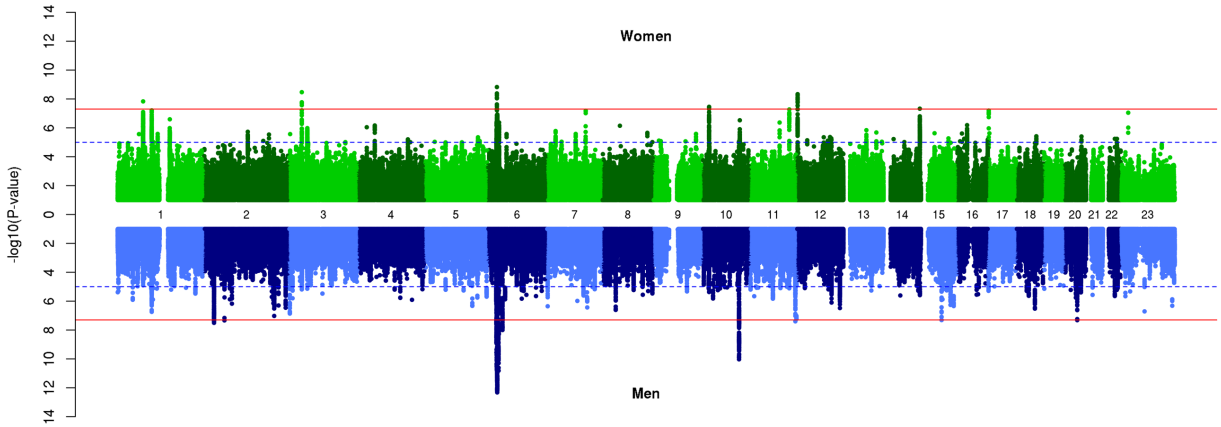
e) Cross-Disorder SCZ-BIP-MDD – European ancestry only



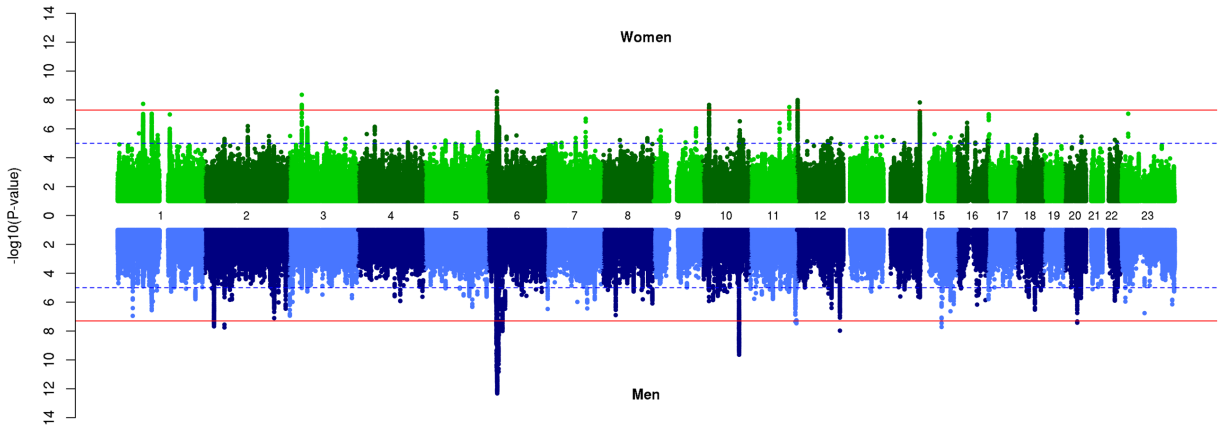
f) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



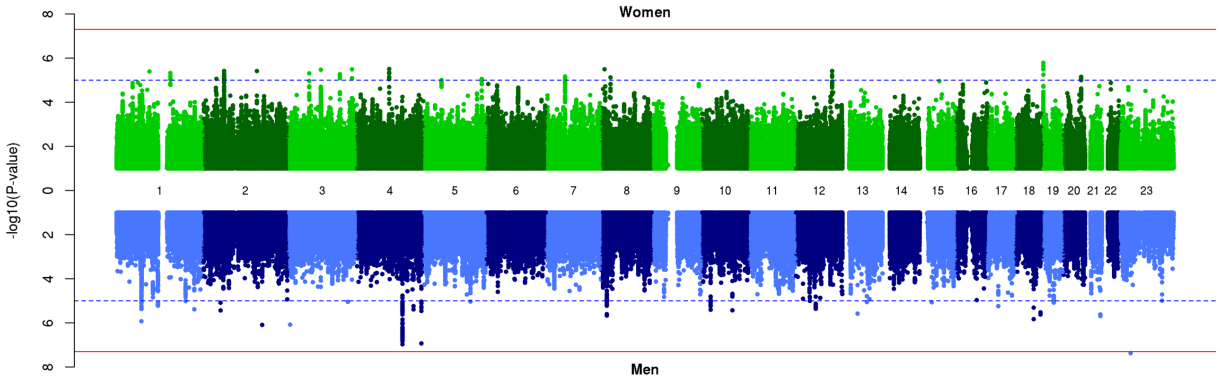
g) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



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



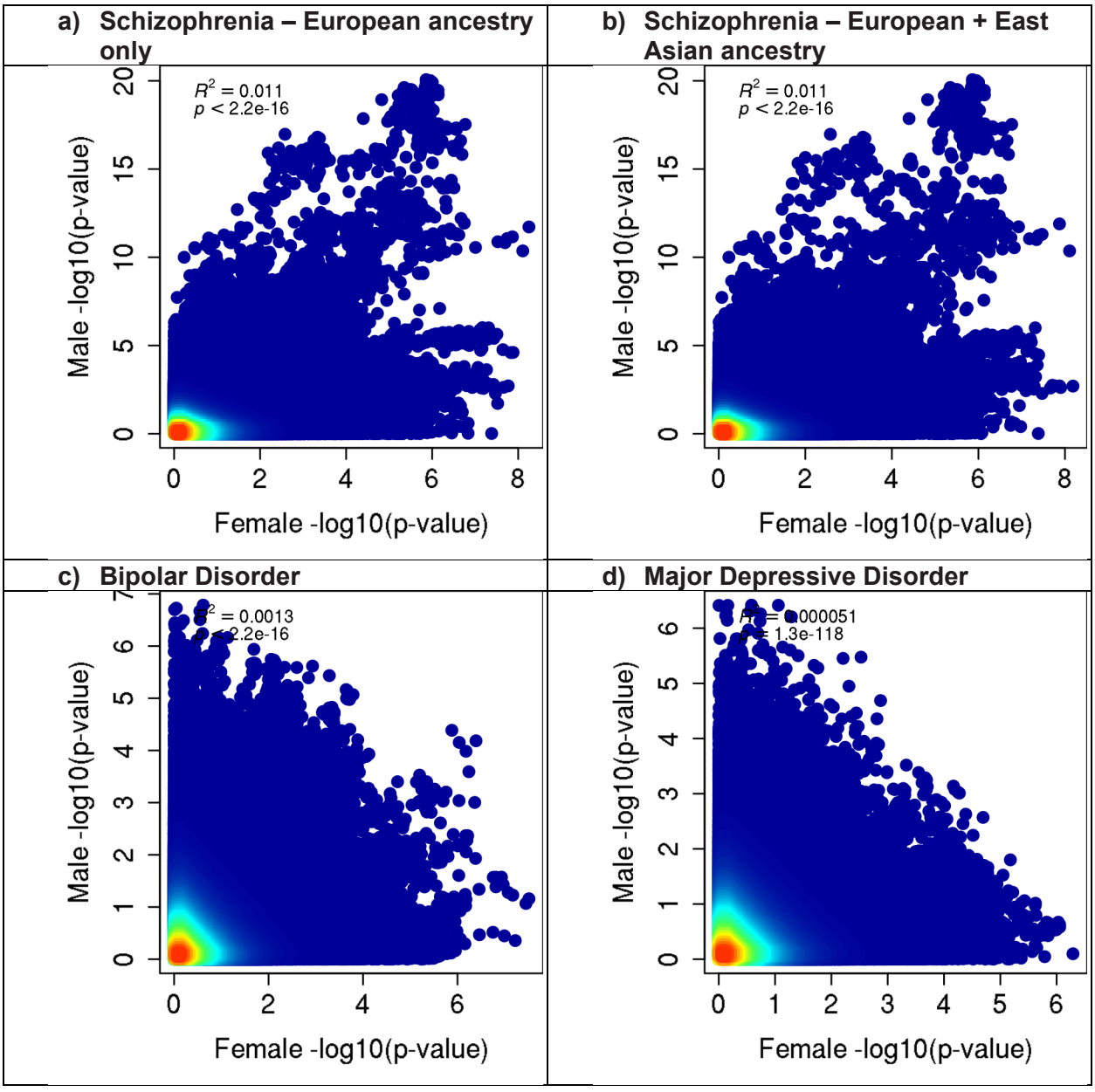
i) Recurrent Major Depressive Disorder



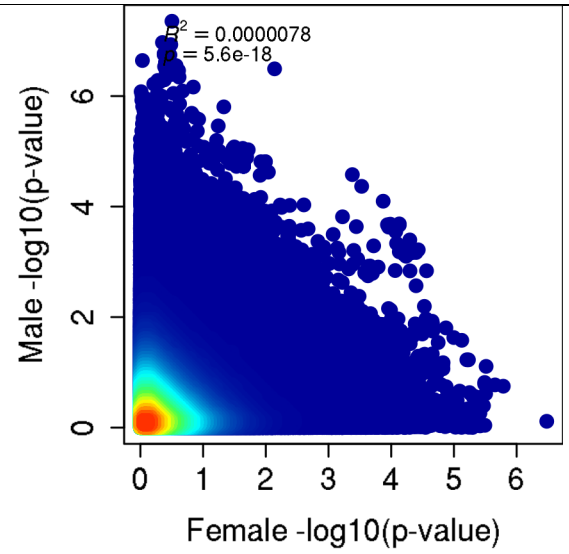
Supplementary Figure 4. Scatter plots of female vs male associations in PGC + iPSYCH

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.

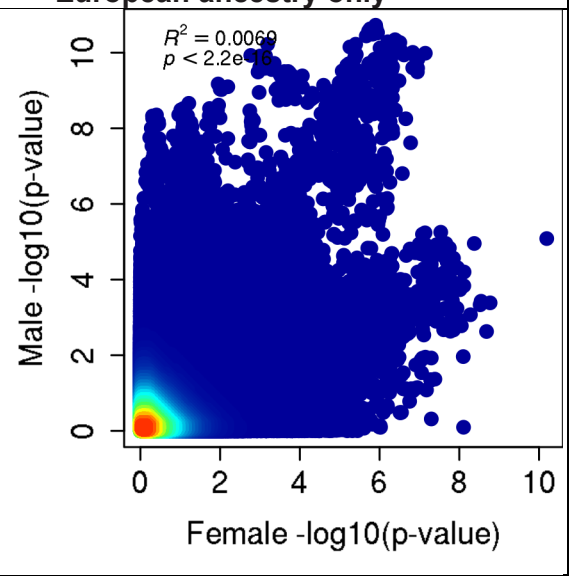
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; R^2 = proportion variance explained.



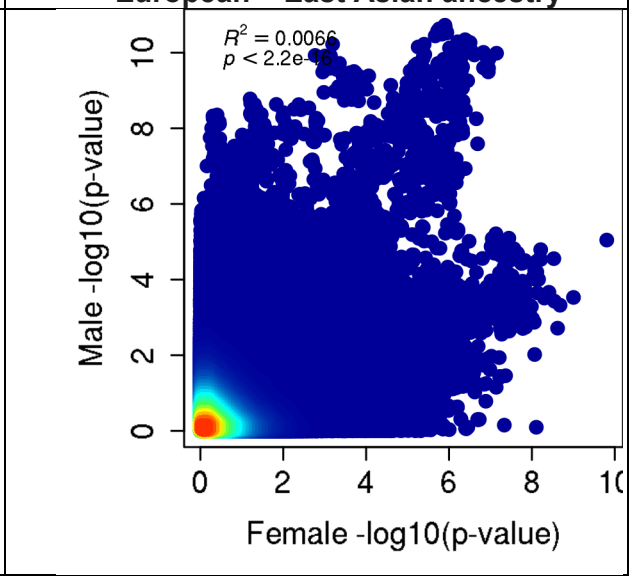
e) Recurrent Major Depressive Disorder

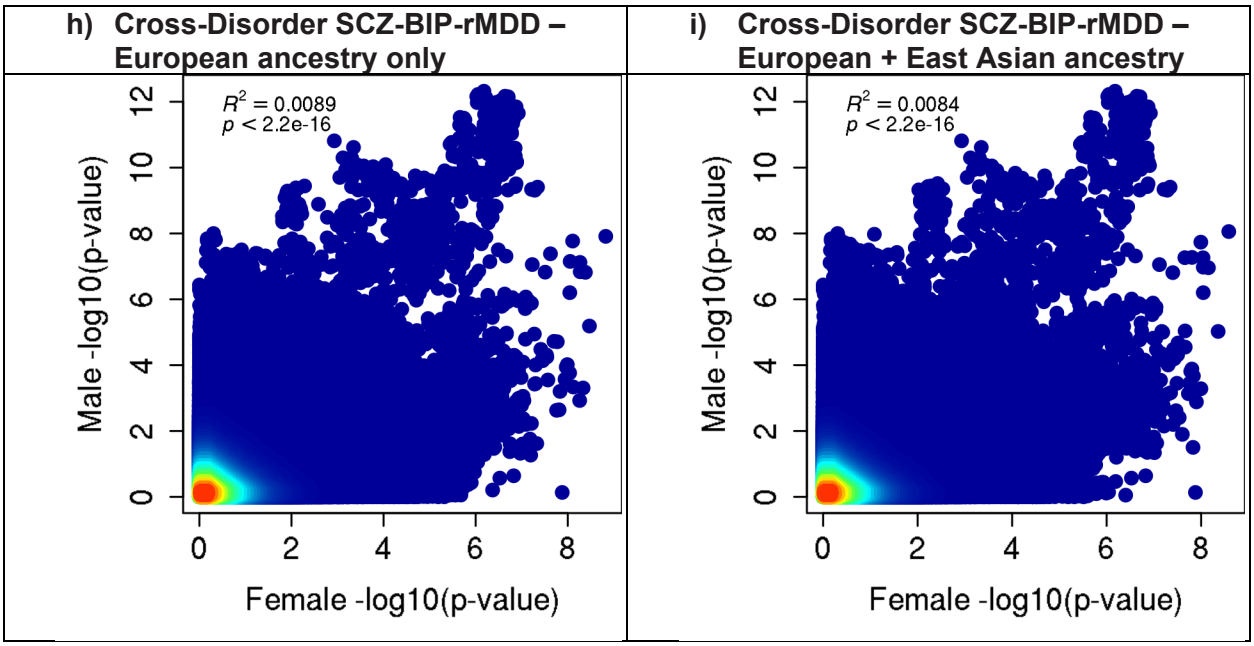


f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



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

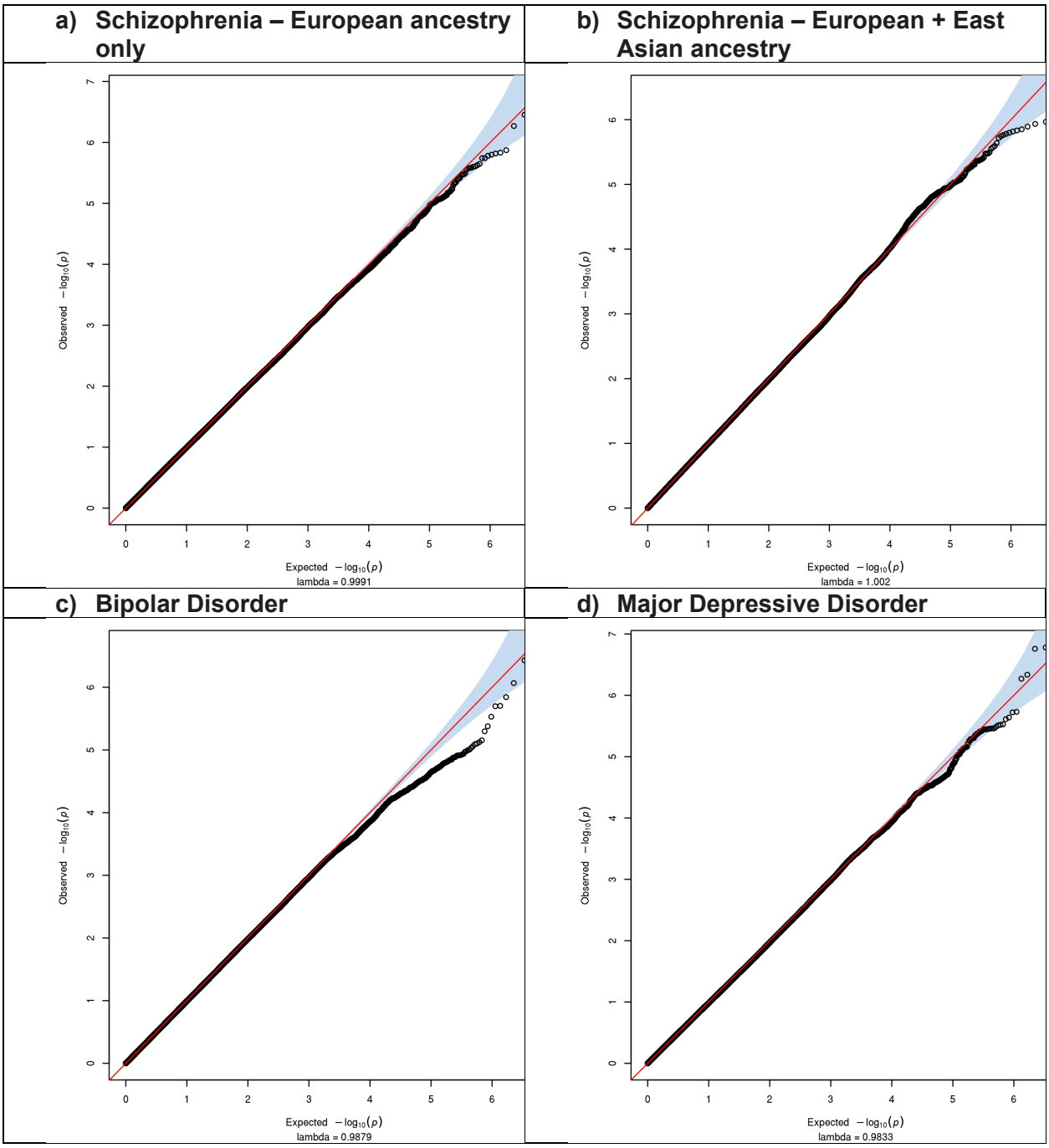



h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only
R^2 = 0.0089
p < 2.2e-16
Male -log10(p-value)
Female -log10(p-value)
0
2
4
6
8
10
12
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry
R^2 = 0.0084
p < 2.2e-16
Male -log10(p-value)
Female -log10(p-value)

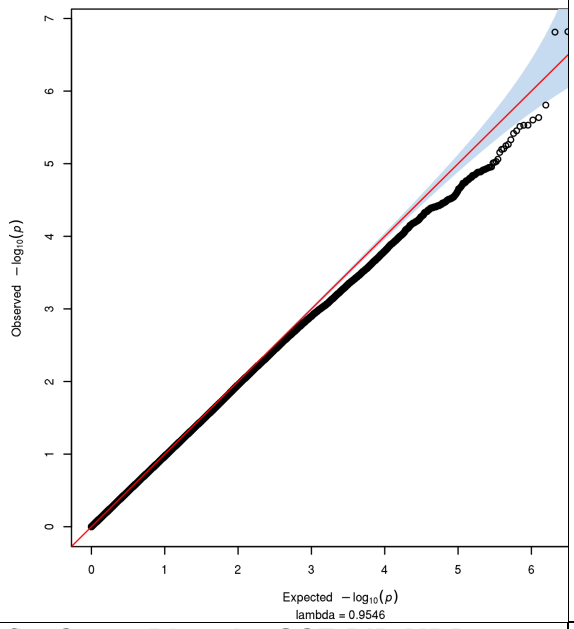
Supplementary Figure 5. Quantile-Quantile (Q-Q) plots for GxS interaction in PGC + iPSYCH

The 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.

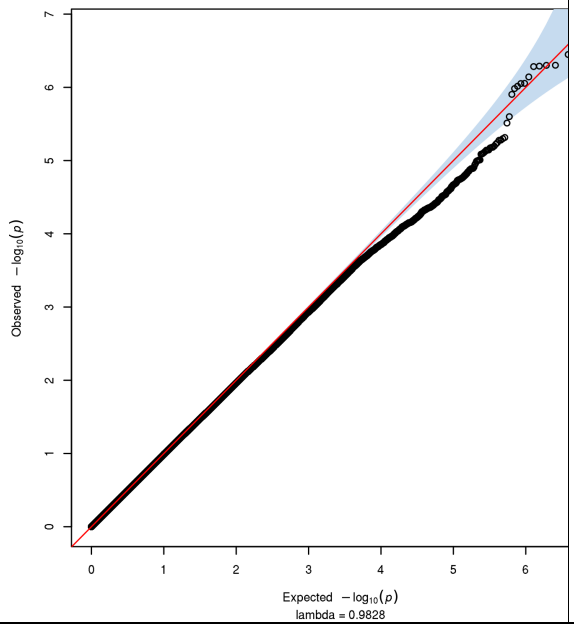
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia



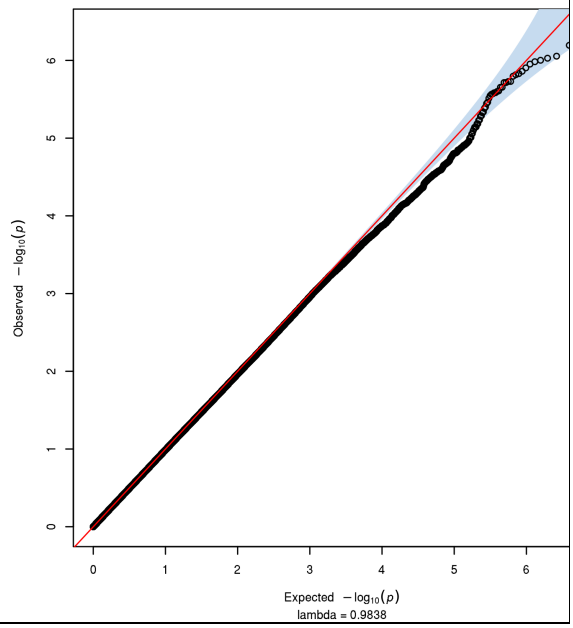
e) Recurrent Major Depressive Disorder



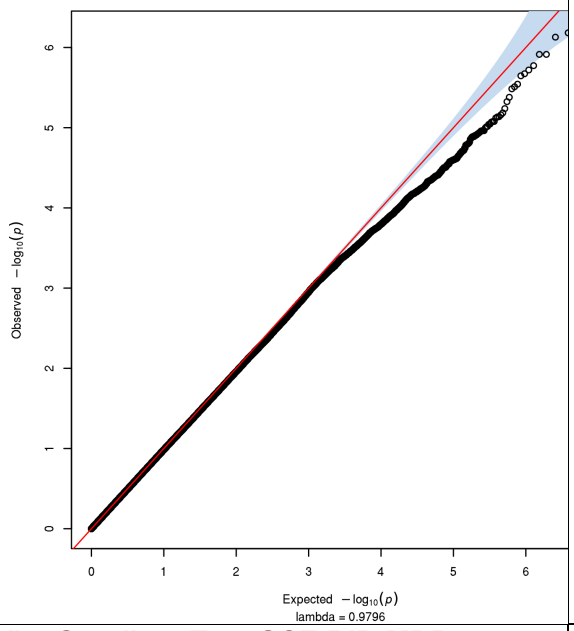
f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



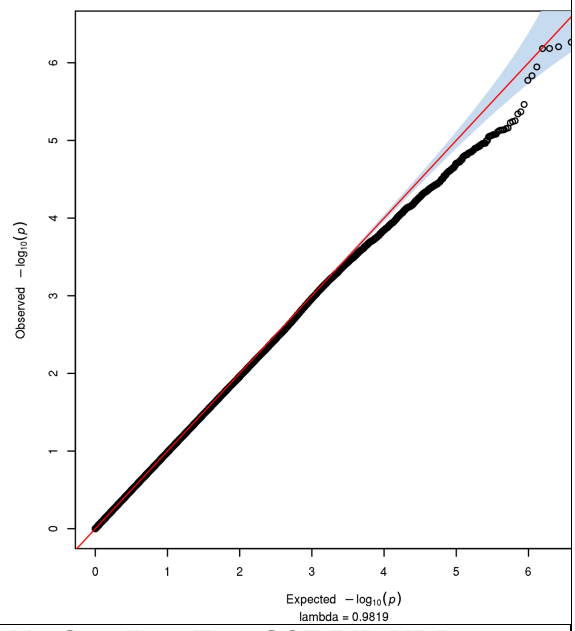
g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



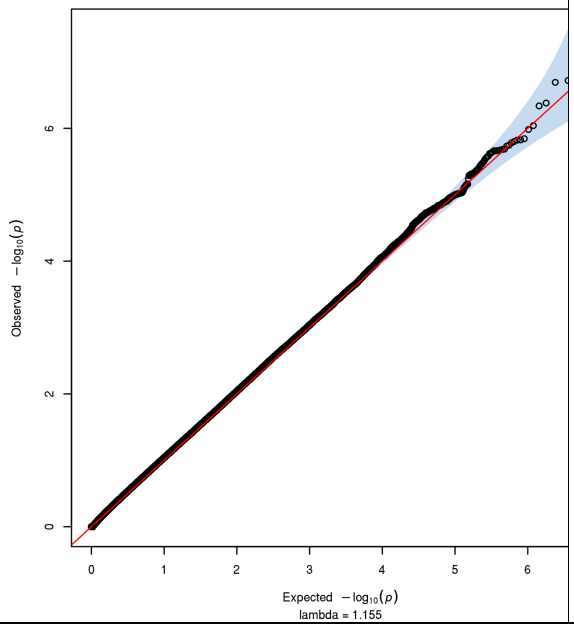
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



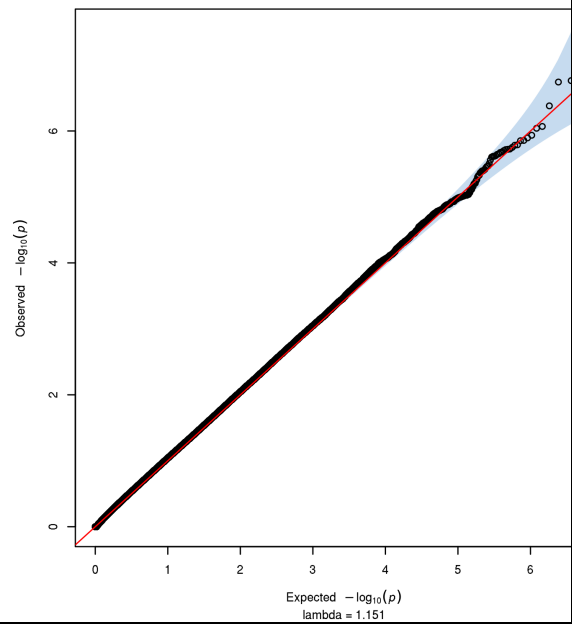
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry



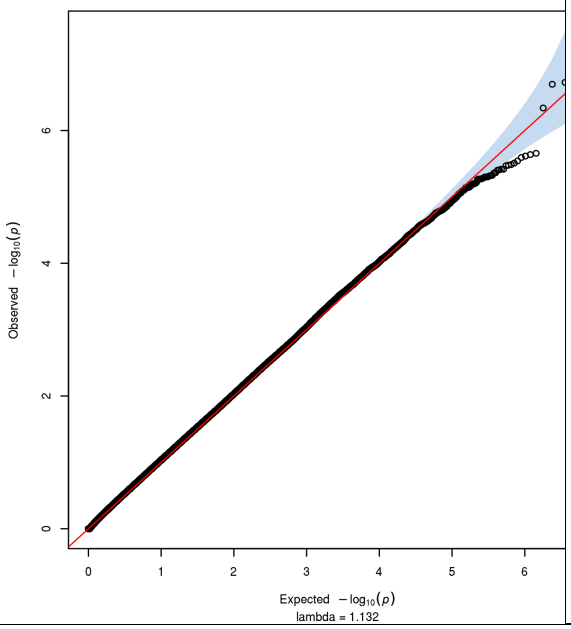
j) Omnibus Test SCZ-BIP-MDD – European ancestry only



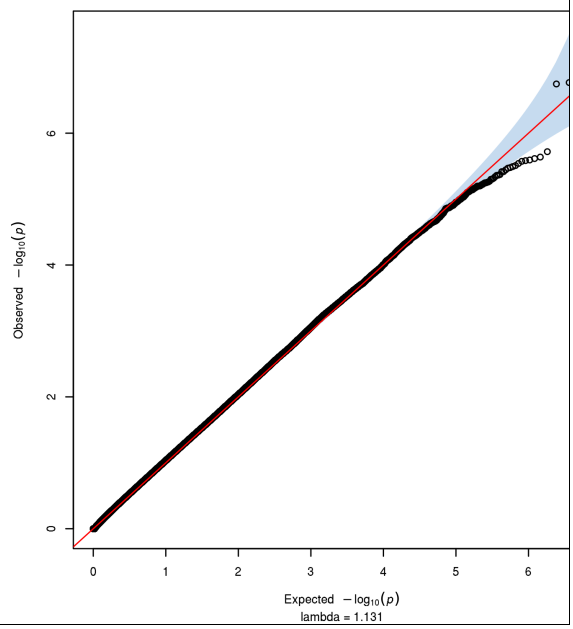
k) Omnibus Test SCZ-BIP-MDD – European + East Asian ancestry



l) Omnibus Test SCZ-BIP-rMDD – European ancestry only



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

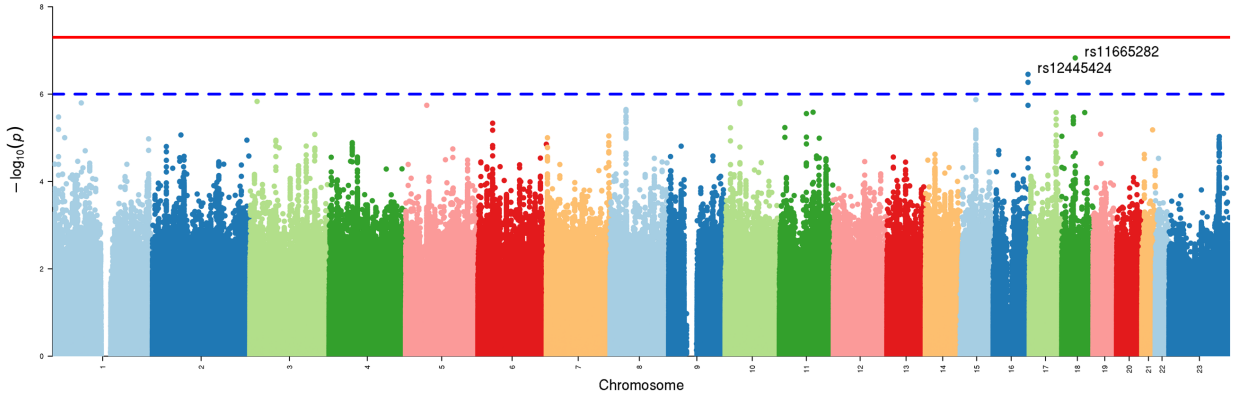


Supplementary Figure 6. Manhattan plots of the GxS interaction GWAS in PGC + iPSYCH

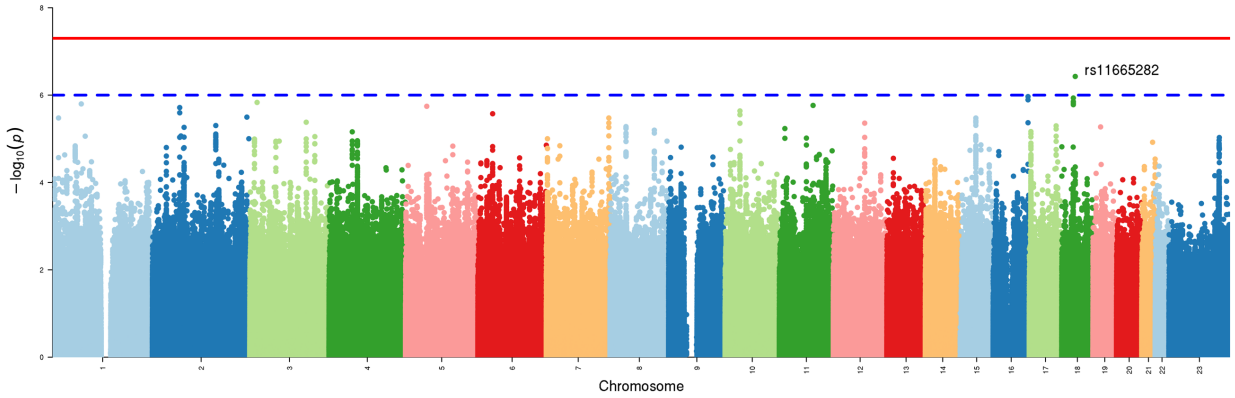
Negative log10-transformed p-values for each variant (each dot) (y-axis) are plotted by chromosomal position (x-axis). The red and blue lines represent the thresholds for genome-wide significant association ($p = 5\times10^{-8}$) and suggestive association ($p = 1\times10^{-5}$), respectively. P-values 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

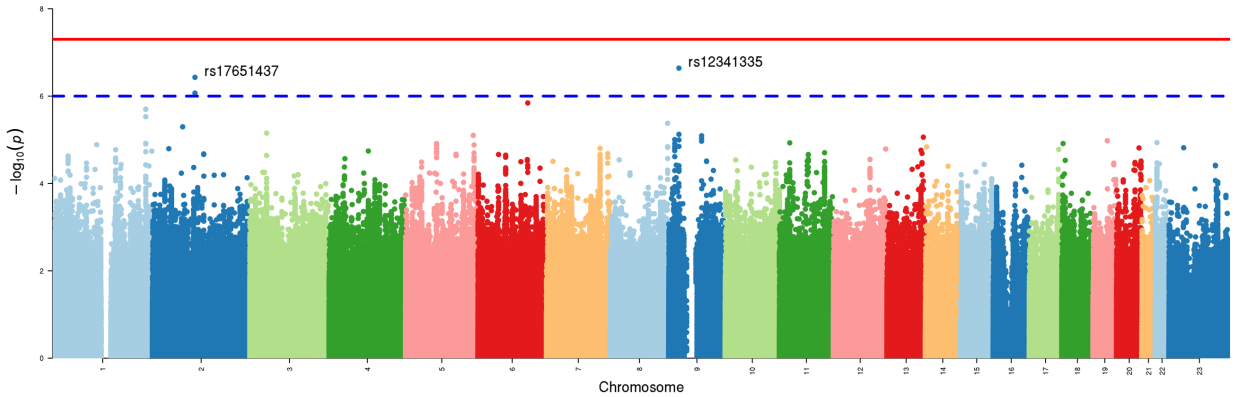
a) Schizophrenia – European ancestry only



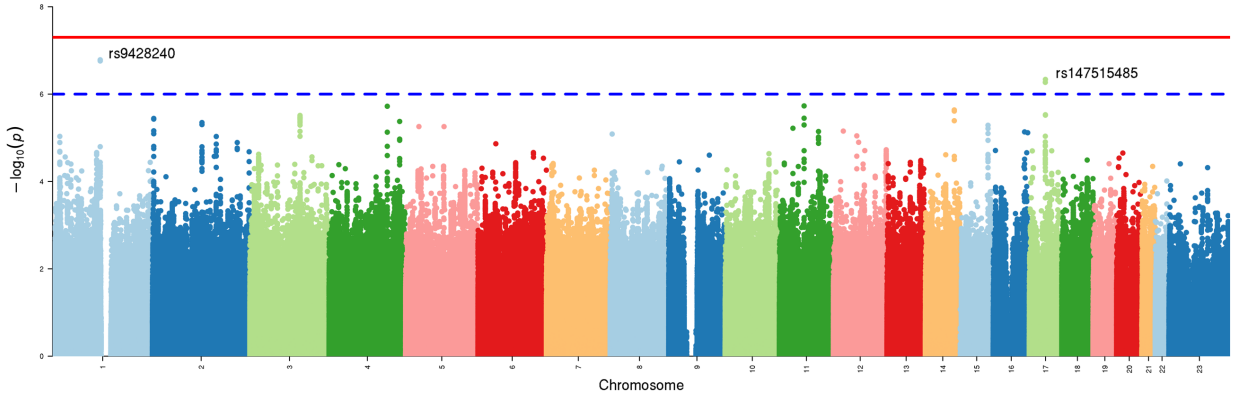
b) Schizophrenia – European + East Asian ancestry



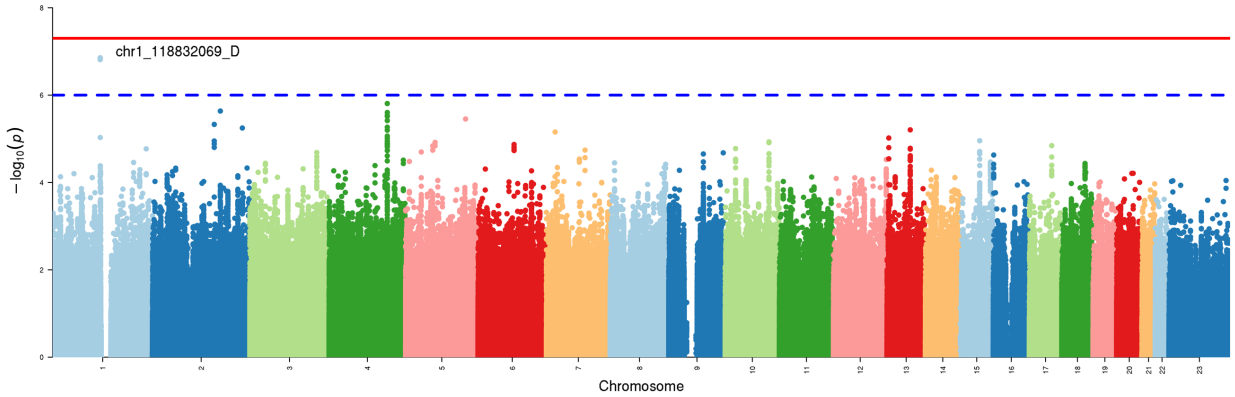
c) Bipolar Disorder



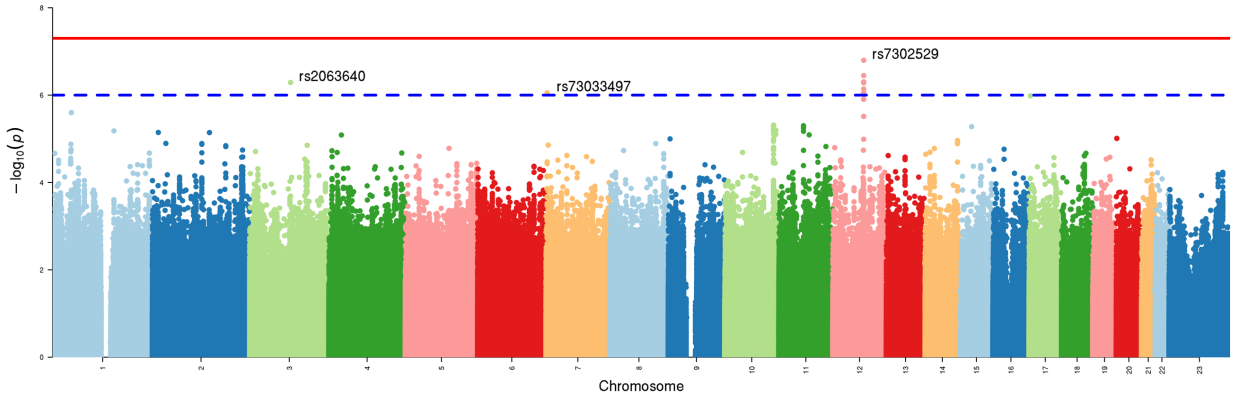
d) Major Depressive Disorder



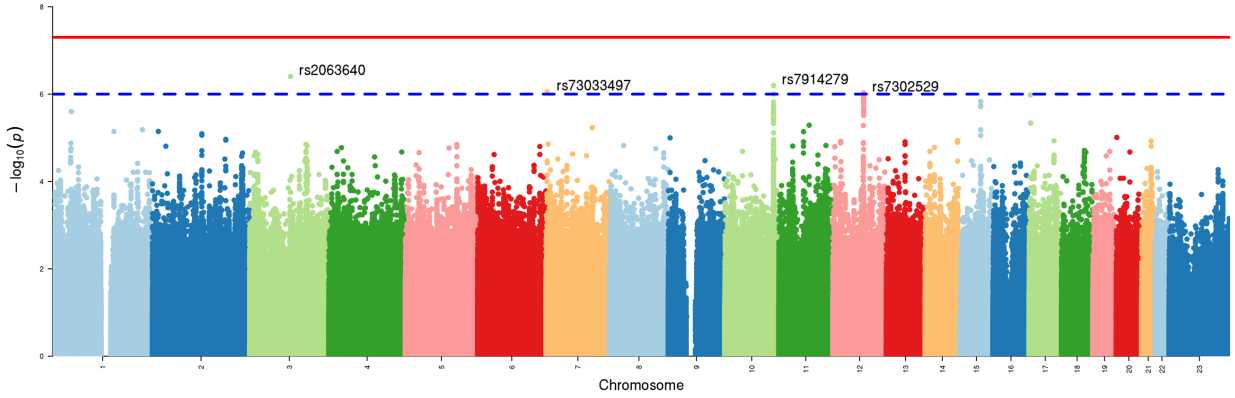
e) Recurrent Major Depressive Disorders



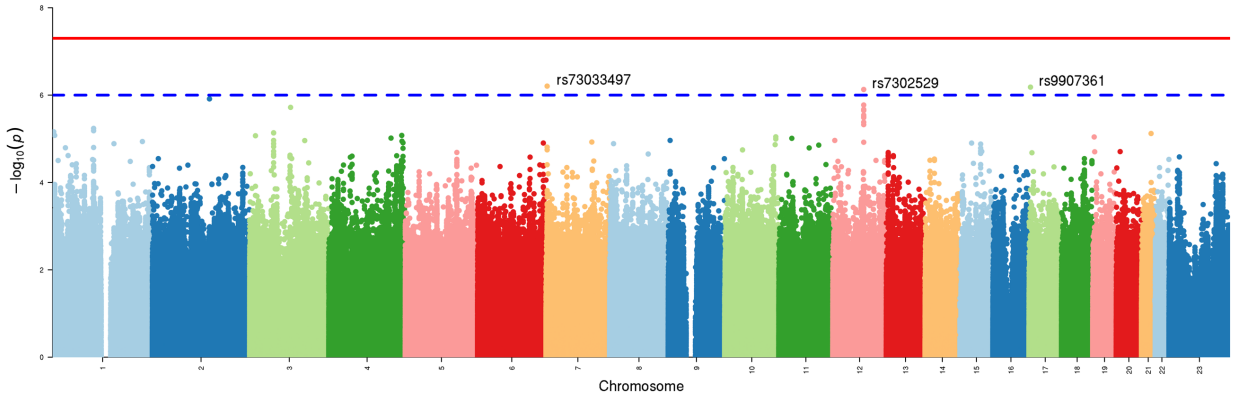
f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



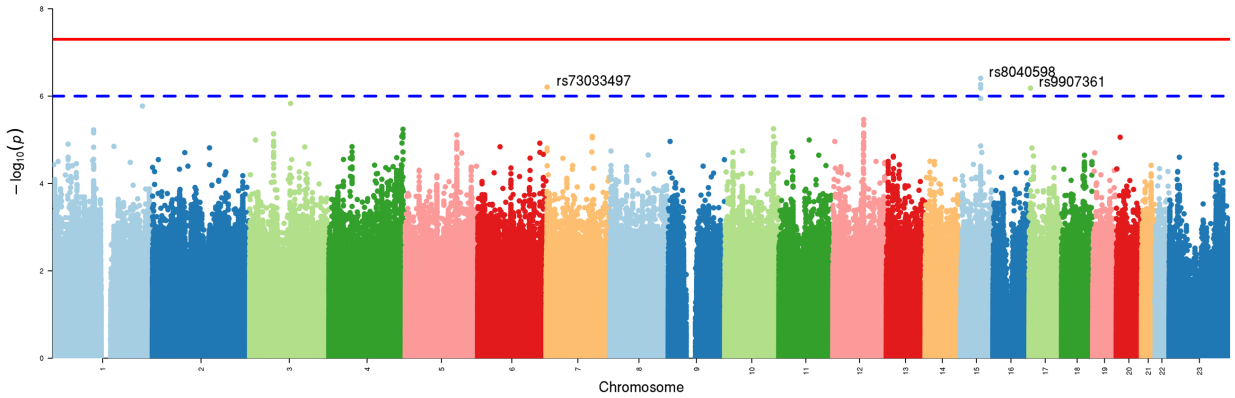
g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



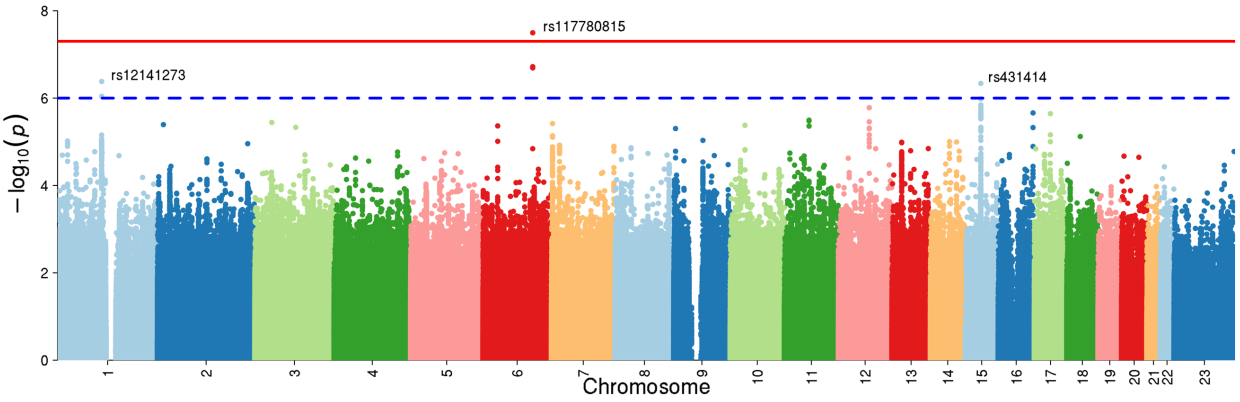
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



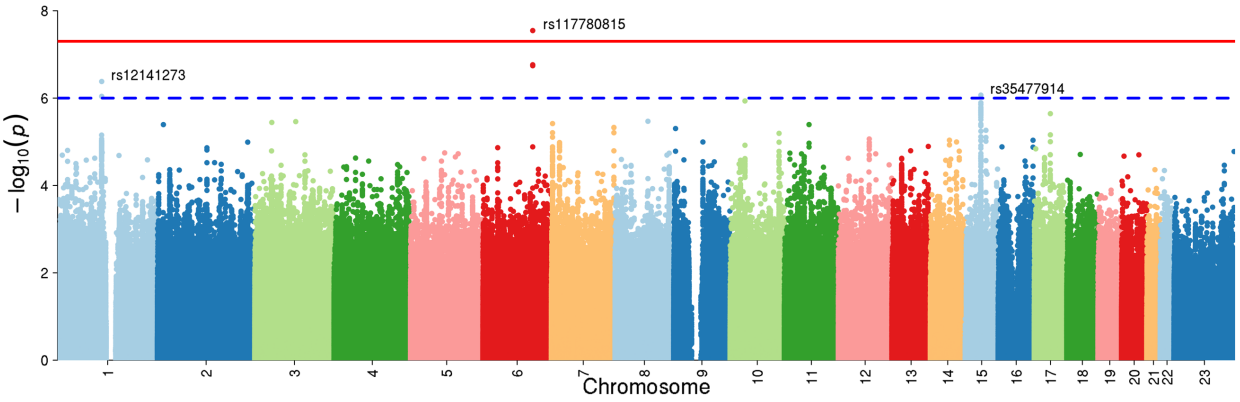
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry



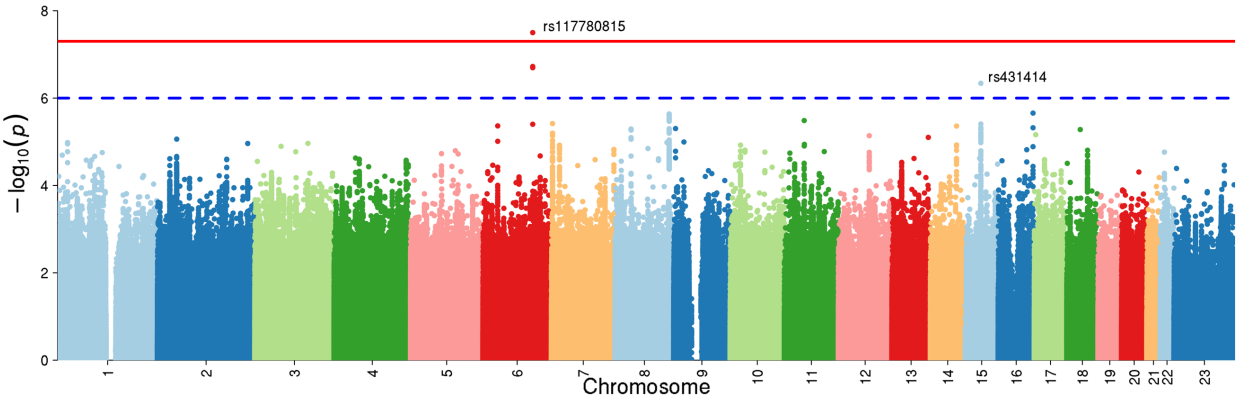
j) Omnibus Test SCZ-BIP-MDD – European ancestry only



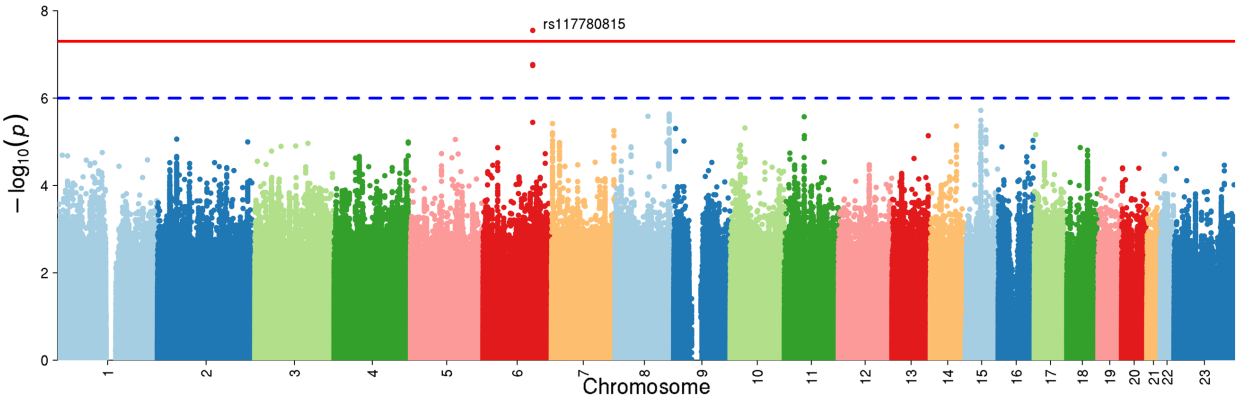
k) Omnibus Test SCZ-BIP-MDD – European + East Asian ancestry



l) Omnibus Test SCZ-BIP-rMDD – European ancestry only



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

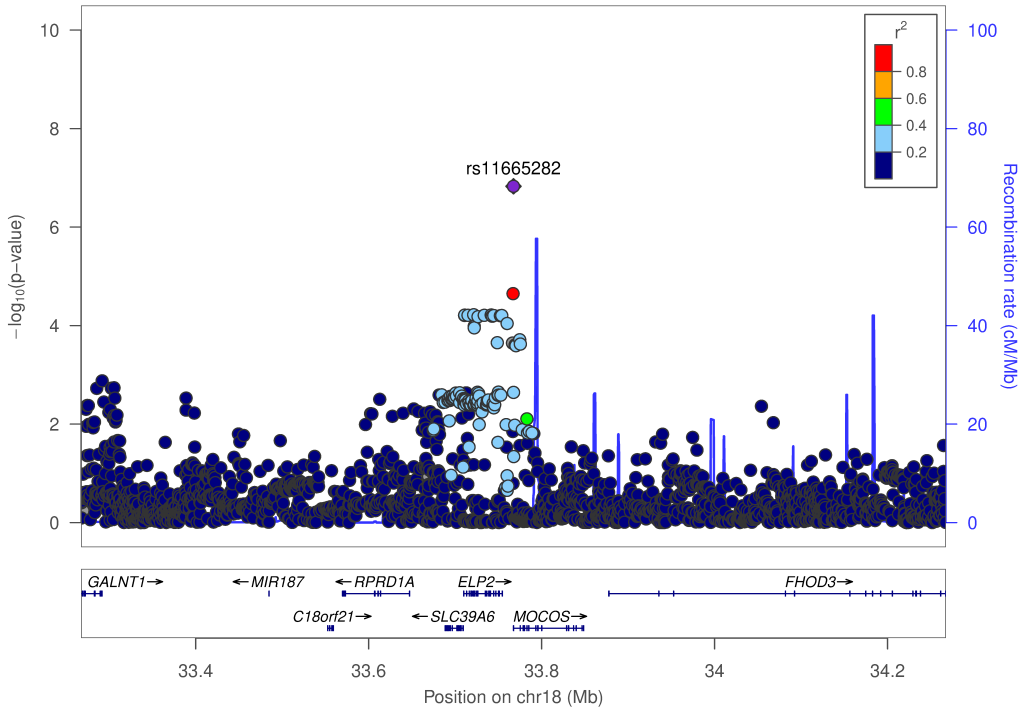


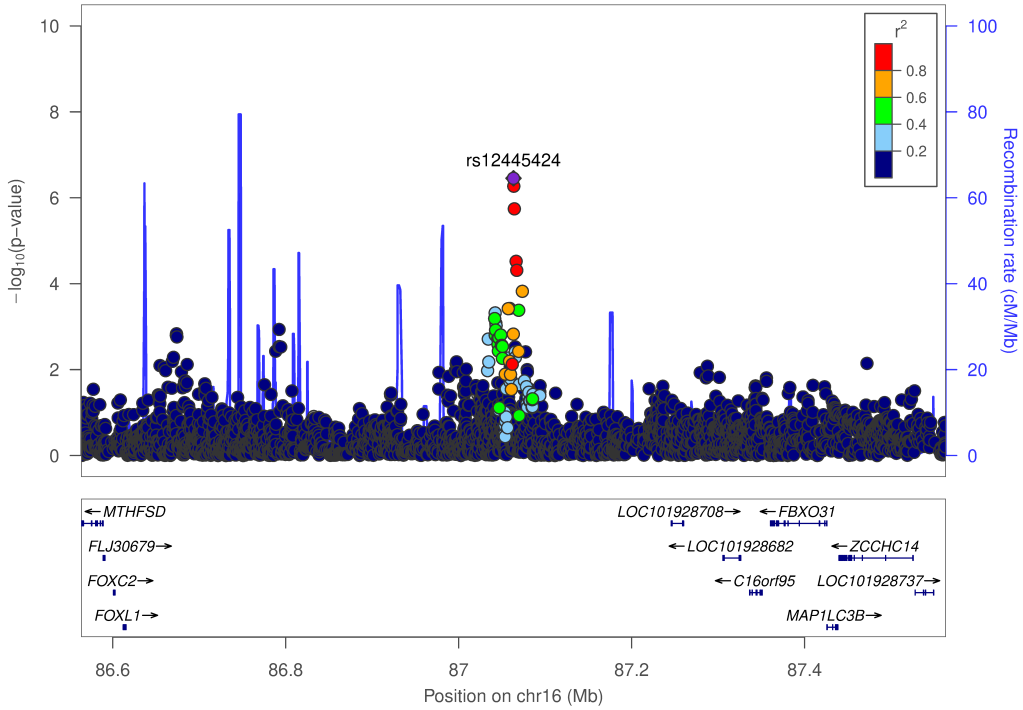
Supplementary Figure 7. LocusZoom plots for loci with GxS interaction in PGC + iPSYCH

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

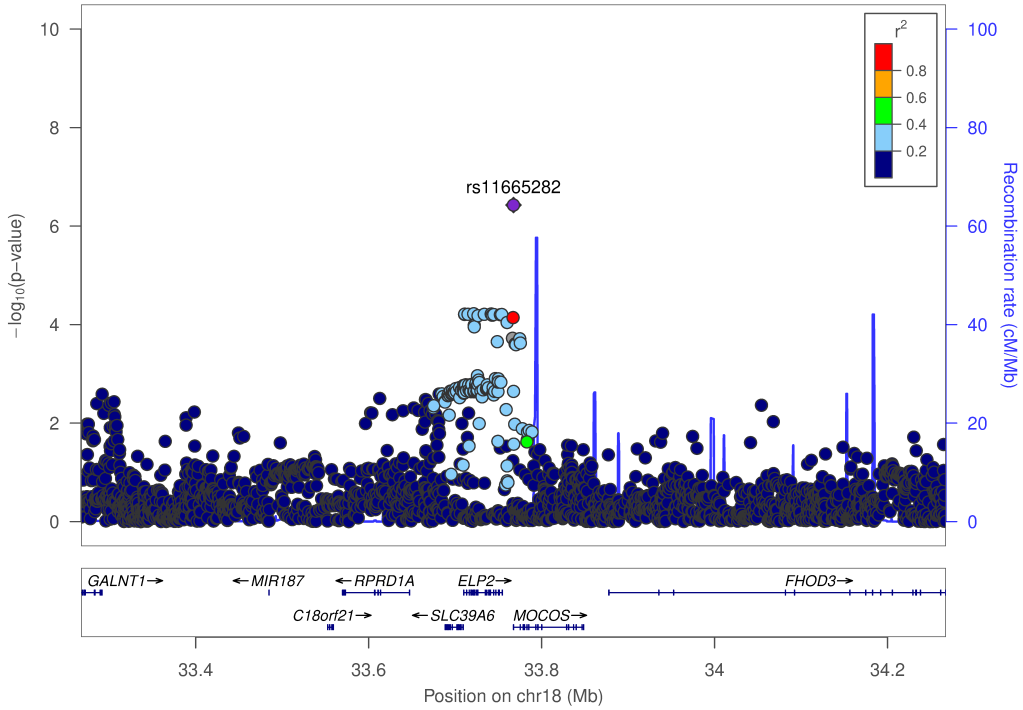
Abbreviations: chr = chromosome; cM = centimorgans; Mb = megabases; r^2 = linkage disequilibrium level; BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia

a) Schizophrenia – European ancestry only

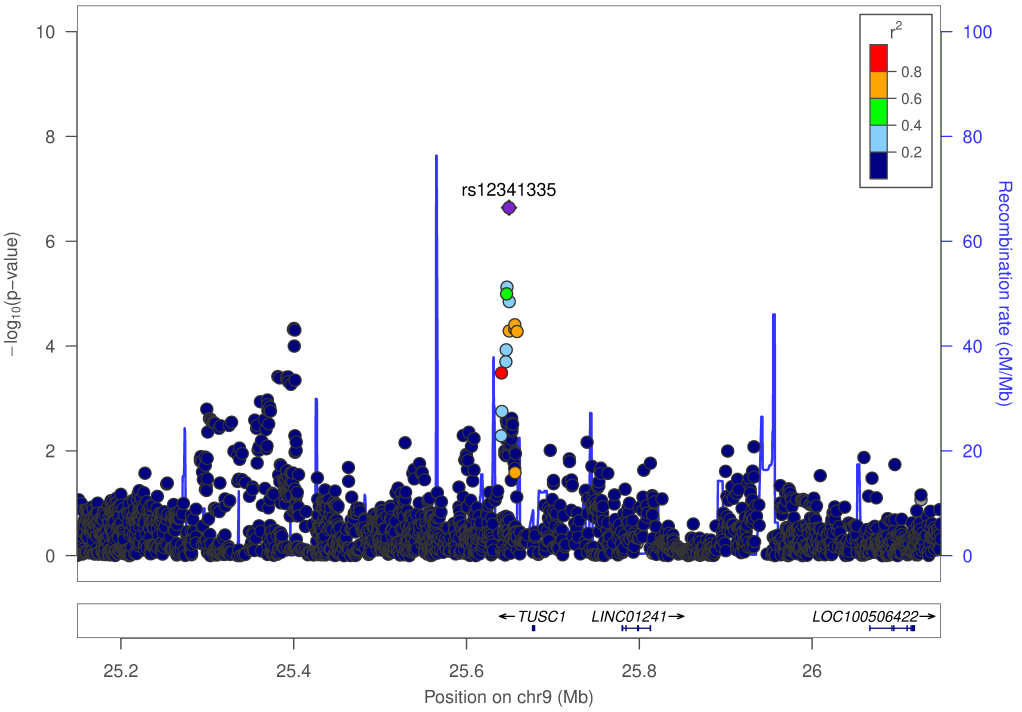


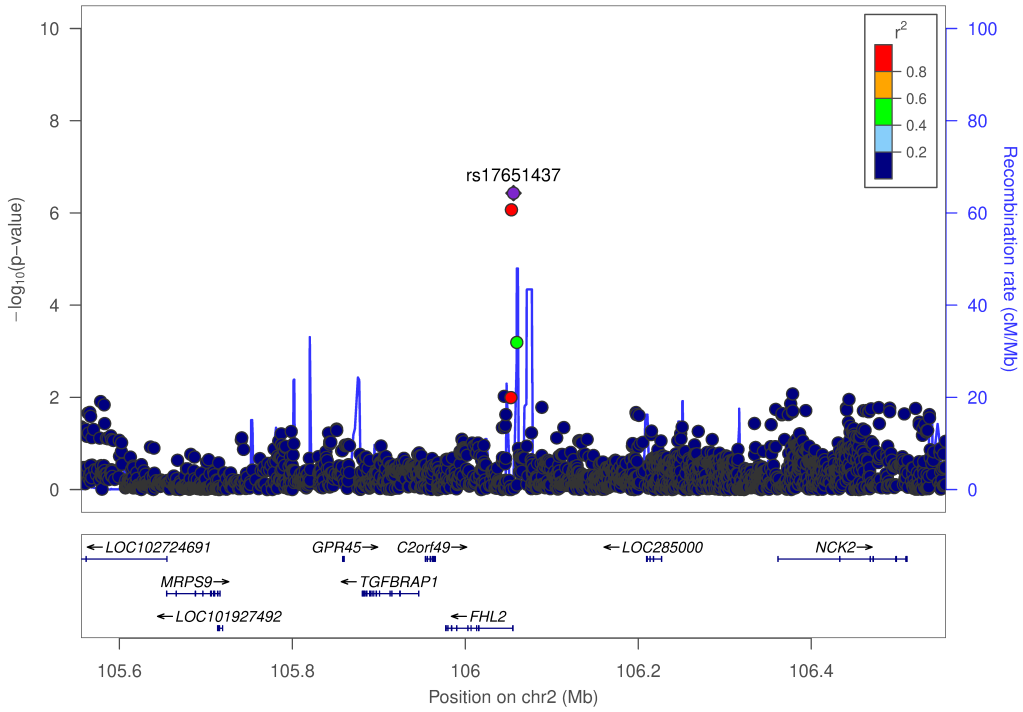


b) Schizophrenia – European + East Asian ancestry

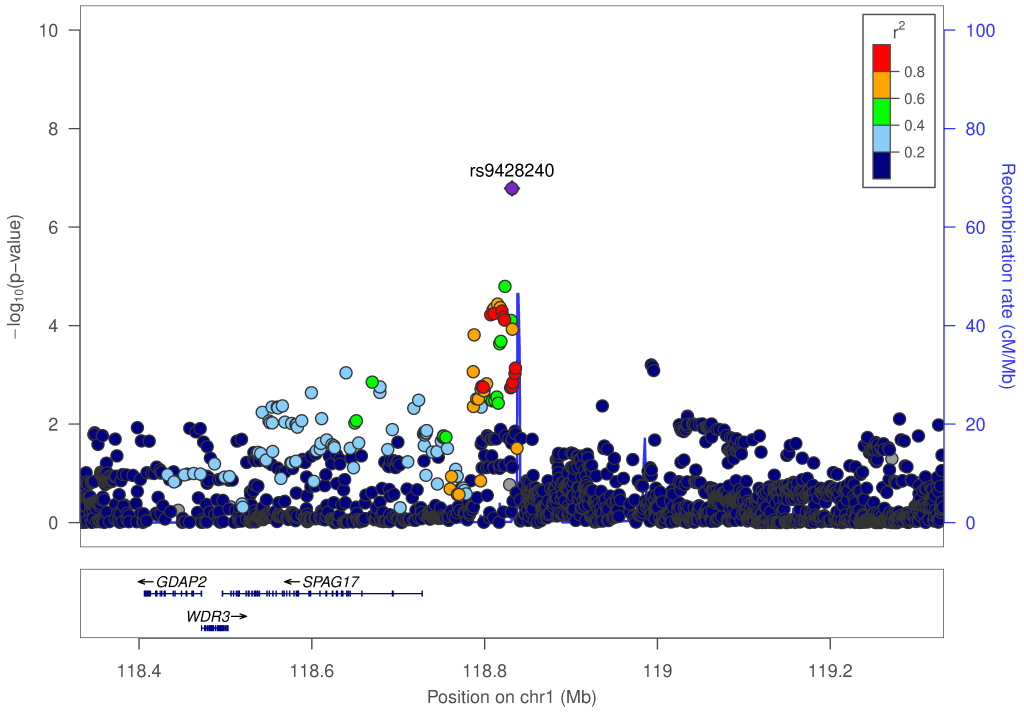


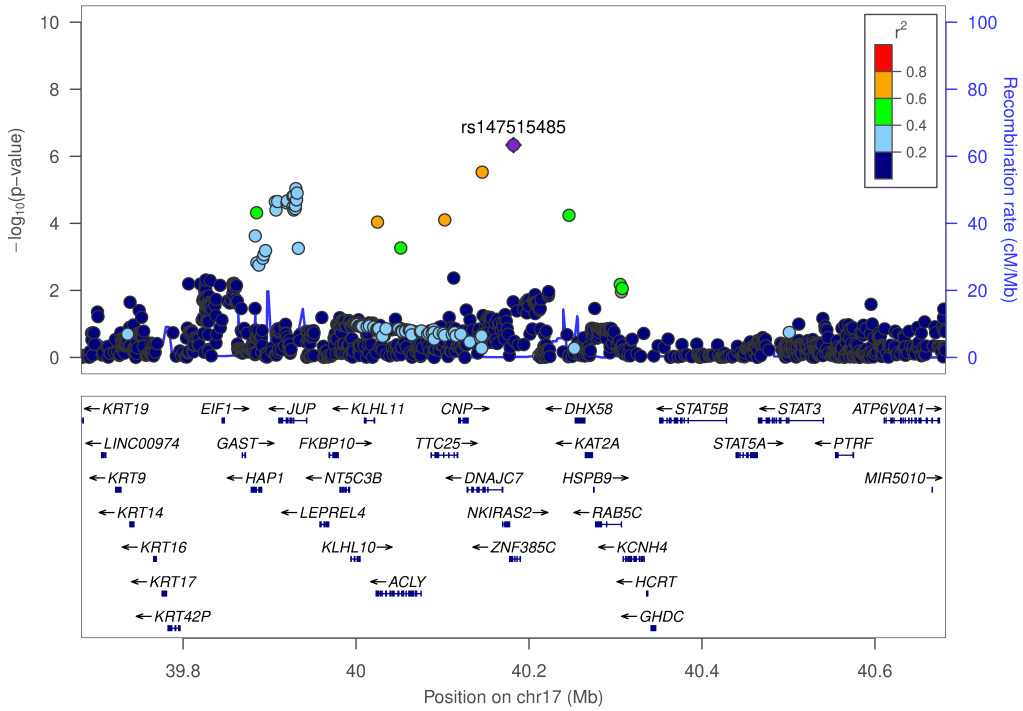
c) Bipolar Disorder



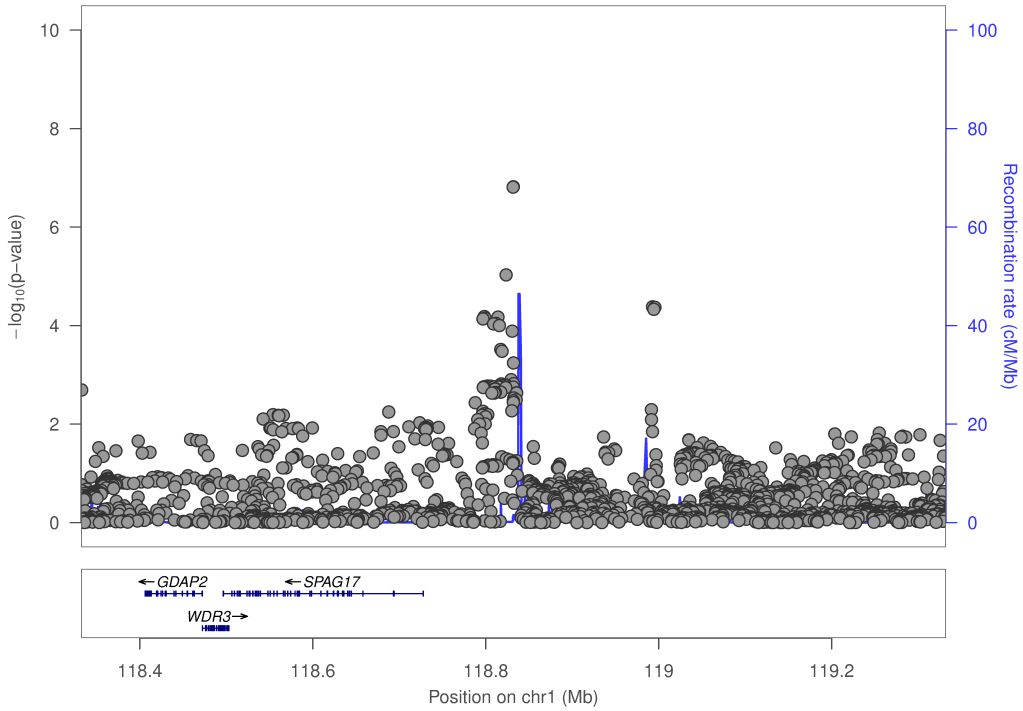


d) Major Depressive Disorder

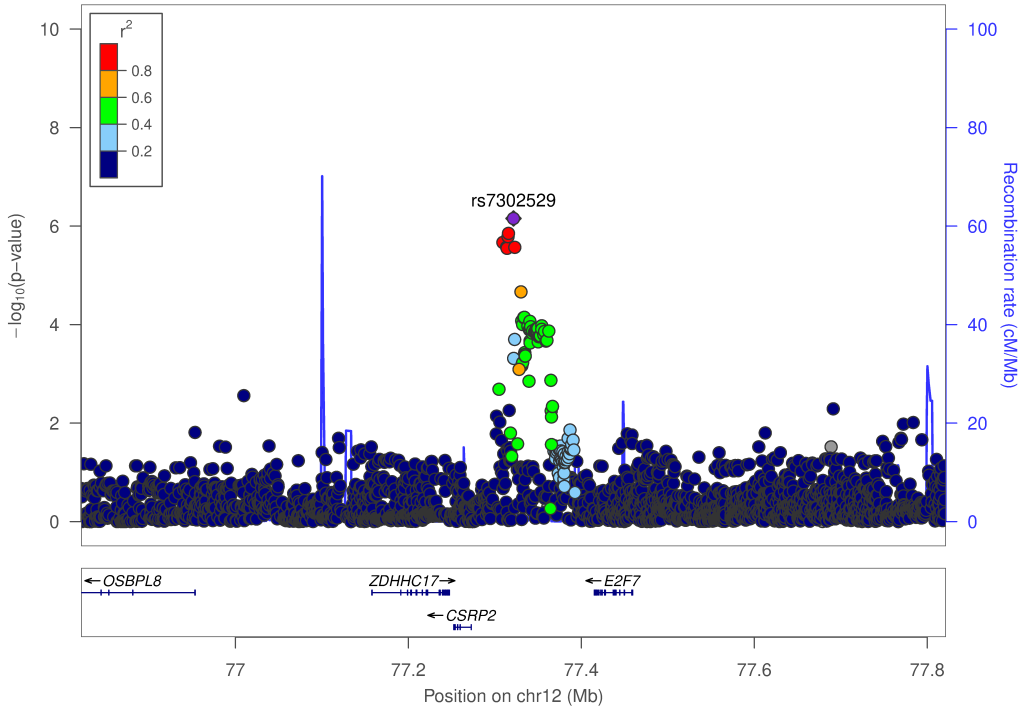


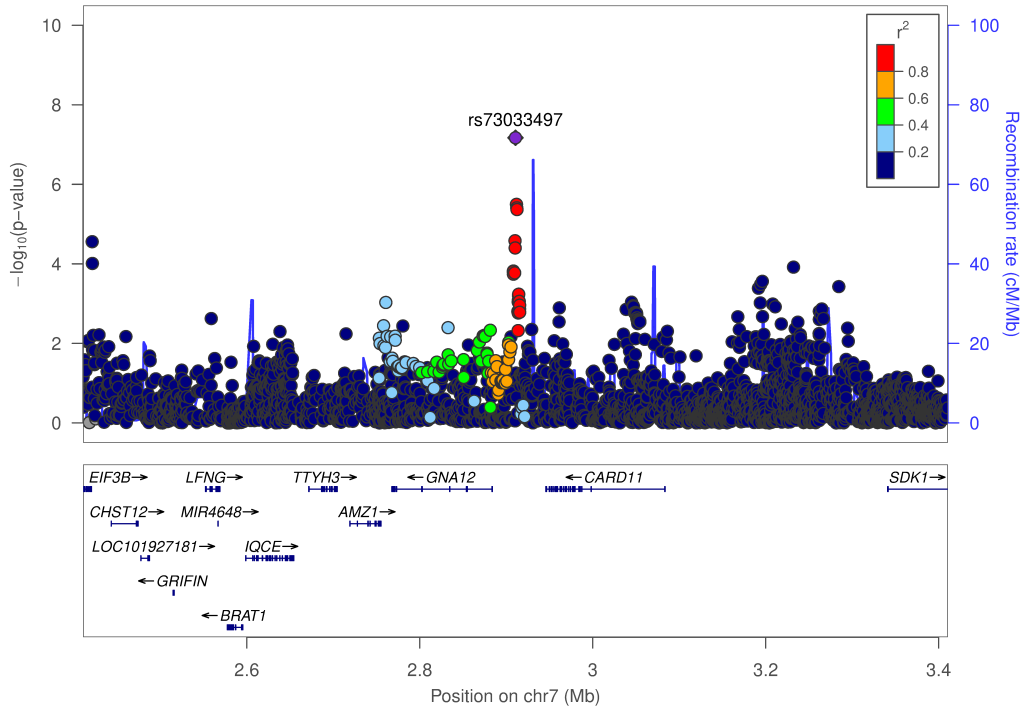


e) Recurrent Major Depressive Disorder

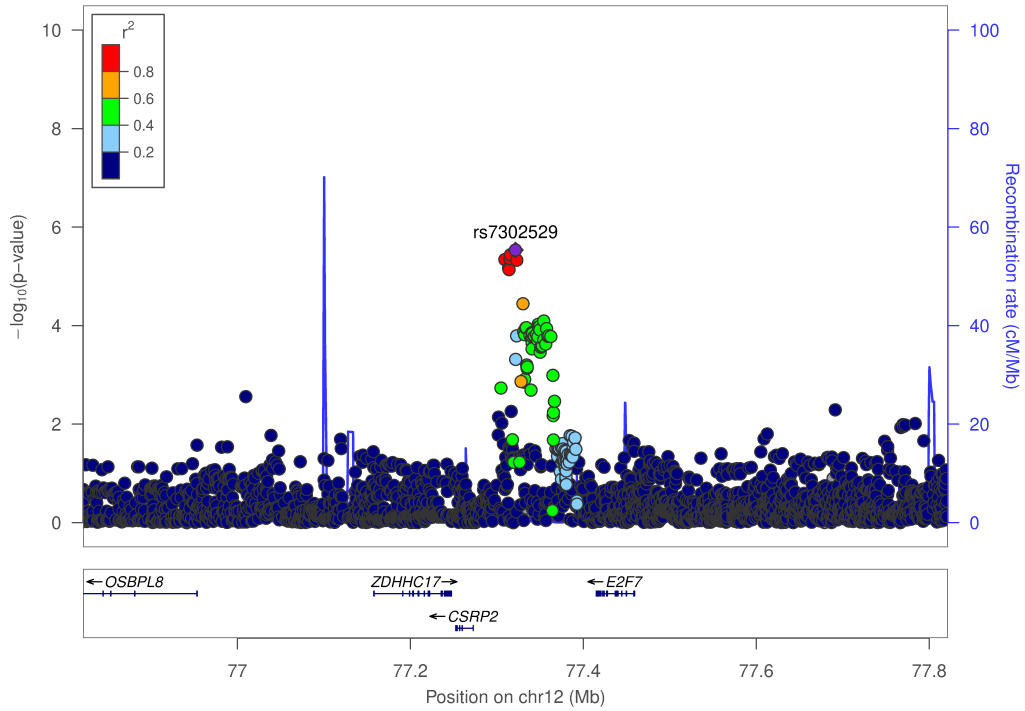


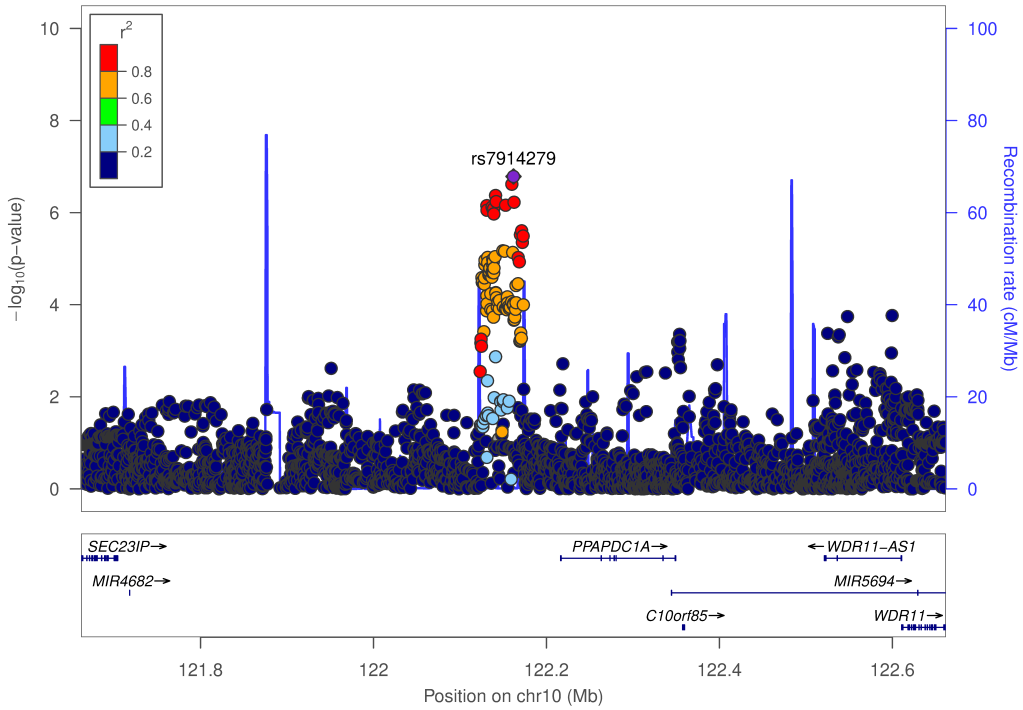
f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



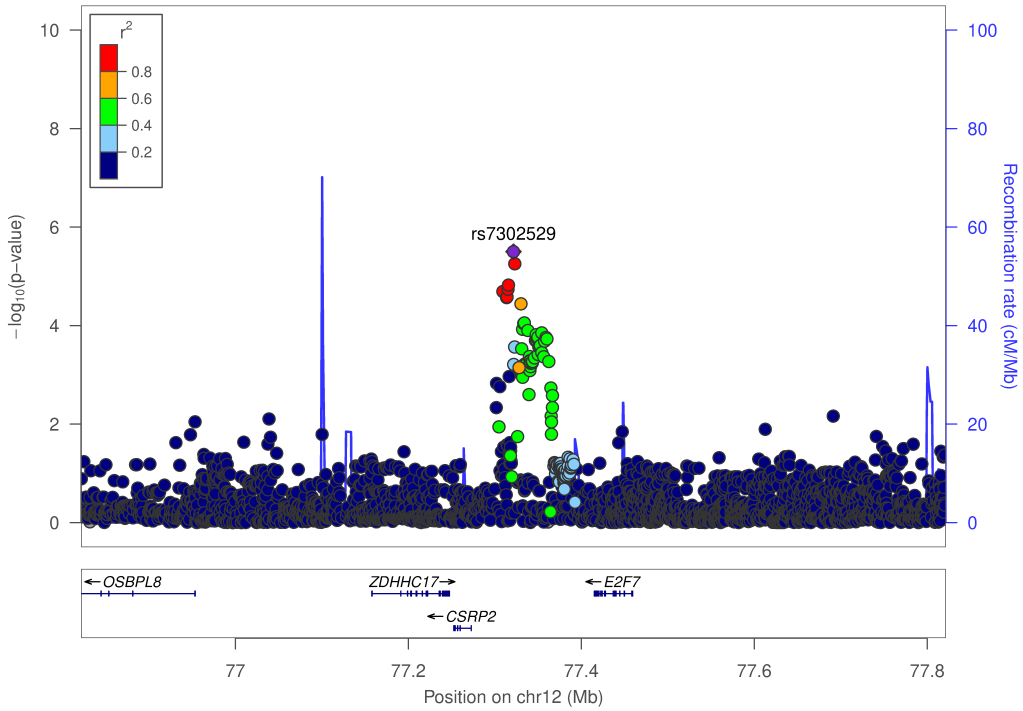


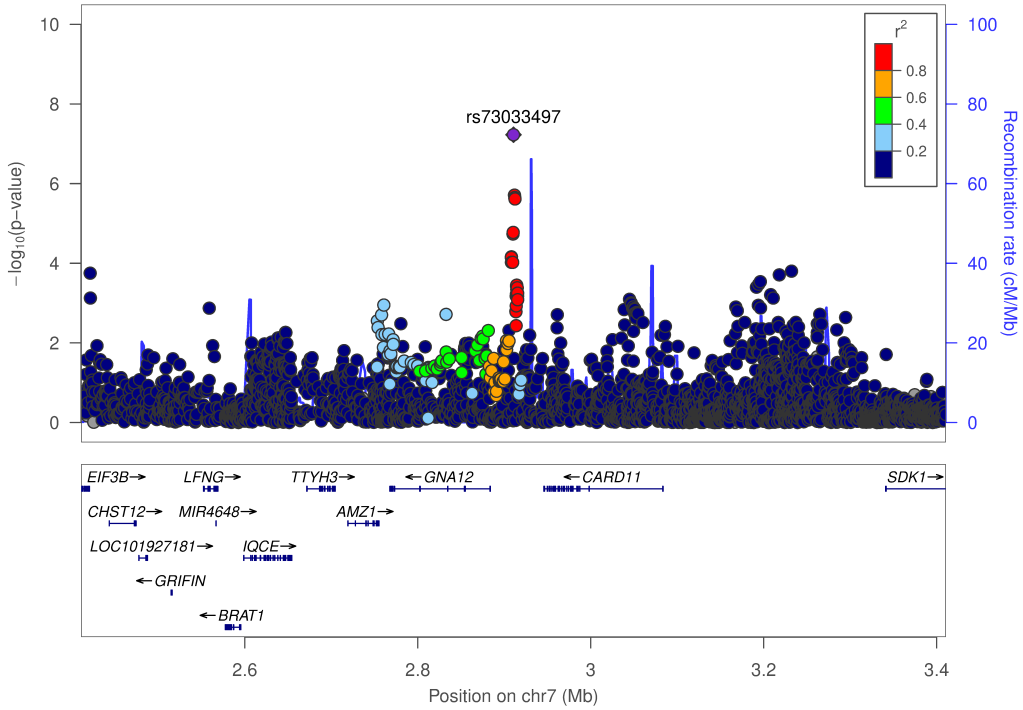
g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



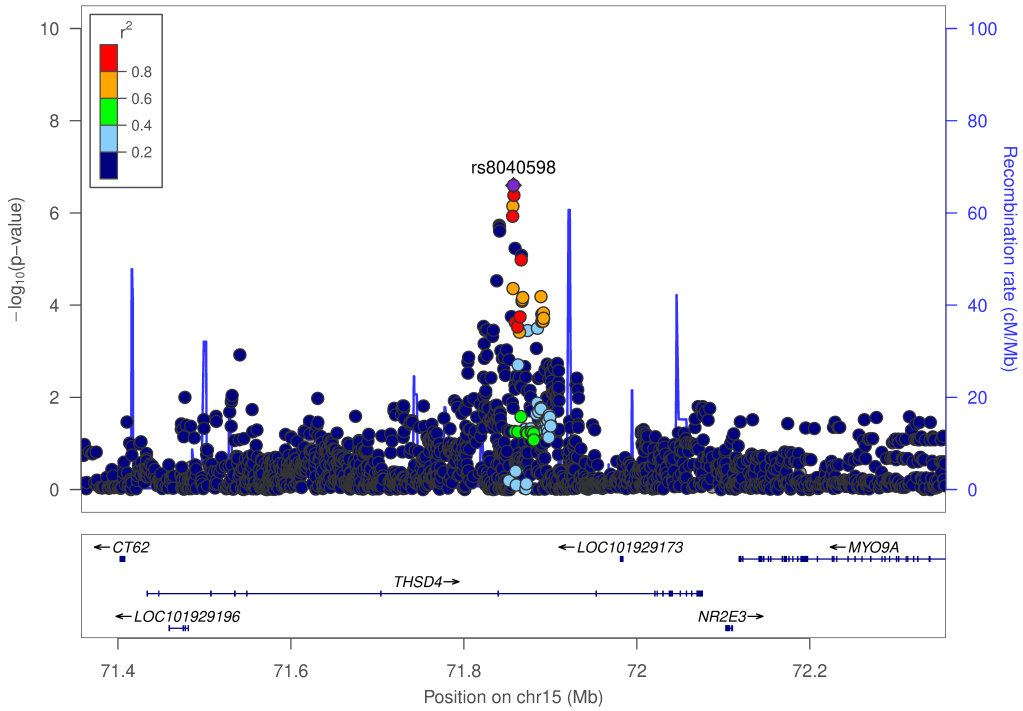


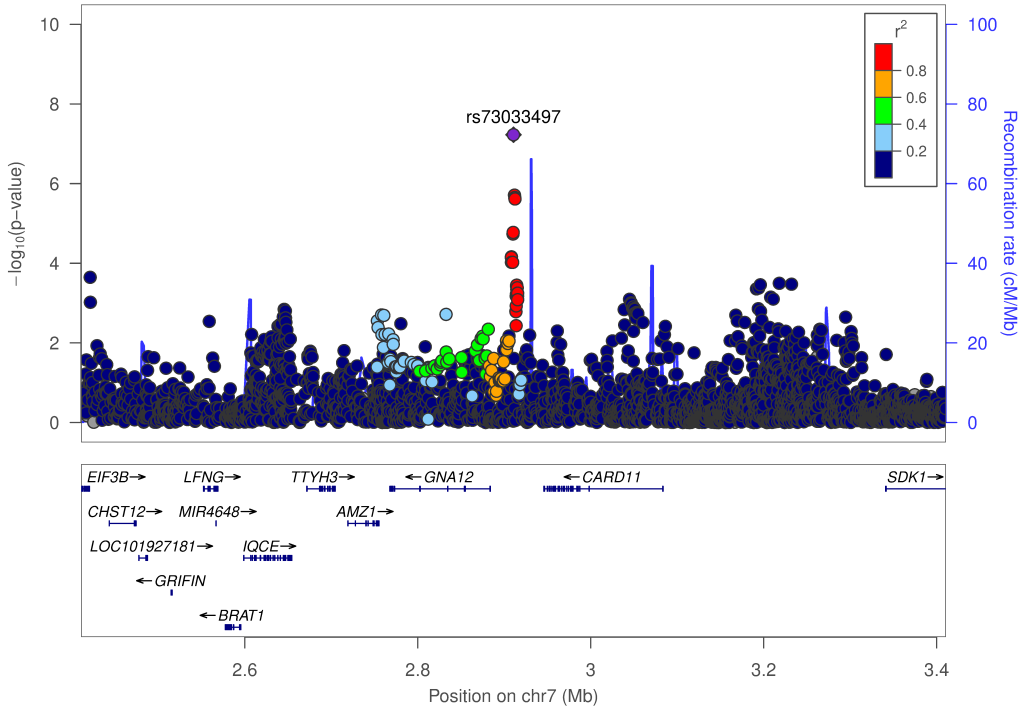
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



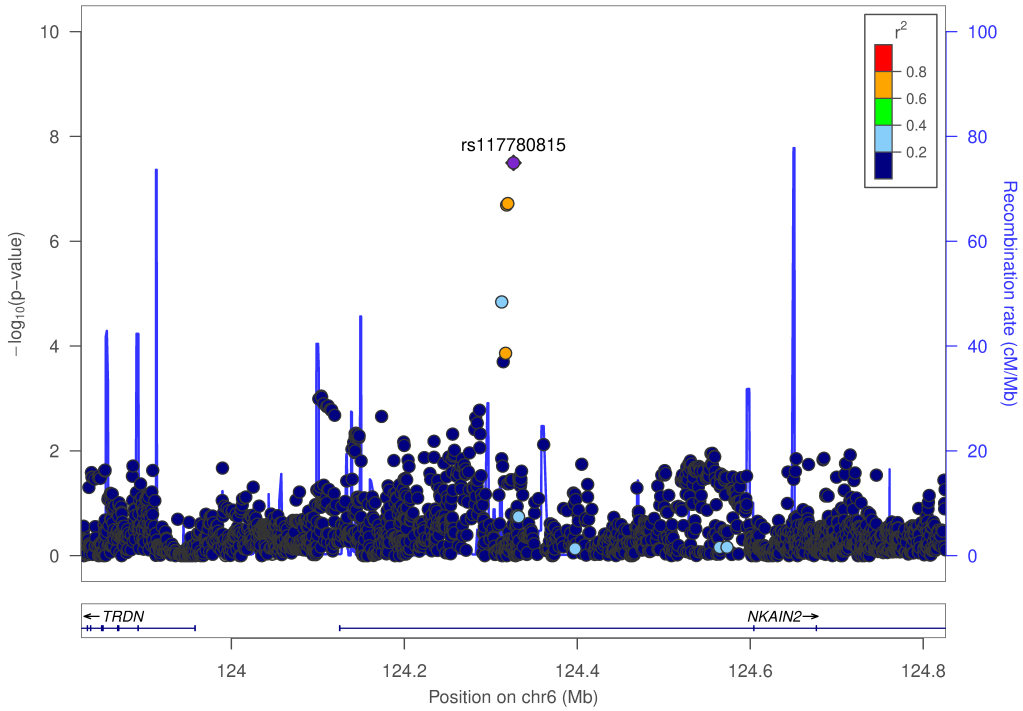


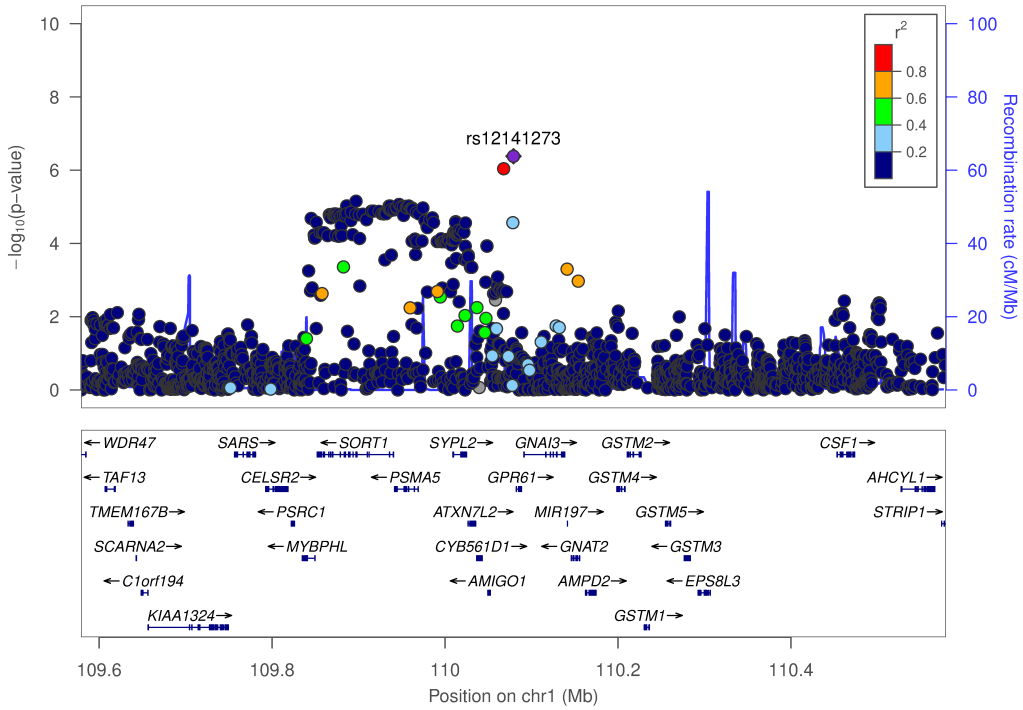
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry



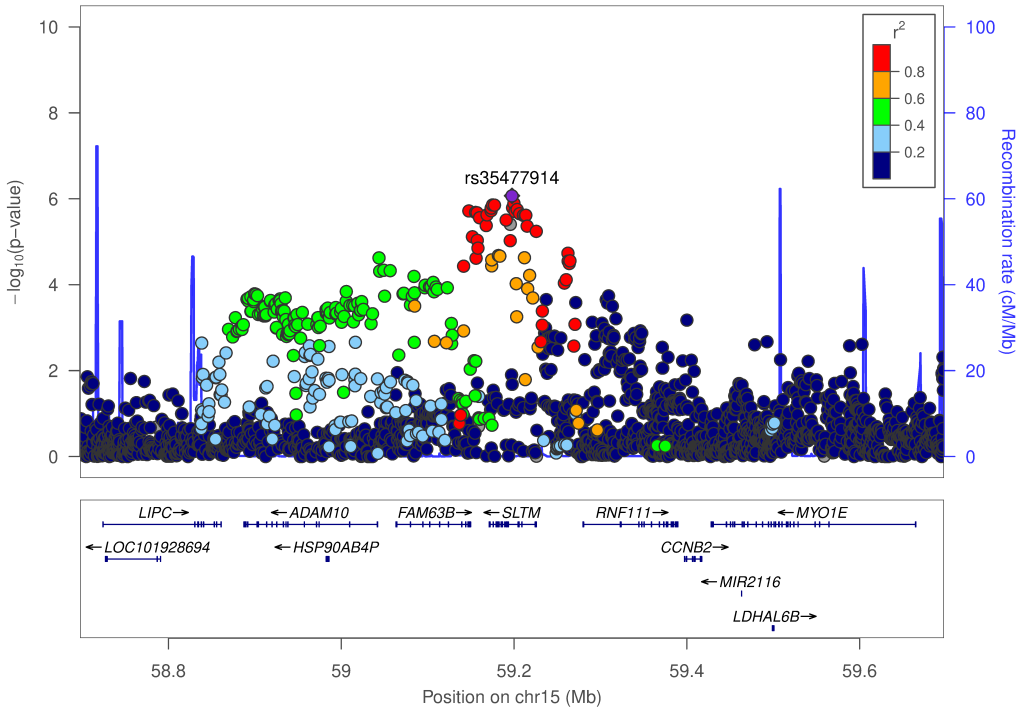


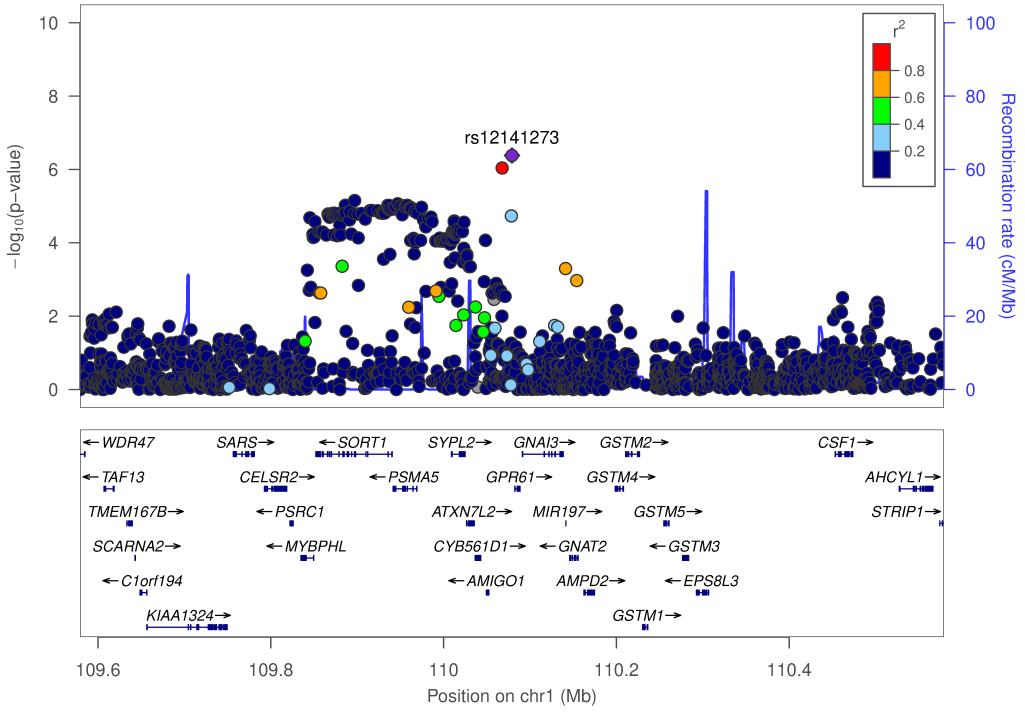
j) Omnibus Test SCZ-BIP-MDD – European ancestry

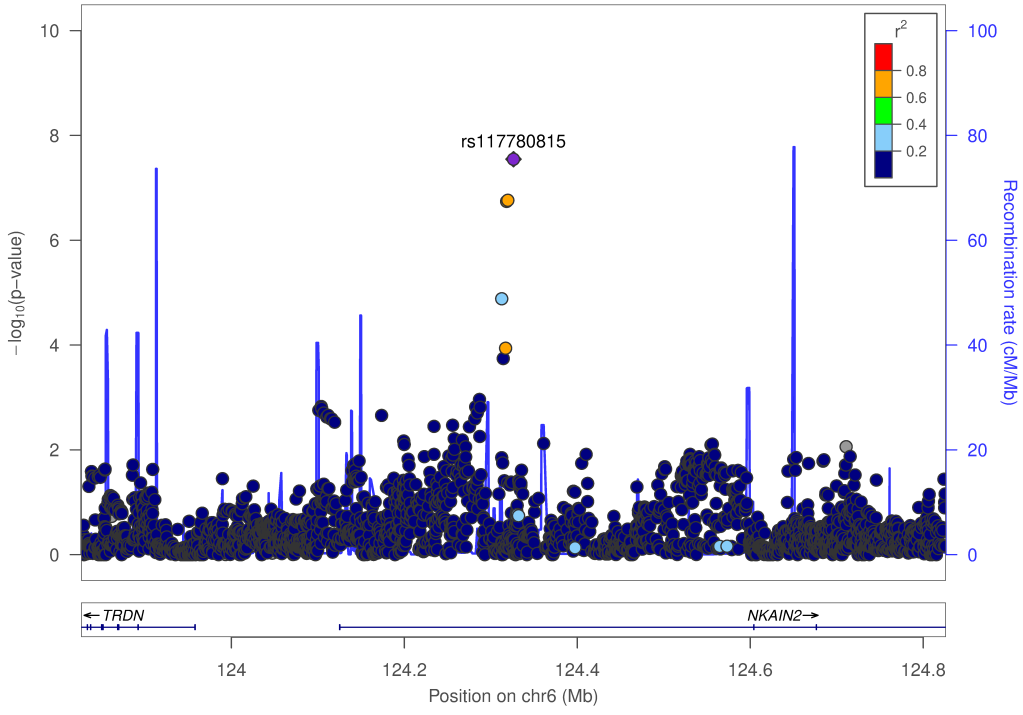




k) Omnibus Test SCZ-BIP-MDD – European + East Asian ancestry




rs12141273
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
WDR47
SARS
SORT1
SYPL2
GNAI3
GSTM2
CSF1
TAF13
CELSR2
PSMA5
GPR61
GSTM4
AHCYL1
TMEM167B
PSRC1
ATXN7L2
MIR197
GSTM5
STRIP1
SCARNA2
MYBPHL
CYB561D1
GNAT2
GSTM3
C1orf194
AMIGO1
AMPD2
EPS8L3
KIAA1324
GSTM1
Position on chr1 (Mb)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r²
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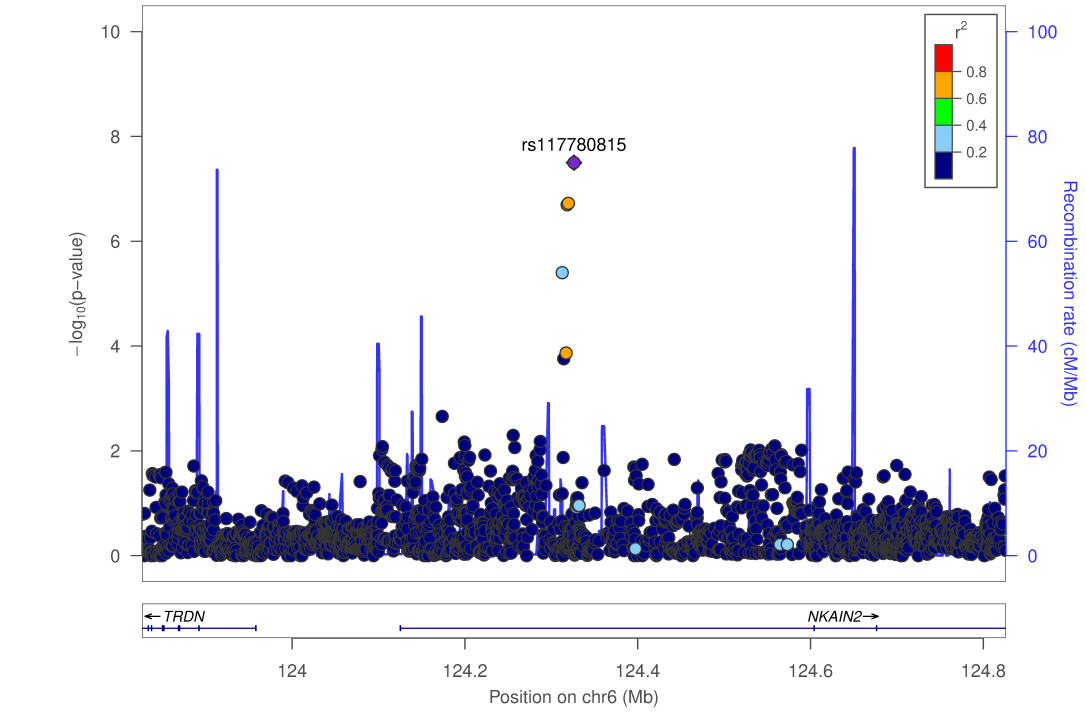
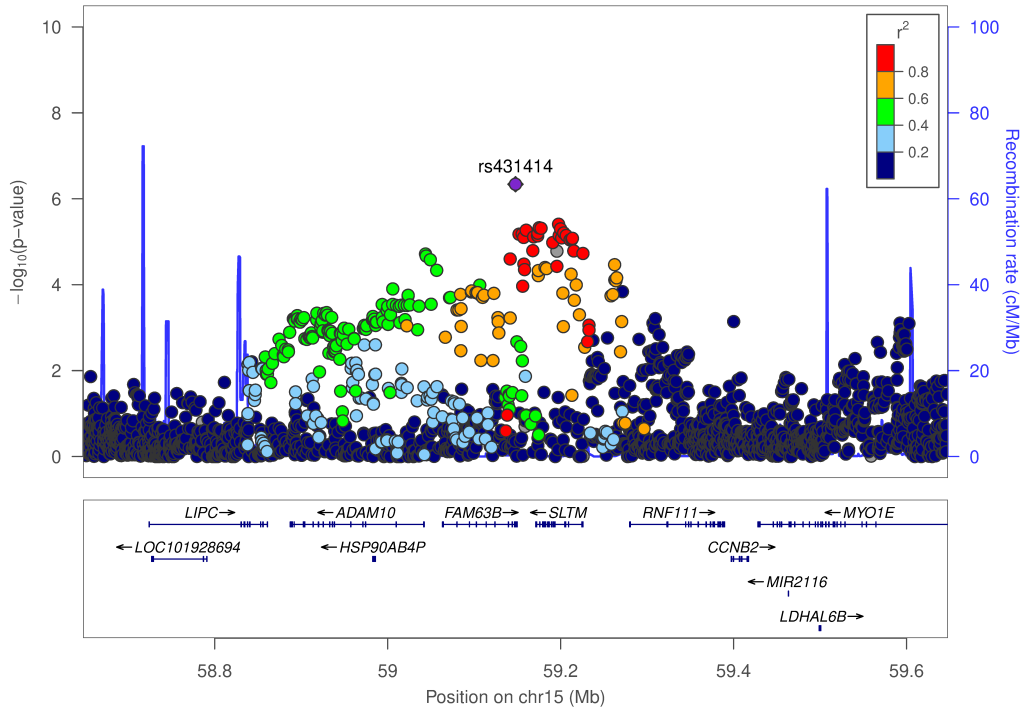
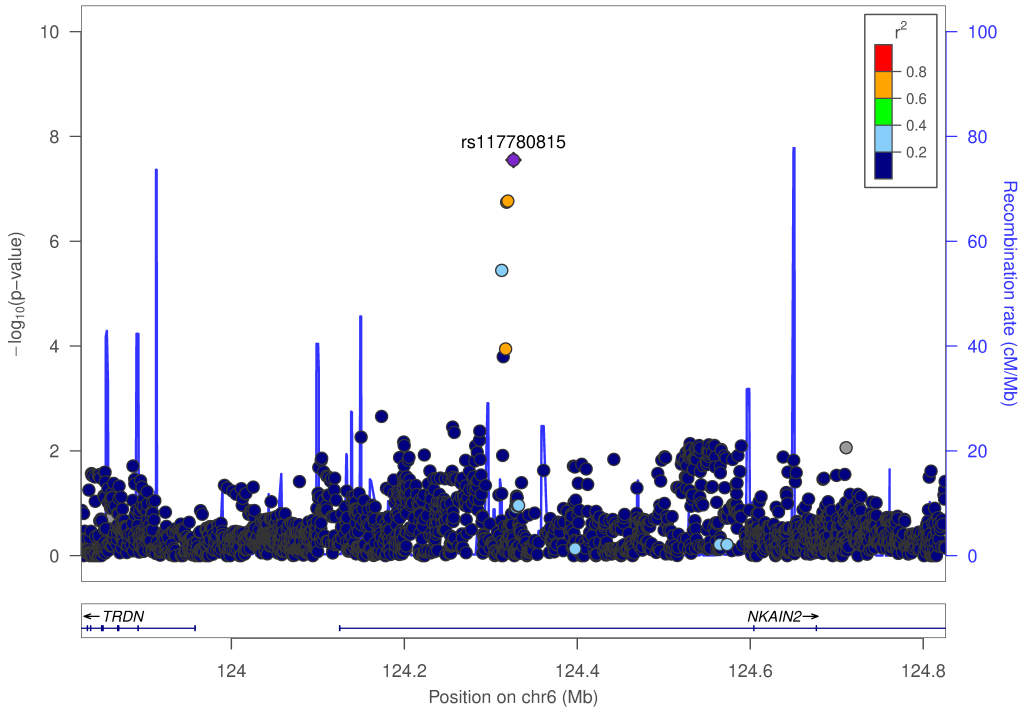
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
TRDN
NKAIN2
Position on chr6 (Mb)

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





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

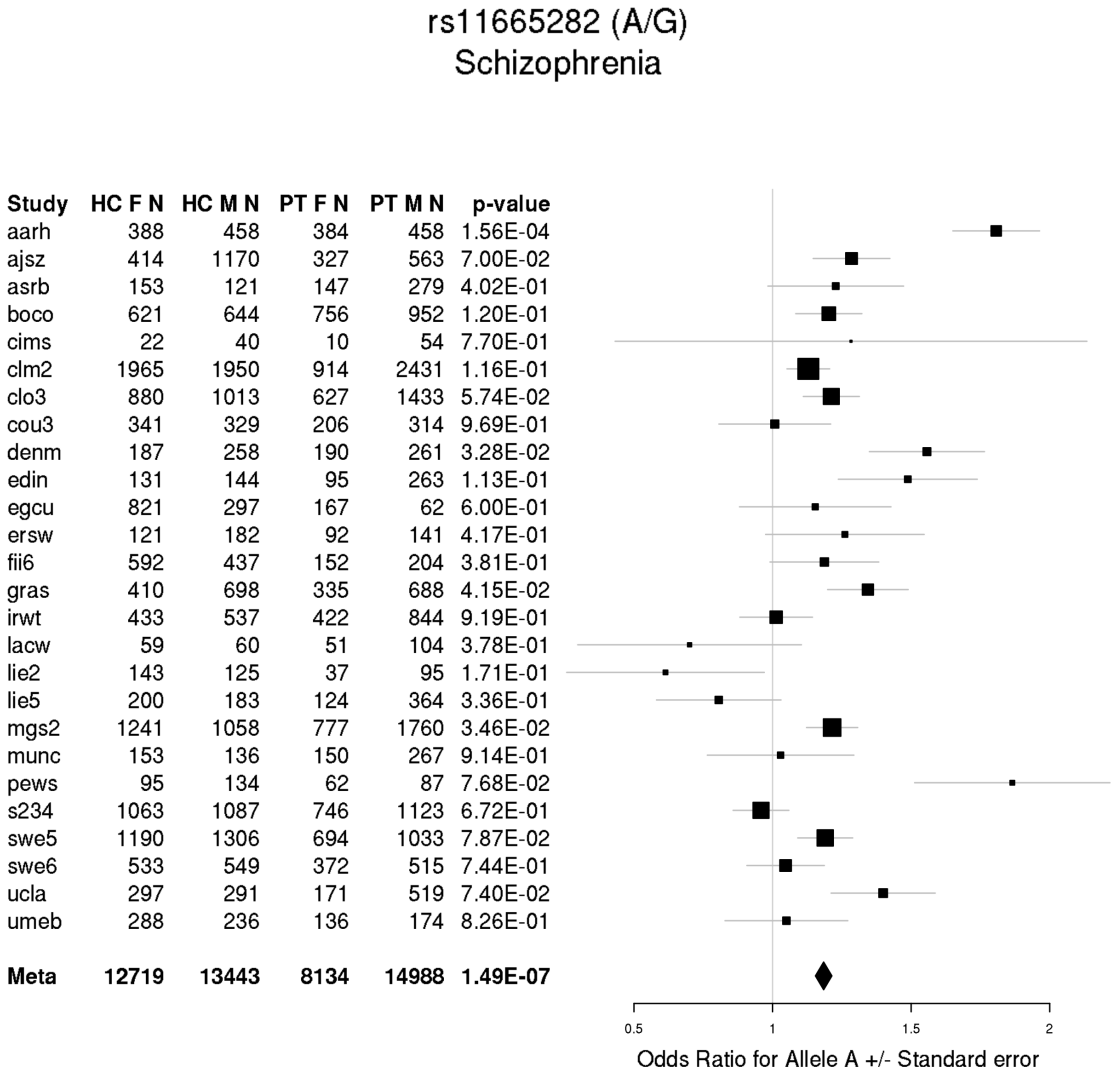


Supplementary Figure 8. Forest plots for PGC + iPSYCH

Plots were generated using the rmeta package in R for loci (index SNPs) with GxS interaction $p < 1\times10^{-6}$.

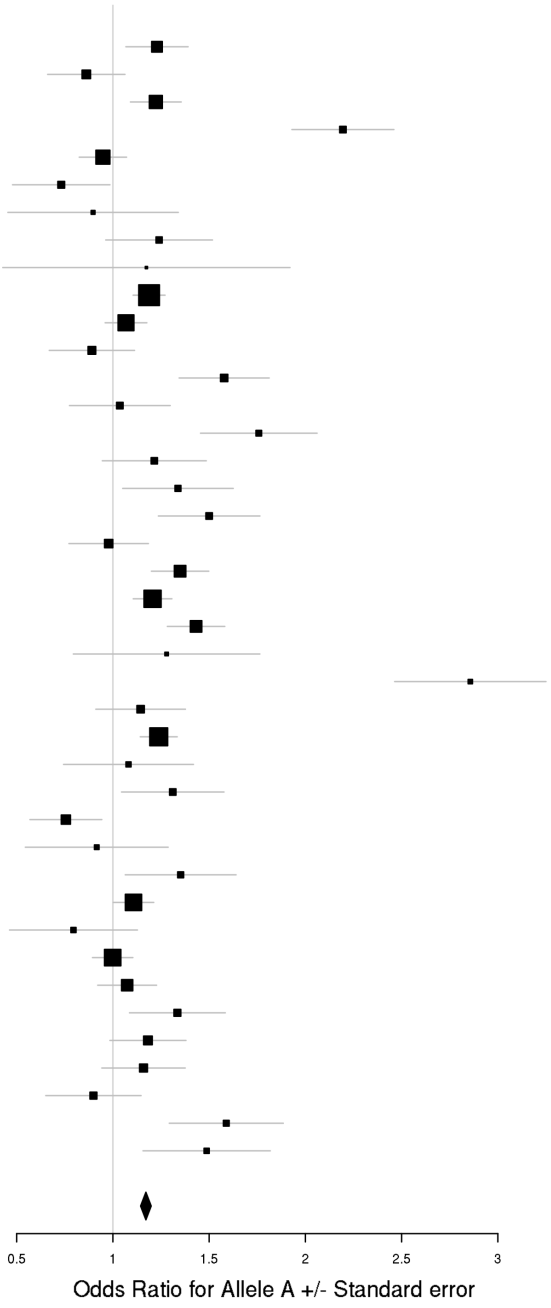
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; HC F N = number of female healthy controls; HC M N = number of male healthy controls; PT F N = number of female patients; PT M N = number of male patients; Study = cohort abbreviation used by PGC;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

a) Schizophrenia – European ancestry only



rs12445424 (A/G)
Schizophrenia

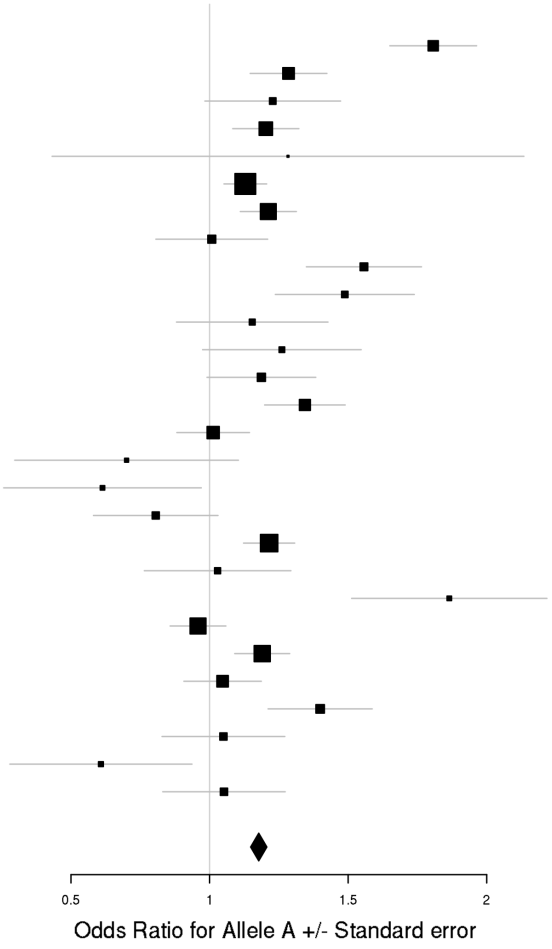
Study	HC F N	HC M N	PT F N	PT M N	p-value
aarh	393	463	387	465	2.02E-01
aber	244	440	182	530	4.59E-01
ajsz	414	1173	327	567	1.26E-01
asrb	154	122	148	280	2.99E-03
boco	628	650	764	960	6.64E-01
buls	317	288	104	91	2.16E-01
cati	21	90	90	304	8.06E-01
caws	145	125	131	260	4.37E-01
cims	22	40	11	54	8.30E-01
clm2	1981	1964	924	2455	3.75E-02
clo3	886	1019	631	1444	5.46E-01
cou3	342	333	208	319	6.02E-01
denm	189	261	193	266	5.10E-02
dubl	579	237	79	176	8.93E-01
edin	135	146	99	265	6.23E-02
egcu	828	299	169	62	4.70E-01
ersw	123	182	93	143	3.11E-01
fi3m	466	452	85	101	1.24E-01
fii6	596	438	153	207	9.14E-01
gras	415	708	342	688	4.45E-02
ipsy	791	1645	1325	1470	6.22E-02
irwt	443	549	428	859	1.60E-02
lacw	59	60	51	105	6.12E-01
lie2	144	125	37	95	7.55E-03
lie5	204	183	126	365	5.62E-01
mgs2	1273	1074	790	1792	2.63E-02
msaf	58	80	121	200	8.17E-01
munc	155	136	149	261	3.09E-01
pewb	907	867	142	398	1.34E-01
pews	96	139	63	87	8.13E-01
port	131	78	133	213	2.94E-01
s234	1081	1108	761	1141	3.36E-01
swe1	102	101	95	116	4.90E-01
swe5	1200	1313	697	1041	9.90E-01
swe6	537	550	372	518	6.40E-01
top8	202	201	162	215	2.45E-01
ucla	300	295	171	522	3.97E-01
uclo	281	203	144	358	4.94E-01
umeb	293	241	139	177	6.66E-01
umes	337	287	80	103	1.18E-01
zhh1	98	92	63	127	2.30E-01
Meta	**17548**	**18757**	**11158**	**19800**	**3.52E-07**



b) Schizophrenia – European + East Asian ancestry

rs11665282 (A/G)
Schizophrenia

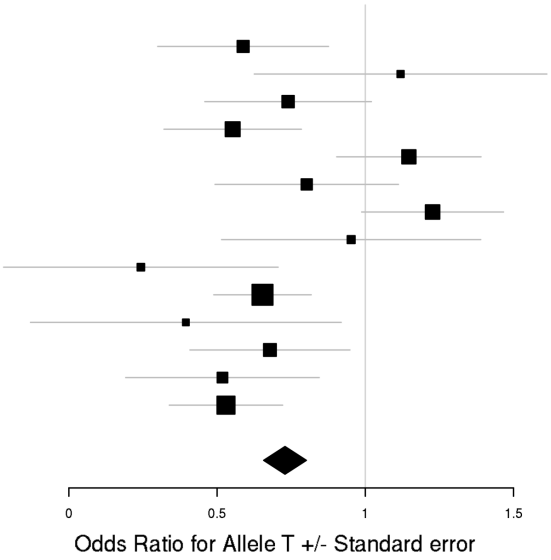
Study	HC F N	HC M N	PT F N	PT M N	p-value
aarh	388	458	384	458	1.56E-04
ajsz	414	1170	327	563	7.00E-02
asrb	153	121	147	279	4.02E-01
boco	621	644	756	952	1.20E-01
cims	22	40	10	54	7.70E-01
clm2	1965	1950	914	2431	1.16E-01
clo3	880	1013	627	1433	5.74E-02
cou3	341	329	206	314	9.69E-01
denm	187	258	190	261	3.28E-02
edin	131	144	95	263	1.13E-01
egcu	821	297	167	62	6.00E-01
ersw	121	182	92	141	4.17E-01
fii6	592	437	152	204	3.81E-01
gras	410	698	335	688	4.15E-02
irwt	433	537	422	844	9.19E-01
lacw	59	60	51	104	3.78E-01
lie2	143	125	37	95	1.71E-01
lie5	200	183	124	364	3.36E-01
mgs2	1241	1058	777	1760	3.46E-02
munc	153	136	150	267	9.14E-01
pews	95	134	62	87	7.68E-02
s234	1063	1087	746	1123	6.72E-01
swe5	1190	1306	694	1033	7.87E-02
swe6	533	549	372	515	7.44E-01
ucla	297	291	171	519	7.40E-02
umeb	288	236	136	174	8.26E-01
jpn1	212	212	231	248	1.30E-01
tcr1	327	560	285	556	8.20E-01
Meta	**13258**	**14215**	**8650**	**15792**	**3.74E-07**



c) Bipolar Disorder

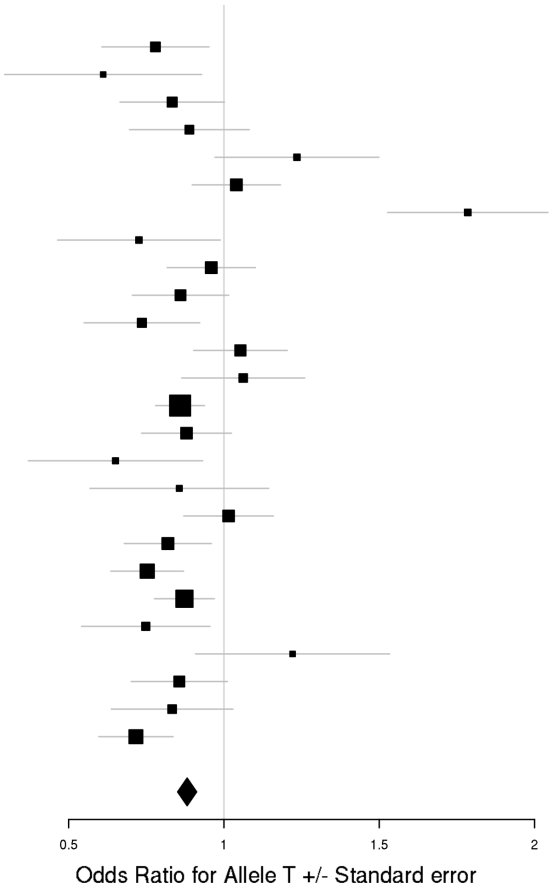
rs12341335 (T/C)
Bipolar Disorder

Study	HC F N	HC M N	PT F N	PT M N	p-value
bmau	891	901	189	140	6.52E-02
bmg2	211	232	117	64	8.20E-01
bmg3	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

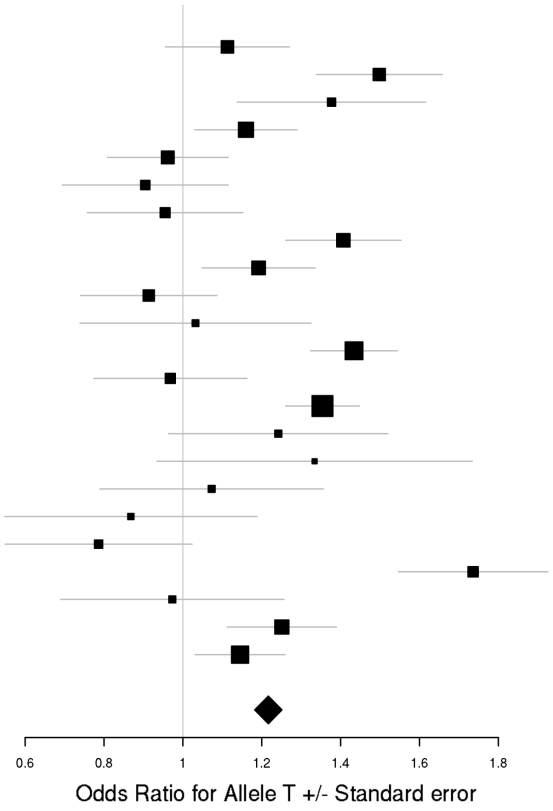
Study	HC F N	HC M N	PT F N	PT M N	p-value
bmau	889	898	185	140	1.48E-01
bmg2	210	231	116	63	1.20E-01
bmg3	587	281	282	194	2.78E-01
bmpo	207	471	249	159	5.41E-01
bmsp	143	143	137	111	4.24E-01
bonn	596	605	340	316	7.82E-01
dub1	560	236	78	71	2.46E-02
edi1	133	141	159	119	2.22E-01
fat2	577	480	417	302	7.69E-01
fran	916	684	261	189	3.31E-01
gain	191	206	314	295	9.92E-02
gsk1	527	369	412	239	7.32E-01
hal2	233	242	231	170	7.61E-01
icuk	1661	1723	1710	757	5.31E-02
may1	375	376	556	374	3.74E-01
mich	156	135	9	3	1.26E-01
rom3	103	87	134	94	5.90E-01
st2c	551	632	361	272	9.17E-01
stp1	378	406	502	417	1.56E-01
swa2	1103	1122	516	361	1.53E-02
swei	1693	1820	779	460	1.58E-01
top7	188	184	251	185	1.61E-01
top8	130	159	78	55	5.23E-01
ucl2	242	445	395	319	3.15E-01
uclo	283	211	242	172	3.51E-01
wtcc	499	456	977	576	5.24E-03
Meta	**13131**	**12743**	**9691**	**6413**	**3.72E-07**



d) Major Depressive Disorder

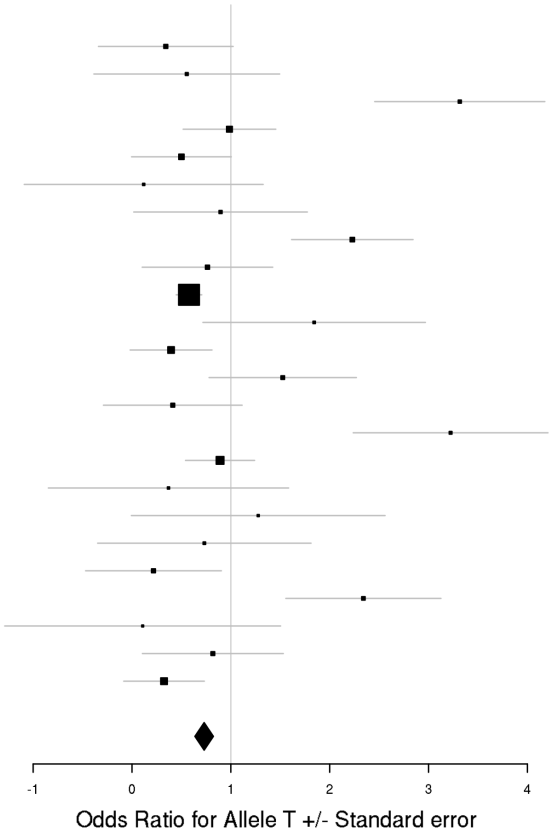
rs9428240 (T/C)
Major Depressive Disorder

Study	HC F N	HC M N	PT F N	PT M N	p-value
boma	530	536	377	210	4.96E-01
col3	605	818	358	148	1.14E-02
edi2	138	146	221	151	1.81E-01
gens	535	784	713	291	2.53E-01
gep3	1346	1351	329	141	7.98E-01
grdg	292	176	365	106	6.33E-01
grnd	232	241	683	143	8.15E-01
gsk2	577	276	563	284	1.93E-02
i2b3	531	534	532	266	2.21E-01
mmi2	277	227	314	267	6.01E-01
mmo4	185	193	136	130	9.15E-01
nes1	976	627	1021	471	1.06E-03
qi6c	364	223	346	151	8.67E-01
rad3	820	557	1315	550	1.17E-03
rage	103	113	213	111	4.36E-01
rai2	178	161	90	19	4.71E-01
rau2	195	182	174	48	8.03E-01
rde4	208	306	93	40	6.58E-01
rot4	570	422	181	63	3.10E-01
shp0	493	638	254	119	3.62E-03
shpt	223	276	119	46	9.23E-01
stm2	422	503	551	368	1.06E-01
twg2	1182	1417	773	321	2.33E-01
Meta	**10982**	**10707**	**9721**	**4444**	**1.64E-07**



rs147515485 (T/C)
Major Depressive Disorder

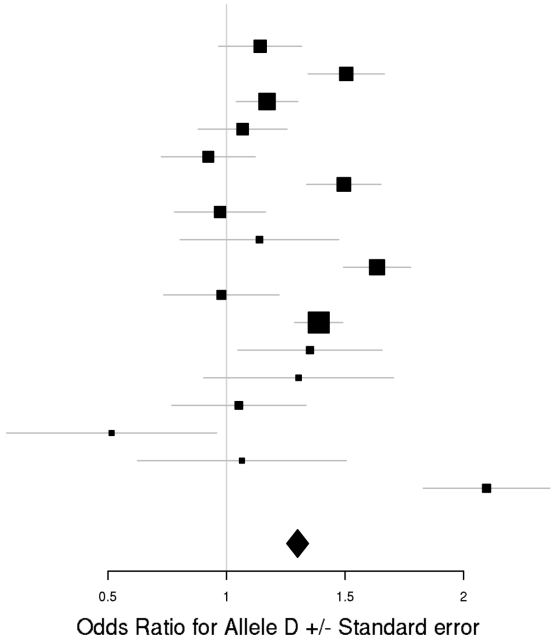
Study	HC F N	HC M N	PT F N	PT M N	p-value
boma	531	531	376	210	1.15E-01
col3	603	807	355	148	5.30E-01
edi2	137	146	220	151	1.63E-01
gens	530	777	706	291	9.76E-01
gep3	1337	1341	324	141	1.69E-01
grdg	292	173	361	104	7.74E-02
grnd	230	238	681	142	9.00E-01
gsk2	574	277	559	285	1.92E-01
i2b3	527	529	532	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
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**



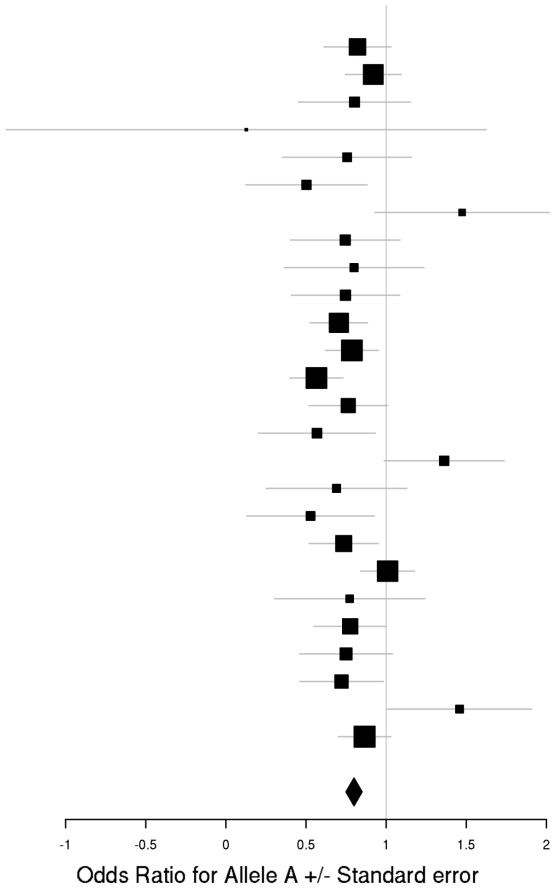
f) Cross-Disorder SCZ-BIP-MDD – European ancestry only

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	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	bmg2	210	226	117	64	4.03E-01
BIP	bmg3	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	**17550**	**17448**	**17634**	**16697**	**1.60E-07**

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

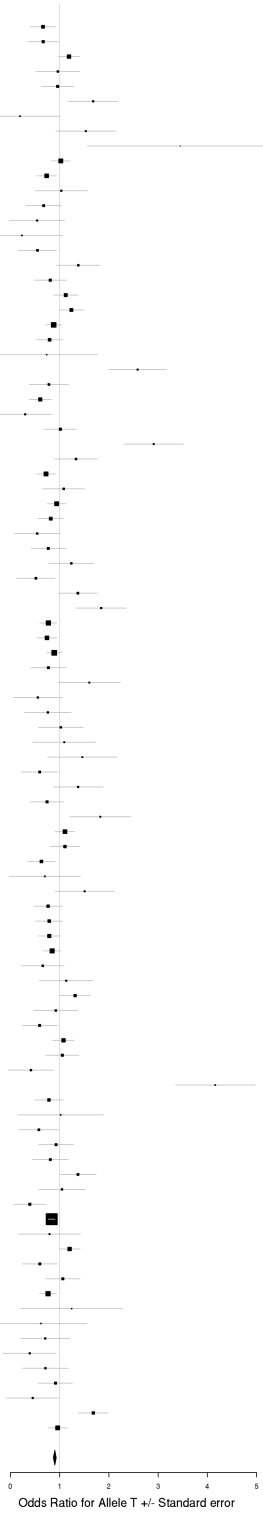
Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	383	455	380	454	3.47E-01
SCZ	ajsz	410	1155	320	561	6.30E-01
SCZ	buls	312	281	101	91	5.29E-01
SCZ	cims	20	33	11	52	1.69E-01
SCZ	cou3	89	73	200	310	4.88E-01
SCZ	dubl	315	129	78	175	6.91E-02
SCZ	edin	37	37	98	262	4.76E-01
SCZ	egcu	815	294	165	61	3.88E-01
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**



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

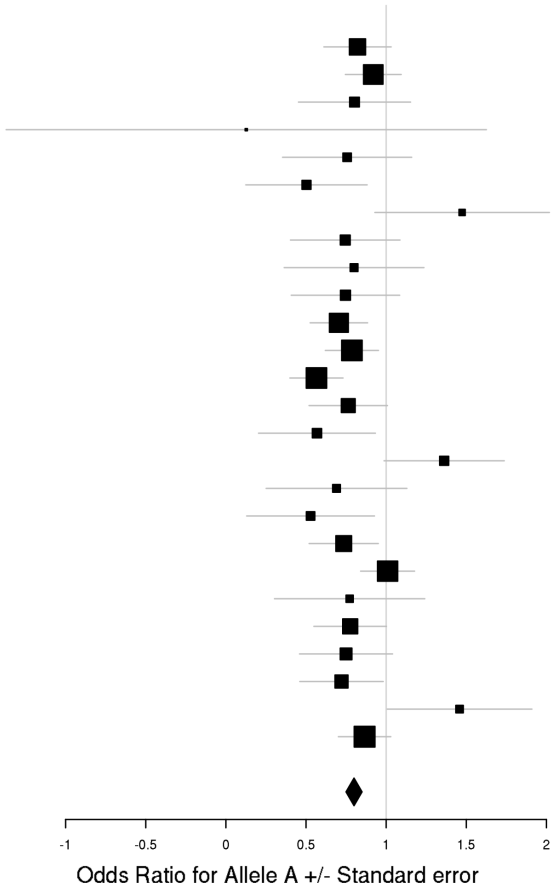
rs7914279 (T/G)
Cross-Disorder SCZ-BIP-MDD

Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	389	463	387	464	1.07E-01
SCZ	aber	243	438	182	528	1.86E-01
SCZ	ajsz	414	1171	327	567	4.16E-01
SCZ	asrb	153	121	147	280	9.31E-01
SCZ	boco	160	160	755	951	8.98E-01
SCZ	buls	317	288	104	91	3.10E-01
SCZ	cati	8	44	90	304	4.22E-02
SCZ	caws	65	63	129	256	4.80E-01
SCZ	cims	20	33	11	52	5.13E-01
SCZ	clm2	679	667	919	2444	9.05E-01
SCZ	clo3	689	820	628	1433	1.23E-01
SCZ	cou3	92	73	202	316	9.51E-01
SCZ	denm	188	259	193	266	2.74E-01
SCZ	dubl	319	129	79	176	2.74E-01
SCZ	edin	37	37	98	264	7.76E-02
SCZ	egcu	828	299	169	62	1.22E-01
SCZ	ersw	121	178	92	142	4.66E-01
SCZ	fi3m	458	450	82	101	5.11E-01
SCZ	fii6	594	437	153	207	6.34E-01
SCZ	gras	411	705	339	688	3.85E-01
SCZ	ipsy	789	1639	1320	1464	4.15E-01
SCZ	irwt	435	547	425	857	4.00E-01
SCZ	lacw	23	21	51	104	7.68E-01
SCZ	lie2	143	124	37	94	1.07E-01
SCZ	lie5	203	182	126	361	5.38E-01
SCZ	mgs2	527	381	785	1783	2.52E-02
SCZ	msaf	57	80	121	200	2.76E-02
SCZ	pewb	886	857	140	396	9.65E-01
SCZ	pews	96	138	63	87	7.71E-02
SCZ	port	131	78	133	212	5.05E-01
SCZ	s234	518	549	744	1131	8.05E-02
SCZ	swe1	99	97	94	116	8.54E-01
SCZ	swe5	583	652	689	1033	7.35E-01
SCZ	swe6	258	283	360	511	4.27E-01
SCZ	top8	102	102	160	214	1.84E-01
SCZ	ucla	278	281	169	522	4.49E-01
SCZ	uclo	143	95	144	358	6.40E-01
SCZ	umeb	185	150	109	155	8.72E-02
SCZ	umes	267	235	72	93	4.23E-01
SCZ	zhh1	97	91	63	127	2.30E-01
SCZ	hok2	1342	666	153	322	1.25E-01
SCZ	jpn1	215	212	238	253	1.42E-01
SCZ	tcr1	336	570	289	562	4.47E-01
BIP	bmau	895	894	184	140	4.58E-01
BIP	bmg2	210	226	117	64	4.57E-01
BIP	bmg3	158	54	288	197	2.39E-01
BIP	bmsp	144	145	137	113	5.60E-01
BIP	bonn	150	141	345	318	9.62E-01
BIP	dub1	283	115	77	70	8.89E-01
BIP	edi1	43	38	154	118	5.90E-01
BIP	fat2	254	170	411	301	1.59E-01
BIP	gain	85	65	314	294	5.25E-01
BIP	gsk1	406	299	415	239	3.75E-01
BIP	hal2	65	73	234	170	3.30E-01
BIP	icuk	628	678	1720	754	6.06E-01
BIP	ipsy	255	295	606	357	7.28E-01
BIP	may1	375	374	558	373	9.35E-02
BIP	mich	69	60	9	3	6.19E-01
BIP	rom3	107	87	135	96	4.91E-01
BIP	st2c	400	499	361	271	3.61E-01
BIP	stp1	287	313	502	415	3.88E-01
BIP	swa2	581	573	499	350	2.97E-01
BIP	swei	871	897	763	459	3.49E-01
BIP	top7	104	104	250	182	3.26E-01
BIP	top8	128	154	81	56	8.19E-01
BIP	ucl2	242	442	394	324	3.68E-01
BIP	uclo	139	110	239	170	8.52E-01
BIP	ume4	139	121	298	184	1.40E-01
BIP	usc2	657	435	632	655	7.30E-01
BIP	wtcc	204	186	972	573	8.75E-01
MDD	boma	131	149	376	207	5.89E-02
MDD	cof3	61	65	74	46	7.77E-02
MDD	col3	608	819	358	148	3.93E-01
MDD	edi2	36	37	220	151	9.82E-01
MDD	gens	130	195	713	291	1.65E-01
MDD	gep3	382	361	328	141	8.26E-01
MDD	grdg	290	176	365	106	5.63E-01
MDD	grnd	199	211	682	143	3.93E-01
MDD	gsk2	134	65	561	284	9.23E-01
MDD	i2b3	238	253	530	266	4.25E-03
MDD	ipsy	6544	6544	5075	5075	9.26E-03
MDD	mmo4	185	193	137	130	7.15E-01
MDD	nes1	951	618	1020	472	3.86E-01
MDD	qi6c	362	221	346	152	1.43E-01
MDD	qio2	297	222	403	159	8.57E-01
MDD	rad3	694	485	1297	548	1.13E-01
MDD	rage	29	34	211	108	8.33E-01
MDD	ral2	172	156	89	19	6.07E-01
MDD	rau2	196	181	175	48	4.86E-01
MDD	rde4	208	303	92	40	7.90E-02
MDD	rot4	570	422	180	63	4.59E-01
MDD	shp0	494	637	254	119	7.96E-01
MDD	shpt	224	276	119	46	1.32E-01
MDD	stm2	280	357	551	368	8.19E-02
MDD	twg2	1111	1334	757	316	8.23E-01
	Meta	**36283**	**36727**	**37168**	**37239**	**6.39E-07**



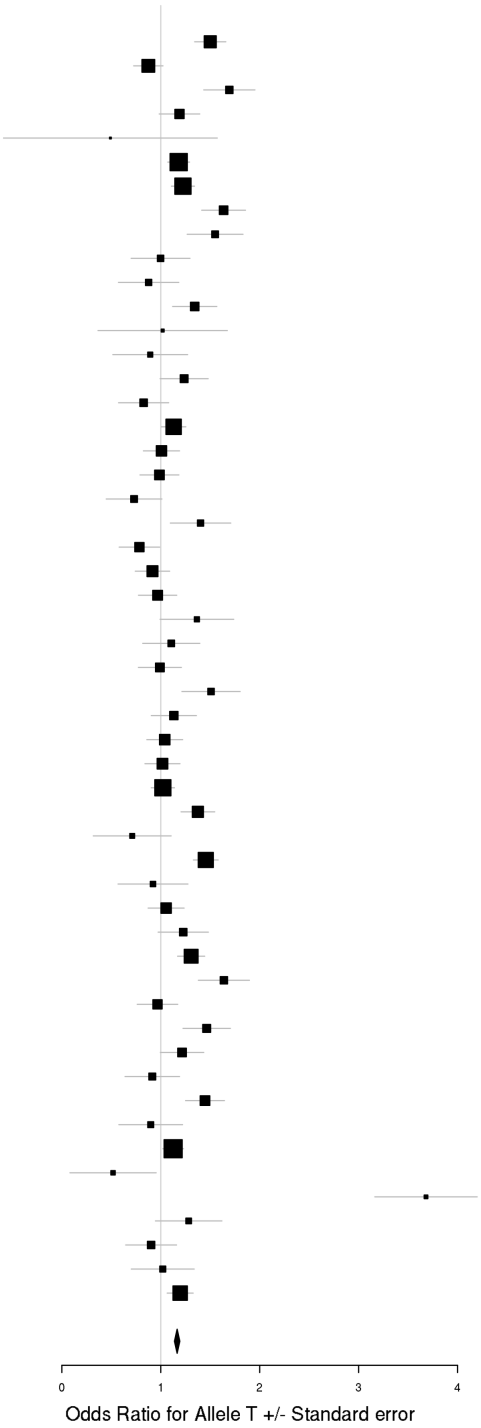
rs73033497 (A/T)
Cross-Disorder SCZ-BIP-MDD

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

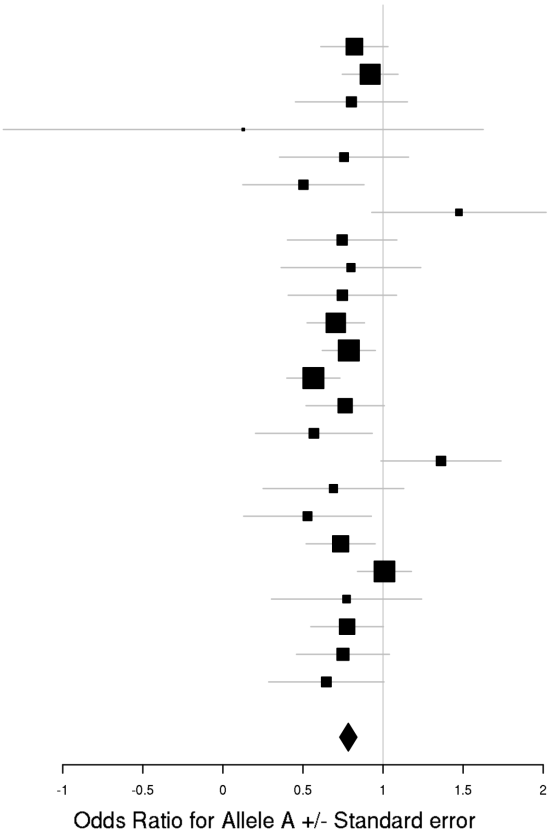
Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	391	463	387	465	9.74E-03
SCZ	ajsz	414	1171	327	567	3.63E-01
SCZ	asrb	153	121	148	280	4.17E-02
SCZ	boco	160	160	761	952	3.97E-01
SCZ	cims	20	33	11	52	5.10E-01
SCZ	clm2	671	657	908	2393	1.28E-01
SCZ	clo3	684	818	627	1435	8.16E-02
SCZ	denm	188	259	193	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	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
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	bmg2	210	226	117	64	4.03E-01
BIP	bmg3	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

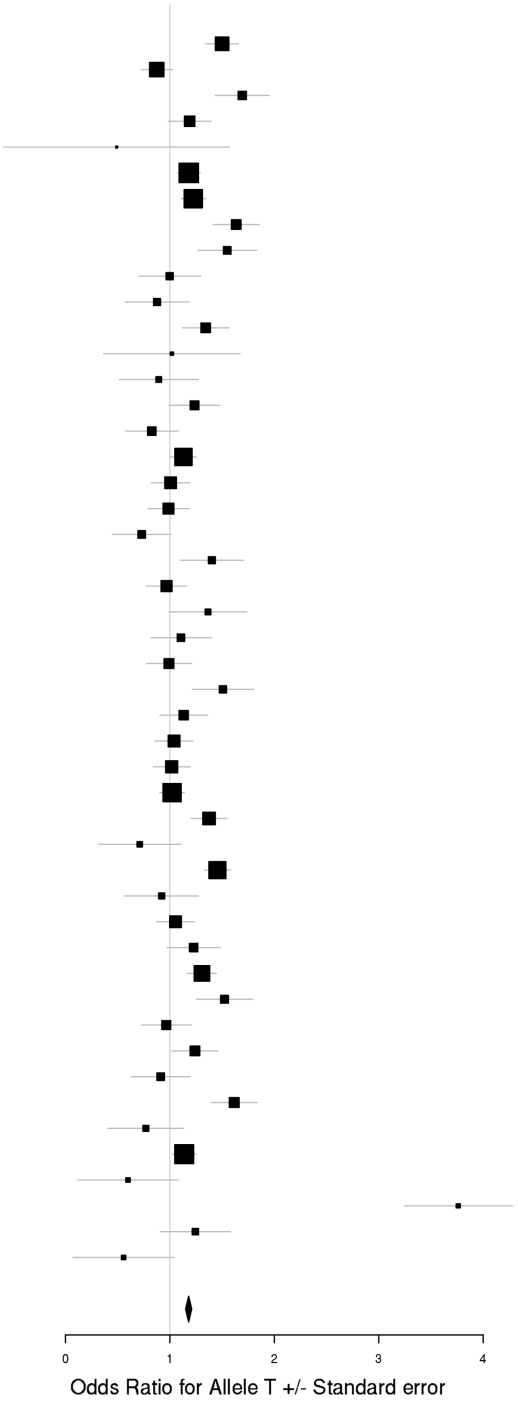
rs73033497 (A/T)
Cross-Disorder SCZ-BIP-RMDD

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
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**



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

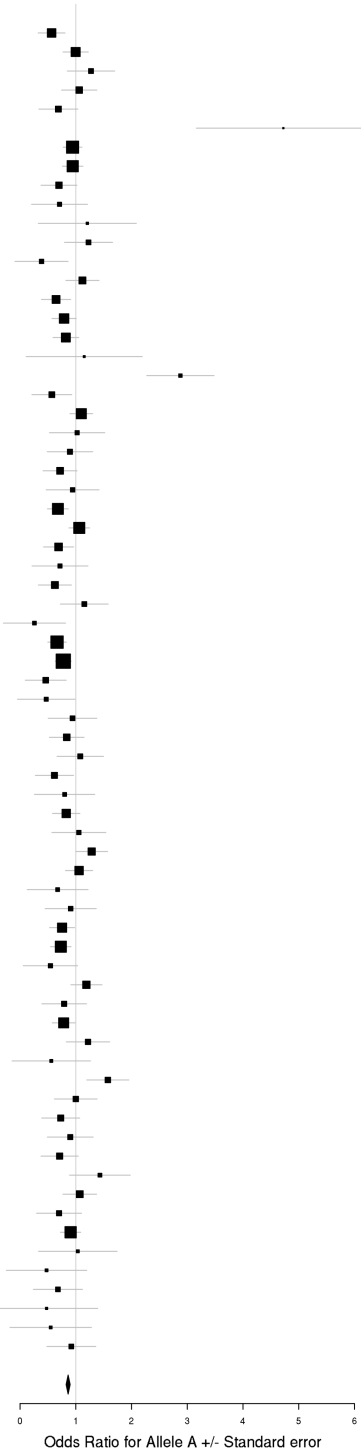
Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	391	463	387	465	9.74E-03
SCZ	ajsz	414	1171	327	567	3.63E-01
SCZ	asrb	153	121	148	280	4.17E-02
SCZ	boco	160	160	761	952	3.97E-01
SCZ	cims	20	33	11	52	5.10E-01
SCZ	clm2	671	657	908	2393	1.28E-01
SCZ	clo3	684	818	627	1435	8.16E-02
SCZ	denm	188	259	193	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	bmg2	210	226	117	64	4.03E-01
BIP	bmg3	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
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

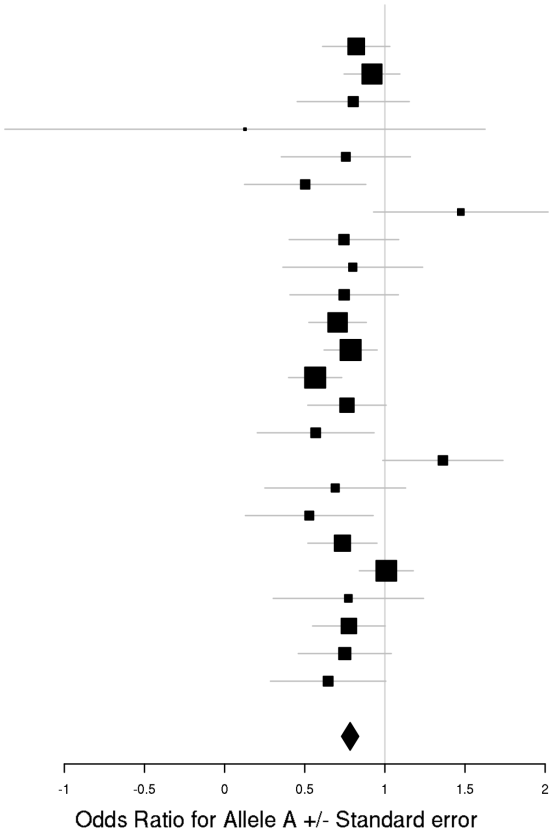
rs8040598 (A/G)
Cross-Disorder SCZ-BIP-RMDD

Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	391	463	387	465	1.79E-02
SCZ	ajsz	414	1171	327	567	9.91E-01
SCZ	asrb	153	121	148	280	5.70E-01
SCZ	boco	160	160	761	952	8.52E-01
SCZ	buls	315	288	104	91	2.83E-01
SCZ	cims	20	33	11	52	3.20E-01
SCZ	clm2	681	668	923	2450	7.24E-01
SCZ	clo3	692	824	629	1442	7.56E-01
SCZ	denm	188	259	193	266	2.63E-01
SCZ	dubl	318	129	79	176	4.90E-01
SCZ	edin	37	37	98	264	8.31E-01
SCZ	egcu	828	299	169	62	6.33E-01
SCZ	ersw	121	178	92	142	4.48E-02
SCZ	fi3m	469	457	85	101	7.04E-01
SCZ	fii6	594	437	153	207	9.44E-02
SCZ	gras	415	707	342	693	2.76E-01
SCZ	irwt	434	546	424	855	3.93E-01
SCZ	lacw	23	21	51	104	8.93E-01
SCZ	lie2	144	124	37	94	8.01E-02
SCZ	lie5	204	182	126	363	1.15E-01
SCZ	mgs2	527	381	783	1777	6.40E-01
SCZ	msaf	57	79	121	198	9.62E-01
SCZ	munc	156	136	150	266	7.86E-01
SCZ	pewb	885	856	140	396	2.76E-01
SCZ	pews	96	138	63	87	9.01E-01
SCZ	s234	517	548	744	1131	3.86E-02
SCZ	swe5	585	654	690	1034	7.45E-01
SCZ	swe6	259	283	360	511	1.69E-01
SCZ	top8	102	101	160	214	5.05E-01
SCZ	ucla	278	282	170	522	1.12E-01
SCZ	umeb	185	150	110	156	7.40E-01
SCZ	umes	269	235	72	93	1.49E-02
SCZ	hok2	1344	668	154	322	1.30E-02
SCZ	tcr1	336	570	289	563	7.50E-02
BIP	bmau	895	895	184	140	3.38E-02
BIP	bmg2	210	226	117	64	1.41E-01
BIP	bmg3	158	54	288	197	8.90E-01
BIP	bmpo	213	476	250	160	5.69E-01
BIP	bmsp	144	147	138	114	8.53E-01
BIP	bonn	151	142	345	318	1.58E-01
BIP	dub1	281	115	77	70	6.79E-01
BIP	fran	934	693	262	189	4.42E-01
BIP	gain	85	65	314	294	9.12E-01
BIP	gsk1	408	299	415	239	3.77E-01
BIP	may1	375	374	560	374	8.14E-01
BIP	mich	69	60	9	3	4.69E-01
BIP	rom3	107	87	135	96	8.33E-01
BIP	swa2	581	572	496	350	2.06E-01
BIP	swei	873	898	765	459	8.96E-02
BIP	top8	128	155	81	56	2.13E-01
BIP	ucl2	243	442	397	324	5.34E-01
BIP	ume4	139	121	299	184	5.56E-01
BIP	usc2	659	438	635	659	2.29E-01
rMDD	boma	131	149	299	148	6.11E-01
rMDD	cof3	60	64	53	37	4.09E-01
rMDD	gens	130	195	711	290	2.29E-01
rMDD	gep3	382	361	260	85	1.00E+
rMDD	grnd	199	212	677	140	3.53E-01
rMDD	gsk2	134	65	438	227	7.99E-01
rMDD	mmi2	278	228	230	173	3.05E-01
rMDD	mmo4	185	193	105	89	5.09E-01
rMDD	qi3c	369	209	326	253	8.20E-01
rMDD	qi6c	363	221	156	85	3.74E-01
rMDD	rad3	694	485	1005	417	5.90E-01
rMDD	rage	29	34	180	73	9.60E-01
rMDD	rai2	172	154	87	19	3.01E-01
rMDD	rau2	196	182	175	47	3.80E-01
rMDD	rde4	208	303	41	18	4.18E-01
rMDD	rot4	571	422	57	14	4.12E-01
rMDD	shp0	494	637	128	52	8.48E-01
	Meta	**23425**	**22558**	**19829**	**23353**	**3.90E-07**



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	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
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**



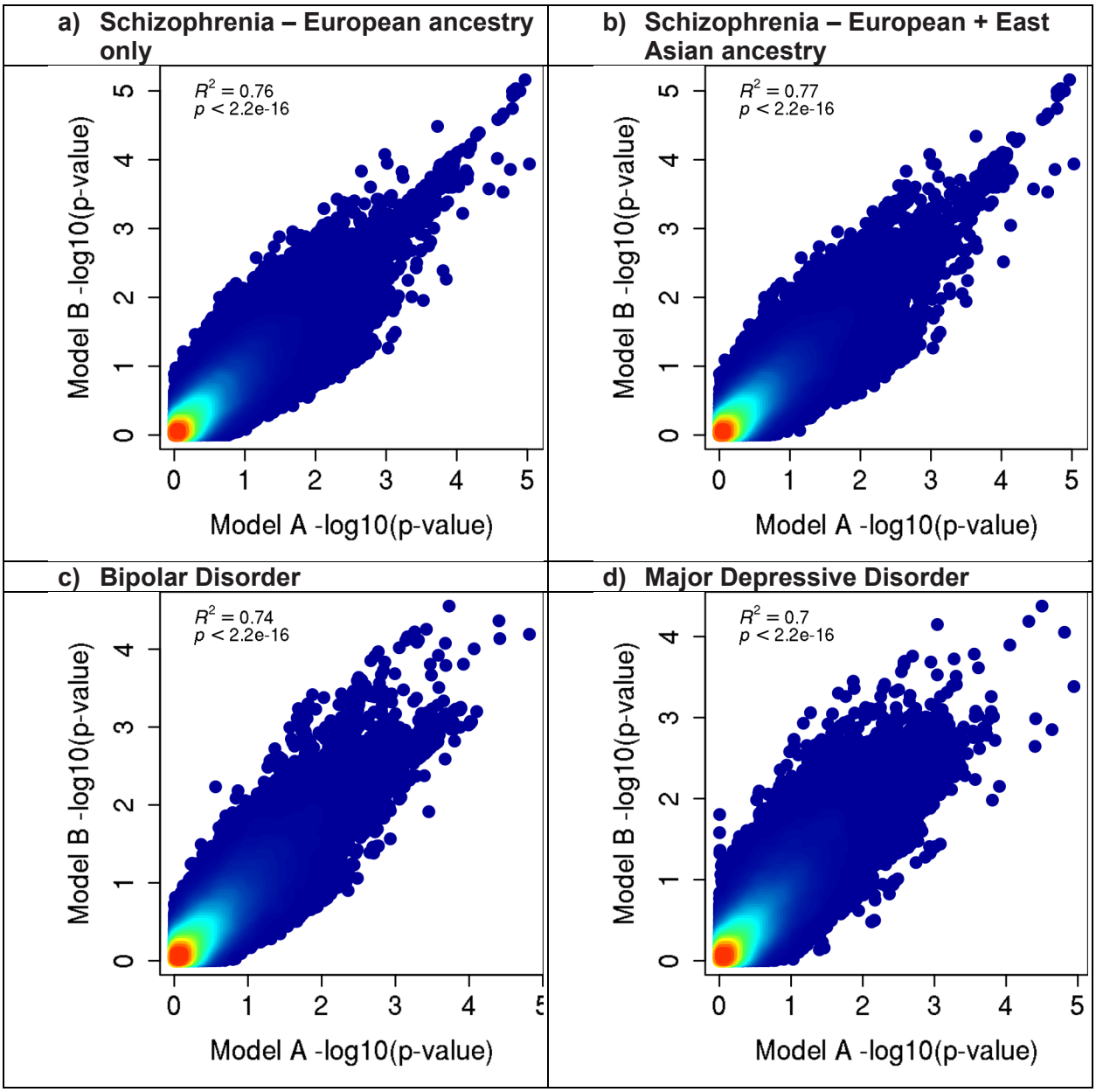
Supplementary Figure 9. X chromosome model comparisons in PGC + iPSYCH

GxS 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.

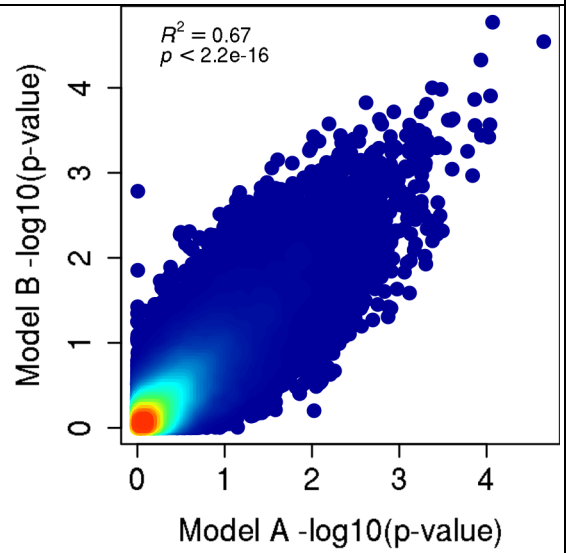
The scatter plots show substantial correlation (R) between *p*-values from the two X chromosome models, indicating the results from the two models did not differ substantially.

Plots were generated using the plot package in R.

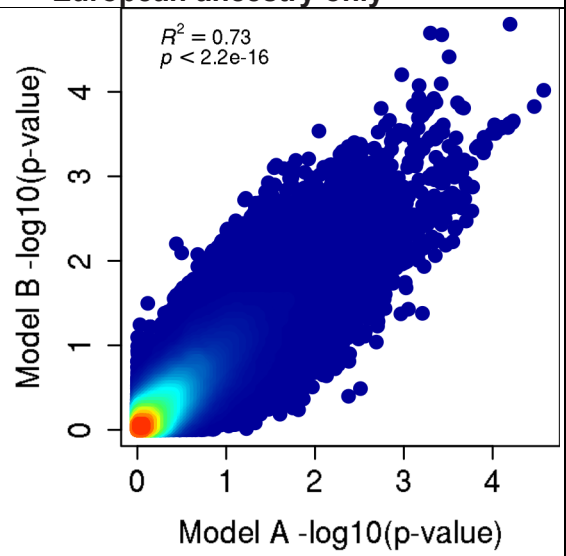
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; R2 = proportion variance explained.



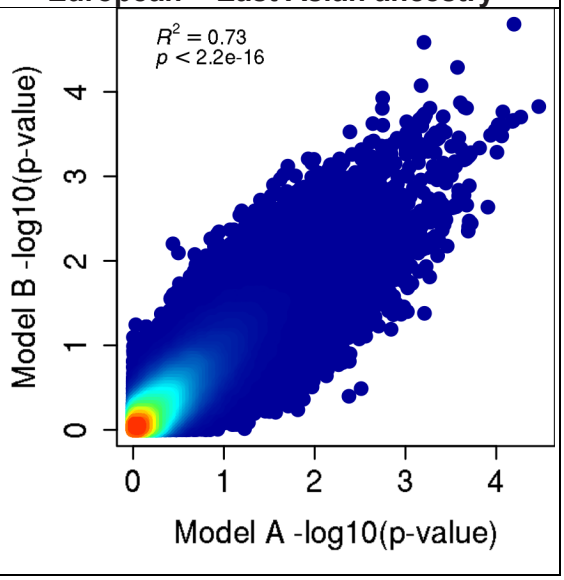
e) Recurrent Major Depressive Disorder

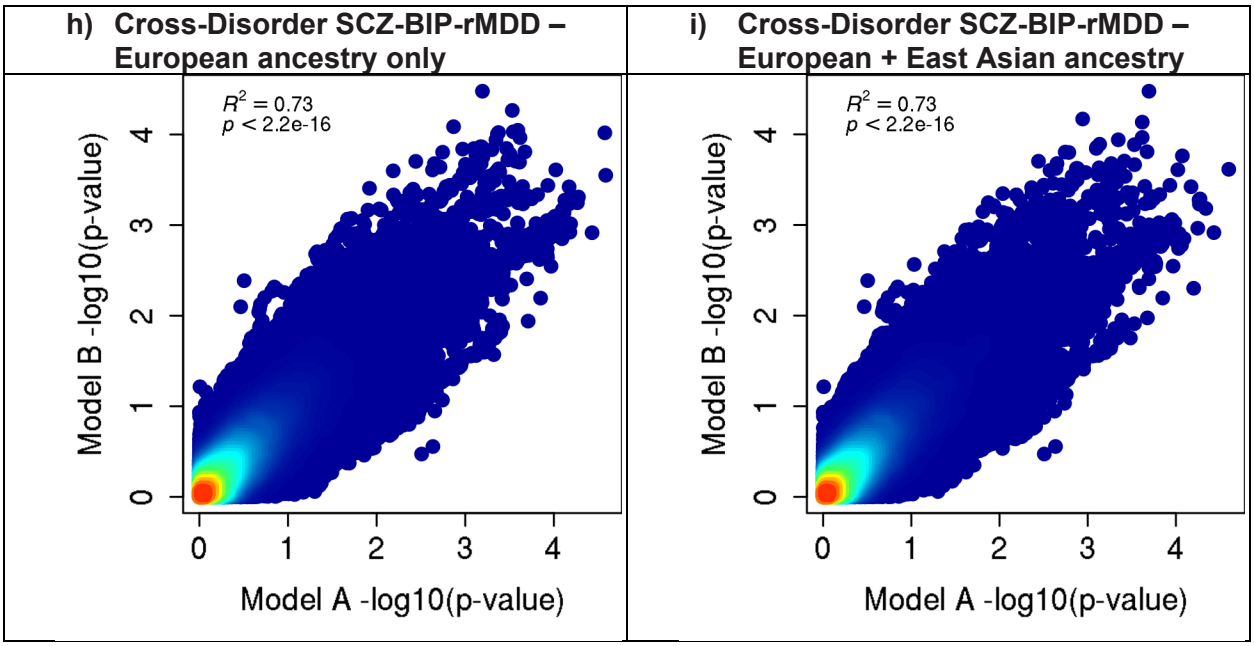


f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



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




h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only
R^2 = 0.73
p < 2.2e-16
Model B -log10(p-value)
Model A -log10(p-value)
0
1
2
3
4
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry
R^2 = 0.73
p < 2.2e-16
Model B -log10(p-value)
Model A -log10(p-value)

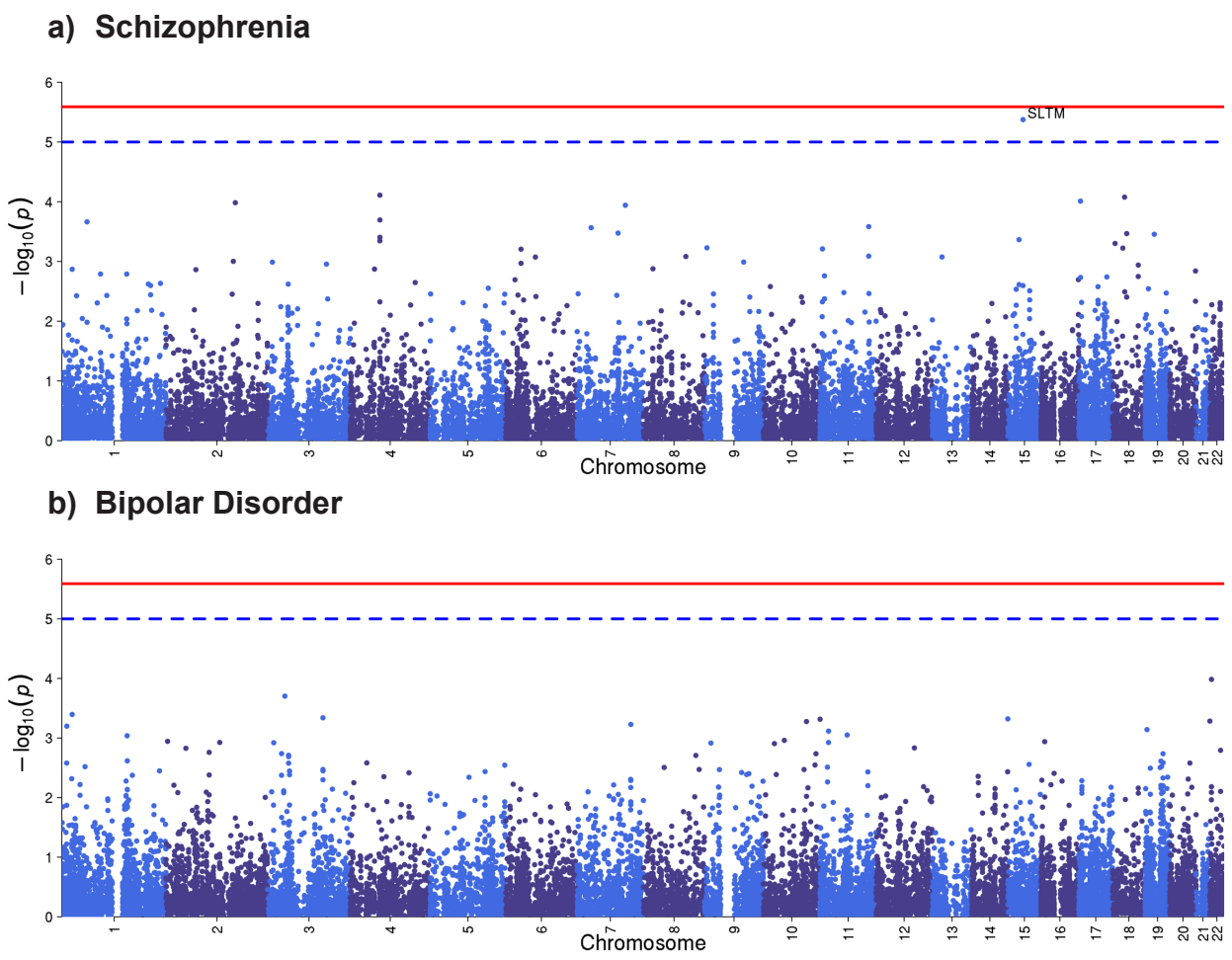
Supplementary Figure 10. Manhattan plots for gene-based GxS tests in PGC + iPSYCH

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.

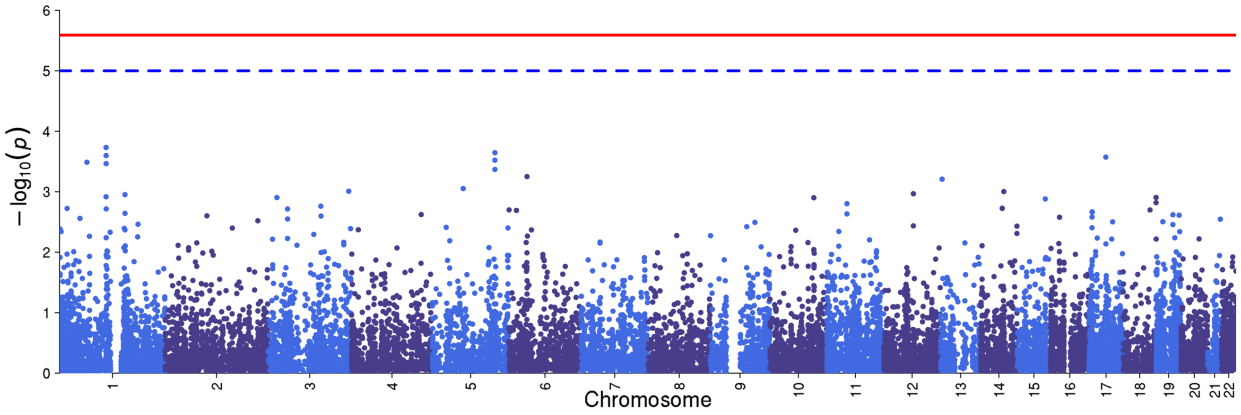
Negative log10-transformed p-values for each gene (y-axis) are plotted by chromosomal position (x-axis). Each dot represents a gene, and the solid red and dotted blue horizontal lines represent the thresholds for genome-wide significant association ($p = 2.57\times10^{-6}$) and suggestive association ($p = 1\times10^{-5}$), respectively.

Plots were generated using the plot package in R.

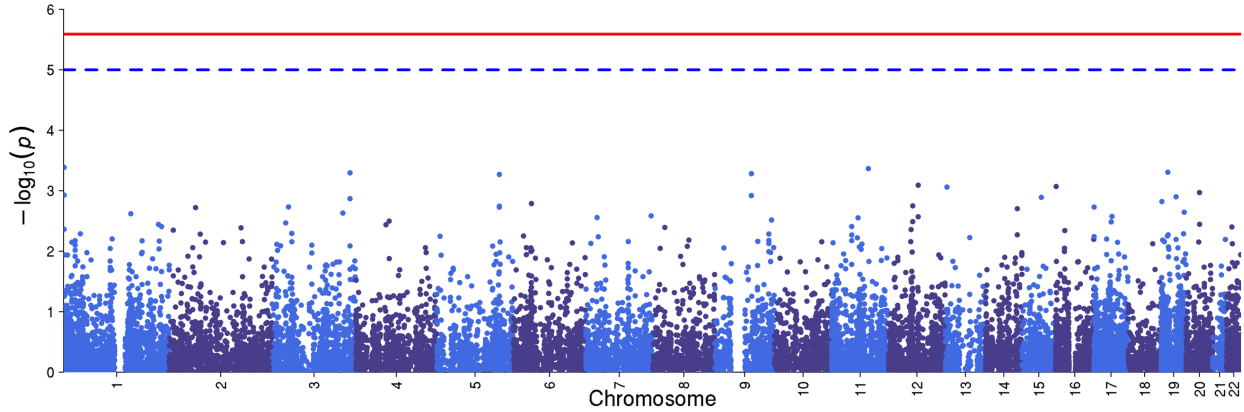
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; SLTM = SAFB Like Transcription Modulator



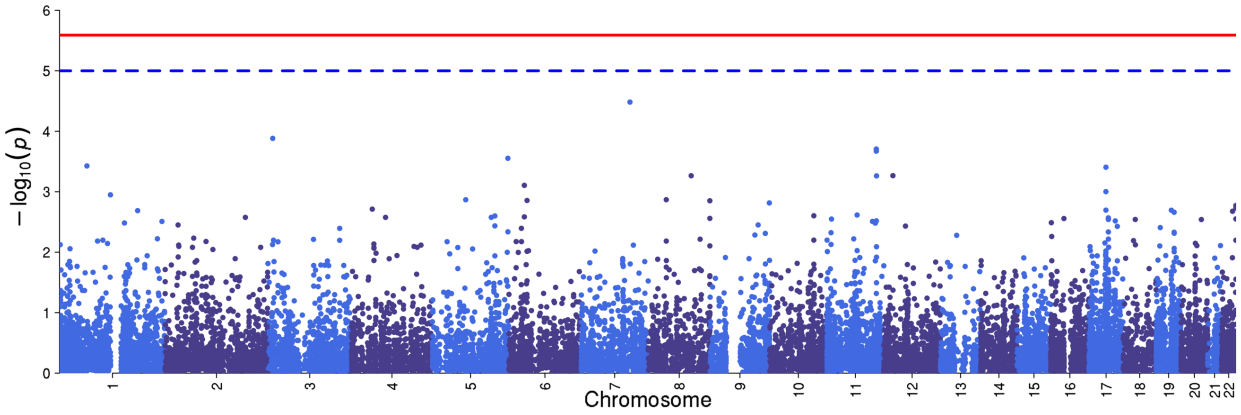
c) Major Depressive Disorder



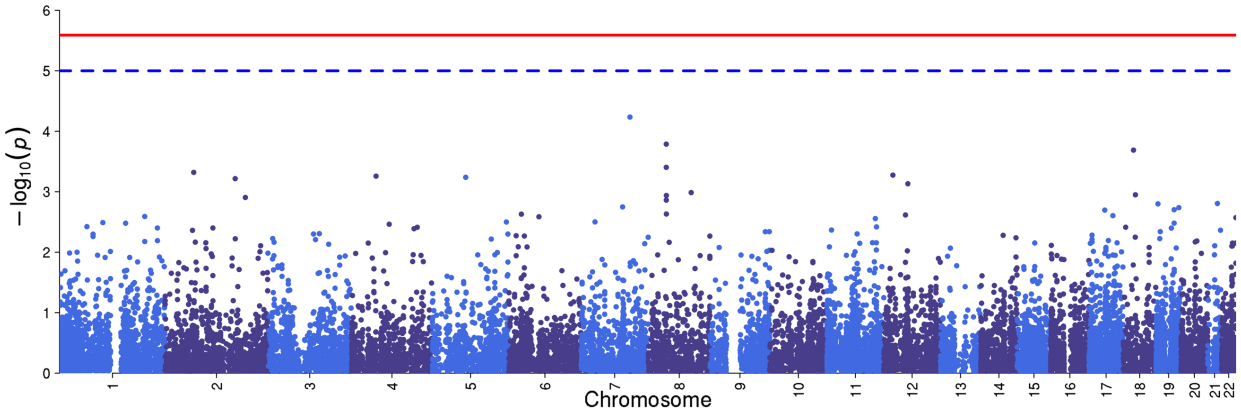
d) Recurrent Major Depressive Disorder



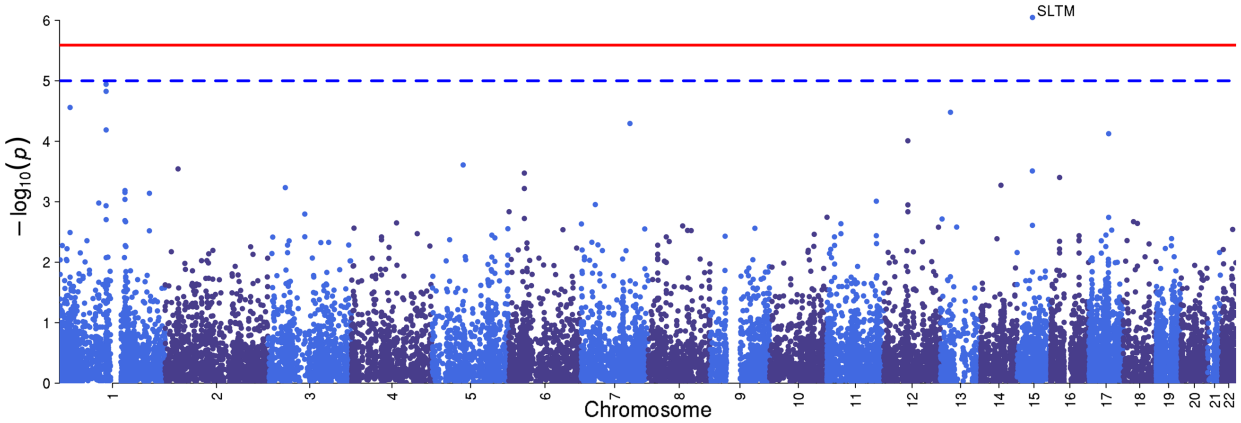
e) Cross-Disorder SCZ-BIP-MDD



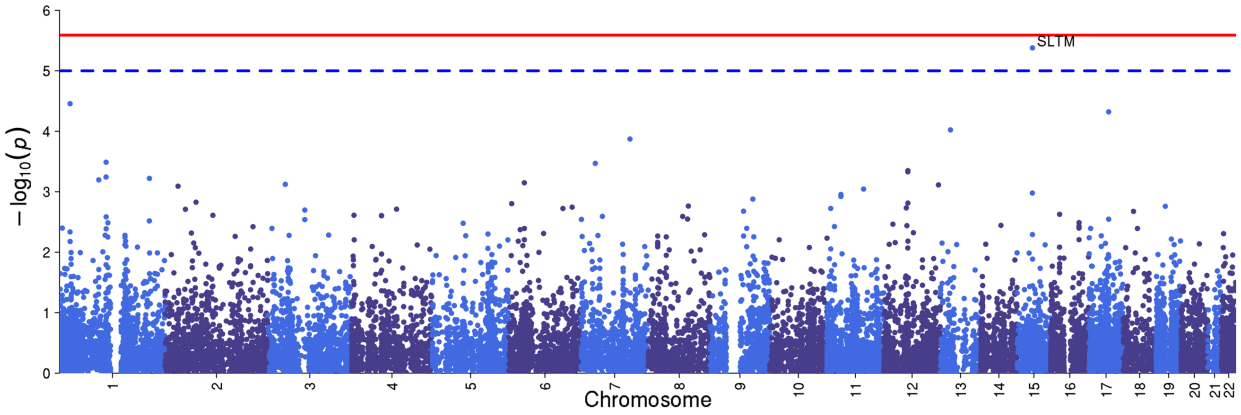
f) Cross-Disorder SCZ-BIP-rMDD



g) Omnibus Test SCZ-BIP-MDD



h) Omnibus Test SCZ-BIP-rMDD



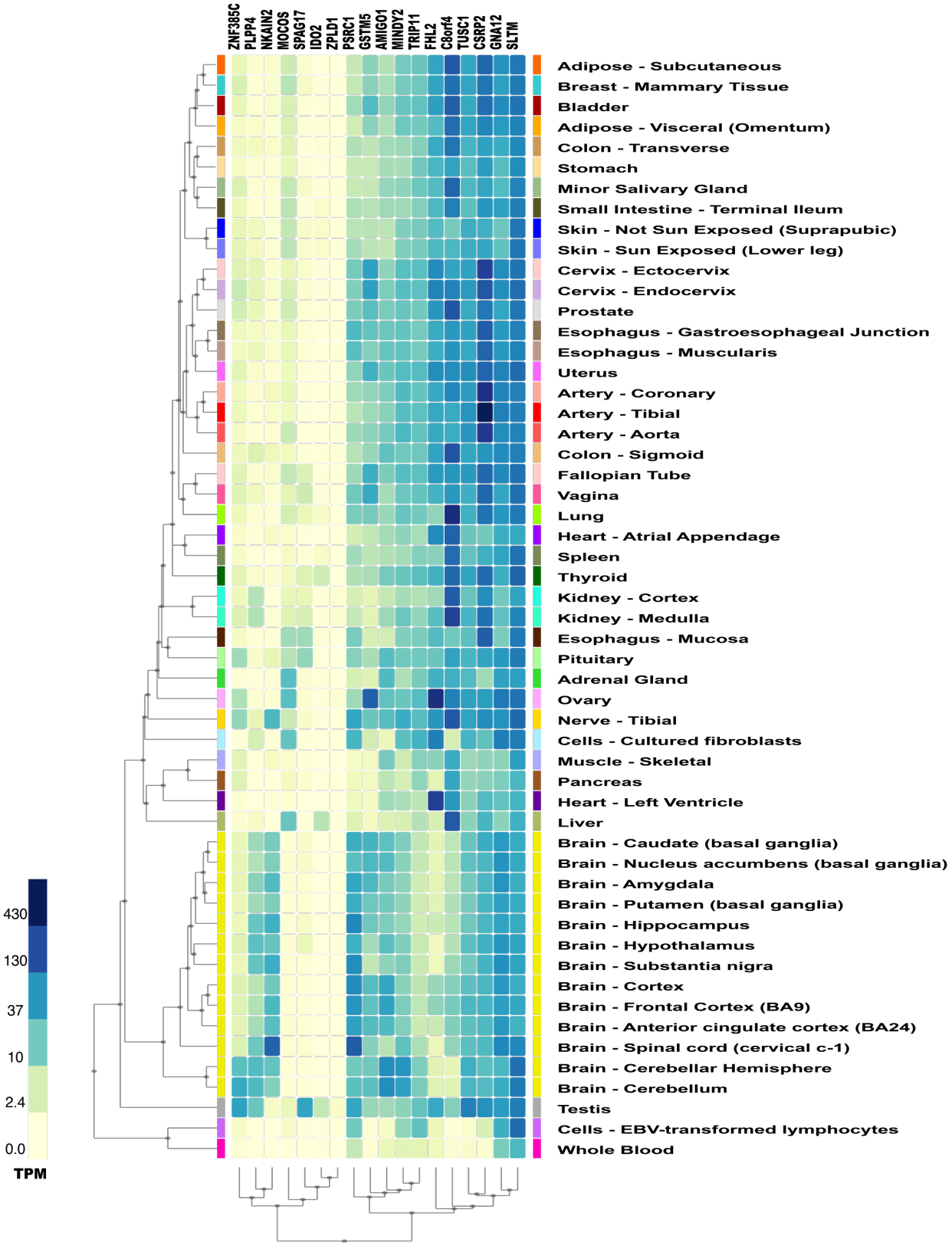
Supplementary Figure 11. GTEx multi-tissue expression for GxS loci

This plot was generated via website gtexportal.org.

Genes were included based on the following thresholds: SNP-based GxS interaction $p < 1\times10^{-6}$ and genes with gene-based test *p*-values $< 2.7\times10^{-6}$.

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.

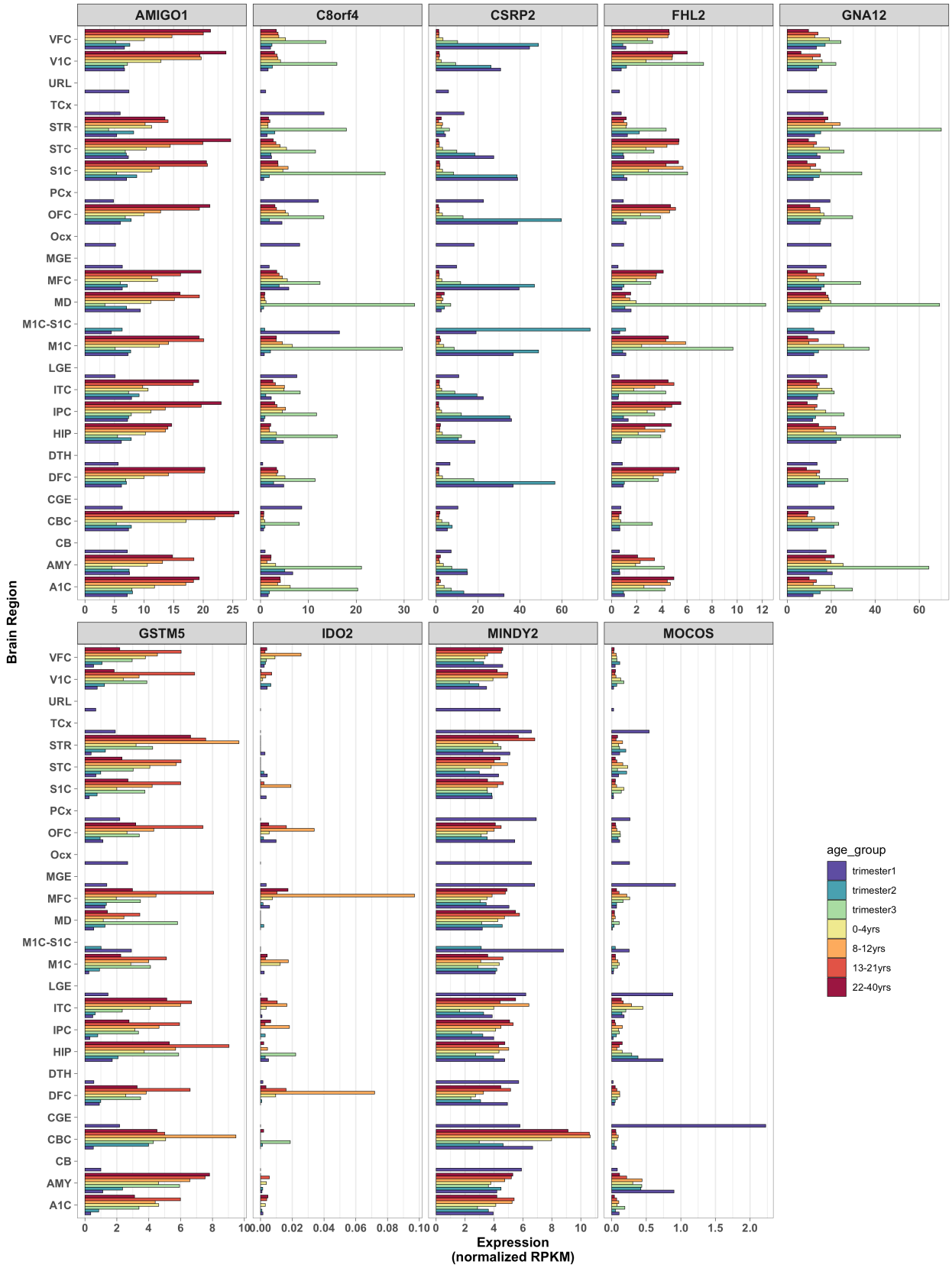

ZNF385C
PLPP4
NKAIN2
MOCOS
SPAG17
IDO2
ZPLD1
PSRC1
GSTM5
AMIGO1
MINDY2
TRIP11
FHL2
C8orf4
TUSC1
CSRP2
GNA12
SLTM
Adipose - Subcutaneous
Breast - Mammary Tissue
Bladder
Adipose - Visceral (Omentum)
Colon - Transverse
Stomach
Minor Salivary Gland
Small Intestine - Terminal Ileum
Skin - Not Sun Exposed (Suprapubic)
Skin - Sun Exposed (Lower leg)
Cervix - Ectocervix
Cervix - Endocervix
Prostate
Esophagus - Gastroesophageal Junction
Esophagus - Muscularis
Uterus
Artery - Coronary
Artery - Tibial
Artery - Aorta
Colon - Sigmoid
Fallopian Tube
Vagina
Lung
Heart - Atrial Appendage
Spleen
Thyroid
Kidney - Cortex
Kidney - Medulla
Esophagus - Mucosa
Pituitary
Adrenal Gland
Ovary
Nerve - Tibial
Cells - Cultured fibroblasts
Muscle - Skeletal
Pancreas
Heart - Left Ventricle
Liver
Brain - Caudate (basal ganglia)
Brain - Nucleus accumbens (basal ganglia)
Brain - Amygdala
Brain - Putamen (basal ganglia)
Brain - Hippocampus
Brain - Hypothalamus
Brain - Substantia nigra
Brain - Cortex
Brain - Frontal Cortex (BA9)
Brain - Anterior cingulate cortex (BA24)
Brain - Spinal cord (cervical c-1)
Brain - Cerebellar Hemisphere
Brain - Cerebellum
Testis
Cells - EBV-transformed lymphocytes
Whole Blood
430
130
37
10
2.4
0.0
TPM

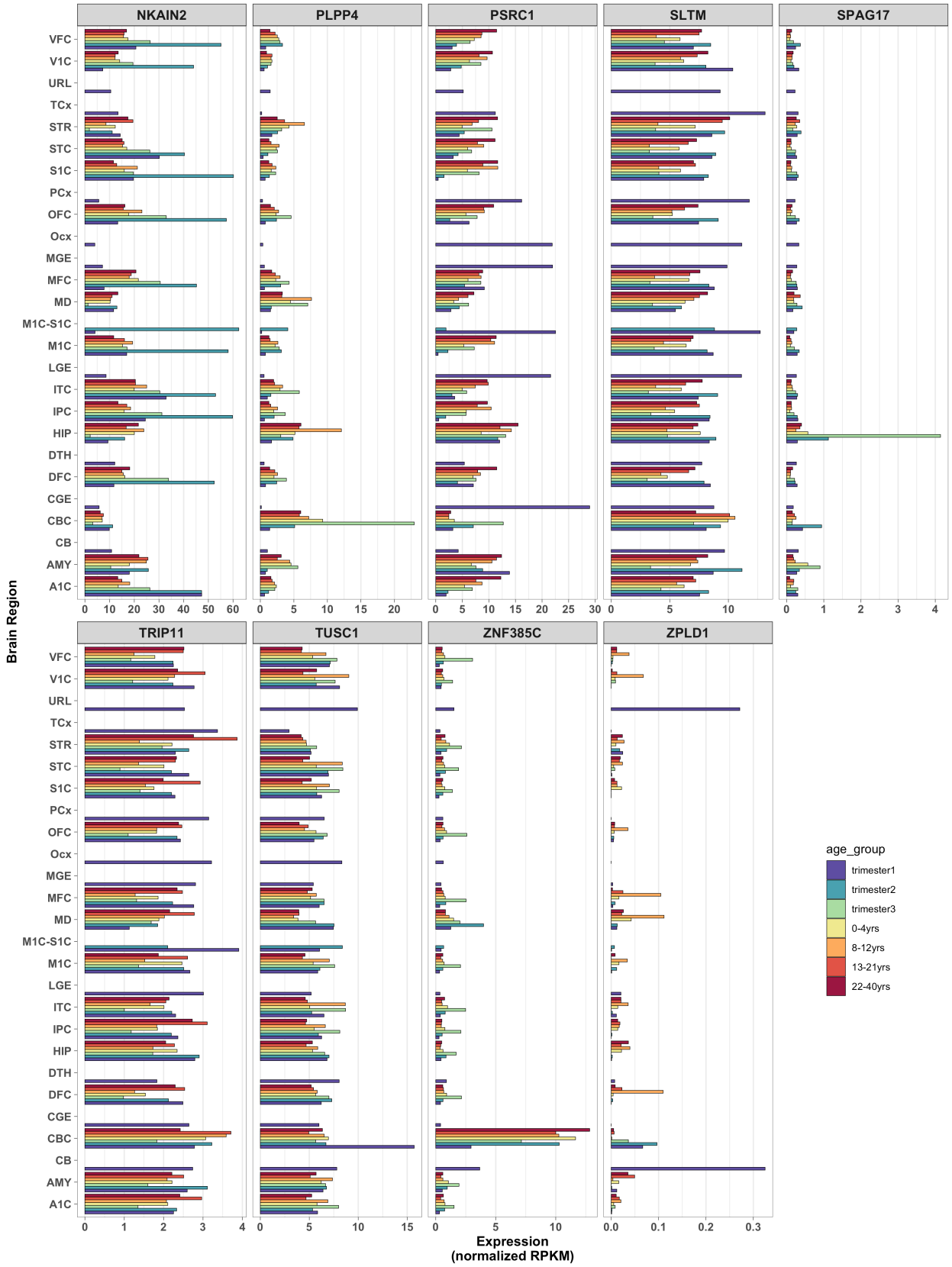
Supplementary Figure 12. Allen Brain Atlas expression across development for GxS loci

Plots were generated using the ggplot 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 GxS interaction $p < 1\times10^{-6}$ and genes with gene-based test p-values $< 2.7\times10^{-6}$.

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

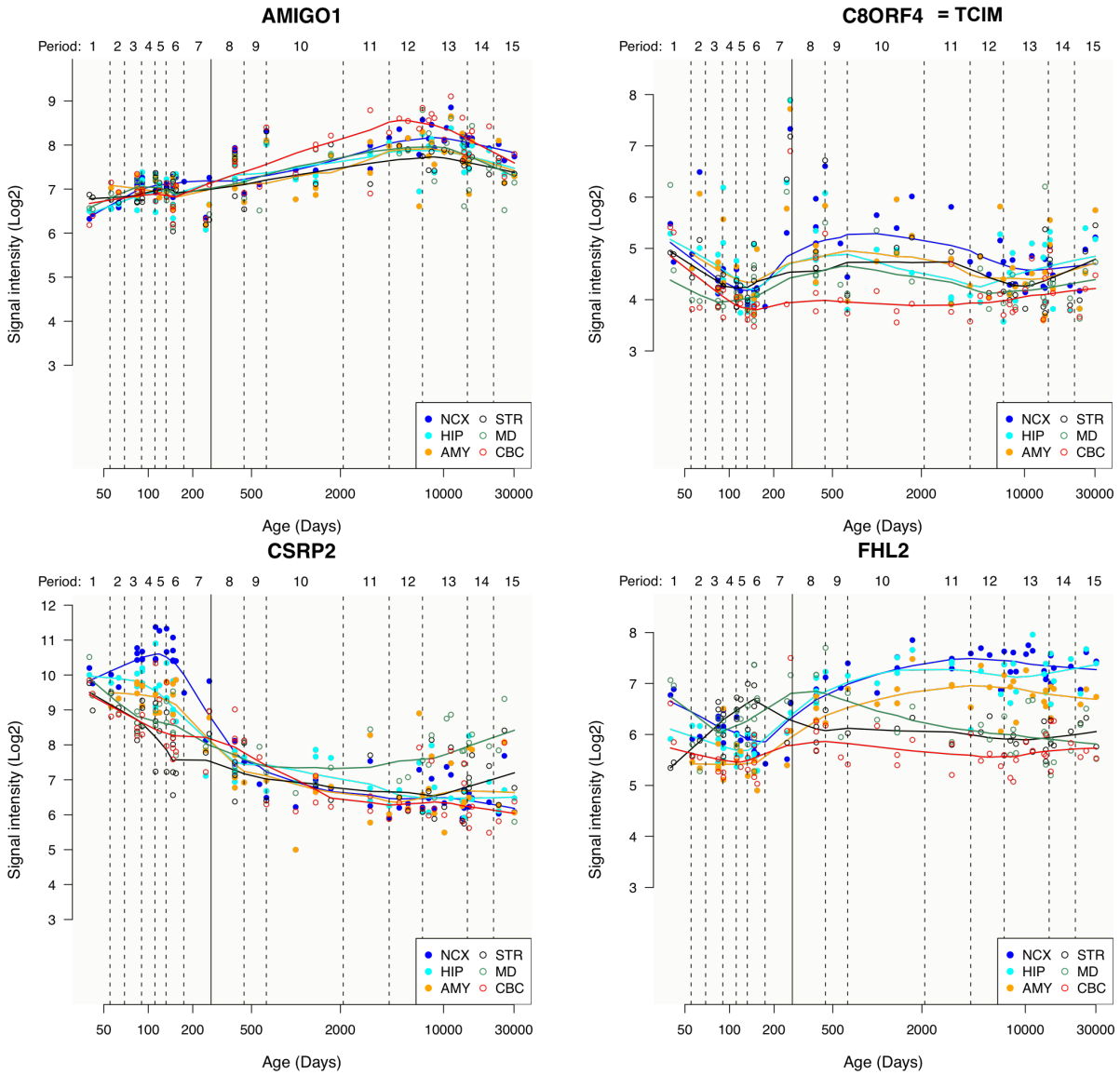

AMIGO1
C8orf4
CSRP2
FHL2
GNA12
GSTM5
IDO2
MINDY2
MOCOS
Brain Region
VFC
V1C
URL
TCx
STR
STC
S1C
PCx
OFC
Ocx
MGE
MFC
MD
M1C-S1C
M1C
LGE
ITC
IPC
HIP
DTH
DFC
CGE
CBC
CB
AMY
A1C
Expression
(normalized RPKM)
age_group
trimester1
trimester2
trimester3
0-4yrs
8-12yrs
13-21yrs
22-40yrs

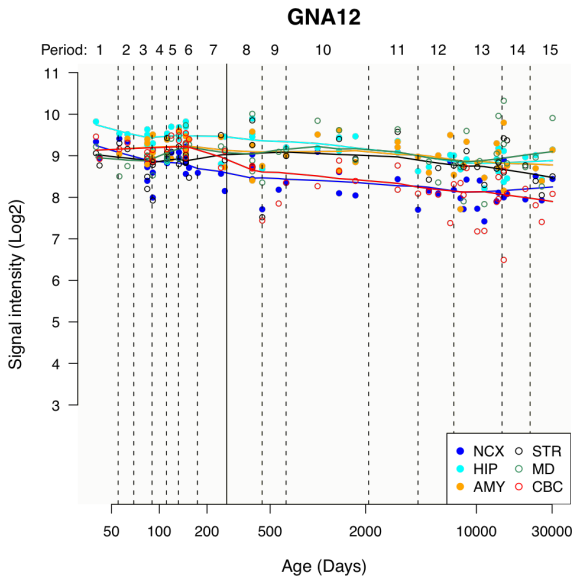

NKAIN2
PLPP4
PSRC1
SLTM
SPAG17
TRIP11
TUSC1
ZNF385C
ZPLD1
Brain Region
VFC
V1C
URL
TCx
STR
STC
S1C
PCx
OFC
Ocx
MGE
MFC
MD
M1C-S1C
M1C
LGE
ITC
IPC
HIP
DTH
DFC
CGE
CBC
CB
AMY
A1C
Expression
(normalized RPKM)
age_group
trimester1
trimester2
trimester3
0-4yrs
8-12yrs
13-21yrs
22-40yrs

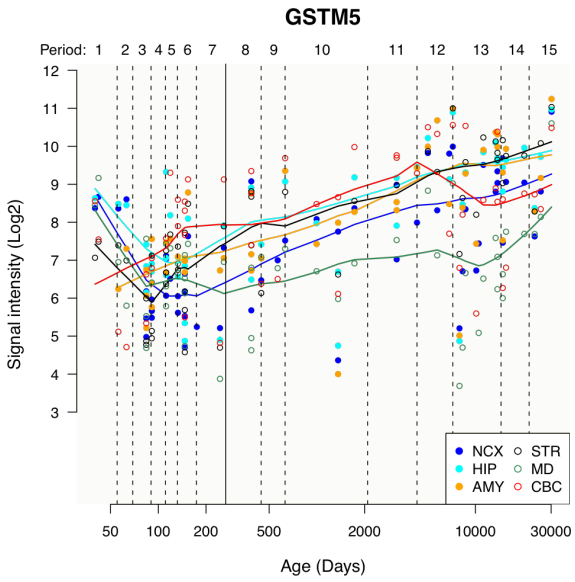
Supplementary Figure 13. Life brain expression course derived from the Human Brain Transcriptome (HBT) Project for GxS loci

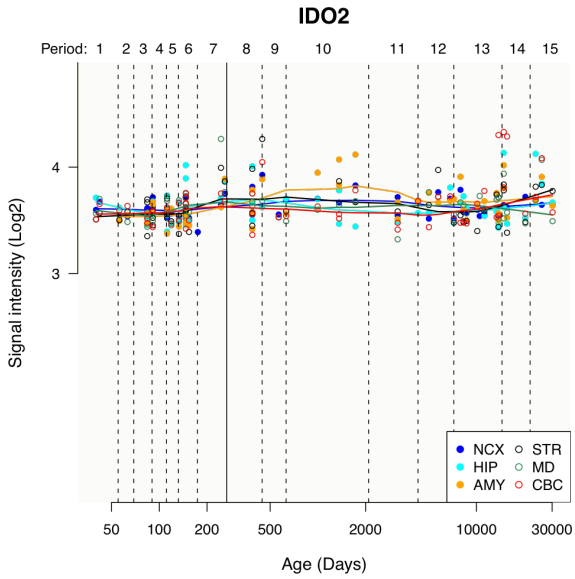
Plots were generated via website hbatlas.org. Genes were included, in alphabetical order, based on the following thresholds: SNP-based GxS interaction $p < 1\times10^{-6}$ and genes with gene-based test *p*-values $< 2.7\times10^{-6}$. Periods 1 through 7 are prenatal; Periods 8 and 9 are infant and 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.

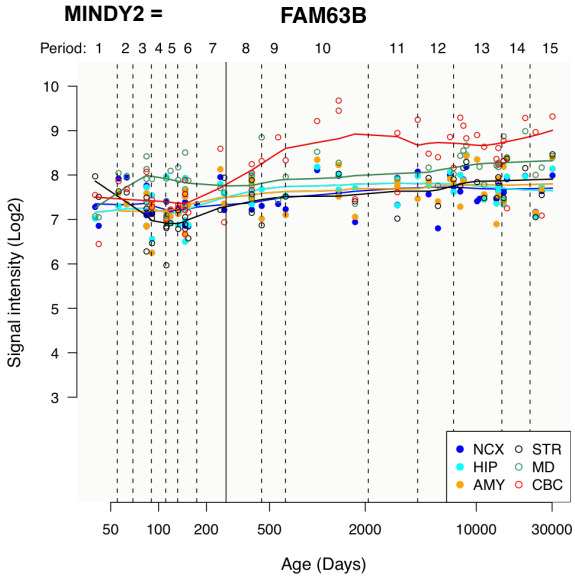
Abbreviations: CBC = cerebellar cortex; MD = mediodorsal nucleus of the thalamus; STR = striatum; AMY = amygdala; HIP = hippocampus; NCX = 11 areas of neocortex.




GNA12
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC


GSTM5
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC


IDO2
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC


MINDY2 = FAM63B
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
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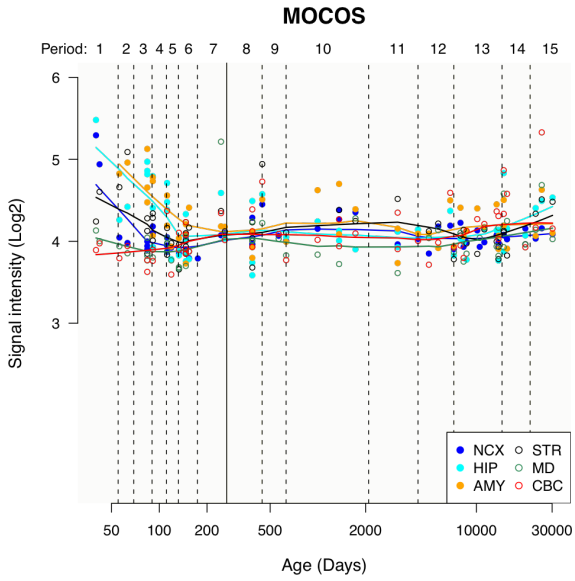
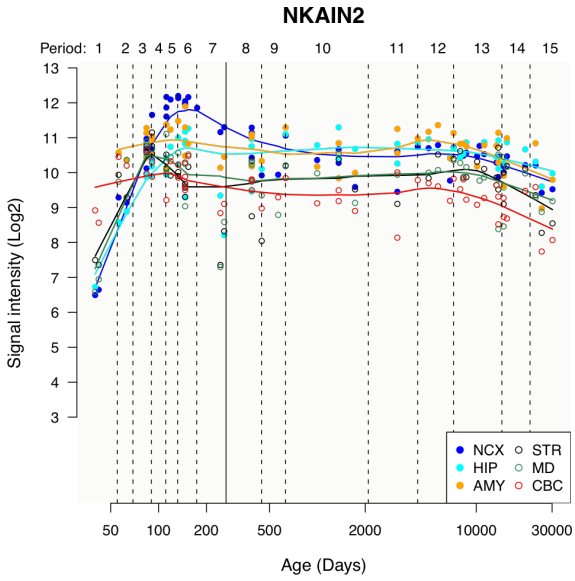
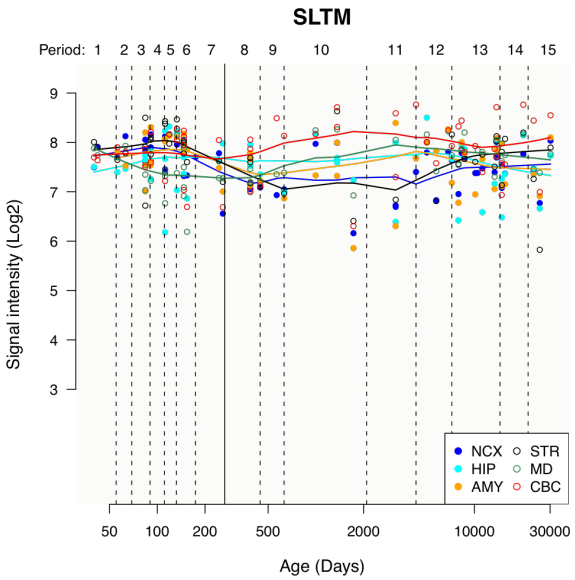
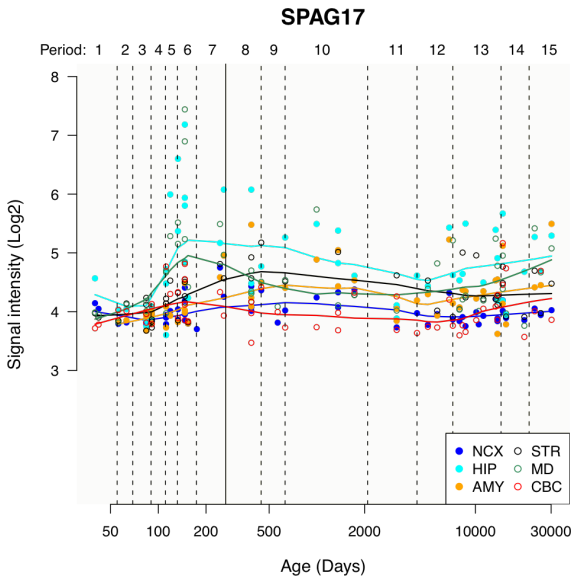
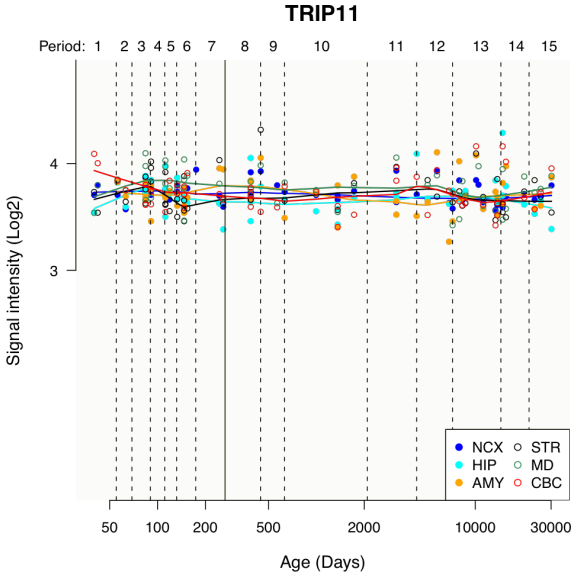
NCX STR
HIP MD
AMY CBC

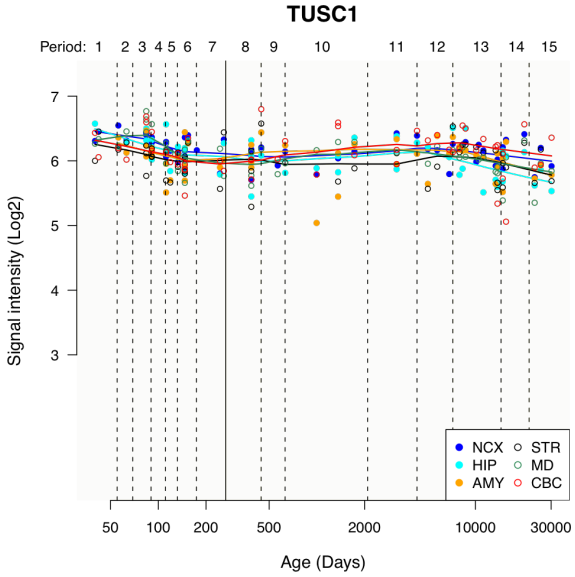

MOCOS
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC

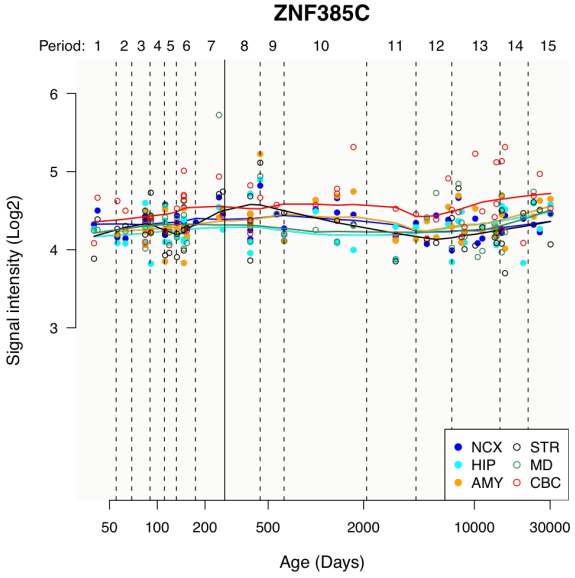

NKAIN2
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC

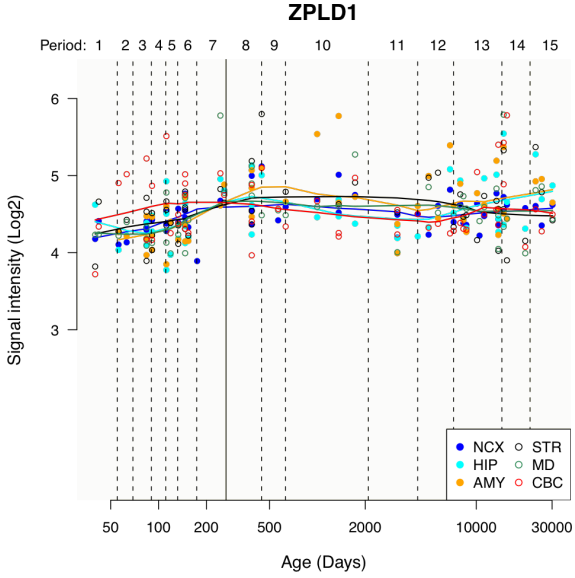

SLTM
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC


SPAG17
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC


TRIP11
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC


TUSC1
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC

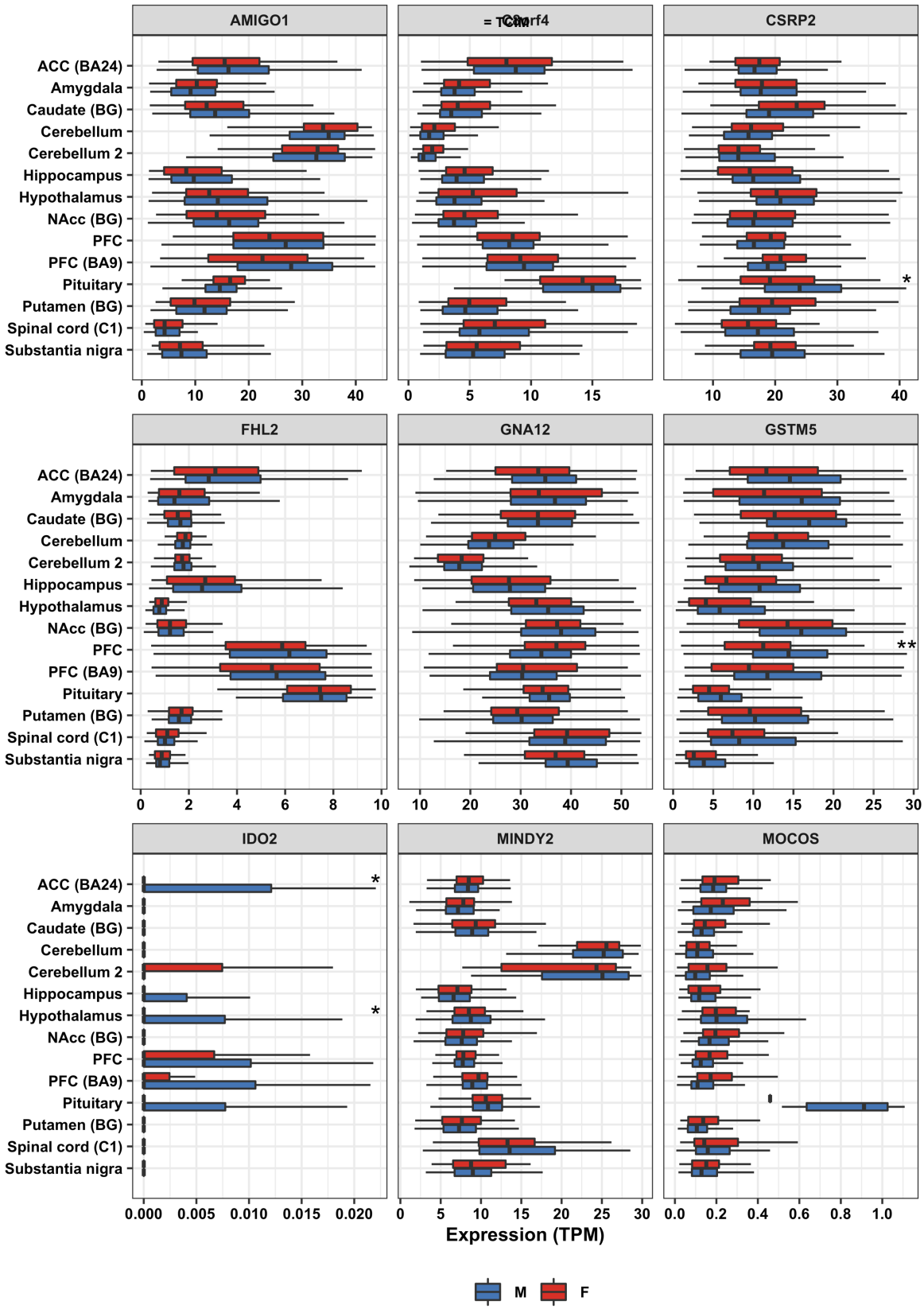

ZNF385C
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC

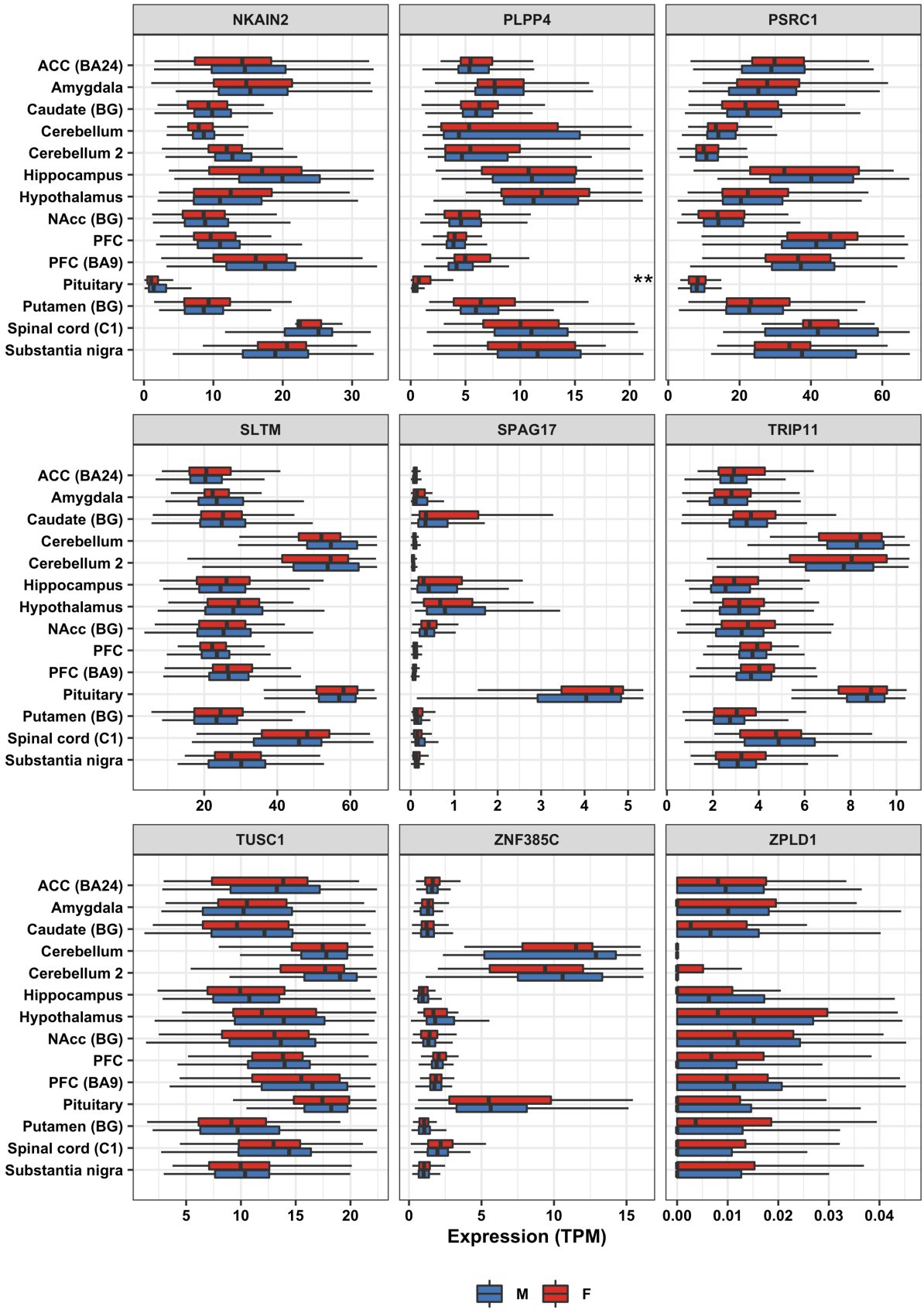

ZPLD1
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC

Supplementary Figure 14. GTEx sex-specific multi-tissue expression for GxS 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 ggplot package in R. Genes were included, in alphabetical order, based on the following thresholds: SNP-based GxS interaction $p < 1\times10^{-6}$ and genes with gene-based test *p*-values < 2.7×10^{-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 mannesr 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.

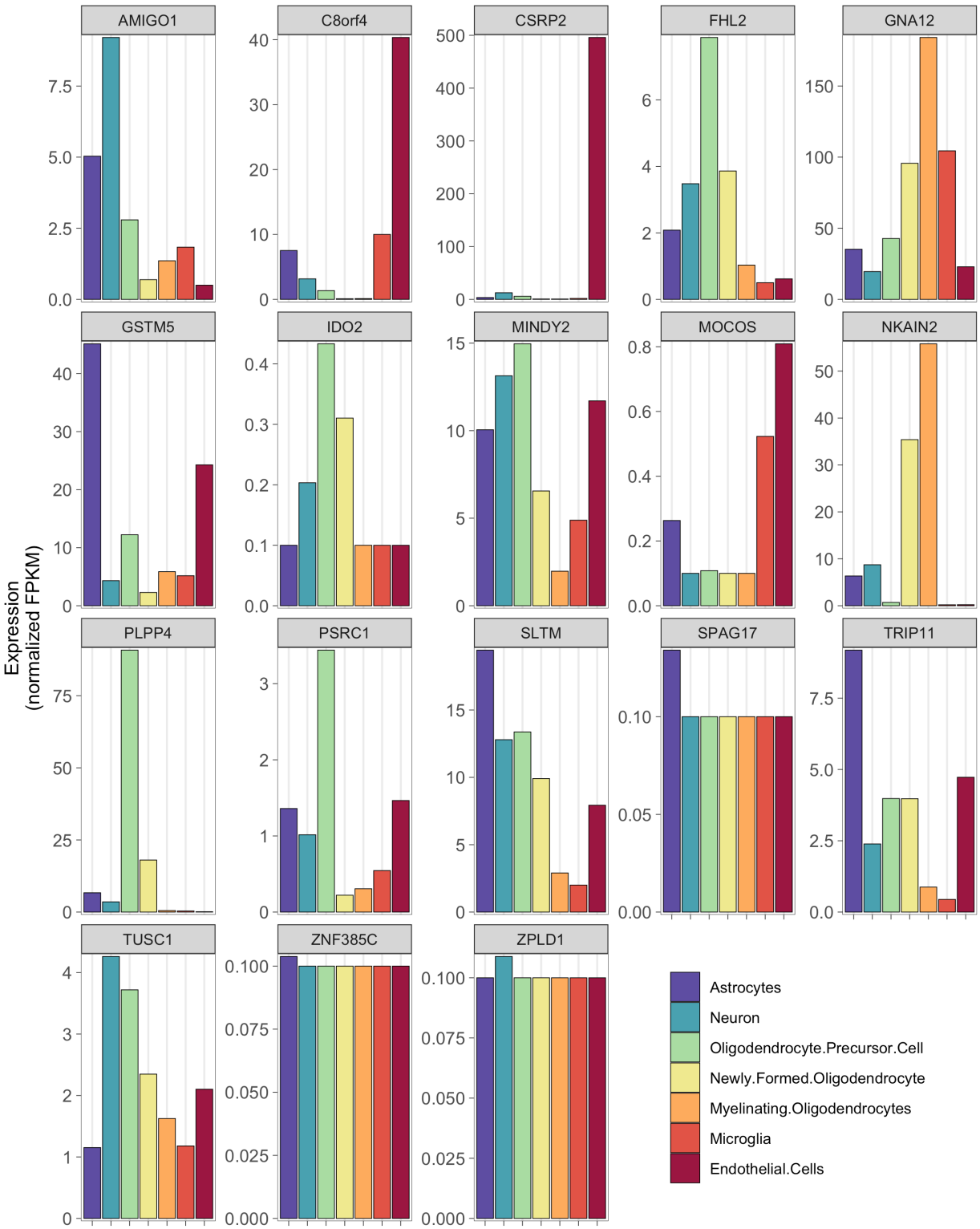

AMIGO1
C9orf4
CSRP2
FHL2
GNA12
GSTM5
IDO2
MINDY2
MOCOS
ACC (BA24)
Amygdala
Caudate (BG)
Cerebellum
Cerebellum 2
Hippocampus
Hypothalamus
NAcc (BG)
PFC
PFC (BA9)
Pituitary
Putamen (BG)
Spinal cord (C1)
Substantia nigra
Expression (TPM)
M
F


NKAIN2
PLPP4
PSRC1
SLTM
SPAG17
TRIP11
TUSC1
ZNF385C
ZPLD1
ACC (BA24)
Amygdala
Caudate (BG)
Cerebellum
Cerebellum 2
Hippocampus
Hypothalamus
NAcc (BG)
PFC
PFC (BA9)
Pituitary
Putamen (BG)
Spinal cord (C1)
Substantia nigra
**
Expression (TPM)
M
F

Supplementary Figure 15. Cell type-specific brain expression derived from the Stanford RNA-Seq database for GxS 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 GxS interaction $p < 1\times10^{-6}$ and genes with gene-based test p-values $< 2.7\times10^{-6}$. Plots were generated using the ggplot 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.


AMIGO1
C8orf4
CSRP2
FHL2
GNA12
GSTM5
IDO2
MINDY2
MOCOS
NKAIN2
PLPP4
PSRC1
SLTM
SPAG17
TRIP11
TUSC1
ZNF385C
ZPLD1
Expression (normalized FPKM)
Astrocytes
Neuron
Oligodendrocyte.Precursor.Cell
Newly.Formed.Oligodendrocyte
Myelinating.Oligodendrocytes
Microglia
Endothelial.Cells

Supplementary Tables PGC only

Supplementary Table 15. Meta-analysis Autosomal GxS interaction loci in PGC

See SupplTable15_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 < 1×10^{-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.

Supplementary Table 16. Omnibus test Autosomal GxS interaction loci in PGC

See SupplTable16_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 < 1×10^{-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.

Supplementary Table 17. Meta-analysis chrX GxS interaction loci in PGC

See SupplTable17_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 < 1×10^{-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.

Supplementary Table 18. Omnibus test chrX GxS interaction loci in PGC

See SupplTable18_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 < 1×10^{-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.

Supplementary Table 19. Credible SNPs for GxS loci in PGC

See SupplTable19_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 $p < 1\times10^{-6}$ 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.

Supplementary Table 20. Gene-based test in PGC

See SupplTable20_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 $< 1\times10^{-4}$ 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; MDD = major depressive disorder; rMDD = recurrent major depressive disorder; SCZ = schizophrenia.

Supplementary Table 21. MSigDB pathway gene set enrichment analyses in PGC

See SupplTable21_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; MDD = major depressive disorder; P_{BONF} = Bonferroni-corrected *p*-value; P_{FDR} = False Discovery Rate-corrected *p*-value; rMDD = recurrent major depressive disorder; SCZ = schizophrenia; SE = Standard Error.

Supplementary Table 22. Selected pathway gene set enrichment analyses in PGC

See SupplTable22_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; MDD = major depressive disorder; MP = Mouse Phenome; P_{FDR} = False Discovery Rate-corrected *p*-value; PGC-NPA = Psychiatric Genomics Consortium – Network and Pathway Analysis Working Group; rMDD = recurrent major depressive disorder; SCZ = schizophrenia; SE = Standard Error.

Supplementary Figures PGC only

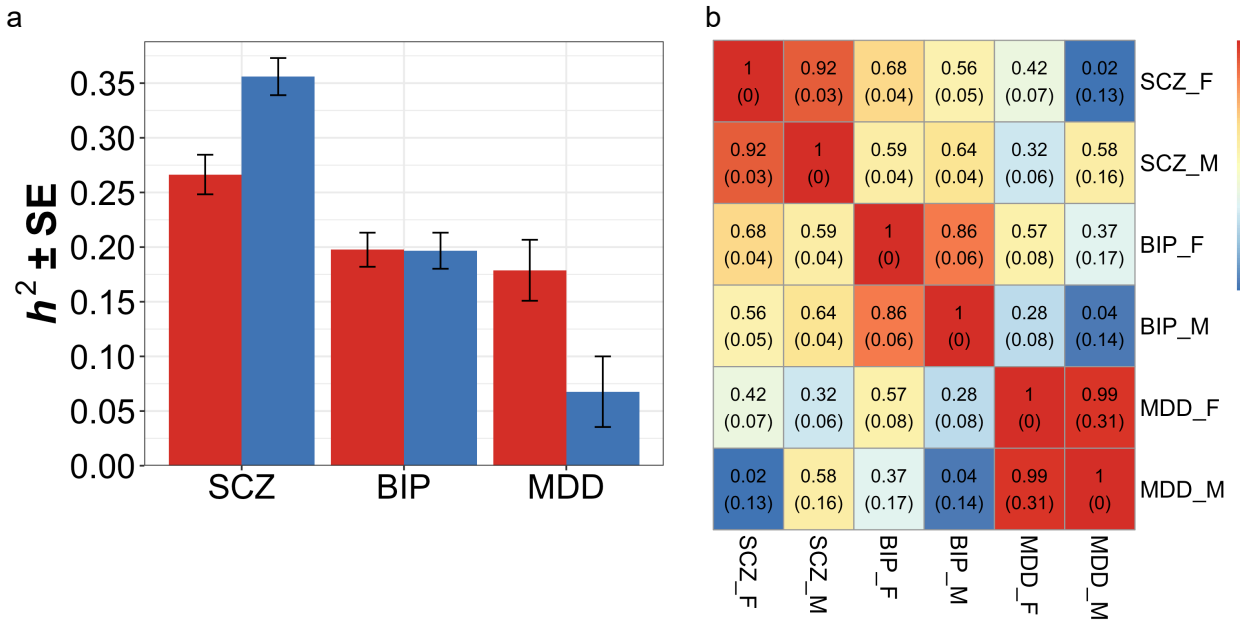
Supplementary Figure 16. LD Score Regression estimates of SNP-based (a) heritability and (b) genetic correlations (SE) in PGC only

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) 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.

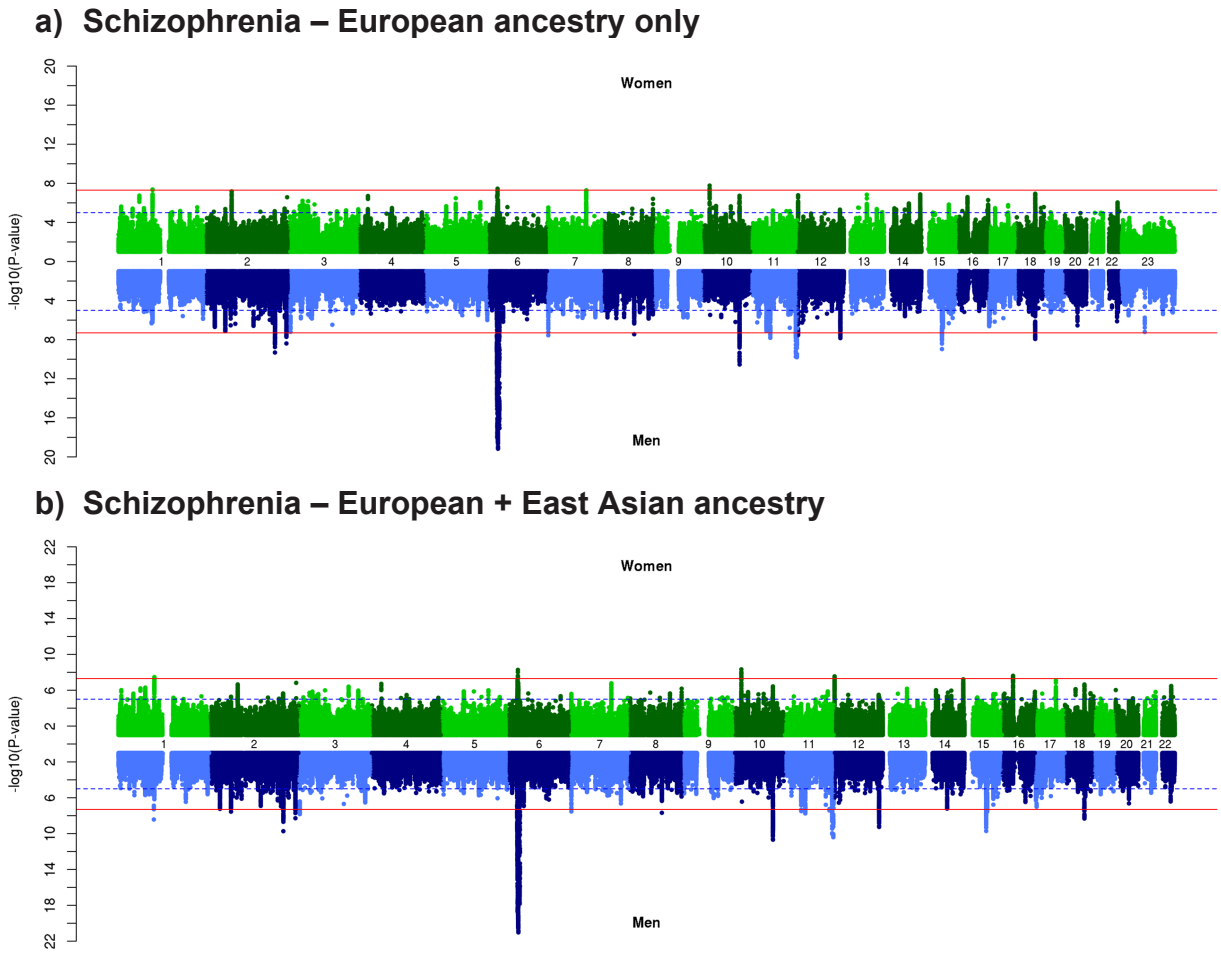


Supplementary Figure 17. Miami plots for sex-stratified analyses in PGC

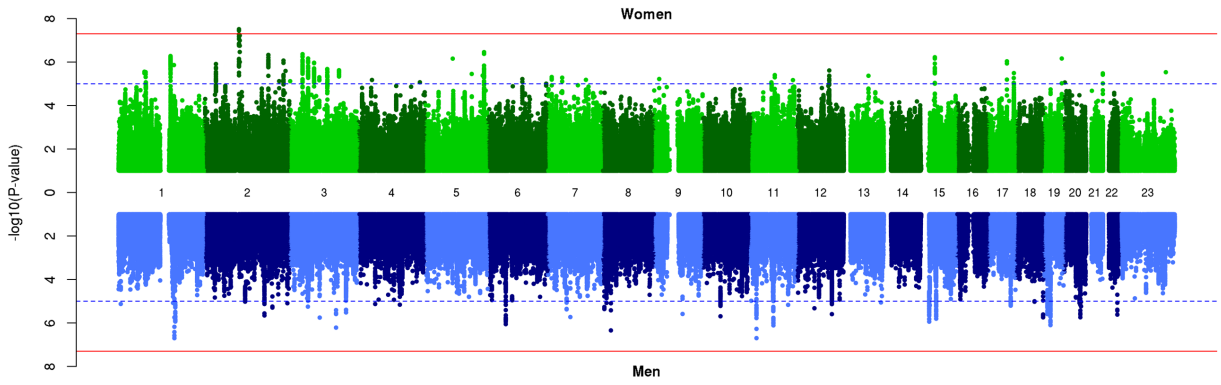
GWAS SNP main effects for men (blue) are plotted downward, and are plotted upward for women (green). Negative log10-transformed p-values for each variant (each dot) (y-axis) are plotted by chromosomal position (x-axis). The solid red and dotted blue horizontal lines represent the thresholds for genome-wide significant association ($p = 5\times10^{-8}$) and suggestive association ($p = 1\times10^{-5}$), 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.

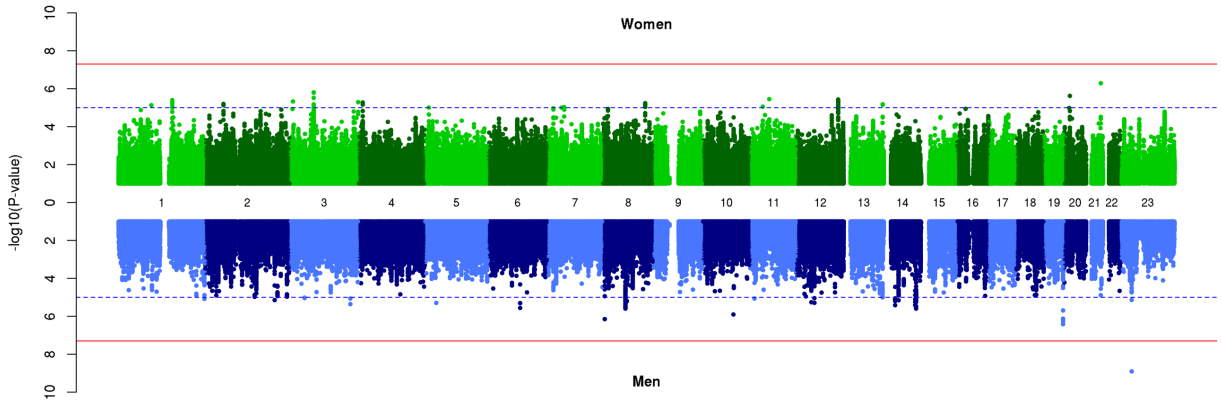
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia



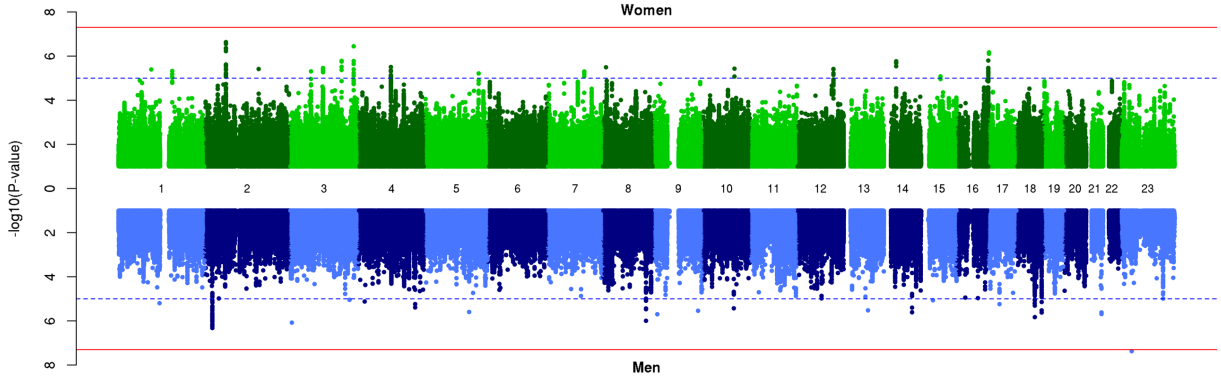
c) Bipolar Disorder



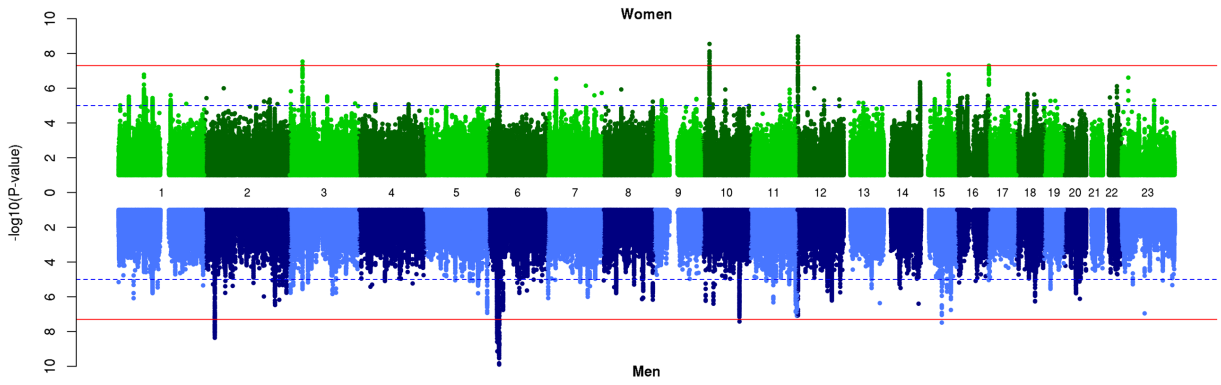
d) Major Depressive Disorder



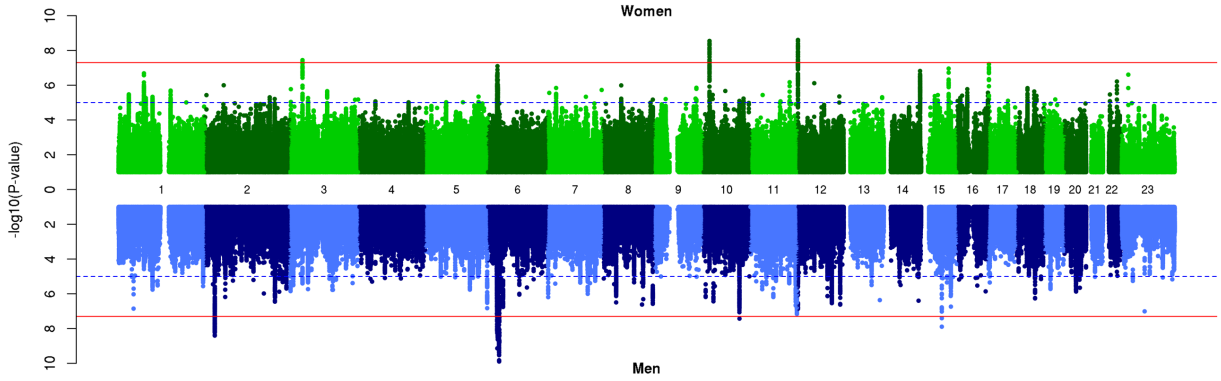
e) Recurrent Major Depressive Disorder



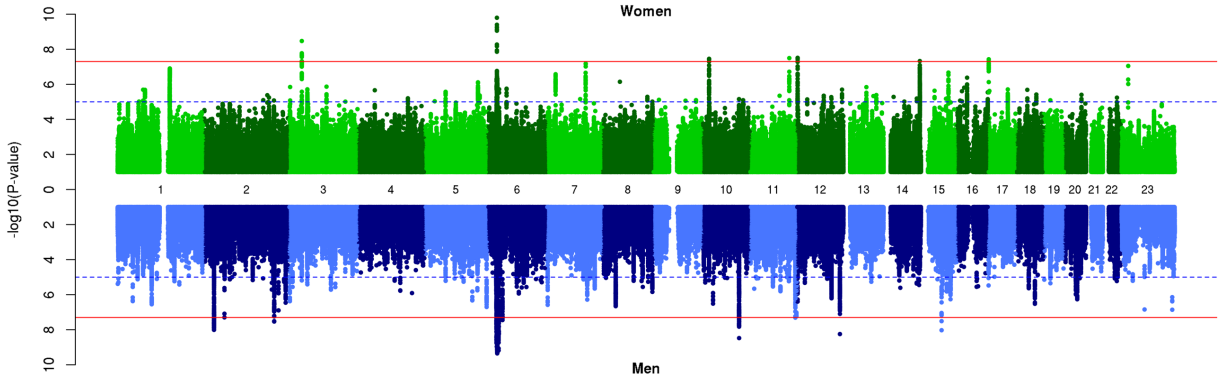
f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



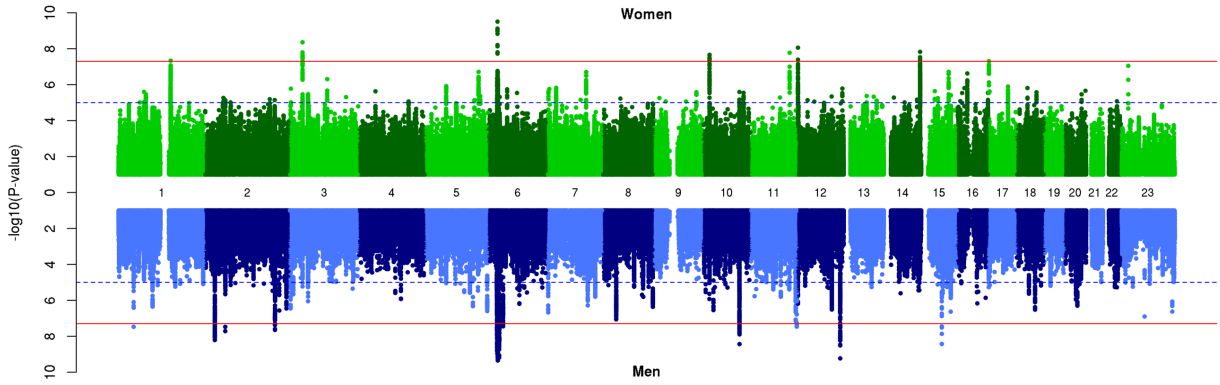
g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



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



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

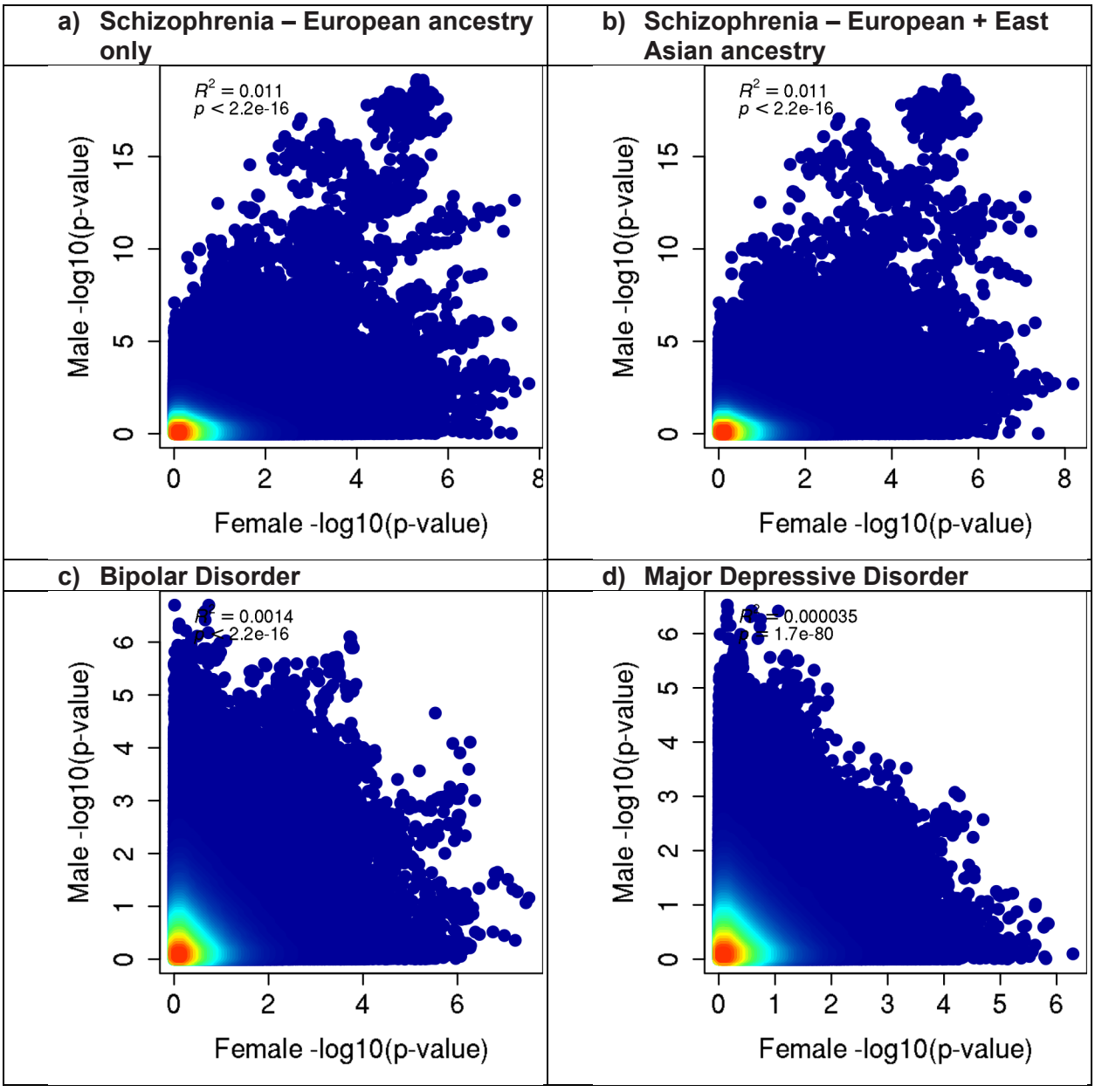


Supplementary Figure 18. Scatter plots of female vs male associations in PGC

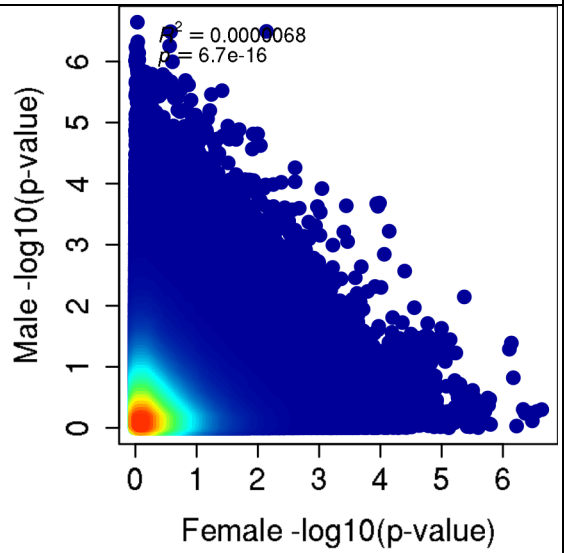
The scatter plots show little correlation (R) between GWAS SNP main effect *p*-values from the two sexes, indicating the strength of association differed substantially between the two sexes.

Plots were generated using the plot package in R.

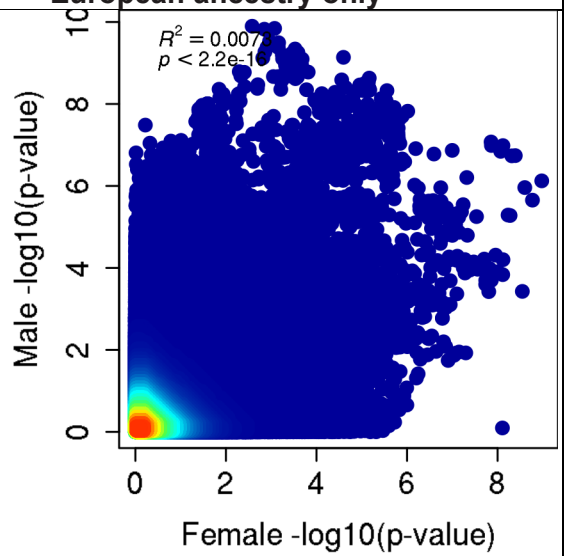
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; R^2 = proportion variance explained.



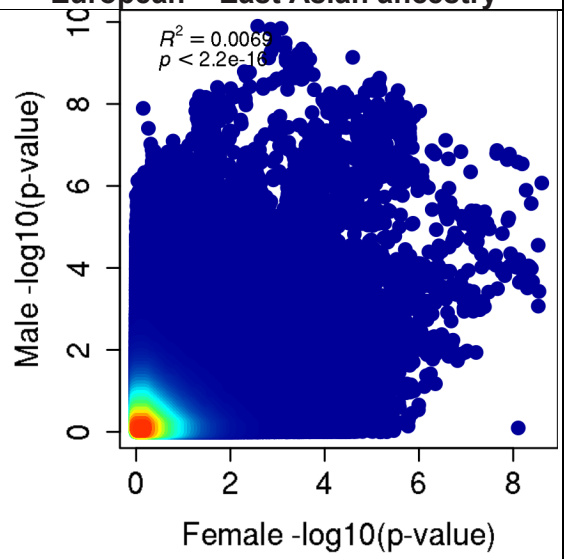
e) Recurrent Major Depressive Disorder

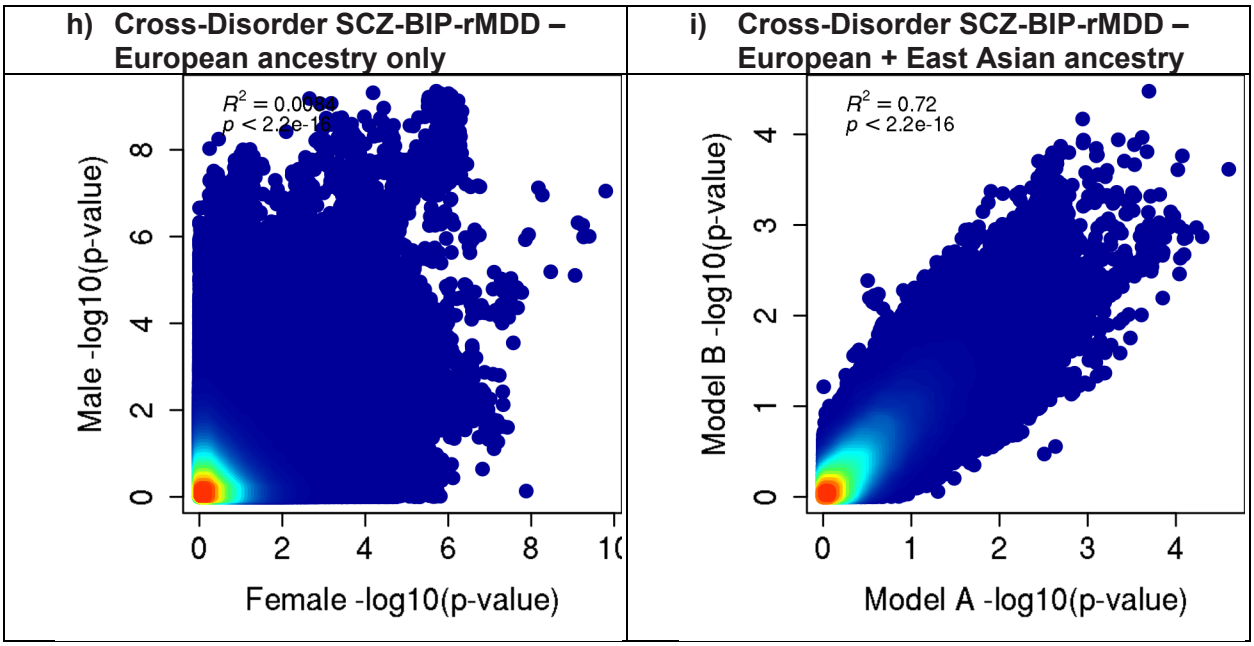


f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



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

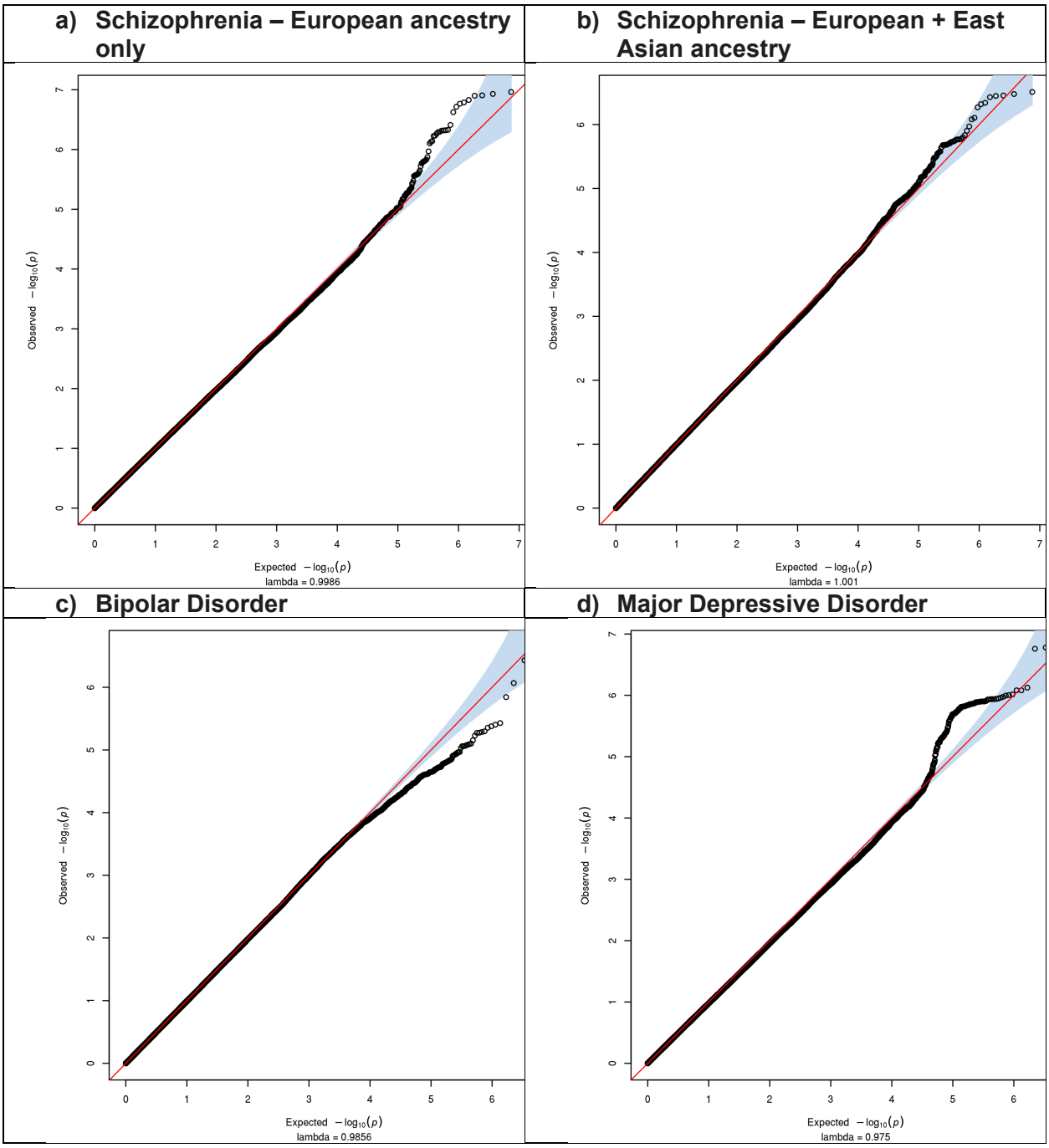



h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only
R^2 = 0.0088
p < 2.2e-16
Male -log10(p-value)
Female -log10(p-value)
0
2
4
6
8
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry
R^2 = 0.72
p < 2.2e-16
Model B -log10(p-value)
Model A -log10(p-value)
0
1
2
3
4

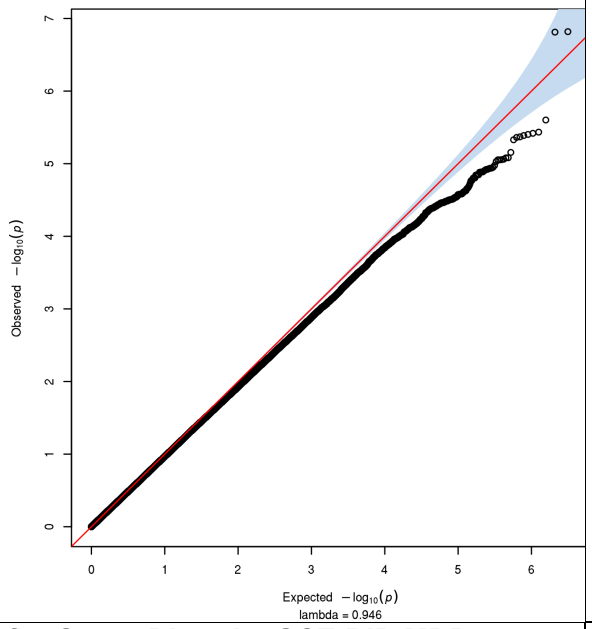
Supplementary Figure 19. Quantile-Quantile (Q-Q) plots for GxS interaction in PGC

The 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.

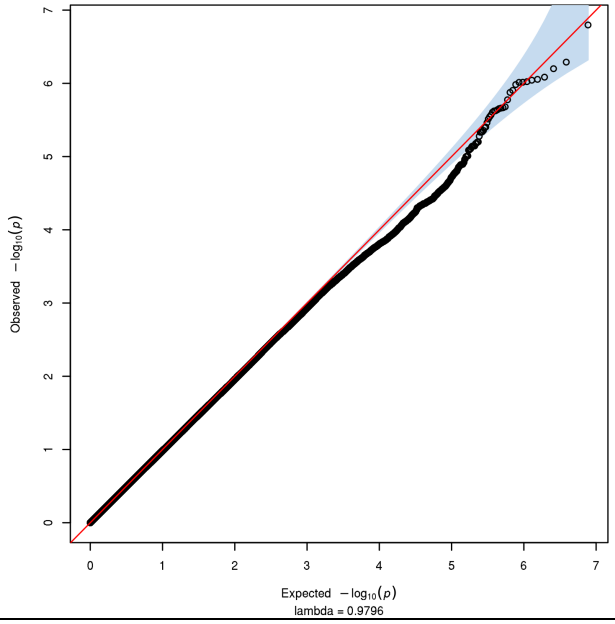
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia



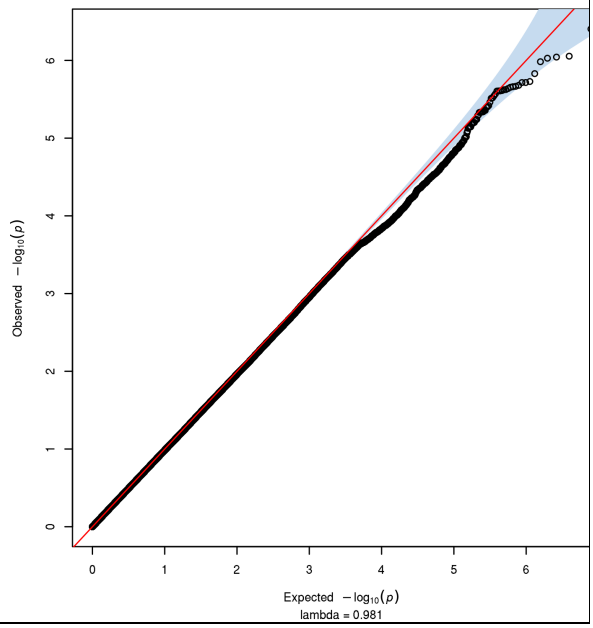
e) Recurrent Major Depressive Disorder



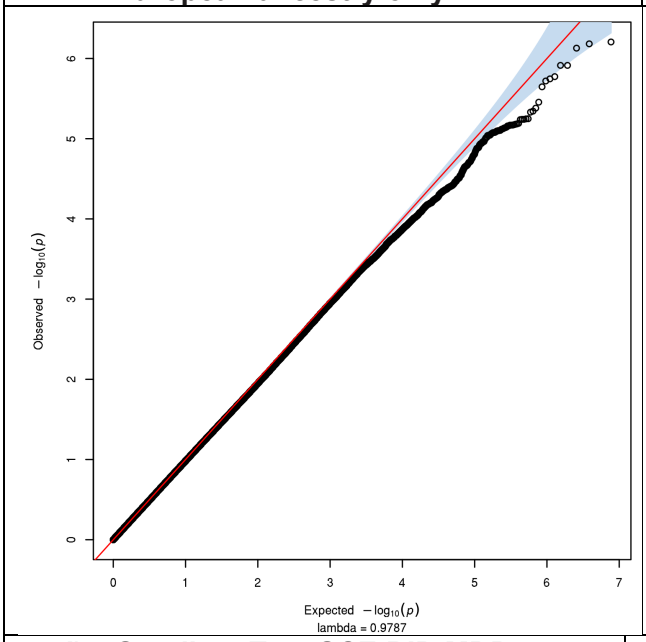
f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



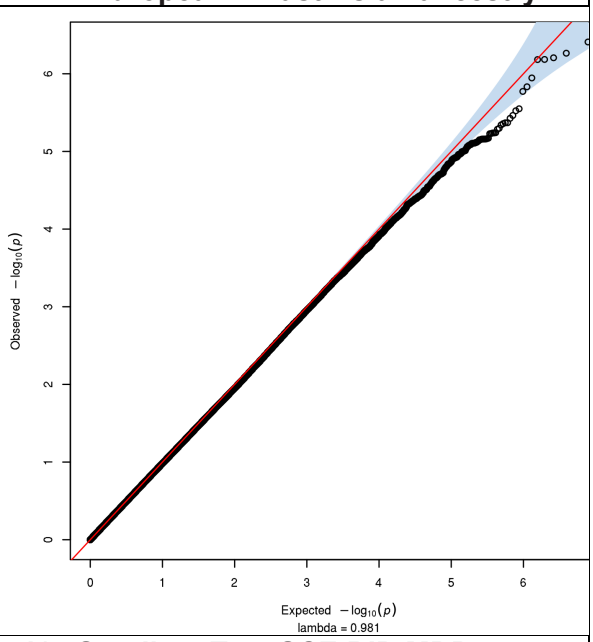
g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



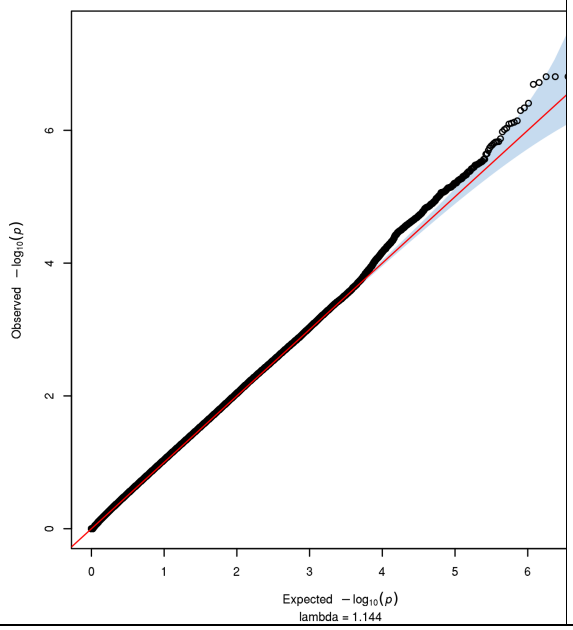
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



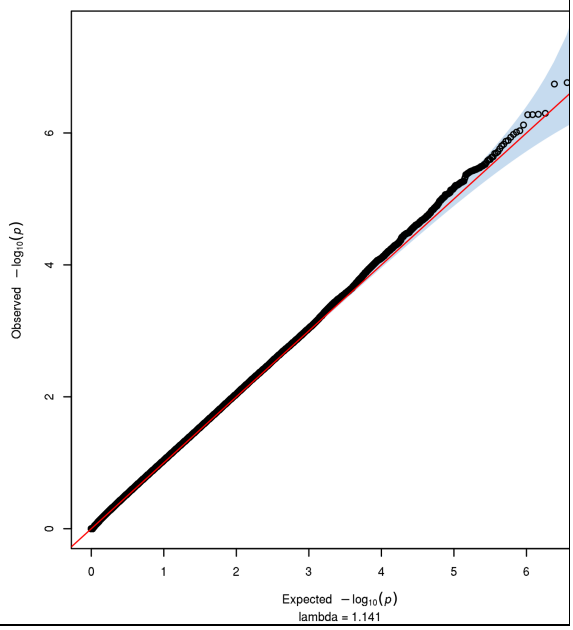
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry



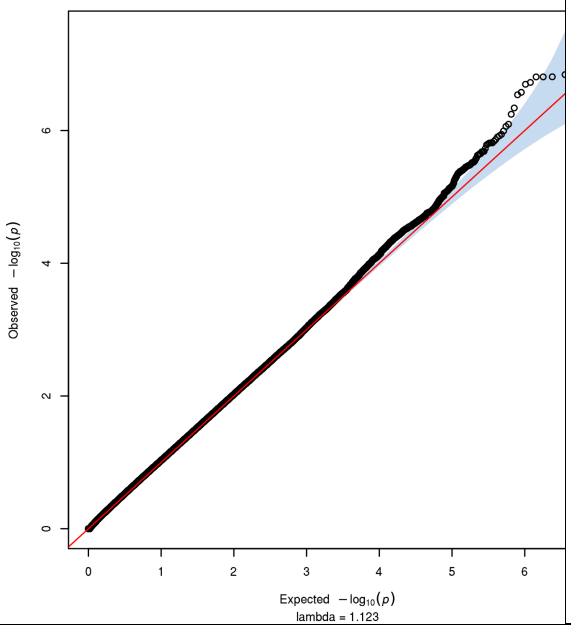
j) Omnibus Test SCZ-BIP-MDD – European ancestry only



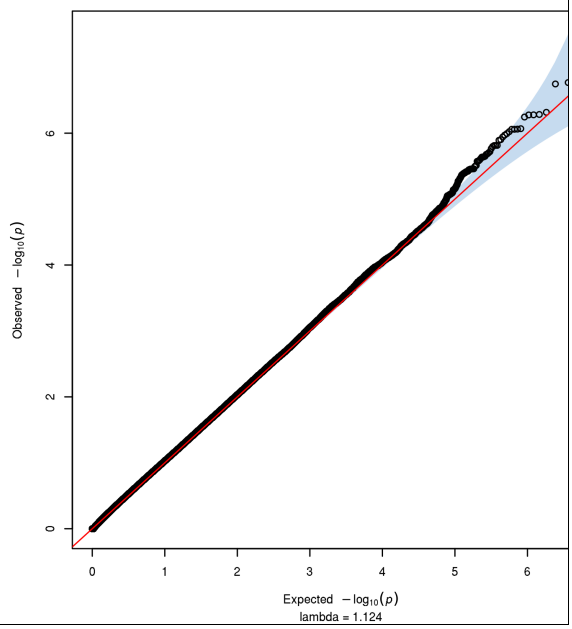
k) Omnibus Test SCZ-BIP-MDD – European + East Asian ancestry



l) Omnibus Test SCZ-BIP-rMDD – European ancestry only



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

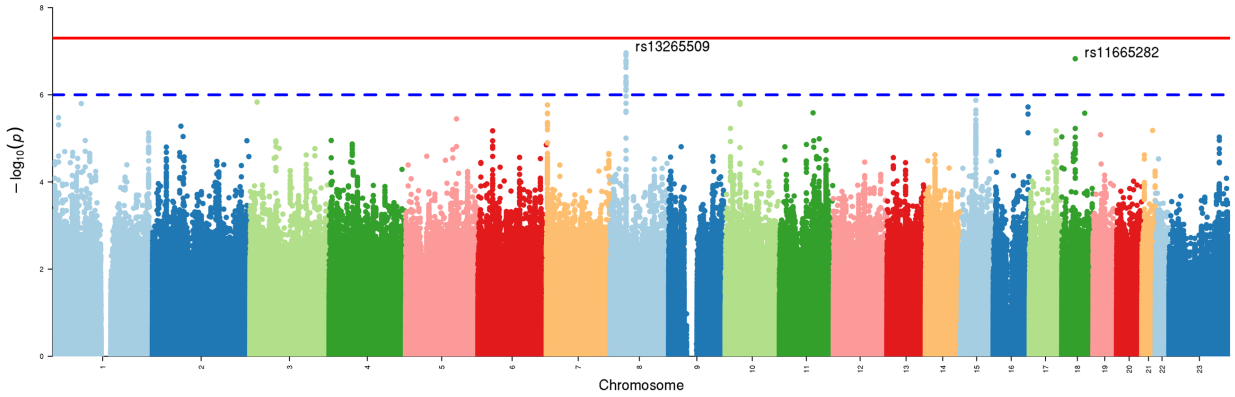


Supplementary Figure 20. Manhattan plots of the GxS interaction GWAS in PGC

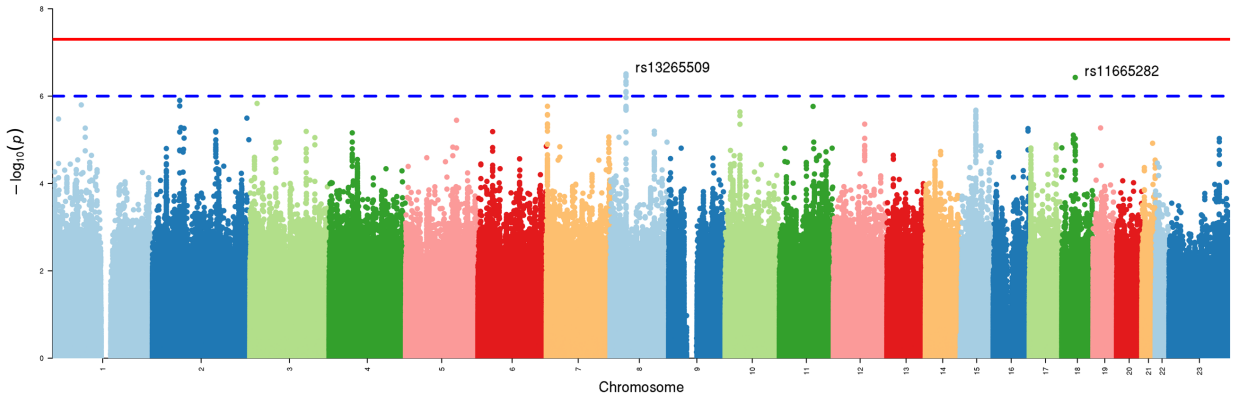
Negative log10-transformed p-values for each variant (each dot) (y-axis) are plotted by chromosomal position (x-axis). The red and blue lines represent the thresholds for genome-wide significant association ($p = 5\times10^{-8}$) and suggestive association ($p = 1\times10^{-5}$), respectively. P-values 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

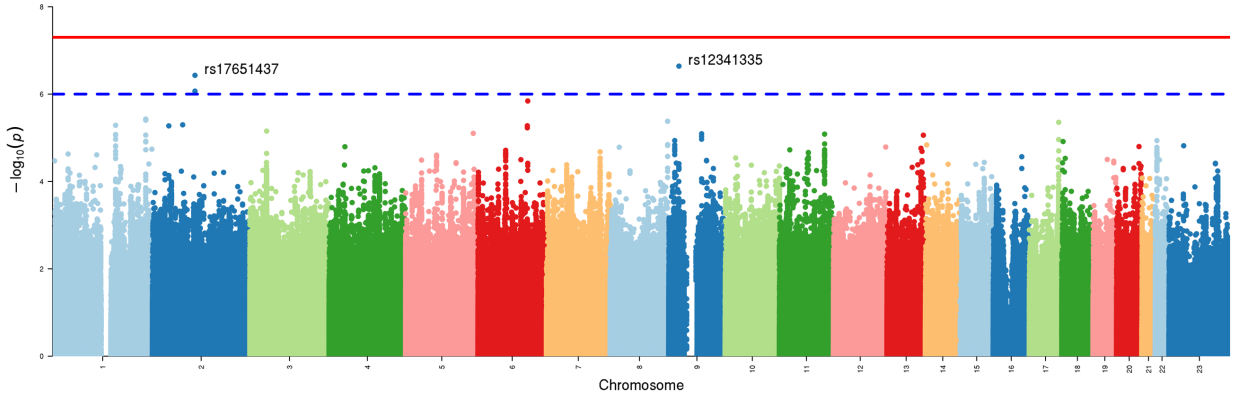
a) Schizophrenia – European ancestry only



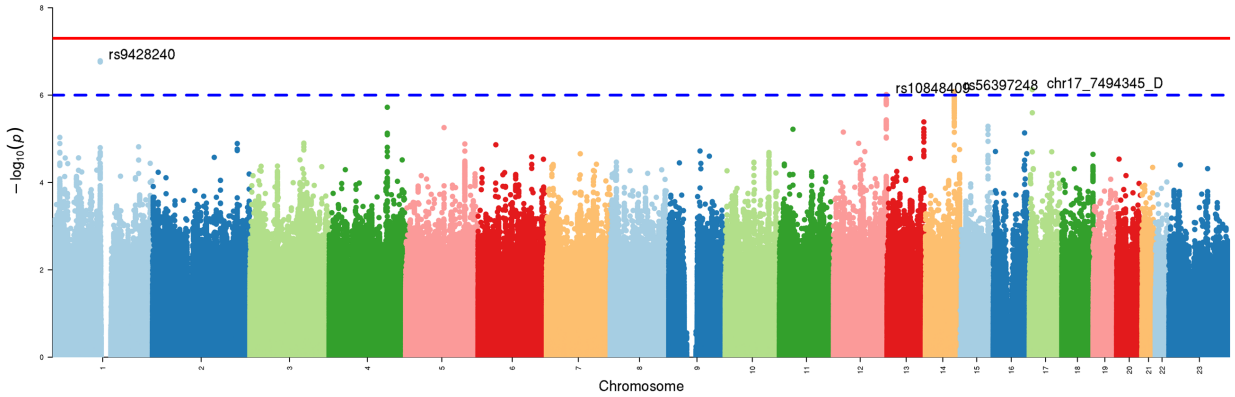
b) Schizophrenia – European + East Asian ancestry



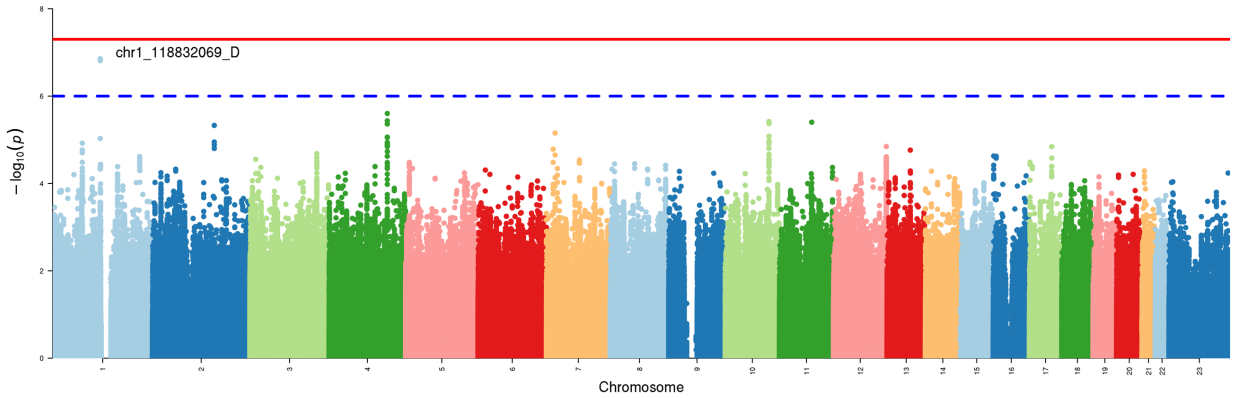
c) Bipolar Disorder



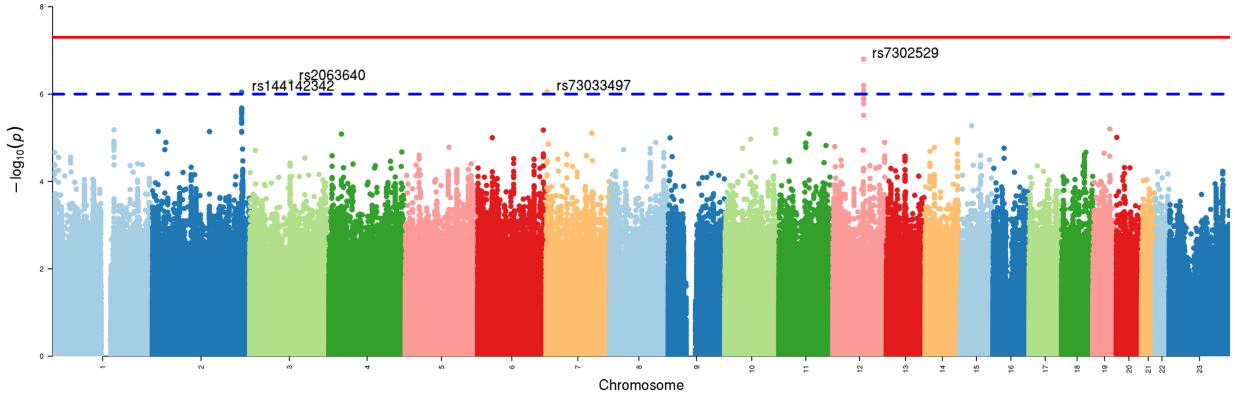
d) Major Depressive Disorder



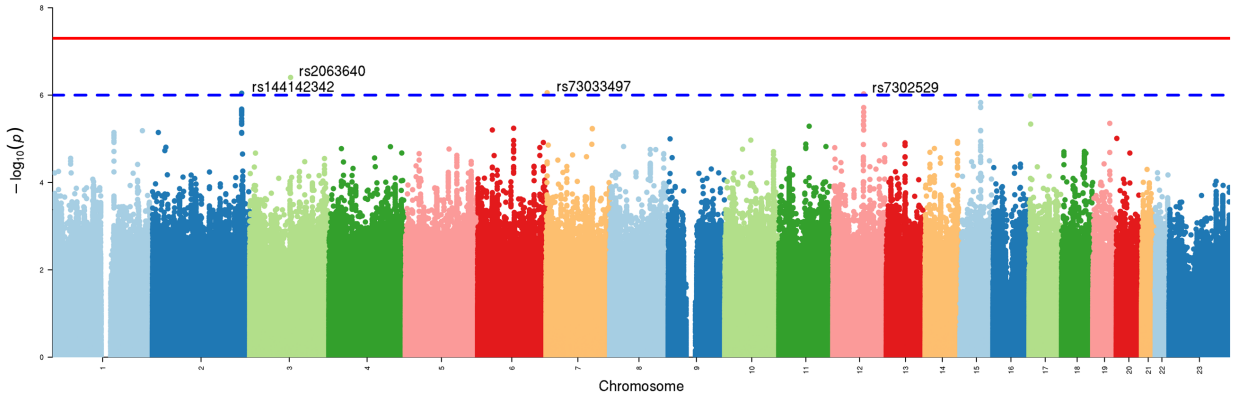
e) Recurrent Major Depressive Disorder



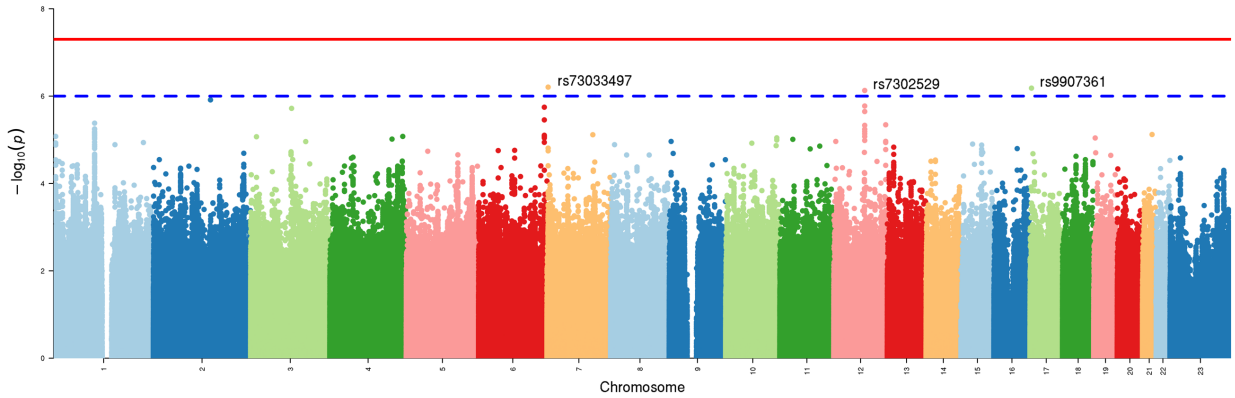
f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



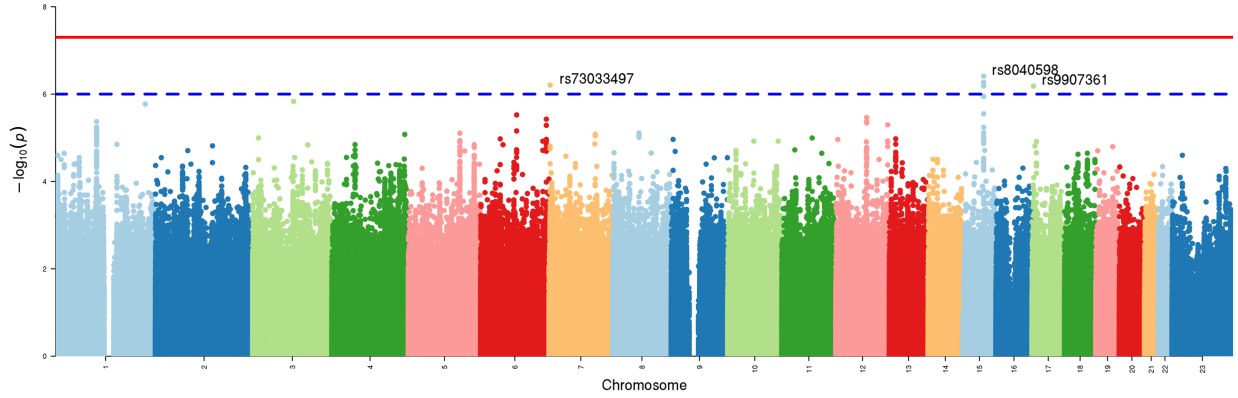
g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry



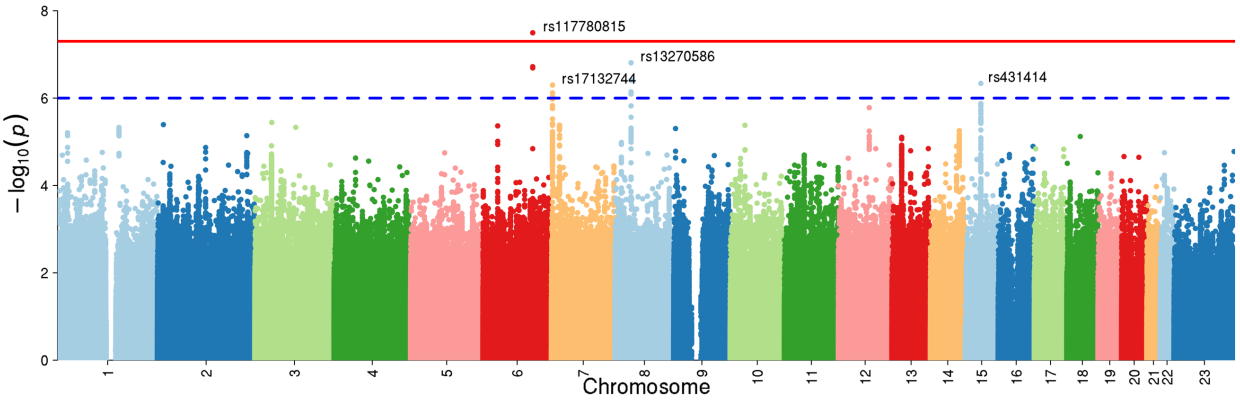
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



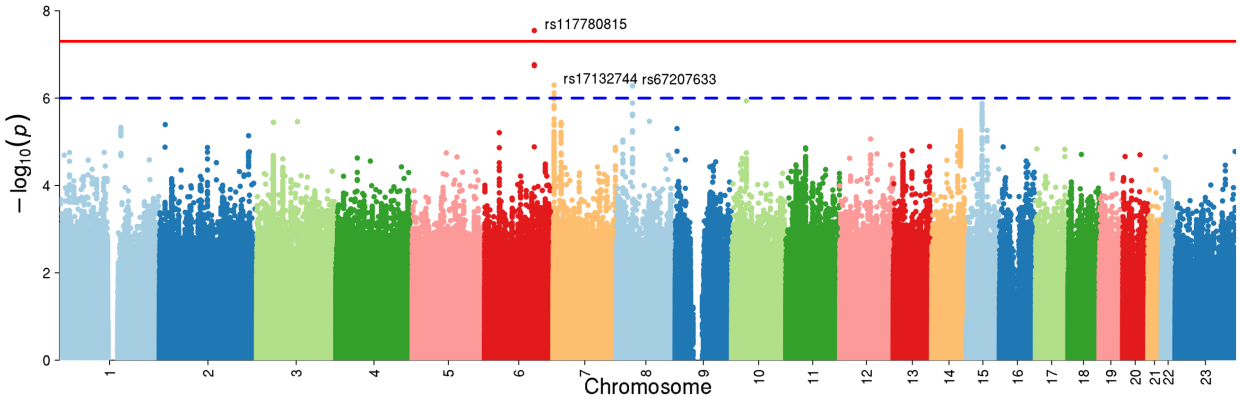
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry



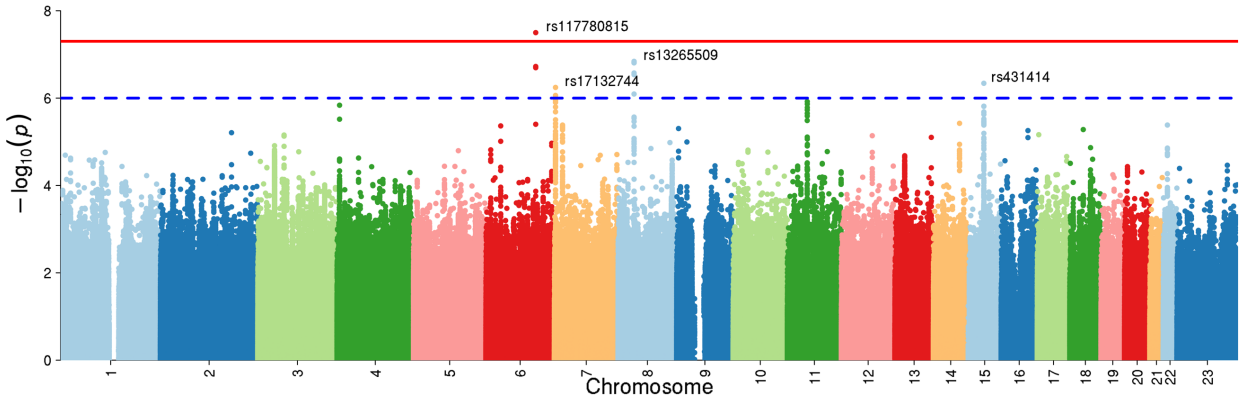
j) Omnibus Test SCZ-BIP-MDD – European ancestry only



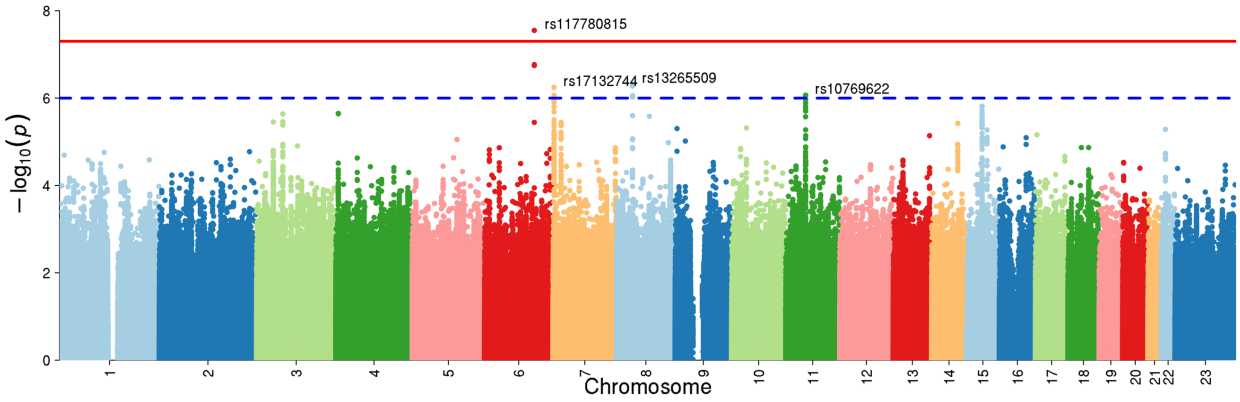
k) Omnibus Test SCZ-BIP-MDD – European + East Asian ancestry



l) Omnibus Test SCZ-BIP-rMDD – European ancestry only



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

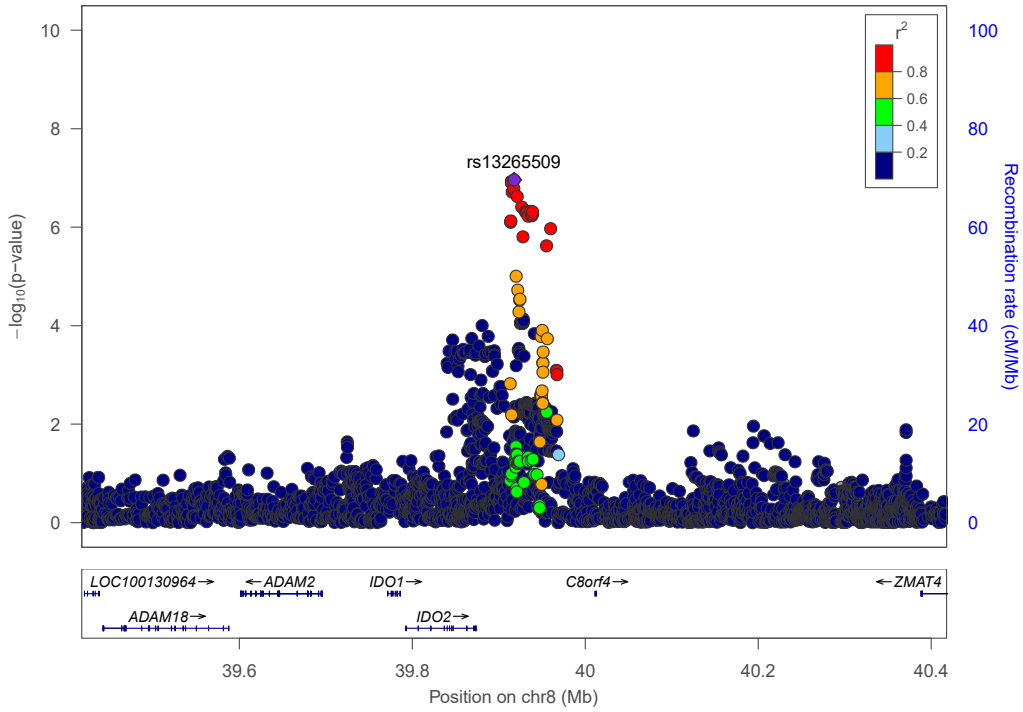


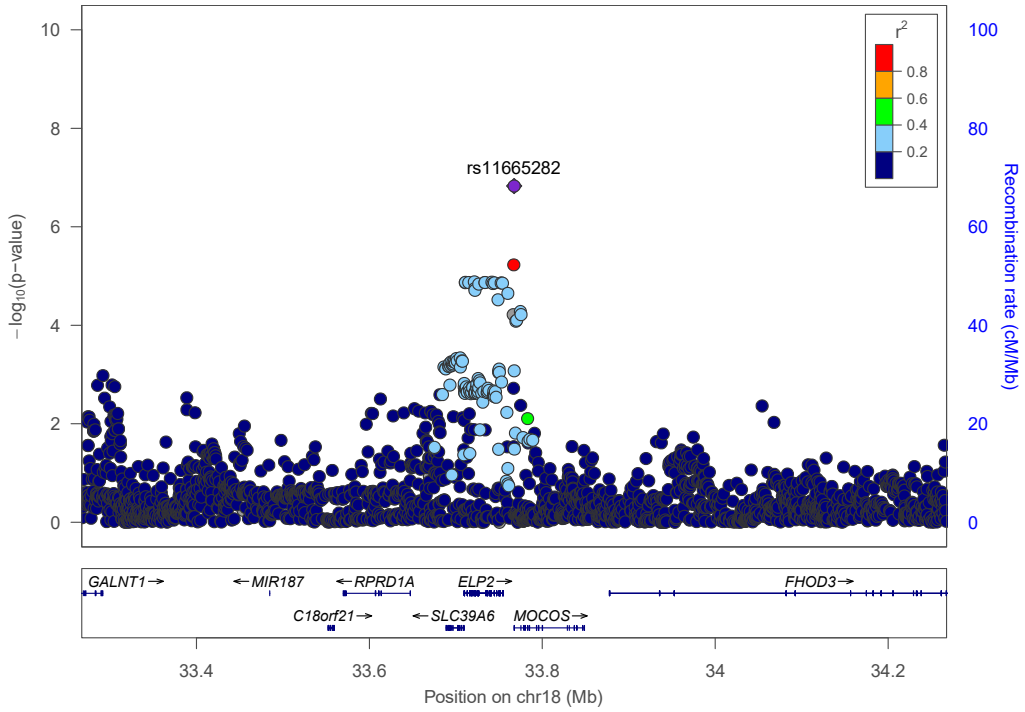
Supplementary Figure 21. LocusZoom plots for loci with GxS interaction in PGC

Plots were generated using the LocusZoom 1.4 Standalone application (49) for loci with GxS interaction $p < 1\times10^{-6}$.

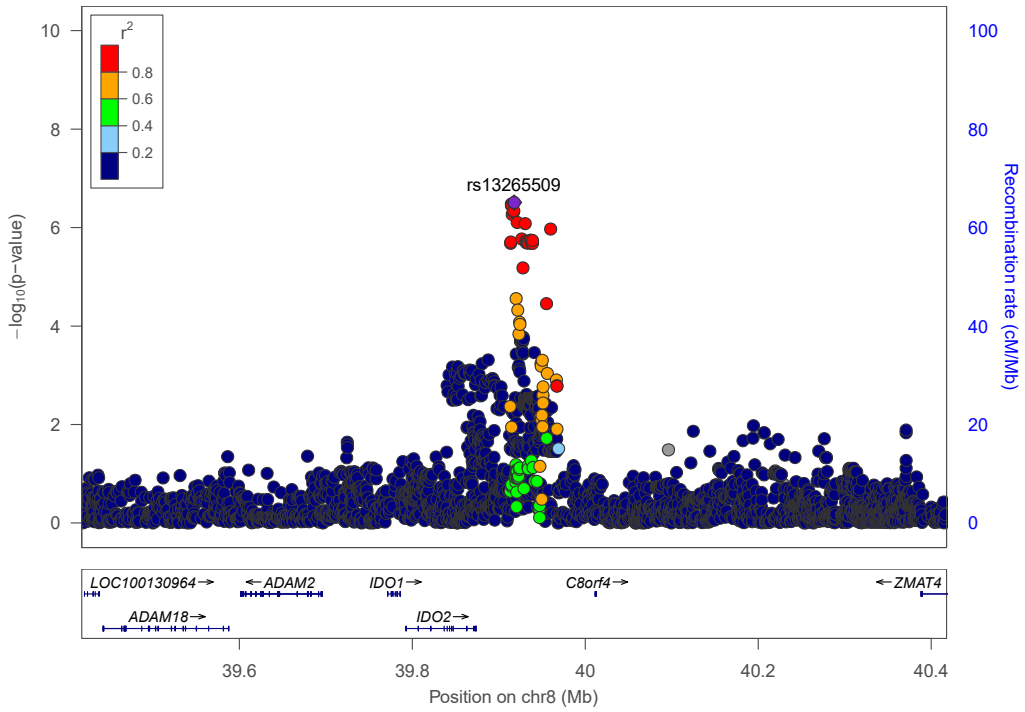
Abbreviations: chr = chromosome; cM = centimorgans; Mb = megabases; r^2 = linkage disequilibrium level; BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia

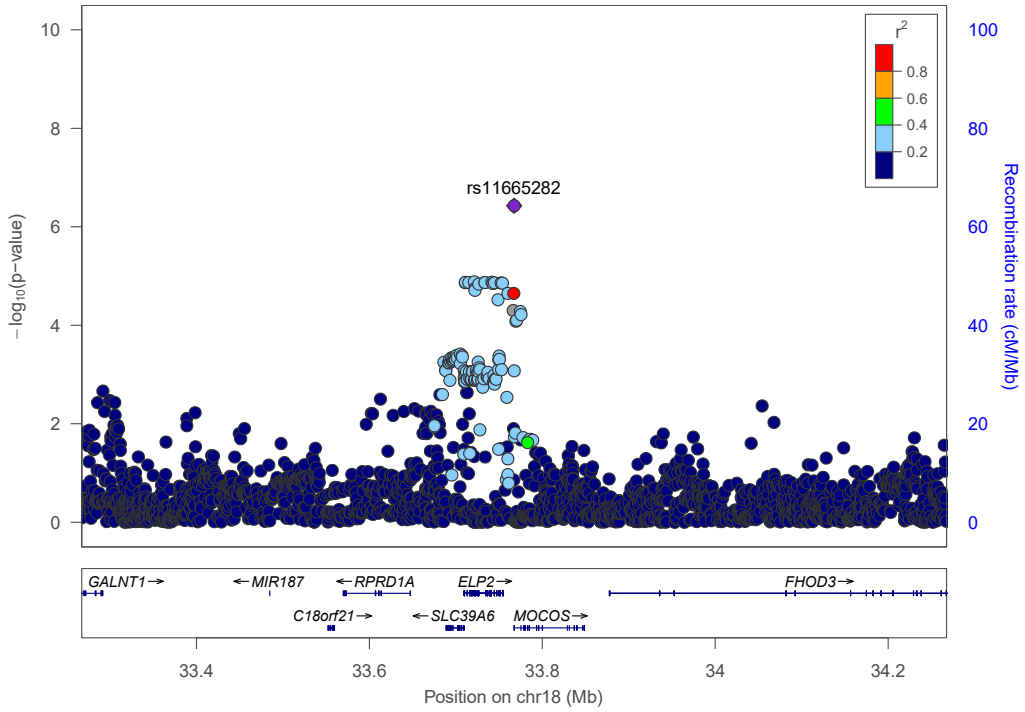
a) Schizophrenia – European ancestry only





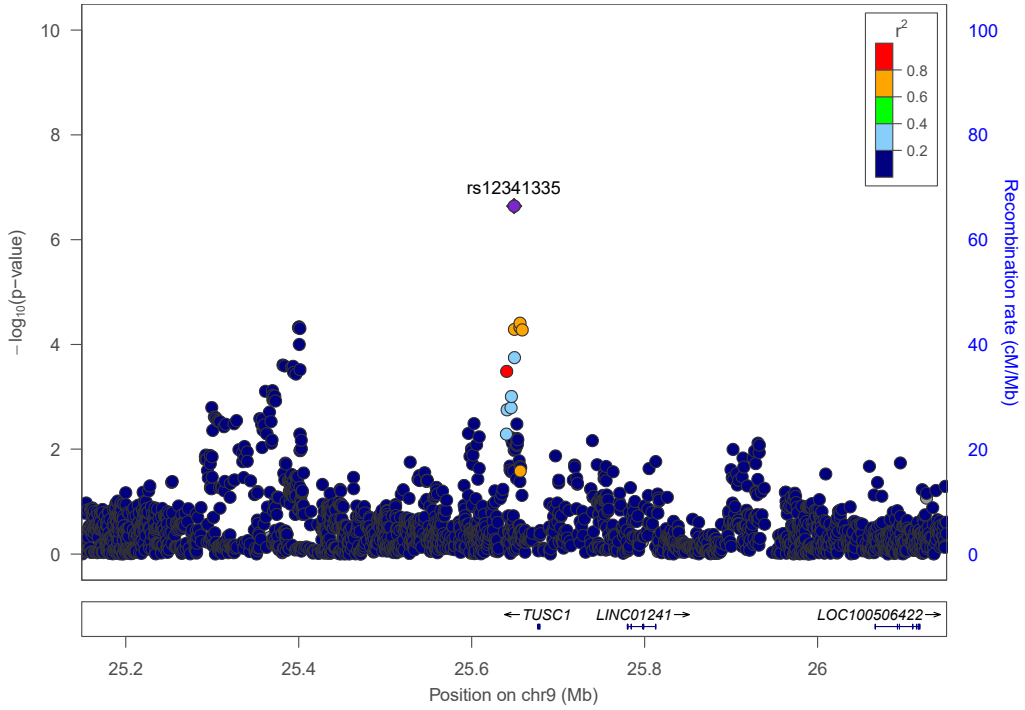
b) Schizophrenia – European + East Asian ancestry

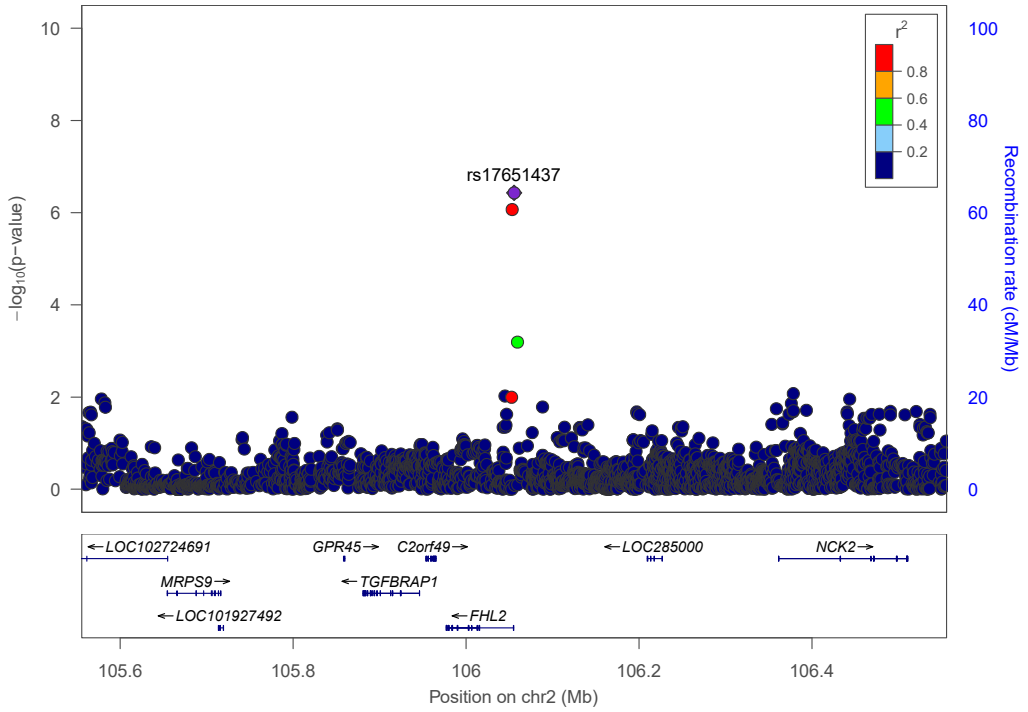




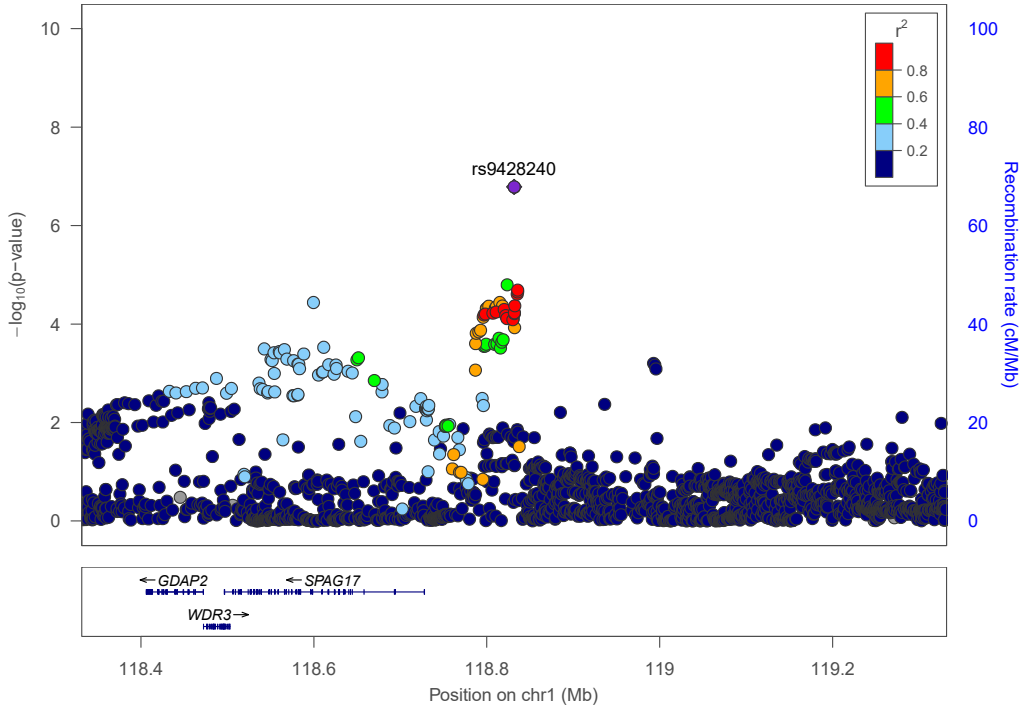
s

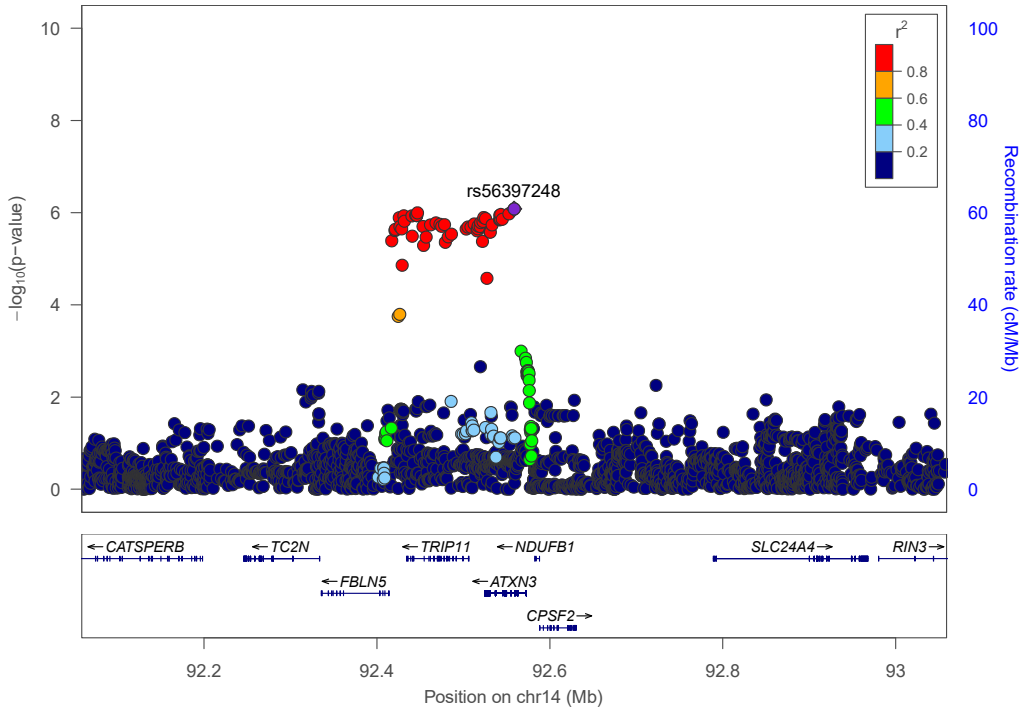
c) Bipolar Disorder



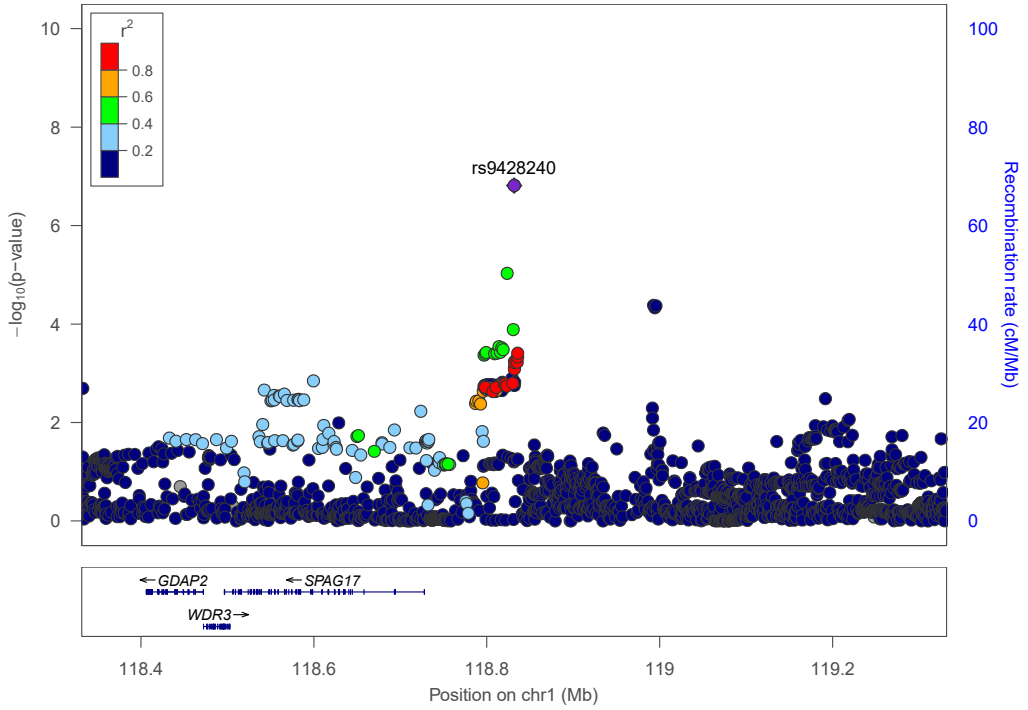


d) Major Depressive Disorder

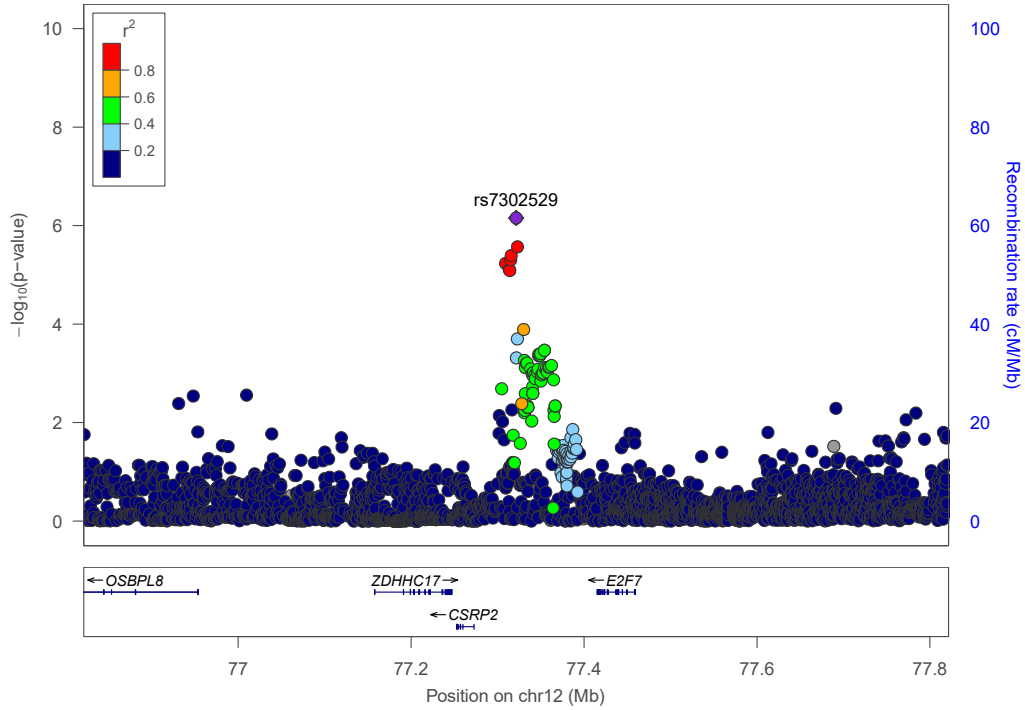


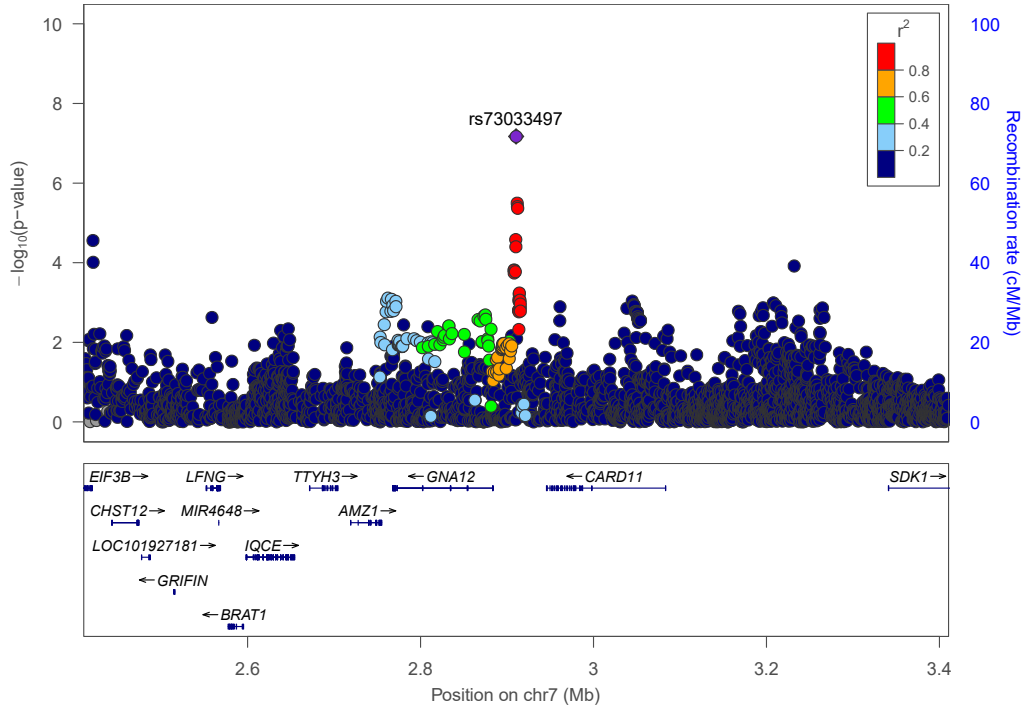


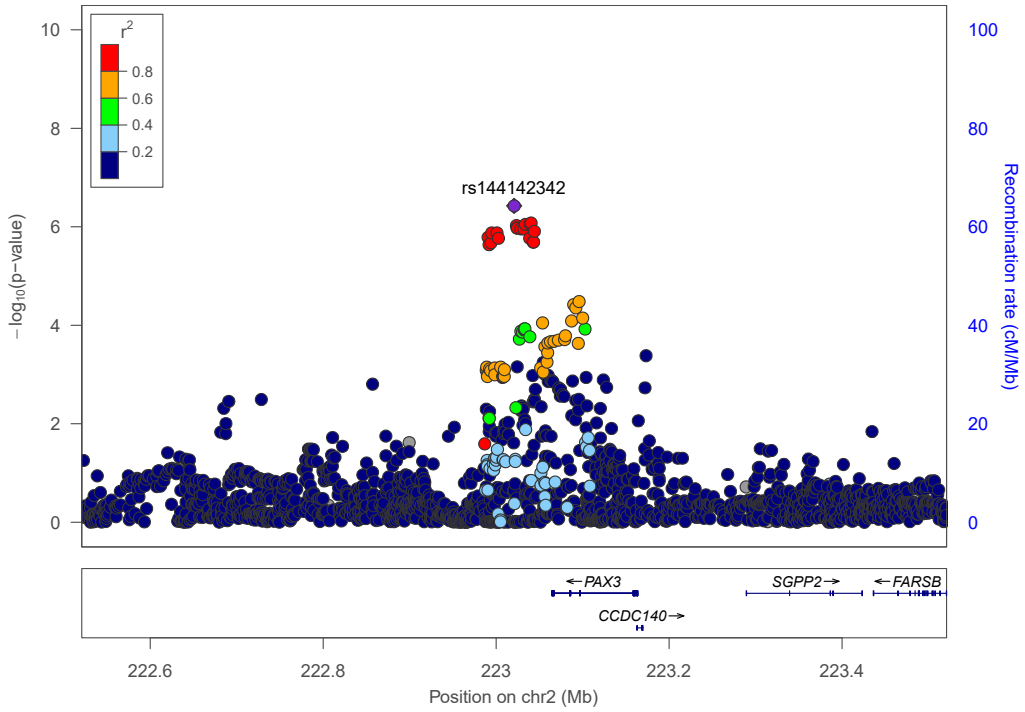
e) Recurrent Major Depressive Disorder



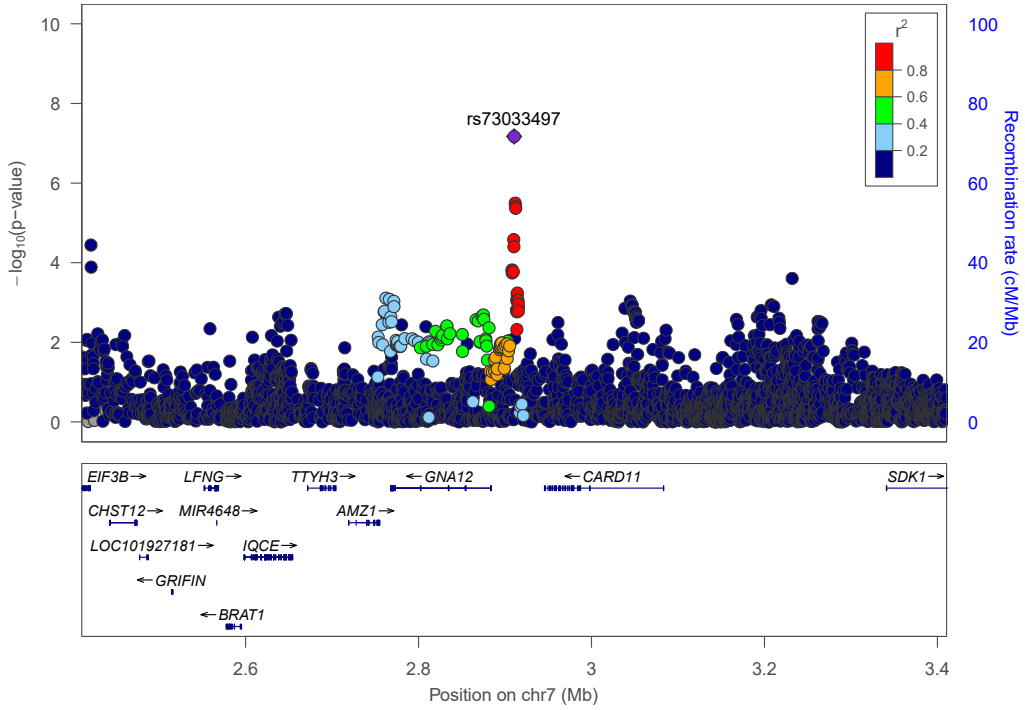
f) Cross-Disorder SCZ-BIP-MDD – European ancestry only

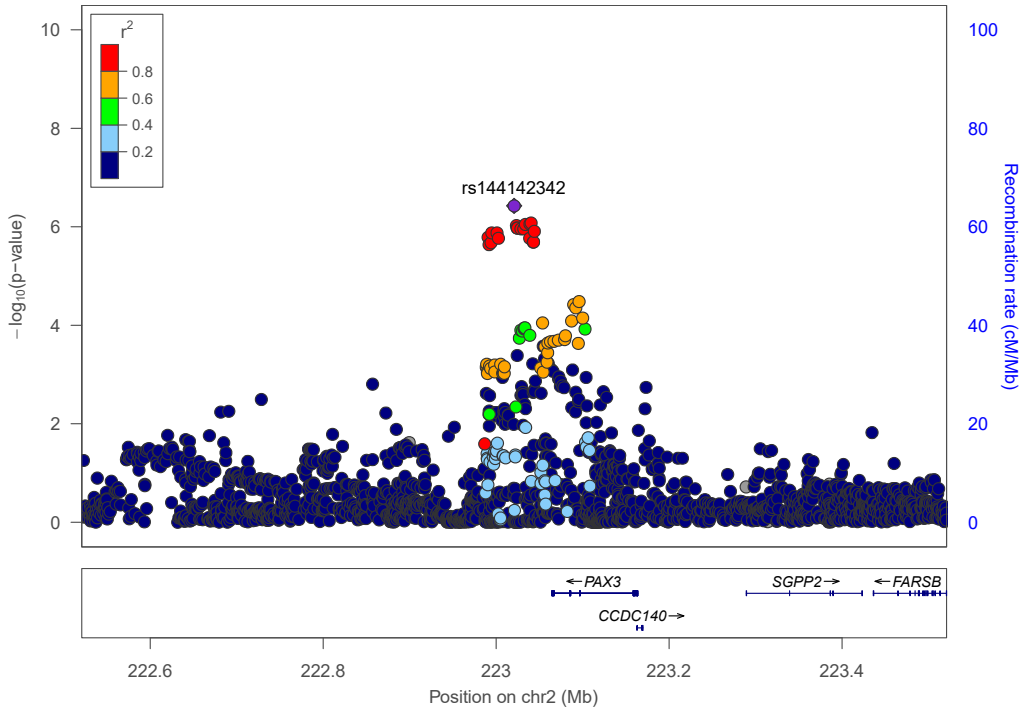


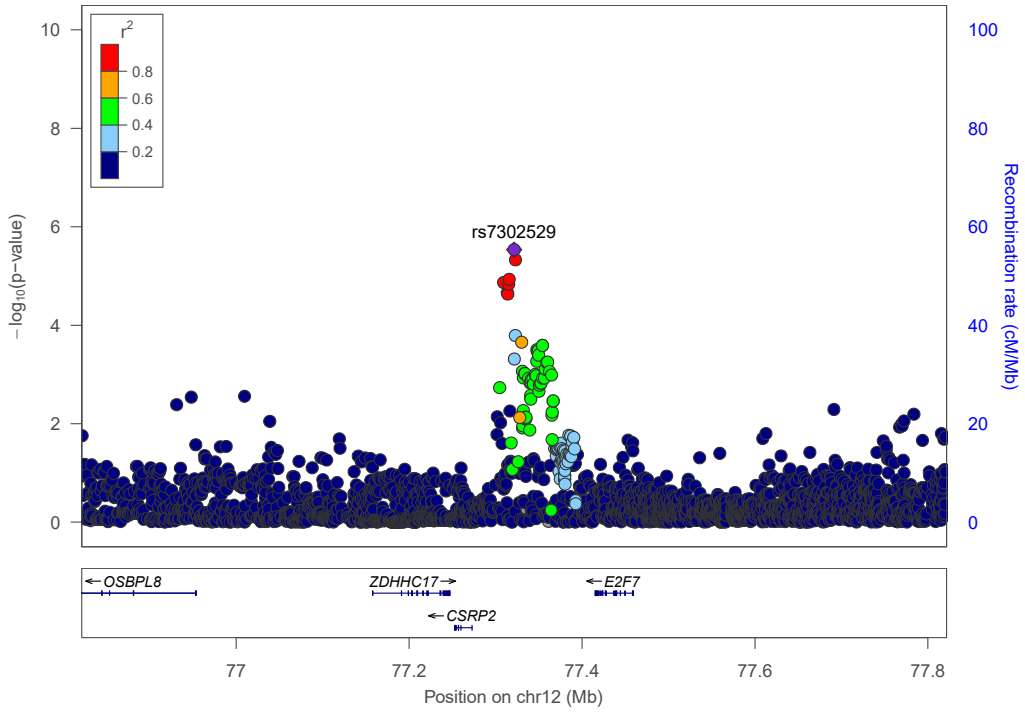




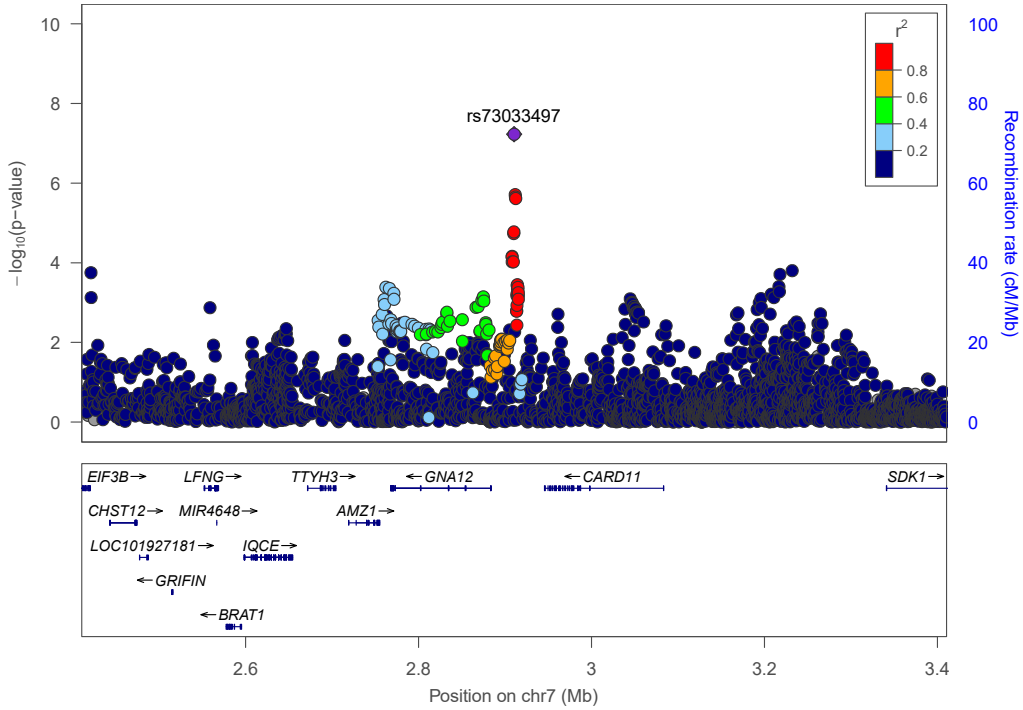
g) Cross-Disorder SCZ-BIP-MDD – European + East Asian ancestry

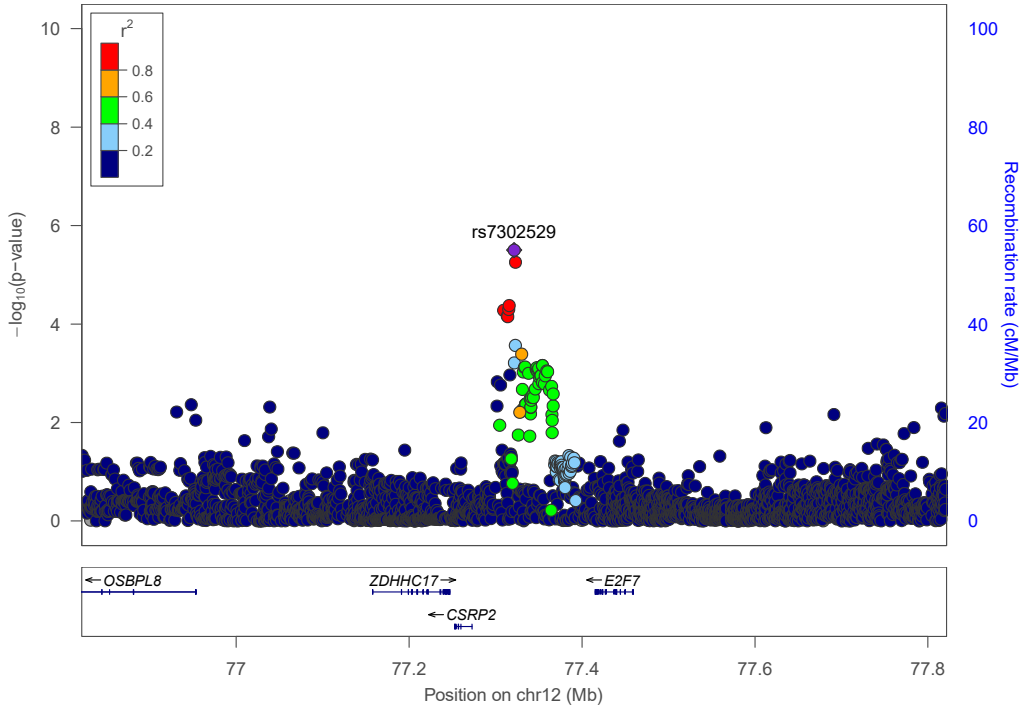



r2
0.8
0.6
0.4
0.2
rs144142342
− log10(p−value)
Recombination rate (cM/Mb)
PAX3
SGPP2
FARSB
CCDC140
Position on chr2 (Mb)

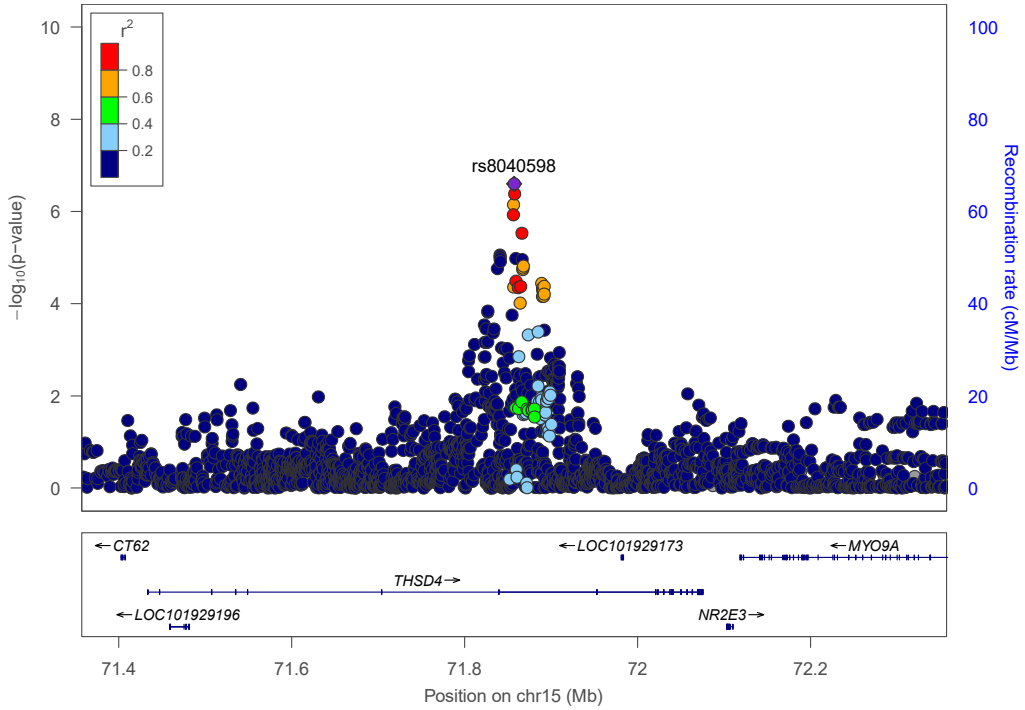

r2
0.8
0.6
0.4
0.2
rs7302529
− log10(p−value)
Recombination rate (cM/Mb)
OSBPL8
ZDHHC17
E2F7
CSRP2
Position on chr12 (Mb)

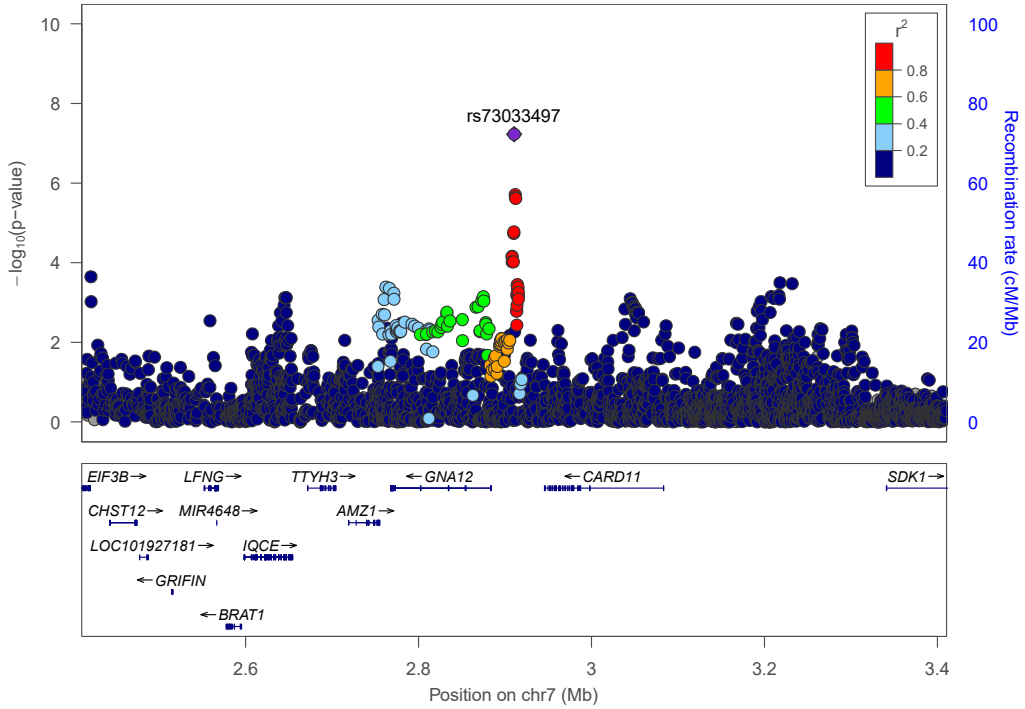
h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only



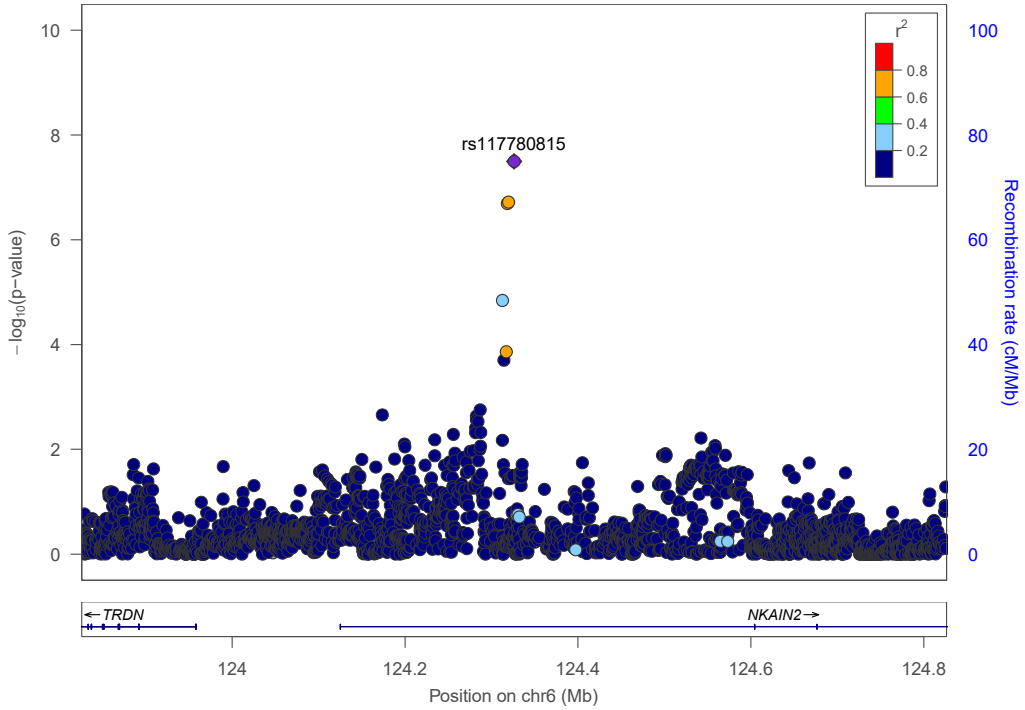


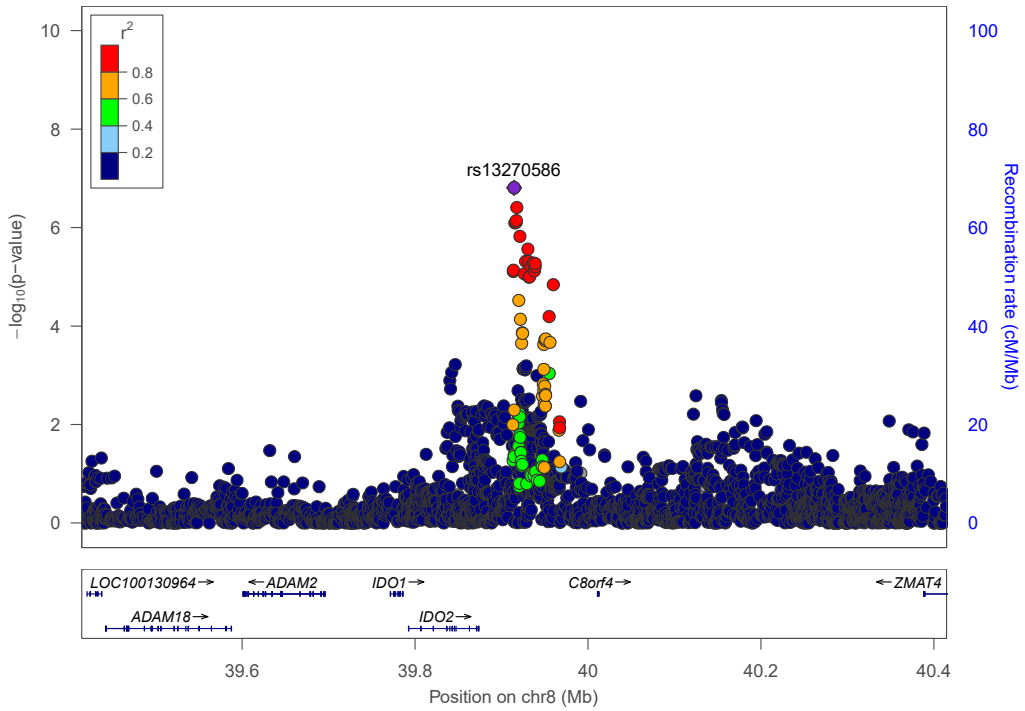
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry

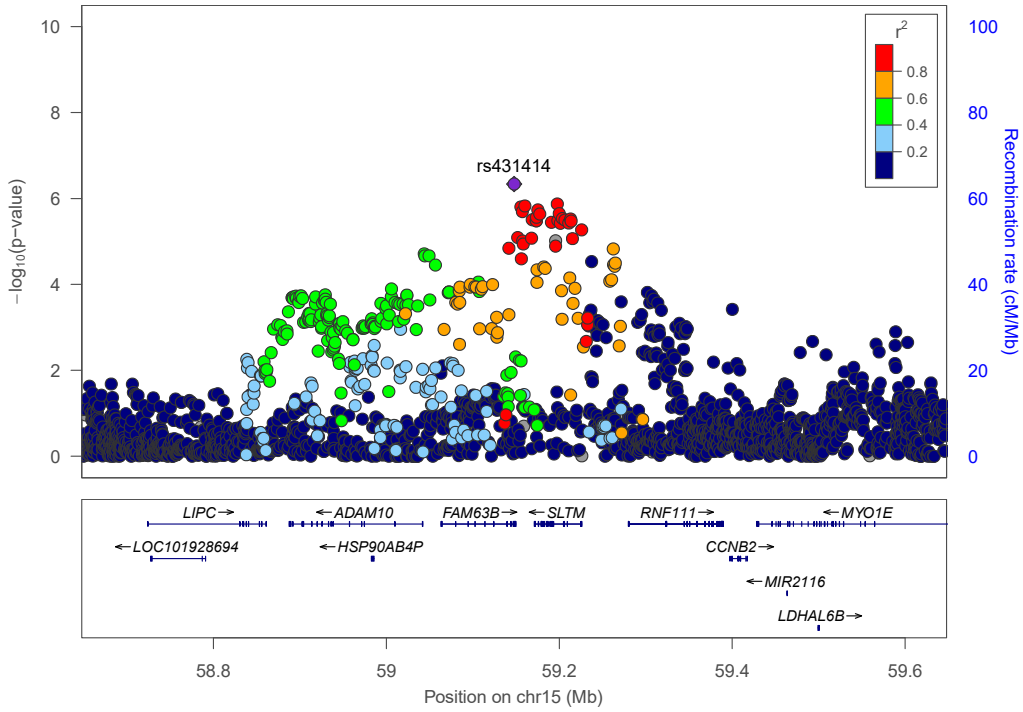


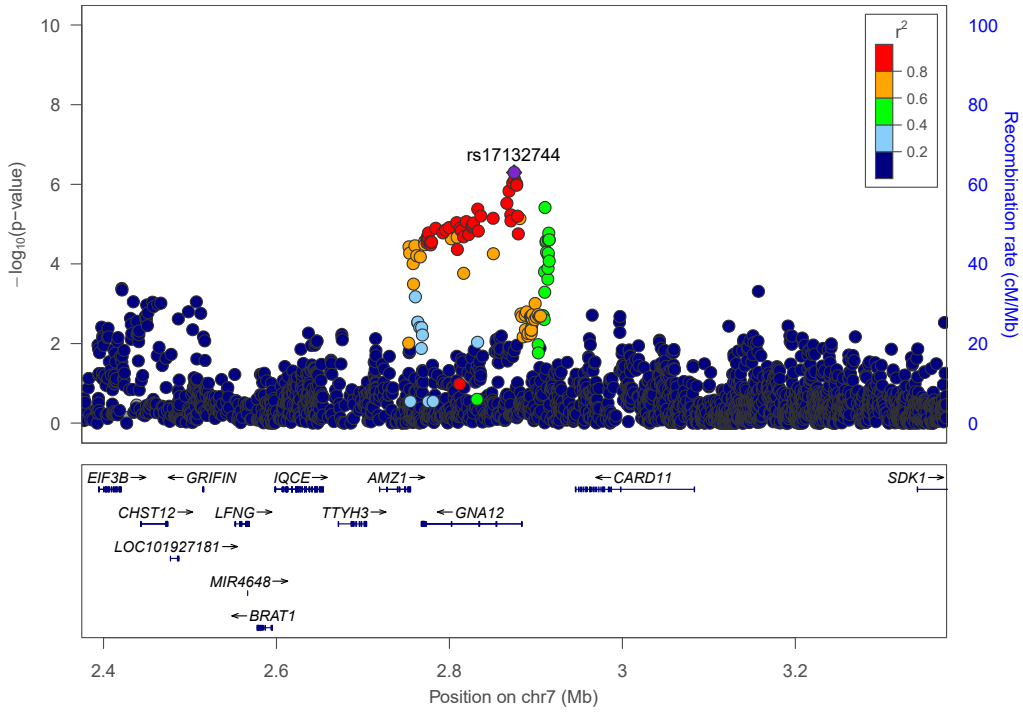


j) Omnibus Test SCZ-BIP-MDD – European ancestry

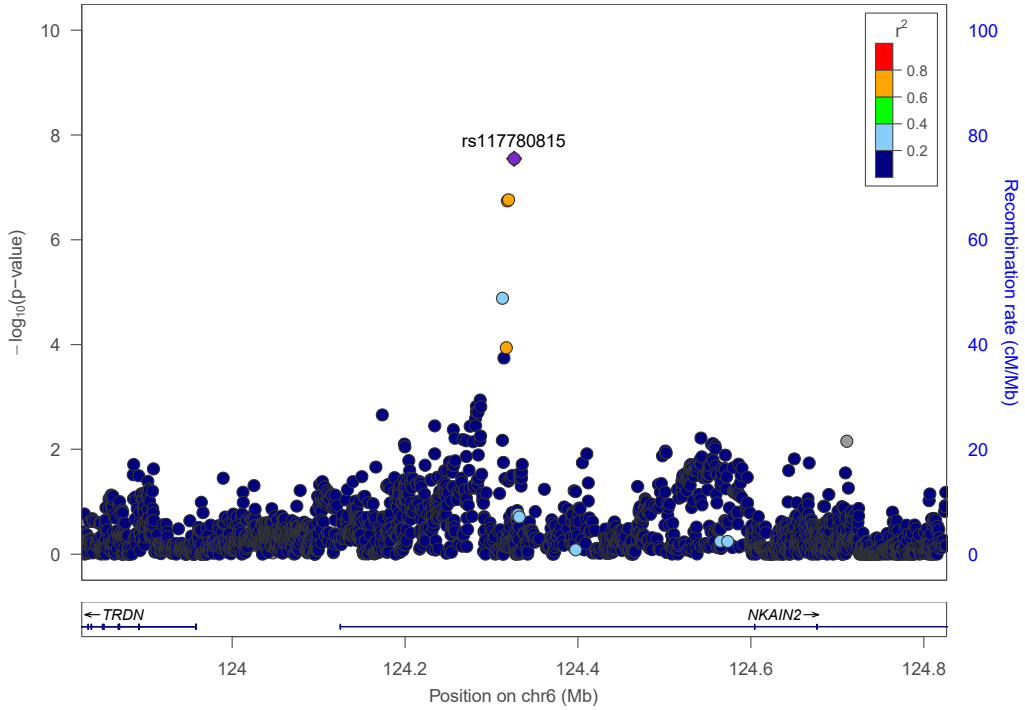


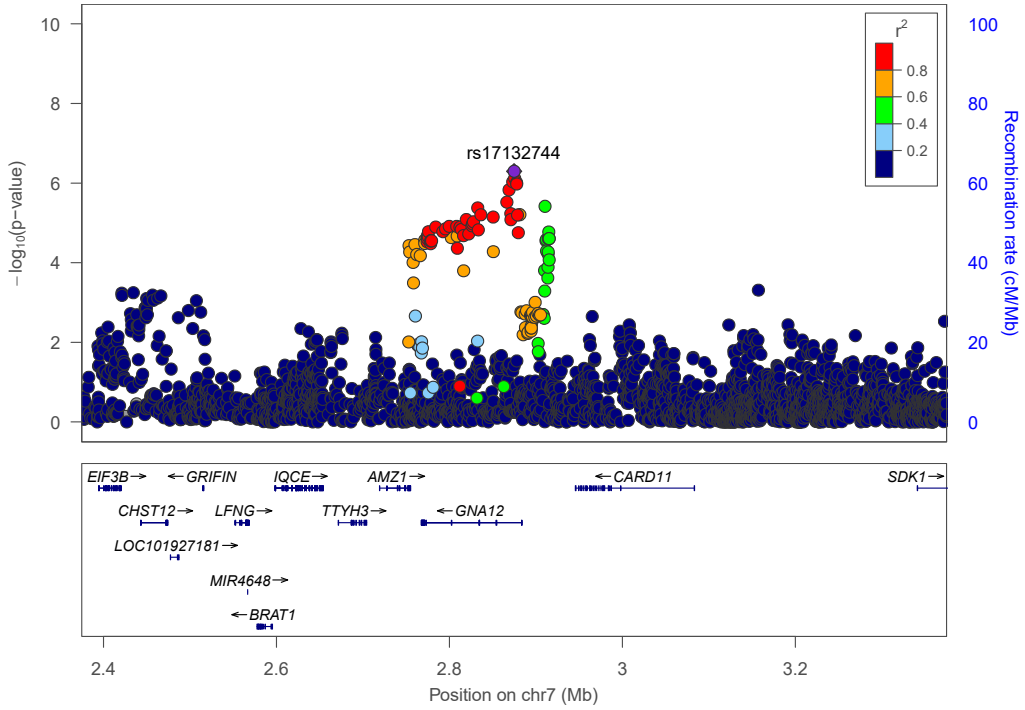


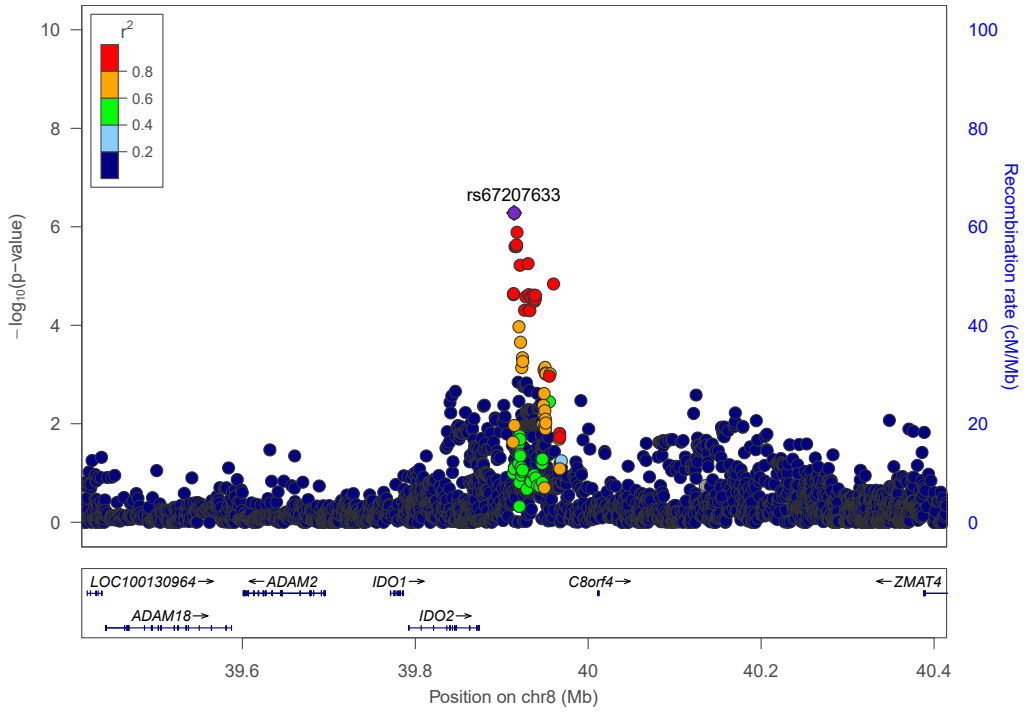

rs431414
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
LIPC
ADAM10
FAM63B
SLTM
RNF111
MYO1E
LOC101928694
HSP90AB4P
CCNB2
MIR2116
LDHAL6B
Position on chr15 (Mb)


rs17132744
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
EIF3B
GRIFIN
IQCE
AMZ1
CARD11
SDK1
CHST12
LFNG
TTYH3
GNA12
LOC101927181
MIR4648
BRAT1
Position on chr7 (Mb)

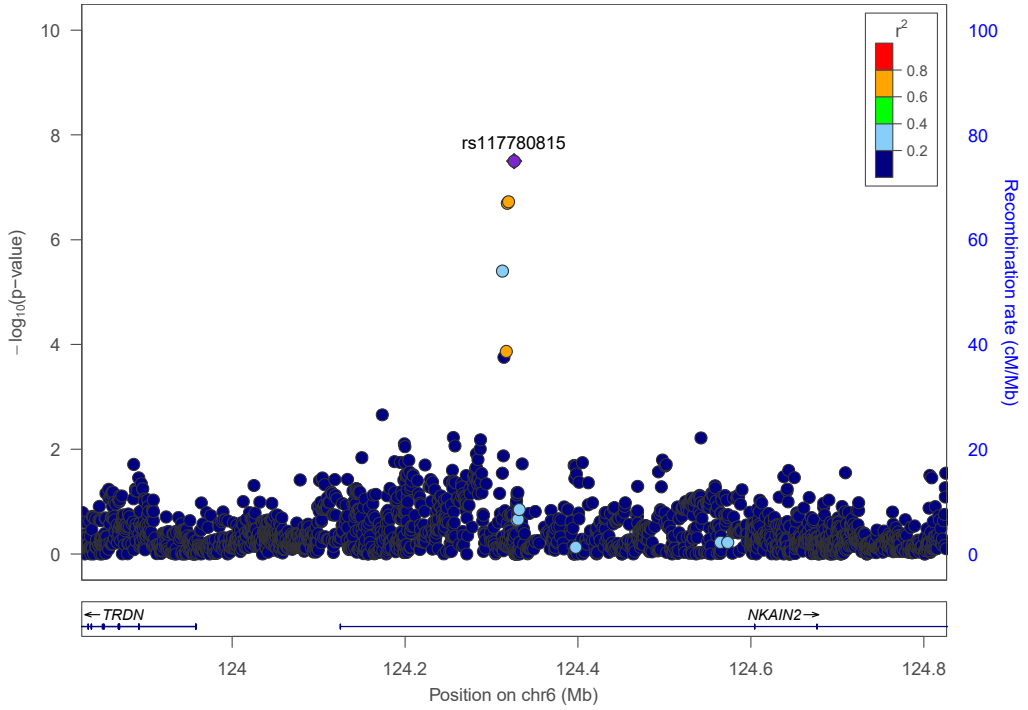
k) Omnibus Test SCZ-BIP-MDD – European + East Asian ancestry

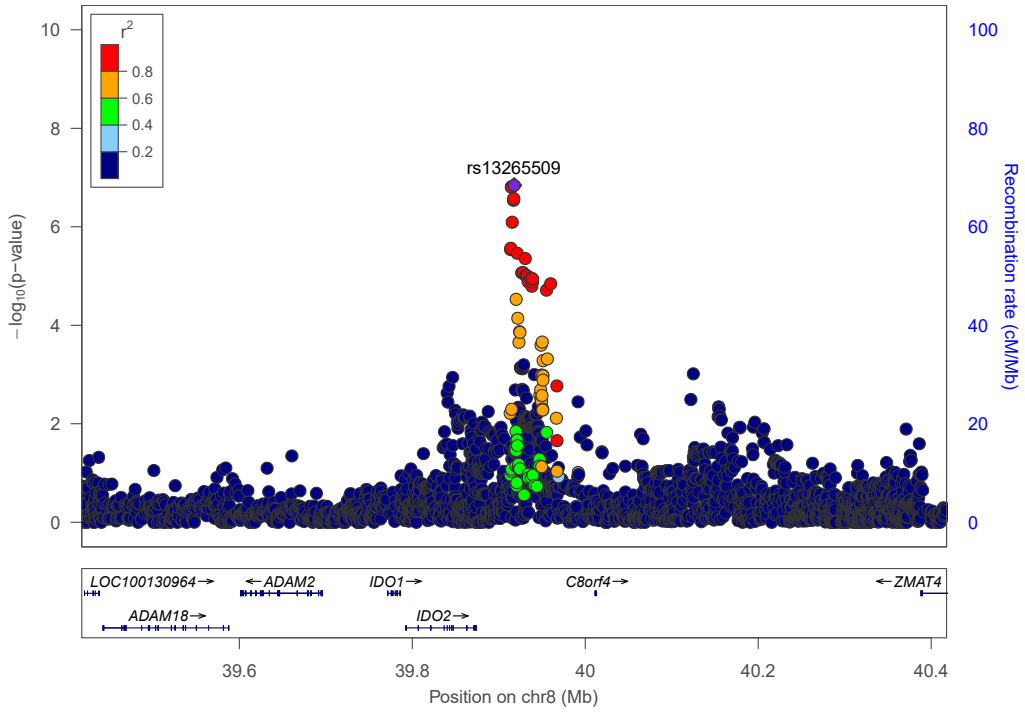


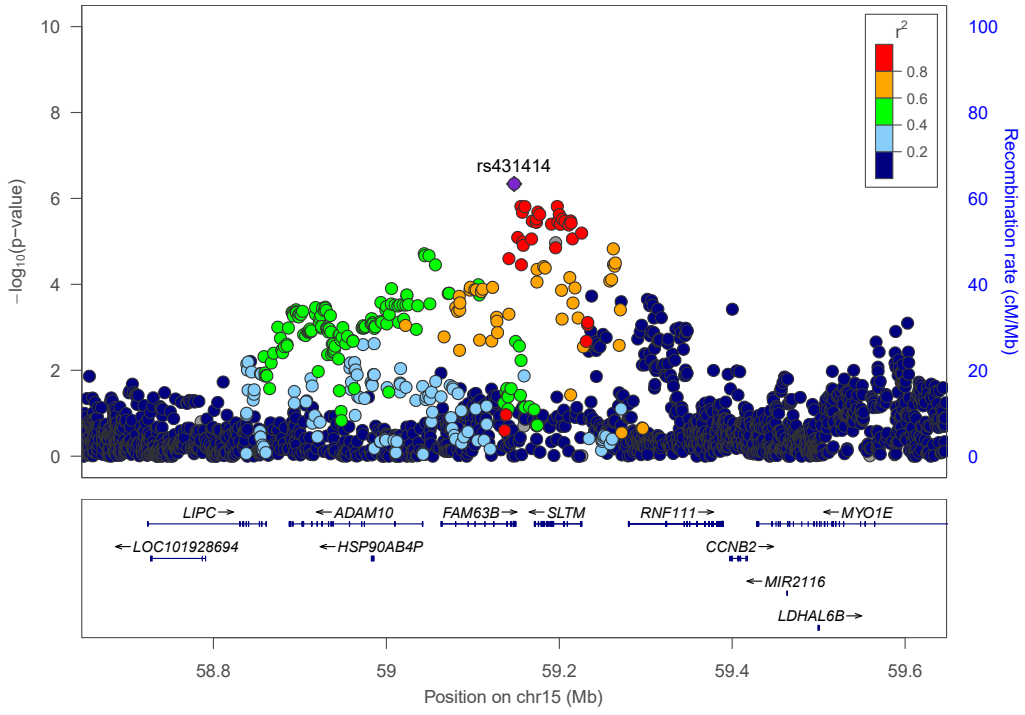


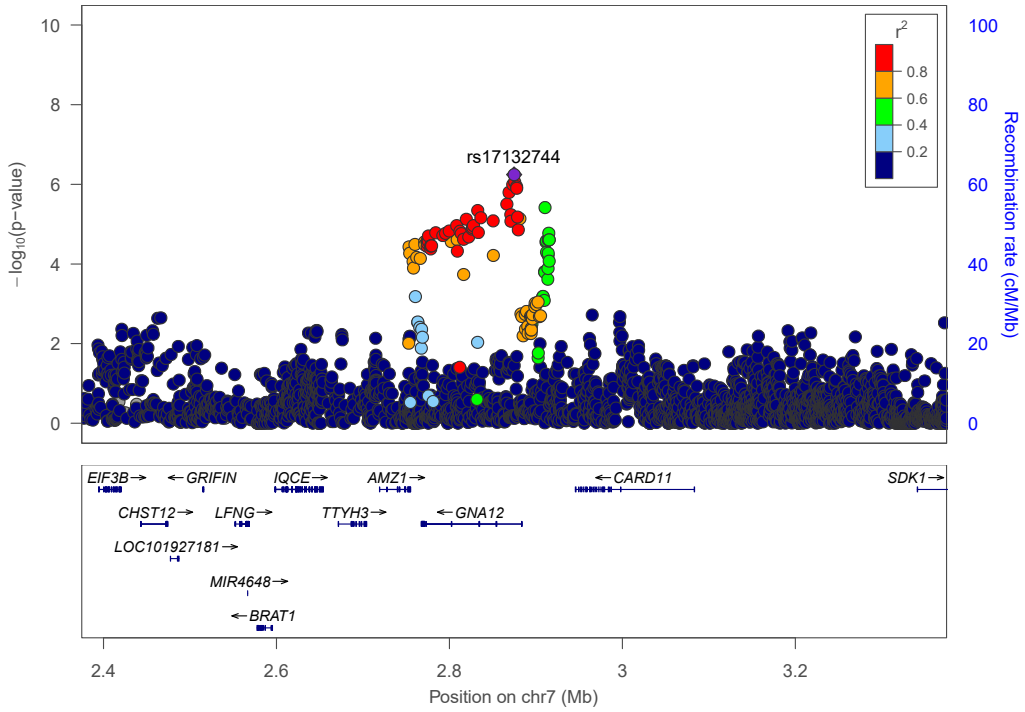


I) Omnibus Test SCZ-BIP-rMDD – European ancestry

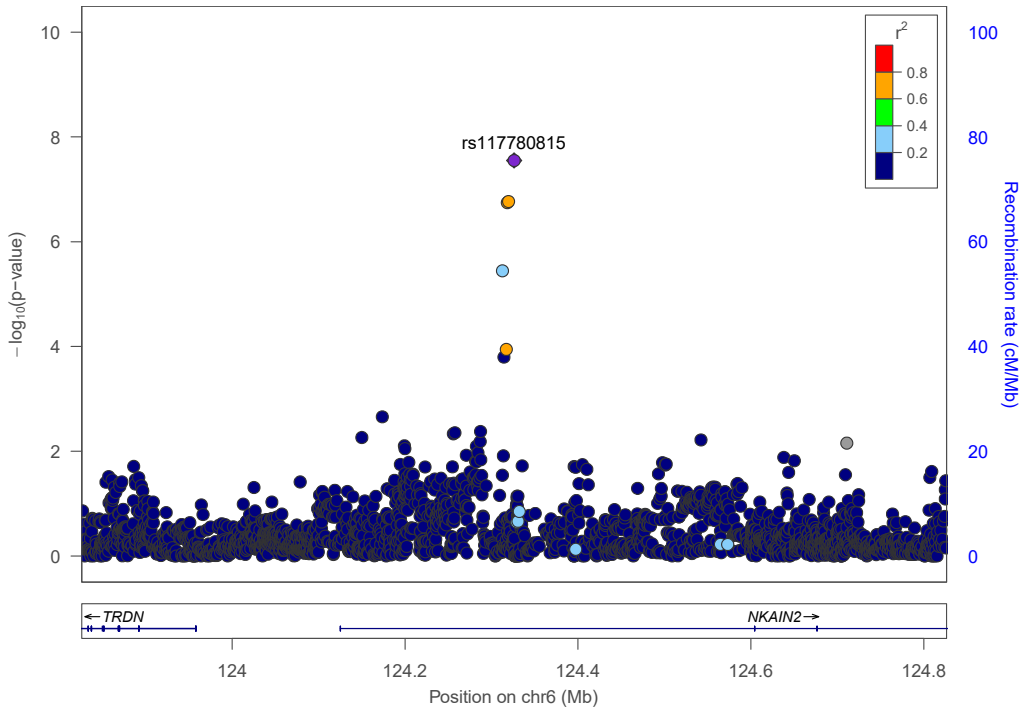


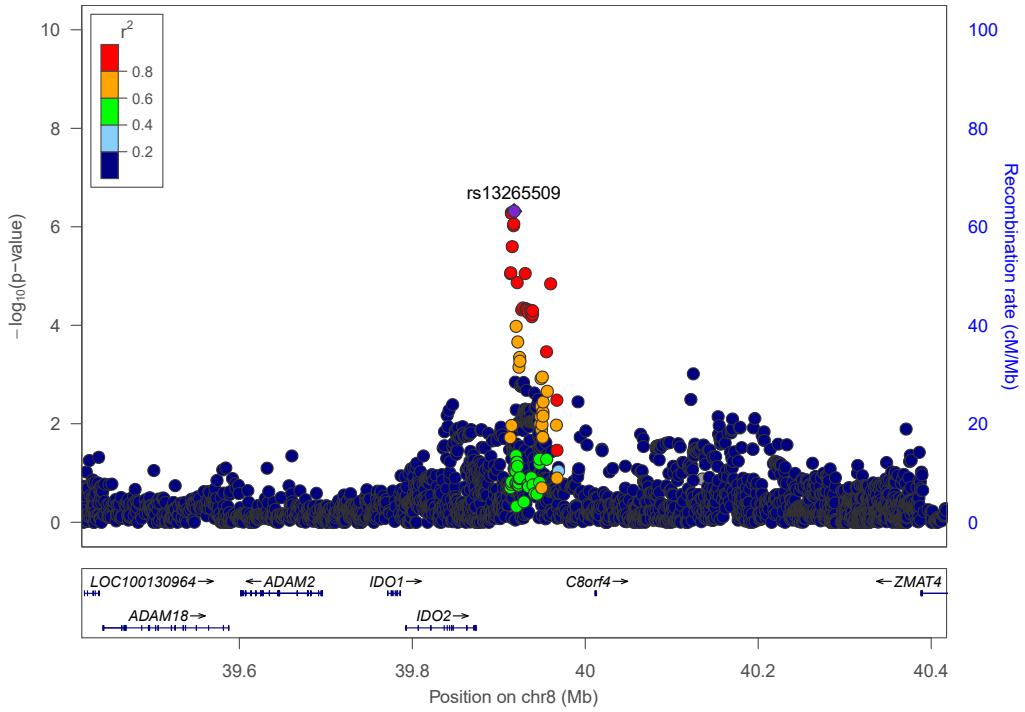

r2
0.8
0.6
0.4
0.2
rs13265509
−log10(p−value)
Recombination rate (cM/Mb)
LOC100130964
ADAM2
IDO1
C8orf4
ZMAT4
ADAM18
IDO2
Position on chr8 (Mb)

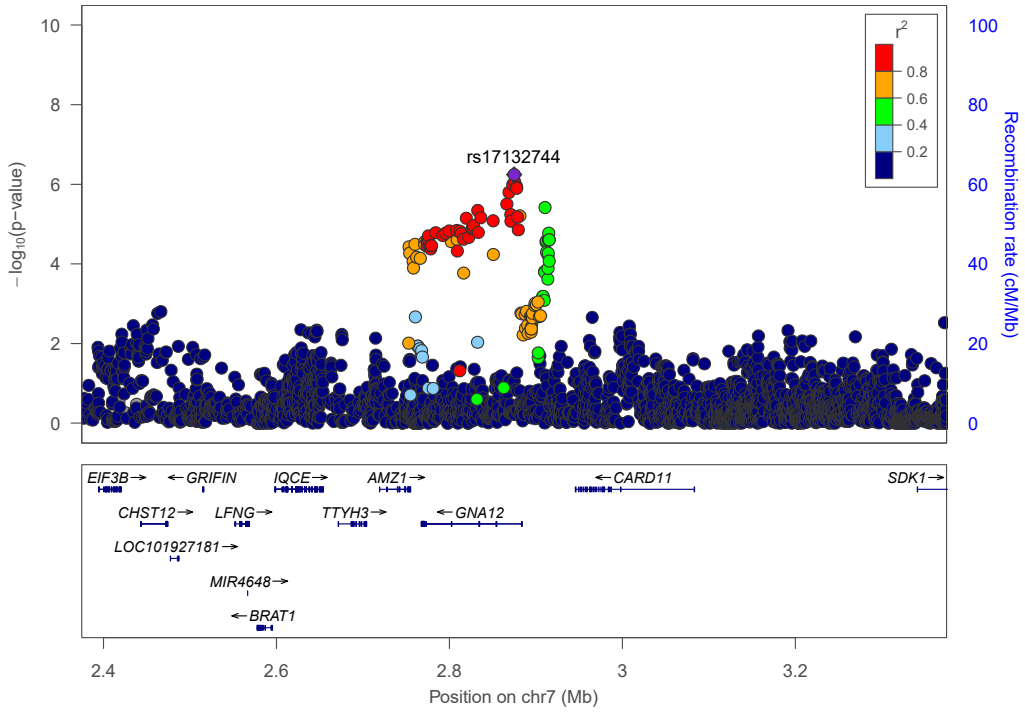

r2
0.8
0.6
0.4
0.2
rs431414
−log10(p−value)
Recombination rate (cM/Mb)
LIPC
ADAM10
FAM63B
SLTM
RNF111
MYO1E
LOC101928694
HSP90AB4P
CCNB2
MIR2116
LDHAL6B
Position on chr15 (Mb)

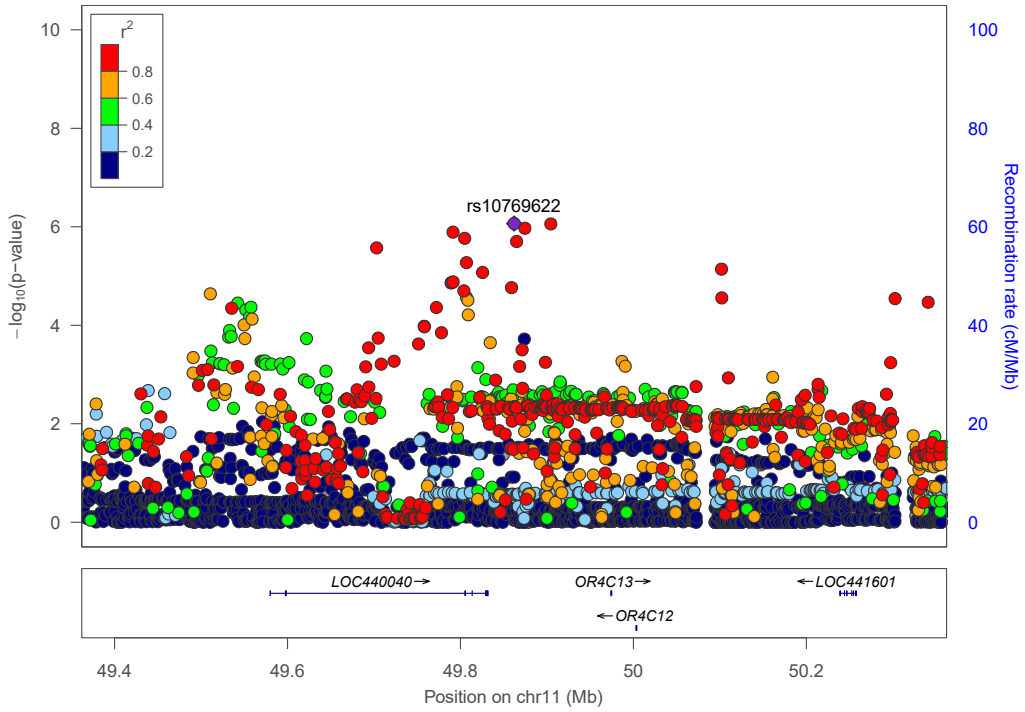


m) Omnibus Test SCZ-BIP-rMDD – European + East Asian ancestry




r²
0.8
0.6
0.4
0.2
rs13265509
−log10(p−value)
Recombination rate (cM/Mb)
LOC100130964
ADAM2
IDO1
C8orf4
ZMAT4
ADAM18
IDO2
Position on chr8 (Mb)


r²
0.8
0.6
0.4
0.2
rs17132744
−log10(p−value)
Recombination rate (cM/Mb)
EIF3B
GRIFIN
IQCE
AMZ1
CARD11
SDK1
CHST12
LFNG
TTYH3
GNA12
LOC101927181
MIR4648
BRAT1
Position on chr7 (Mb)

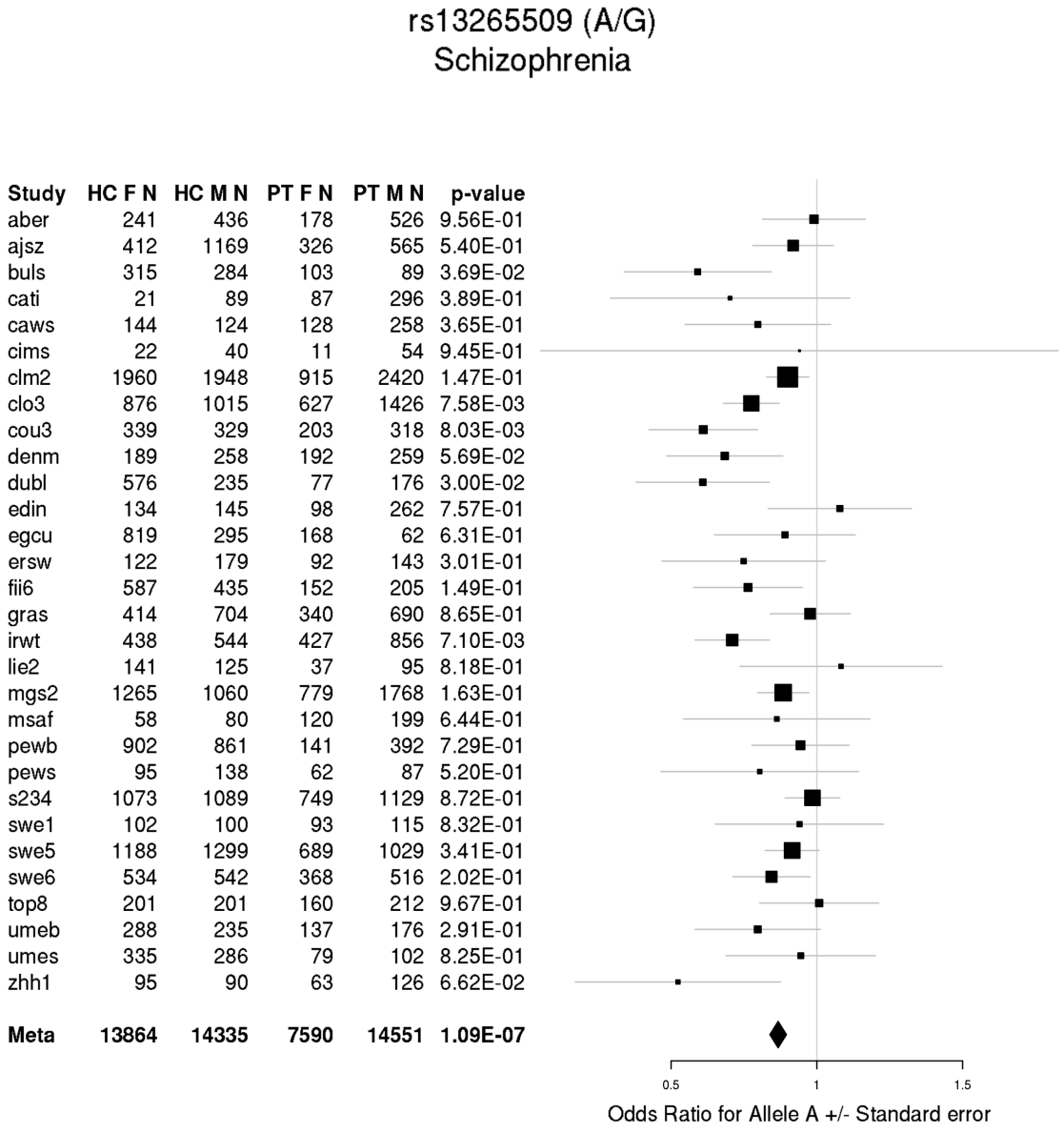

r2
0.8
0.6
0.4
0.2
rs10769622
− log10(p−value)
Recombination rate (cM/Mb)
LOC440040
OR4C13
LOC441601
OR4C12
Position on chr11 (Mb)

Supplementary Figure 22. Forest plots for PGC

Plots were generated using the rmeta package in R for loci (index SNPs) with GxS interaction $p < 1\times10^{-6}$.

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

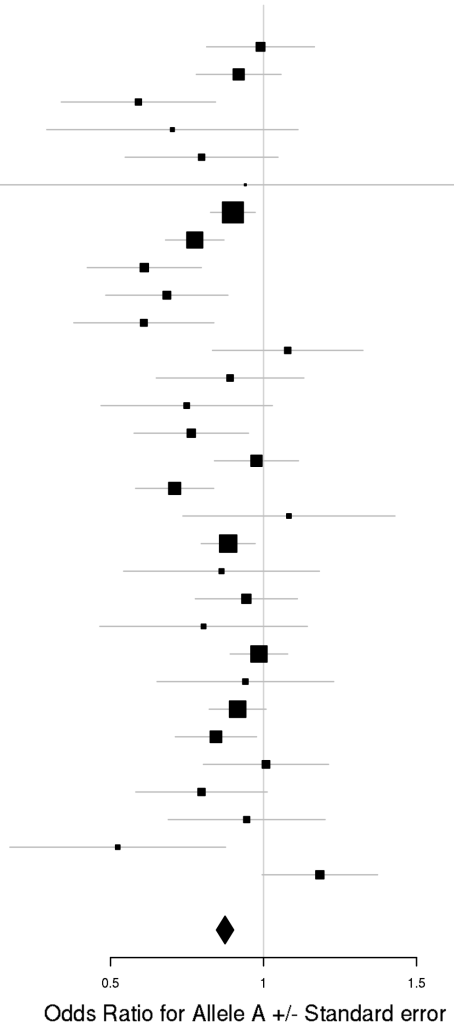


Study	HC F N	HC M N	PT F N	PT M N	p-value
aber	241	436	178	526	9.56E-01
ajsz	412	1169	326	565	5.40E-01
buls	315	284	103	89	3.69E-02
cati	21	89	87	296	3.89E-01
caws	144	124	128	258	3.65E-01
cims	22	40	11	54	9.45E-01
clm2	1960	1948	915	2420	1.47E-01
clo3	876	1015	627	1426	7.58E-03
cou3	339	329	203	318	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

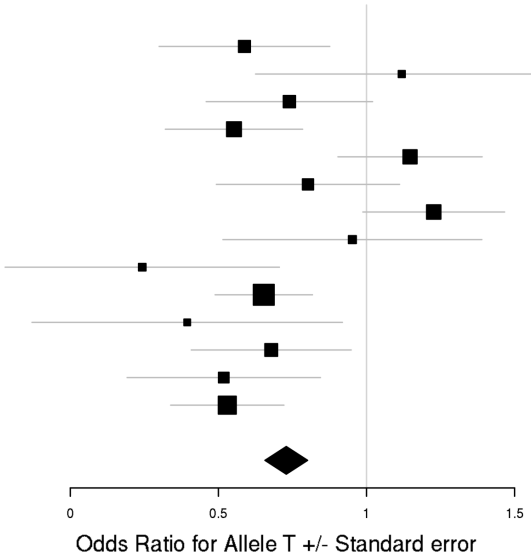
Study	HC F N	HC M N	PT F N	PT M N	p-value
aber	241	436	178	526	9.56E-01
ajsz	412	1169	326	565	5.40E-01
buls	315	284	103	89	3.69E-02
cati	21	89	87	296	3.89E-01
caws	144	124	128	258	3.65E-01
cims	22	40	11	54	9.45E-01
clm2	1960	1948	915	2420	1.47E-01
clo3	876	1015	627	1426	7.58E-03
cou3	339	329	203	318	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
jpn1	215	212	237	252	3.70E-01
Meta	**14079**	**14547**	**7827**	**14803**	**3.10E-07**



c) Bipolar Disorder

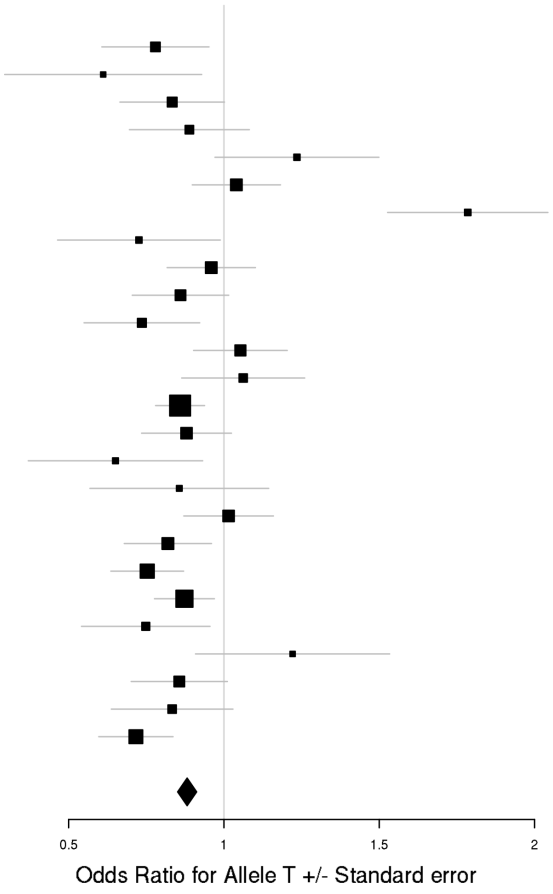
rs12341335 (T/C)
Bipolar Disorder

Study	HC F N	HC M N	PT F N	PT M N	p-value
bmau	891	901	189	140	6.52E-02
bmg2	211	232	117	64	8.20E-01
bmg3	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

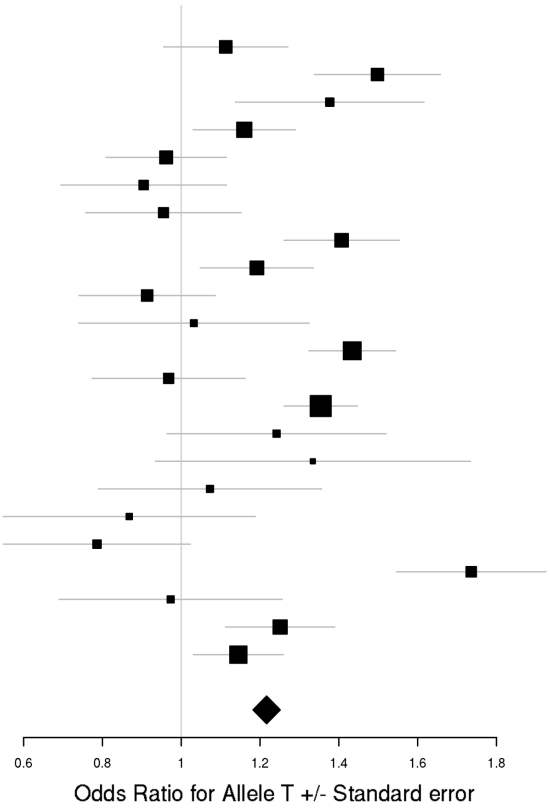
Study	HC F N	HC M N	PT F N	PT M N	p-value
bmau	889	898	185	140	1.48E-01
bmg2	210	231	116	63	1.20E-01
bmg3	587	281	282	194	2.78E-01
bmpo	207	471	249	159	5.41E-01
bmsp	143	143	137	111	4.24E-01
bonn	596	605	340	316	7.82E-01
dub1	560	236	78	71	2.46E-02
edi1	133	141	159	119	2.22E-01
fat2	577	480	417	302	7.69E-01
fran	916	684	261	189	3.31E-01
gain	191	206	314	295	9.92E-02
gsk1	527	369	412	239	7.32E-01
hal2	233	242	231	170	7.61E-01
icuk	1661	1723	1710	757	5.31E-02
may1	375	376	556	374	3.74E-01
mich	156	135	9	3	1.26E-01
rom3	103	87	134	94	5.90E-01
st2c	551	632	361	272	9.17E-01
stp1	378	406	502	417	1.56E-01
swa2	1103	1122	516	361	1.53E-02
swei	1693	1820	779	460	1.58E-01
top7	188	184	251	185	1.61E-01
top8	130	159	78	55	5.23E-01
ucl2	242	445	395	319	3.15E-01
uclo	283	211	242	172	3.51E-01
wtcc	499	456	977	576	5.24E-03
Meta	**13131**	**12743**	**9691**	**6413**	**3.72E-07**



d) Major Depressive Disorder

rs9428240 (T/C)
Major Depressive Disorder

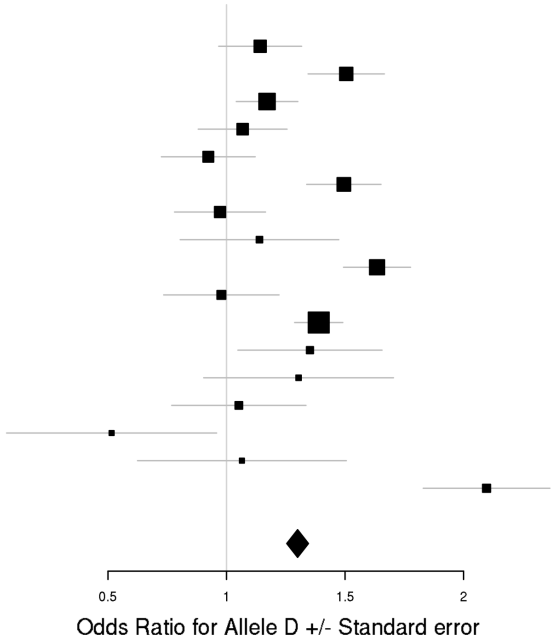
Study	HC F N	HC M N	PT F N	PT M N	p-value
boma	530	536	377	210	4.96E-01
col3	605	818	358	148	1.14E-02
edi2	138	146	221	151	1.81E-01
gens	535	784	713	291	2.53E-01
gep3	1346	1351	329	141	7.98E-01
grdg	292	176	365	106	6.33E-01
grnd	232	241	683	143	8.15E-01
gsk2	577	276	563	284	1.93E-02
i2b3	531	534	532	266	2.21E-01
mmi2	277	227	314	267	6.01E-01
mmo4	185	193	136	130	9.15E-01
nes1	976	627	1021	471	1.06E-03
qi6c	364	223	346	151	8.67E-01
rad3	820	557	1315	550	1.17E-03
rage	103	113	213	111	4.36E-01
rai2	178	161	90	19	4.71E-01
rau2	195	182	174	48	8.03E-01
rde4	208	306	93	40	6.58E-01
rot4	570	422	181	63	3.10E-01
shp0	493	638	254	119	3.62E-03
shpt	223	276	119	46	9.23E-01
stm2	422	503	551	368	1.06E-01
twg2	1182	1417	773	321	2.33E-01
Meta	**10982**	**10707**	**9721**	**4444**	**1.64E-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
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**

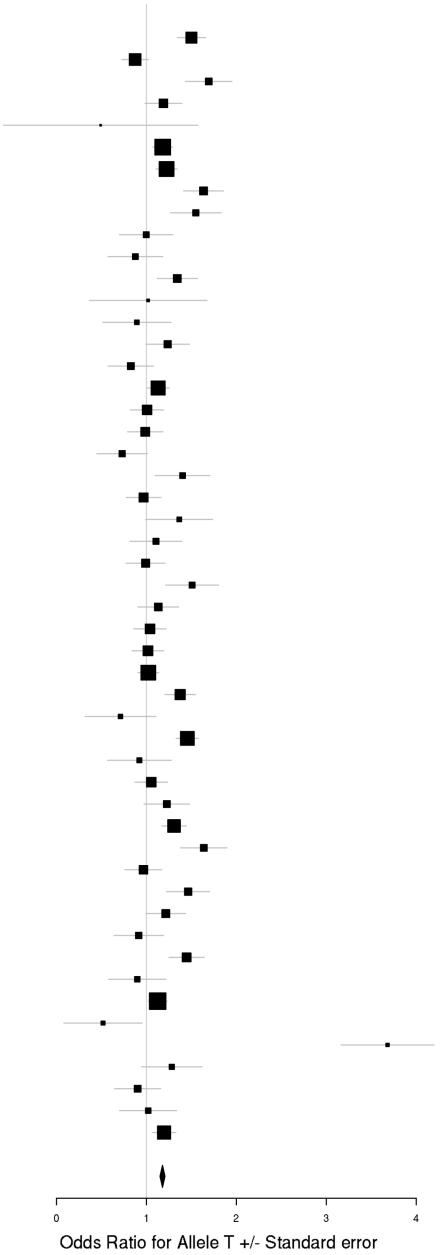


f) Cross-Disorder SCZ-BIP-MDD – European ancestry only

rs7302529 (T/C)

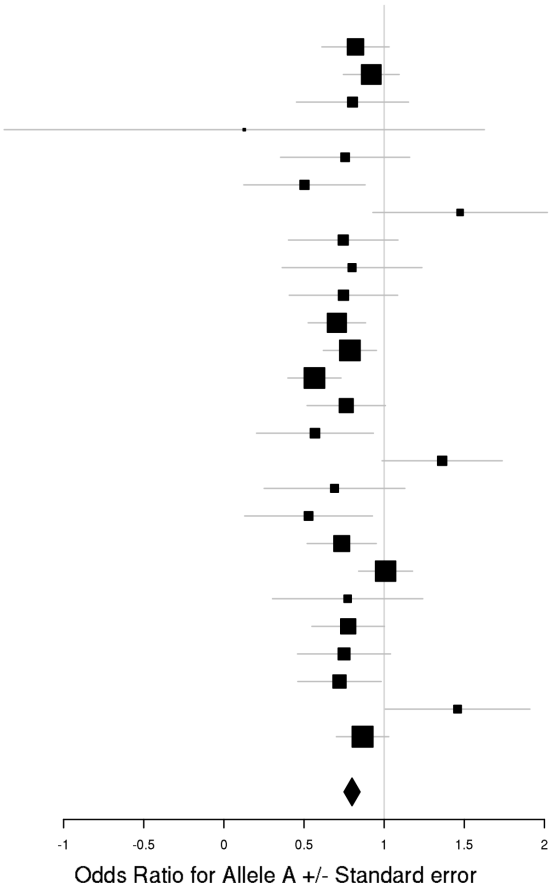
Cross-Disorder SCZ-BIP-MDD

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	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	bmg2	210	226	117	64	4.03E-01
BIP	bmg3	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	**17550**	**17448**	**17634**	**16697**	**1.60E-07**



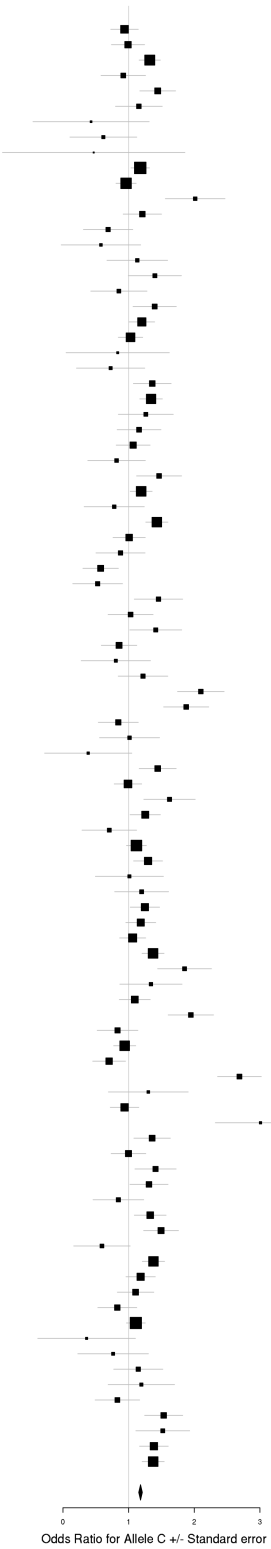
rs73033497 (A/T)
Cross-Disorder SCZ-BIP-MDD

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**



rs144142342 (C/G)
Cross-Disorder SCZ-BIP-MDD

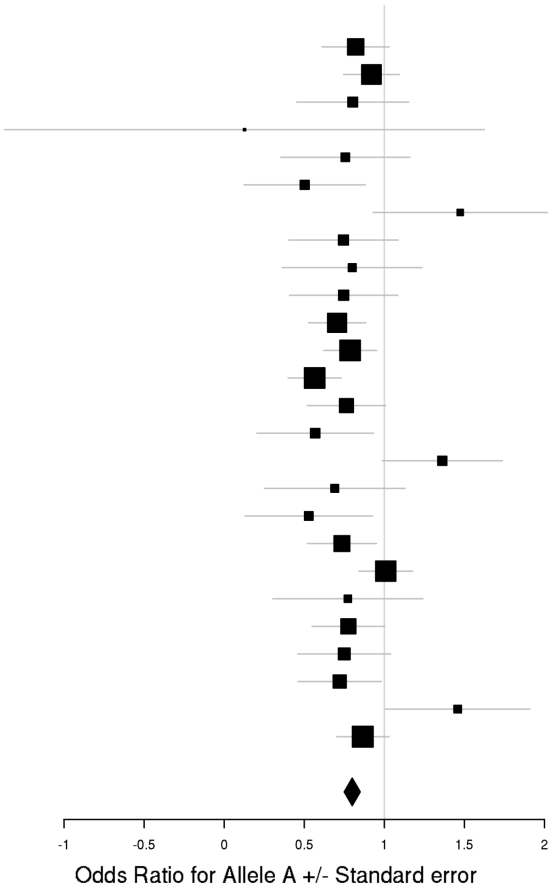
Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	390	462	386	464	7.57E-01
SCZ	aber	243	438	182	527	9.70E-01
SCZ	ajsz	414	1170	327	567	8.31E-02
SCZ	asrb	153	121	148	279	8.02E-01
SCZ	boco	160	160	759	952	1.77E-01
SCZ	buls	316	287	104	91	6.84E-01
SCZ	cati	7	44	90	304	3.37E-01
SCZ	caws	65	63	130	256	3.39E-01
SCZ	cims	20	33	11	52	5.84E-01
SCZ	clm2	680	667	923	2448	2.44E-01
SCZ	clo3	691	823	629	1440	7.96E-01
SCZ	cou3	91	73	202	317	1.23E-01
SCZ	denm	188	259	193	265	5.14E-01
SCZ	dubl	319	129	79	176	3.18E-01
SCZ	edin	37	37	98	264	3.64E-01
SCZ	egcu	827	299	169	62	7.88E-01
SCZ	ersw	121	178	91	142	4.05E-01
SCZ	fi3m	468	457	85	100	7.07E-01
SCZ	fii6	594	437	153	207	3.10E-01
SCZ	gras	413	710	342	694	3.46E-01
SCZ	irwt	435	546	425	857	8.76E-01
SCZ	lacw	23	21	51	104	8.17E-01
SCZ	lie2	144	124	37	94	5.38E-01
SCZ	lie5	204	181	126	362	2.84E-01
SCZ	mgs2	525	379	784	1781	8.65E-02
SCZ	msaf	57	79	121	199	5.77E-01
SCZ	munc	156	136	150	264	6.57E-01
SCZ	pewb	880	854	140	394	7.95E-01
SCZ	pews	96	137	63	86	6.43E-01
SCZ	port	131	78	133	212	2.65E-01
SCZ	s234	515	546	743	1118	2.94E-01
SCZ	swe1	99	98	94	115	5.89E-01
SCZ	swe5	583	653	690	1033	3.34E-02
SCZ	swe6	259	283	360	511	9.74E-01
SCZ	top8	101	100	159	212	7.24E-01
SCZ	ucla	278	282	170	522	3.93E-02
SCZ	uclo	143	95	144	358	9.14E-02
SCZ	umeb	185	149	110	156	3.08E-01
SCZ	umes	269	235	72	93	9.31E-01
SCZ	zhh1	98	91	63	127	3.81E-01
BIP	bmau	894	894	184	140	5.59E-01
BIP	bmg2	210	226	117	63	6.81E-01
BIP	bmg3	158	54	288	197	5.99E-01
BIP	bmpo	213	476	250	159	3.65E-02
BIP	bmsp	143	147	138	114	6.67E-02
BIP	bonn	151	142	345	318	5.73E-01
BIP	dub1	283	115	77	70	9.76E-01
BIP	edi1	43	38	154	118	1.50E-01
BIP	fat2	254	171	414	301	1.92E-01
BIP	fran	932	693	262	189	9.62E-01
BIP	gain	85	65	312	293	2.15E-01
BIP	gsk1	407	299	415	239	3.28E-01
BIP	hal2	65	73	234	171	4.01E-01
BIP	icuk	631	679	1725	757	4.56E-01
BIP	may1	374	374	560	374	2.38E-01
BIP	mich	69	60	8	3	9.82E-01
BIP	rom3	107	86	135	96	6.59E-01
BIP	st2c	399	497	359	269	3.20E-01
BIP	stp1	286	312	502	415	4.55E-01
BIP	swa2	578	569	498	348	7.63E-01
BIP	swei	873	896	764	457	5.81E-02
BIP	top7	103	104	248	181	1.32E-01
BIP	top8	128	155	81	56	5.36E-01
BIP	ucl2	243	441	397	324	7.03E-01
BIP	uclo	138	110	239	170	5.29E-02
BIP	ume4	139	121	299	184	5.50E-01
BIP	usc2	659	438	635	659	7.11E-01
BIP	wtcc	204	185	970	573	1.57E-01
MDD	boma	131	149	377	208	2.94E-03
MDD	cof3	61	65	74	46	6.66E-01
MDD	col3	608	819	358	148	7.68E-01
MDD	edi2	36	37	219	151	1.09E-01
MDD	gens	130	195	713	291	2.69E-01
MDD	gep3	382	361	328	142	9.93E-01
MDD	grdg	290	176	364	106	2.72E-01
MDD	grnd	198	212	682	143	3.51E-01
MDD	gsk2	134	65	561	285	6.59E-01
MDD	i2b3	240	253	533	266	2.38E-01
MDD	mmi2	276	228	314	265	1.30E-01
MDD	mmo4	185	193	137	130	2.25E-01
MDD	nes1	948	618	1018	470	5.72E-02
MDD	qi3c	368	208	498	361	4.51E-01
MDD	qi6c	363	220	347	152	7.17E-01
MDD	qio2	301	223	402	160	5.23E-01
MDD	rad3	694	485	1302	548	4.65E-01
MDD	rage	29	34	211	109	1.69E-01
MDD	ral2	173	157	89	19	6.16E-01
MDD	rau2	196	181	175	48	7.14E-01
MDD	rde4	207	301	93	40	7.26E-01
MDD	rot4	571	422	181	63	5.79E-01
MDD	shp0	492	635	254	118	1.40E-01
MDD	shpt	224	275	118	46	3.06E-01
MDD	stm2	279	356	551	367	1.34E-01
MDD	twg2	1110	1336	763	316	5.76E-02
	Meta	**28753**	**28538**	**30997**	**30441**	**9.06E-07**



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

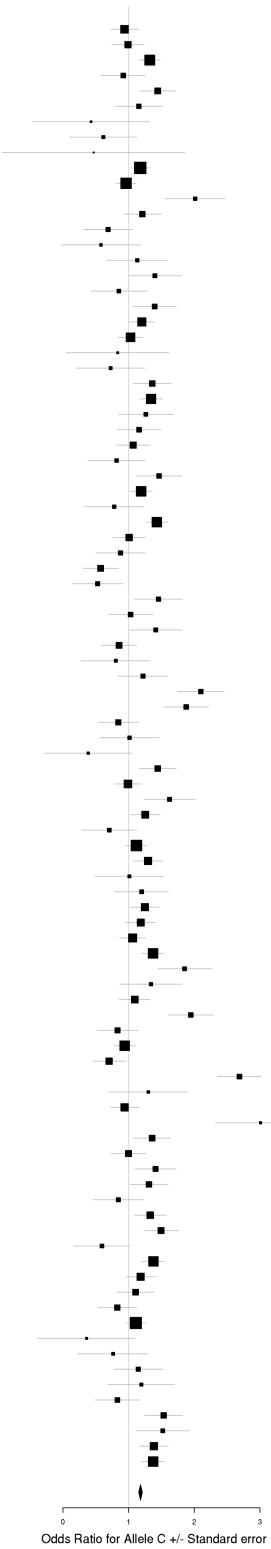
rs73033497 (A/T)
Cross-Disorder SCZ-BIP-MDD

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**



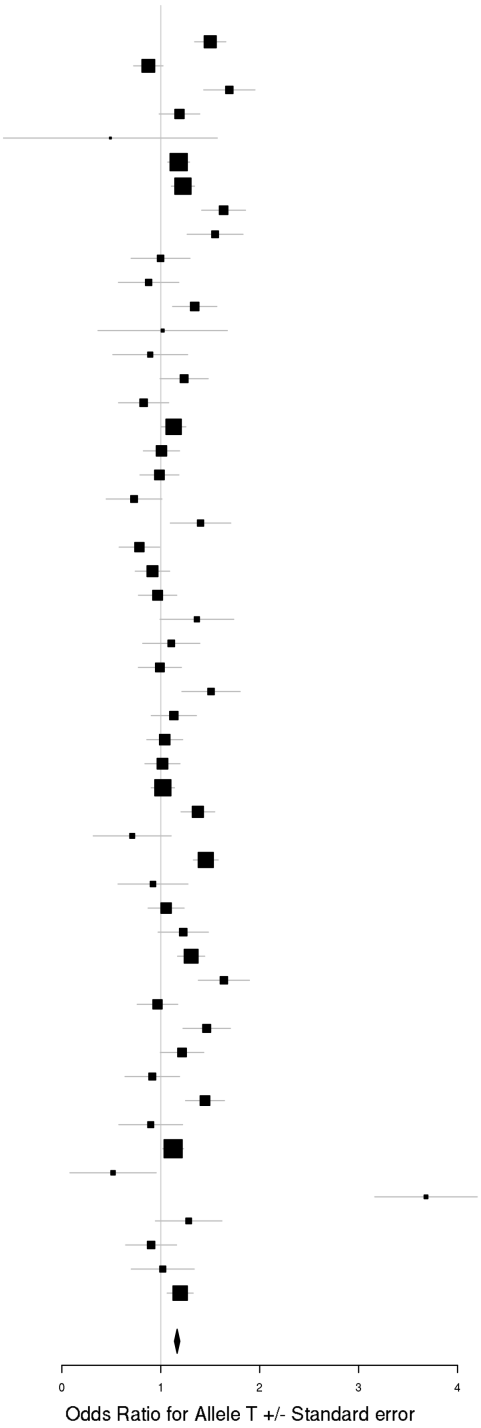
rs144142342 (C/G)
Cross-Disorder SCZ-BIP-MDD

Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	390	462	386	464	7.57E-01
SCZ	aber	243	438	182	527	9.70E-01
SCZ	ajsz	414	1170	327	567	8.31E-02
SCZ	asrb	153	121	148	279	8.02E-01
SCZ	boco	160	160	759	952	1.77E-01
SCZ	buls	316	287	104	91	6.84E-01
SCZ	cati	7	44	90	304	3.37E-01
SCZ	caws	65	63	130	256	3.39E-01
SCZ	cims	20	33	11	52	5.84E-01
SCZ	clm2	680	667	923	2448	2.44E-01
SCZ	clo3	691	823	629	1440	7.96E-01
SCZ	cou3	91	73	202	317	1.23E-01
SCZ	denm	188	259	193	265	5.14E-01
SCZ	dubl	319	129	79	176	3.18E-01
SCZ	edin	37	37	98	264	3.64E-01
SCZ	egcu	827	299	169	62	7.88E-01
SCZ	ersw	121	178	91	142	4.05E-01
SCZ	fi3m	468	457	85	100	7.07E-01
SCZ	fii6	594	437	153	207	3.10E-01
SCZ	gras	413	710	342	694	3.46E-01
SCZ	irwt	435	546	425	857	8.76E-01
SCZ	lacw	23	21	51	104	8.17E-01
SCZ	lie2	144	124	37	94	5.38E-01
SCZ	lie5	204	181	126	362	2.84E-01
SCZ	mgs2	525	379	784	1781	8.65E-02
SCZ	msaf	57	79	121	199	5.77E-01
SCZ	munc	156	136	150	264	6.57E-01
SCZ	pewb	880	854	140	394	7.95E-01
SCZ	pews	96	137	63	86	6.43E-01
SCZ	port	131	78	133	212	2.65E-01
SCZ	s234	515	546	743	1118	2.94E-01
SCZ	swe1	99	98	94	115	5.89E-01
SCZ	swe5	583	653	690	1033	3.34E-02
SCZ	swe6	259	283	360	511	9.74E-01
SCZ	top8	101	100	159	212	7.24E-01
SCZ	ucla	278	282	170	522	3.93E-02
SCZ	uclo	143	95	144	358	9.14E-02
SCZ	umeb	185	149	110	156	3.08E-01
SCZ	umes	269	235	72	93	9.31E-01
SCZ	zhh1	98	91	63	127	3.81E-01
BIP	bmau	894	894	184	140	5.59E-01
BIP	bmg2	210	226	117	63	6.81E-01
BIP	bmg3	158	54	288	197	5.99E-01
BIP	bmpo	213	476	250	159	3.65E-02
BIP	bmsp	143	147	138	114	6.67E-02
BIP	bonn	151	142	345	318	5.73E-01
BIP	dub1	283	115	77	70	9.76E-01
BIP	edi1	43	38	154	118	1.50E-01
BIP	fat2	254	171	414	301	1.92E-01
BIP	fran	932	693	262	189	9.62E-01
BIP	gain	85	65	312	293	2.15E-01
BIP	gsk1	407	299	415	239	3.28E-01
BIP	hal2	65	73	234	171	4.01E-01
BIP	icuk	631	679	1725	757	4.56E-01
BIP	may1	374	374	560	374	2.38E-01
BIP	mich	69	60	8	3	9.82E-01
BIP	rom3	107	86	135	96	6.59E-01
BIP	st2c	399	497	359	269	3.20E-01
BIP	stp1	286	312	502	415	4.55E-01
BIP	swa2	578	569	498	348	7.63E-01
BIP	swei	873	896	764	457	5.81E-02
BIP	top7	103	104	248	181	1.32E-01
BIP	top8	128	155	81	56	5.36E-01
BIP	ucl2	243	441	397	324	7.03E-01
BIP	uclo	138	110	239	170	5.29E-02
BIP	ume4	139	121	299	184	5.50E-01
BIP	usc2	659	438	635	659	7.11E-01
BIP	wtcc	204	185	970	573	1.57E-01
MDD	boma	131	149	377	208	2.94E-03
MDD	cof3	61	65	74	46	6.66E-01
MDD	col3	608	819	358	148	7.68E-01
MDD	edi2	36	37	219	151	1.09E-01
MDD	gens	130	195	713	291	2.69E-01
MDD	gep3	382	361	328	142	9.93E-01
MDD	grdg	290	176	364	106	2.72E-01
MDD	grnd	198	212	682	143	3.51E-01
MDD	gsk2	134	65	561	285	6.59E-01
MDD	i2b3	240	253	533	266	2.38E-01
MDD	mmi2	276	228	314	265	1.30E-01
MDD	mmo4	185	193	137	130	2.25E-01
MDD	nes1	948	618	1018	470	5.72E-02
MDD	qi3c	368	208	498	361	4.51E-01
MDD	qi6c	363	220	347	152	7.17E-01
MDD	qio2	301	223	402	160	5.23E-01
MDD	rad3	694	485	1302	548	4.65E-01
MDD	rage	29	34	211	109	1.69E-01
MDD	ral2	173	157	89	19	6.16E-01
MDD	rau2	196	181	175	48	7.14E-01
MDD	rde4	207	301	93	40	7.26E-01
MDD	rot4	571	422	181	63	5.79E-01
MDD	shp0	492	635	254	118	1.40E-01
MDD	shpt	224	275	118	46	3.06E-01
MDD	stm2	279	356	551	367	1.34E-01
MDD	twg2	1110	1336	763	316	5.76E-02
	Meta	**28753**	**28538**	**30997**	**30441**	**9.06E-07**



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

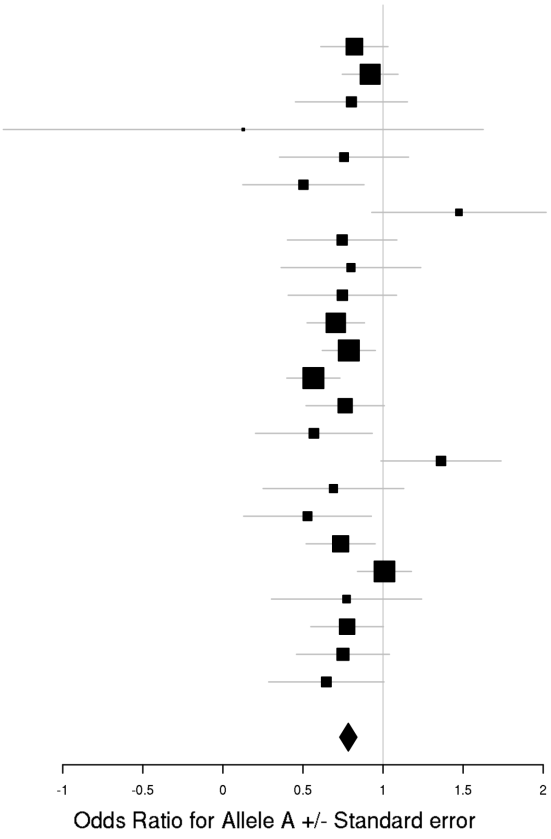
Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	391	463	387	465	9.74E-03
SCZ	ajsz	414	1171	327	567	3.63E-01
SCZ	asrb	153	121	148	280	4.17E-02
SCZ	boco	160	160	761	952	3.97E-01
SCZ	cims	20	33	11	52	5.10E-01
SCZ	clm2	671	657	908	2393	1.28E-01
SCZ	clo3	684	818	627	1435	8.16E-02
SCZ	denm	188	259	193	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	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
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	bmg2	210	226	117	64	4.03E-01
BIP	bmg3	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

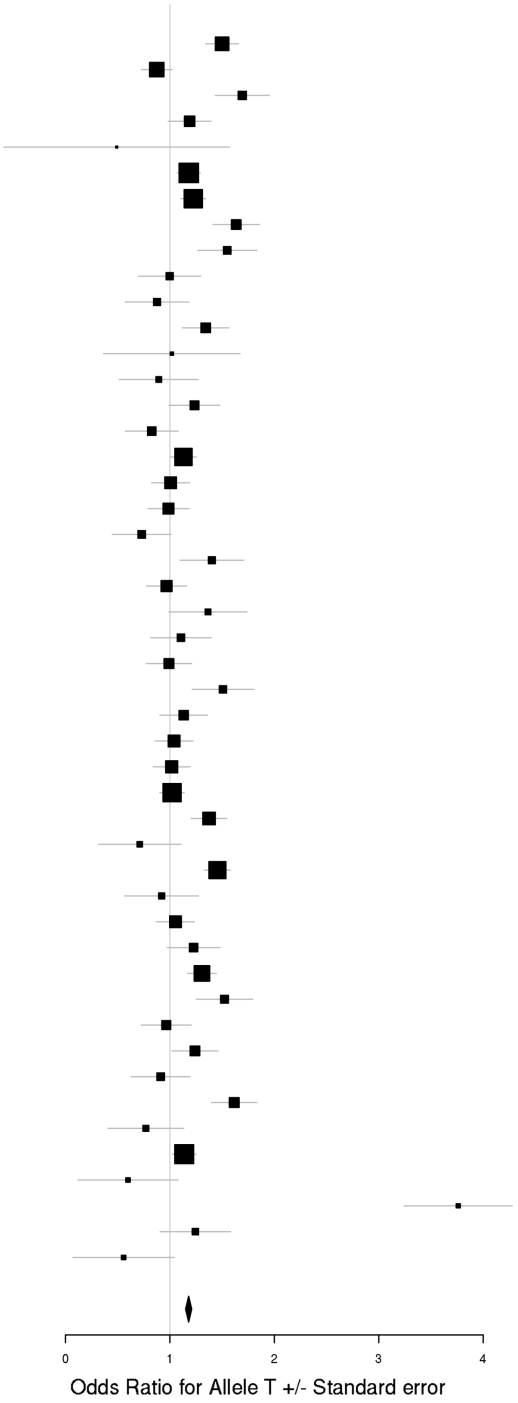
rs73033497 (A/T)
Cross-Disorder SCZ-BIP-RMDD

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
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**



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

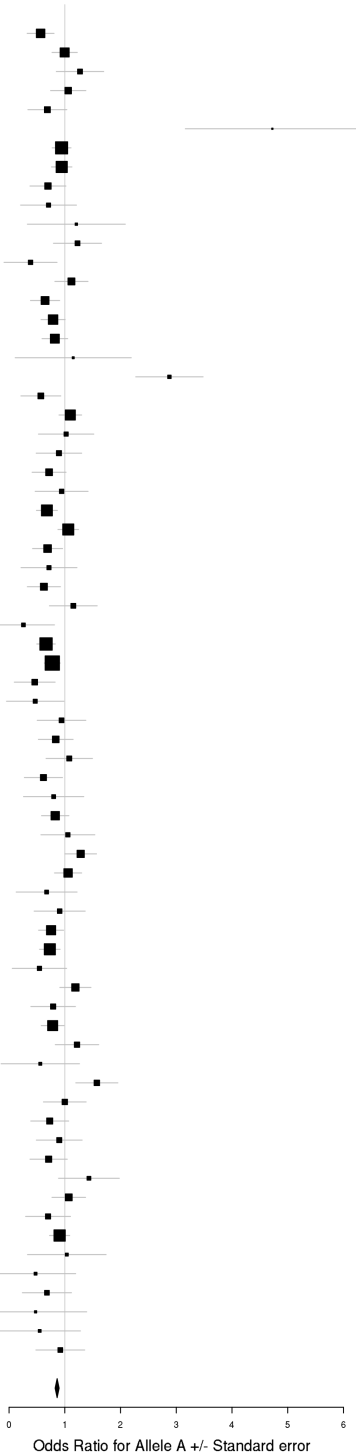
Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	391	463	387	465	9.74E-03
SCZ	ajsz	414	1171	327	567	3.63E-01
SCZ	asrb	153	121	148	280	4.17E-02
SCZ	boco	160	160	761	952	3.97E-01
SCZ	cims	20	33	11	52	5.10E-01
SCZ	clm2	671	657	908	2393	1.28E-01
SCZ	clo3	684	818	627	1435	8.16E-02
SCZ	denm	188	259	193	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	bmg2	210	226	117	64	4.03E-01
BIP	bmg3	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
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

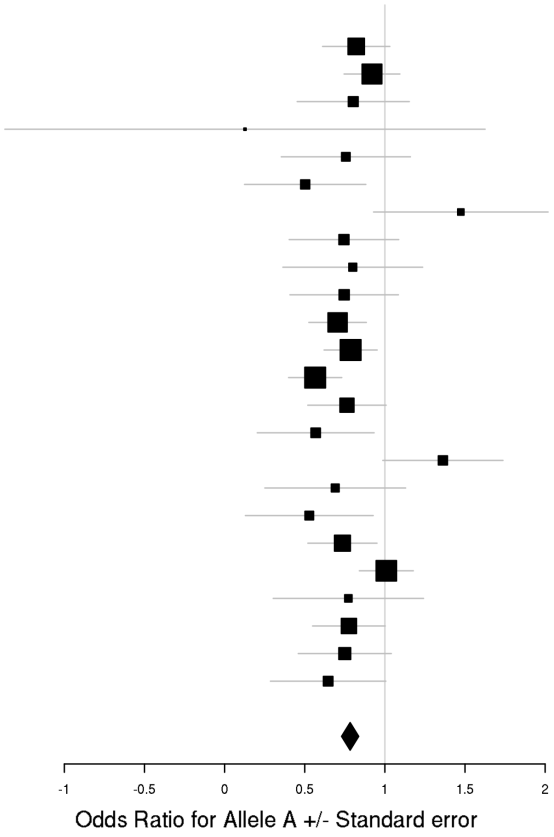
rs8040598 (A/G)
Cross-Disorder SCZ-BIP-RMDD

Dx	Study	HC F N	HC M N	PT F N	PT M N	p-value
SCZ	aarh	391	463	387	465	1.79E-02
SCZ	ajsz	414	1171	327	567	9.91E-01
SCZ	asrb	153	121	148	280	5.70E-01
SCZ	boco	160	160	761	952	8.52E-01
SCZ	buls	315	288	104	91	2.83E-01
SCZ	cims	20	33	11	52	3.20E-01
SCZ	clm2	681	668	923	2450	7.24E-01
SCZ	clo3	692	824	629	1442	7.56E-01
SCZ	denm	188	259	193	266	2.63E-01
SCZ	dubl	318	129	79	176	4.90E-01
SCZ	edin	37	37	98	264	8.31E-01
SCZ	egcu	828	299	169	62	6.33E-01
SCZ	ersw	121	178	92	142	4.48E-02
SCZ	fi3m	469	457	85	101	7.04E-01
SCZ	fii6	594	437	153	207	9.44E-02
SCZ	gras	415	707	342	693	2.76E-01
SCZ	irwt	434	546	424	855	3.93E-01
SCZ	lacw	23	21	51	104	8.93E-01
SCZ	lie2	144	124	37	94	8.01E-02
SCZ	lie5	204	182	126	363	1.15E-01
SCZ	mgs2	527	381	783	1777	6.40E-01
SCZ	msaf	57	79	121	198	9.62E-01
SCZ	munc	156	136	150	266	7.86E-01
SCZ	pewb	885	856	140	396	2.76E-01
SCZ	pews	96	138	63	87	9.01E-01
SCZ	s234	517	548	744	1131	3.86E-02
SCZ	swe5	585	654	690	1034	7.45E-01
SCZ	swe6	259	283	360	511	1.69E-01
SCZ	top8	102	101	160	214	5.05E-01
SCZ	ucla	278	282	170	522	1.12E-01
SCZ	umeb	185	150	110	156	7.40E-01
SCZ	umes	269	235	72	93	1.49E-02
SCZ	hok2	1344	668	154	322	1.30E-02
SCZ	tcr1	336	570	289	563	7.50E-02
BIP	bmau	895	895	184	140	3.38E-02
BIP	bmg2	210	226	117	64	1.41E-01
BIP	bmg3	158	54	288	197	8.90E-01
BIP	bmpo	213	476	250	160	5.69E-01
BIP	bmsp	144	147	138	114	8.53E-01
BIP	bonn	151	142	345	318	1.58E-01
BIP	dub1	281	115	77	70	6.79E-01
BIP	fran	934	693	262	189	4.42E-01
BIP	gain	85	65	314	294	9.12E-01
BIP	gsk1	408	299	415	239	3.77E-01
BIP	may1	375	374	560	374	8.14E-01
BIP	mich	69	60	9	3	4.69E-01
BIP	rom3	107	87	135	96	8.33E-01
BIP	swa2	581	572	496	350	2.06E-01
BIP	swei	873	898	765	459	8.96E-02
BIP	top8	128	155	81	56	2.13E-01
BIP	ucl2	243	442	397	324	5.34E-01
BIP	ume4	139	121	299	184	5.56E-01
BIP	usc2	659	438	635	659	2.29E-01
rMDD	boma	131	149	299	148	6.11E-01
rMDD	cof3	60	64	53	37	4.09E-01
rMDD	gens	130	195	711	290	2.29E-01
rMDD	gep3	382	361	260	85	1.00E+
rMDD	grnd	199	212	677	140	3.53E-01
rMDD	gsk2	134	65	438	227	7.99E-01
rMDD	mmi2	278	228	230	173	3.05E-01
rMDD	mmo4	185	193	105	89	5.09E-01
rMDD	qi3c	369	209	326	253	8.20E-01
rMDD	qi6c	363	221	156	85	3.74E-01
rMDD	rad3	694	485	1005	417	5.90E-01
rMDD	rage	29	34	180	73	9.60E-01
rMDD	rai2	172	154	87	19	3.01E-01
rMDD	rau2	196	182	175	47	3.80E-01
rMDD	rde4	208	303	41	18	4.18E-01
rMDD	rot4	571	422	57	14	4.12E-01
rMDD	shp0	494	637	128	52	8.48E-01
	Meta	**23425**	**22558**	**19829**	**23353**	**3.90E-07**



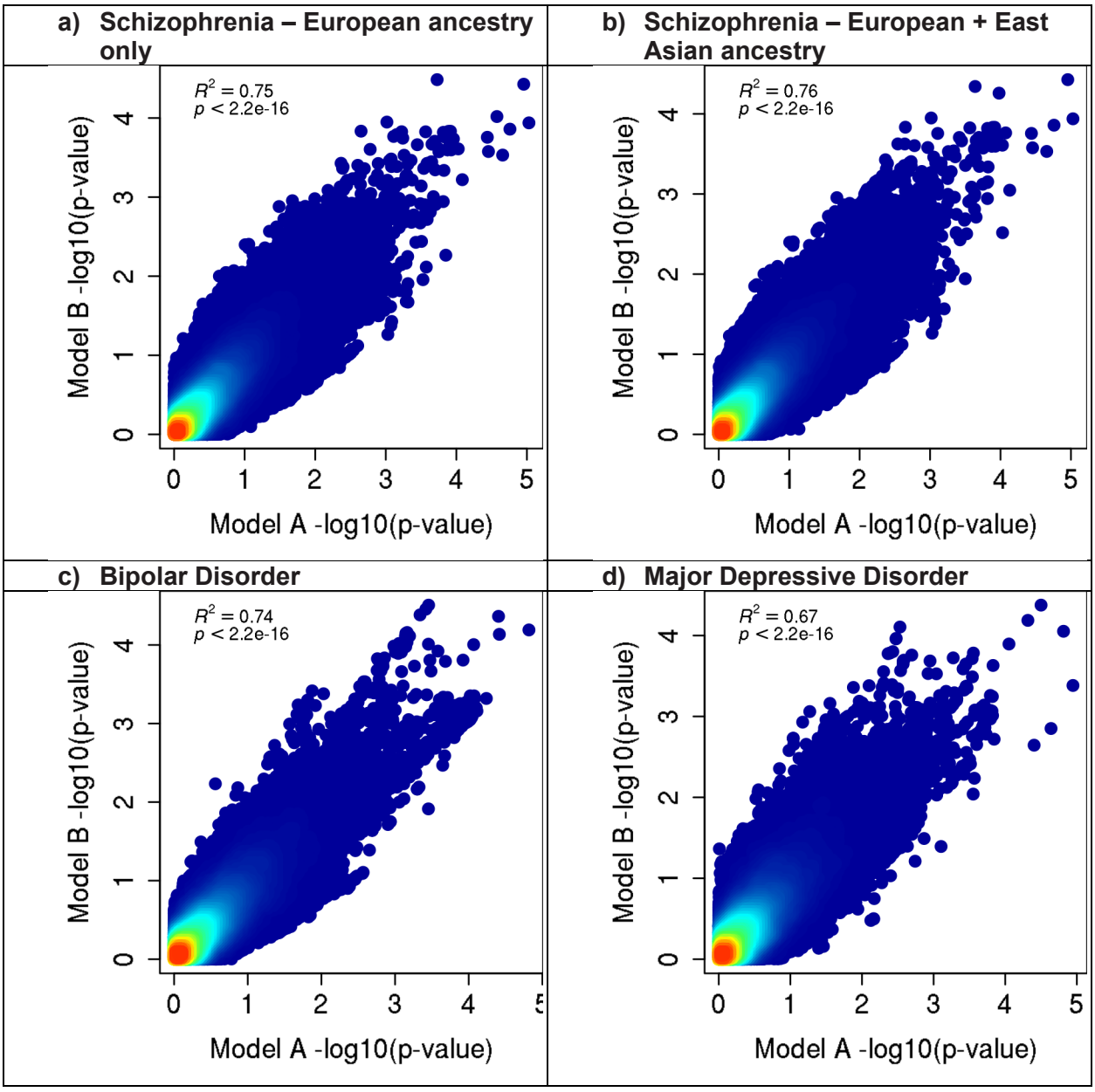
rs73033497 (A/T)
Cross-Disorder SCZ-BIP-RMDD

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	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
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**

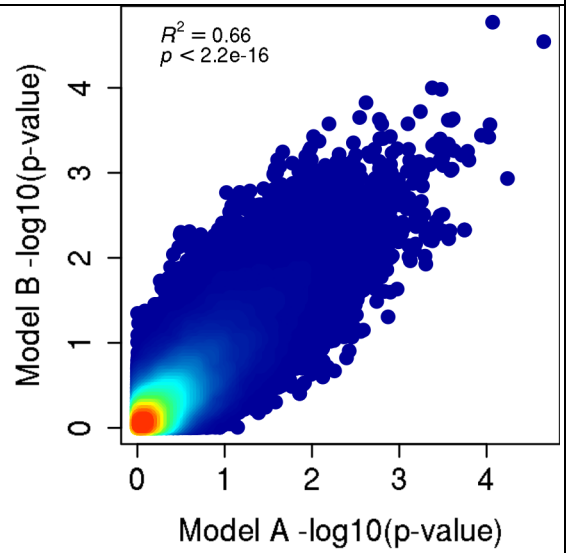


Supplementary Figure 23. X chromosome model comparisons in PGC

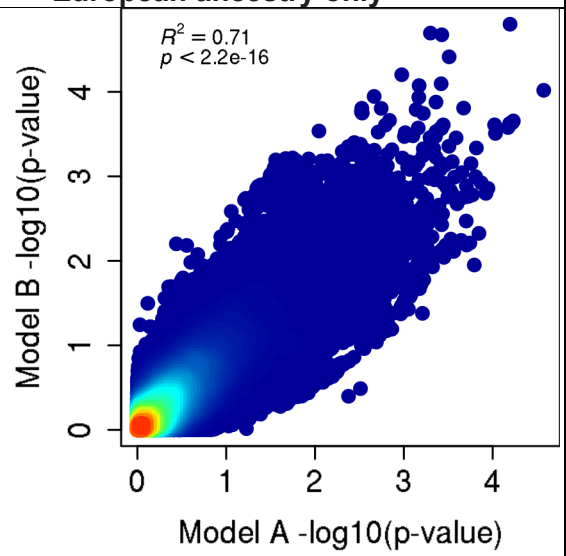
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; HC F N = number of female healthy controls; HC M N = number of male healthy controls; PT F N = number of female patients; PT M N = number of male patients; Study = cohort abbreviation used by PGC;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



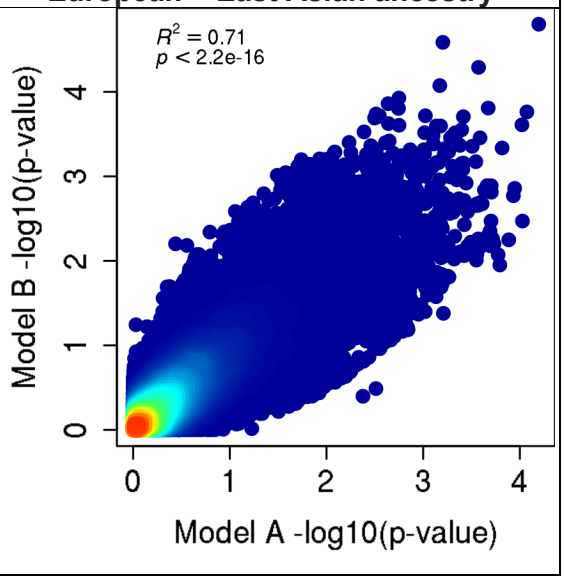
e) Recurrent Major Depressive Disorder

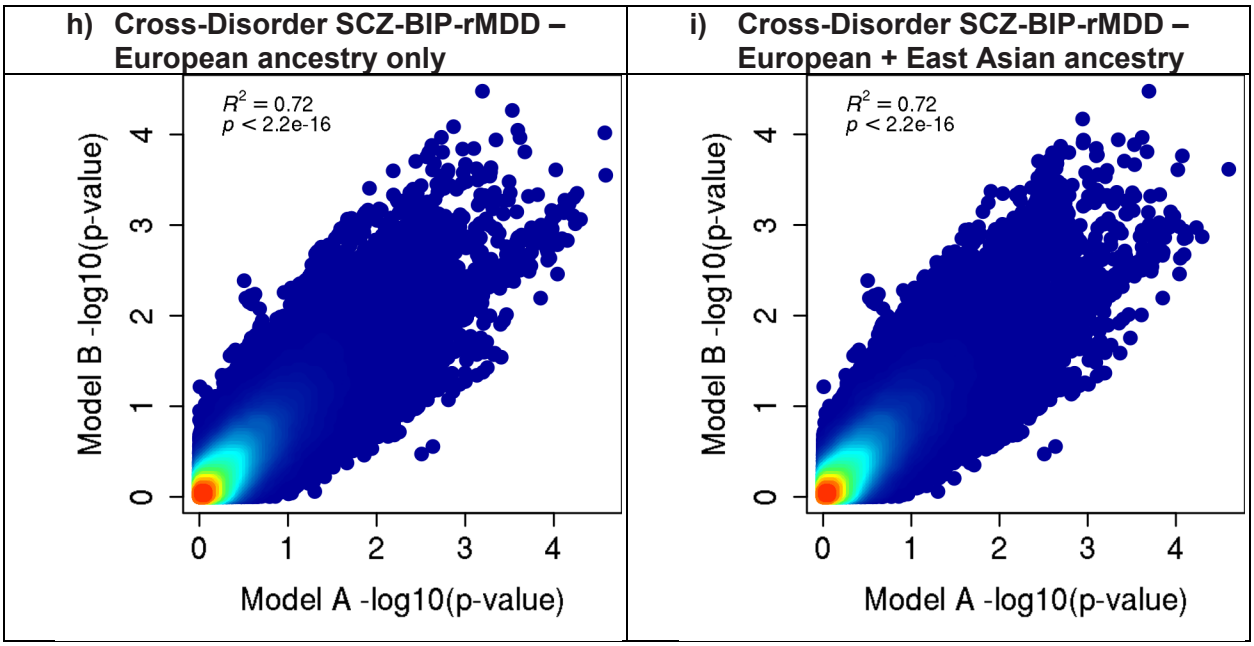


f) Cross-Disorder SCZ-BIP-MDD – European ancestry only



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




h) Cross-Disorder SCZ-BIP-rMDD – European ancestry only
R^2 = 0.72
p < 2.2e-16
Model B -log10(p-value)
Model A -log10(p-value)
0
1
2
3
4
i) Cross-Disorder SCZ-BIP-rMDD – European + East Asian ancestry
R^2 = 0.72
p < 2.2e-16
Model B -log10(p-value)
Model A -log10(p-value)

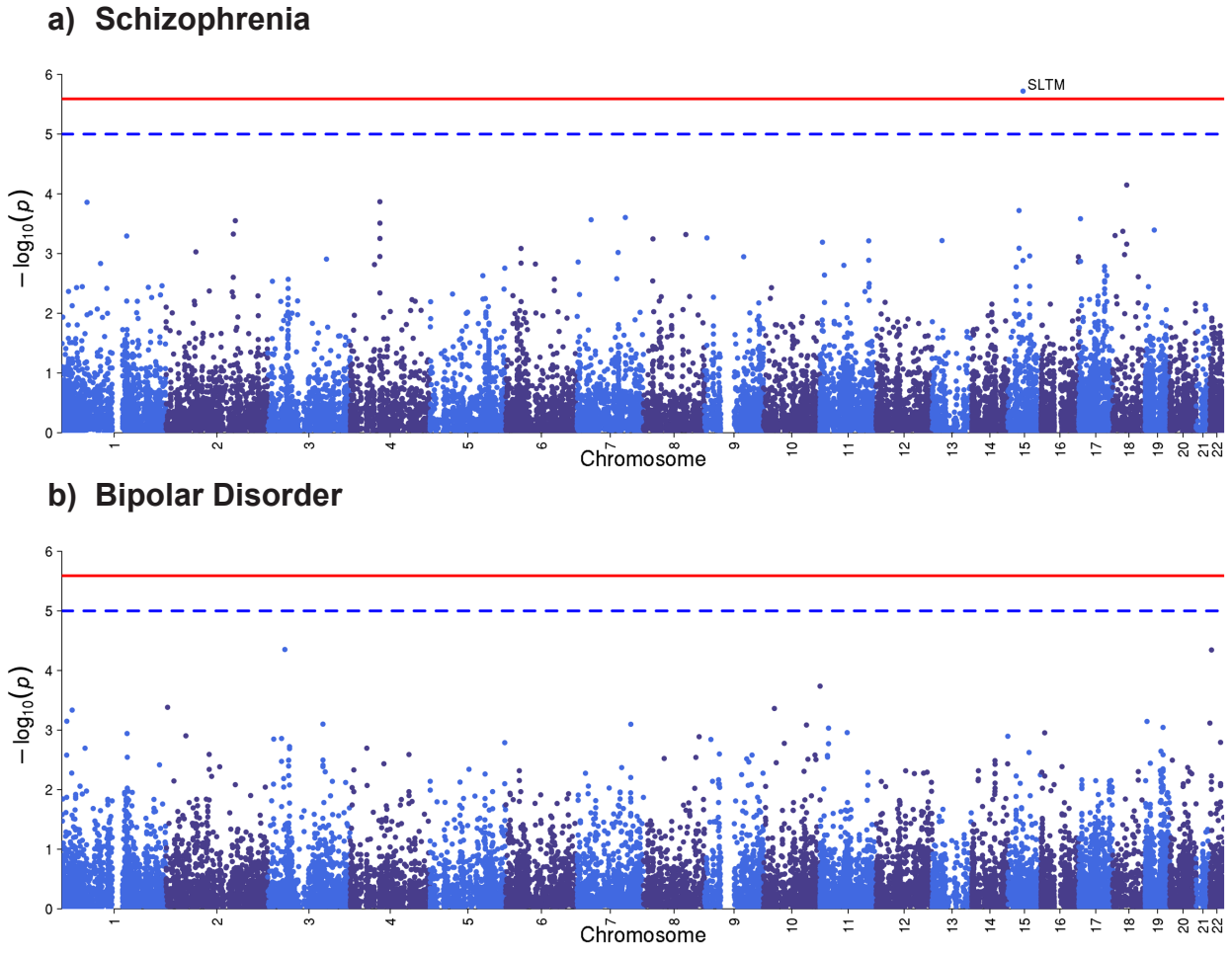
Supplementary Figure 24. Manhattan plots for gene-based GxS tests in PGC

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.

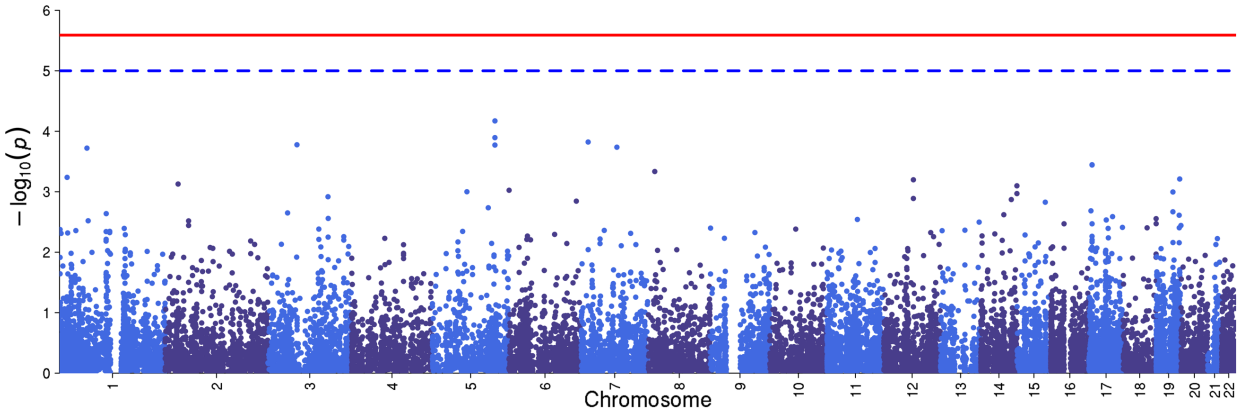
Negative log10-transformed p-values for each gene (y-axis) are plotted by chromosomal position (x-axis). Each dot represents a gene, and the solid red and dotted blue horizontal lines represent the thresholds for genome-wide significant association ($p = 2.57\times10^{-6}$) and suggestive association ($p = 1\times10^{-5}$), respectively.

Plots were generated using the plot package in R.

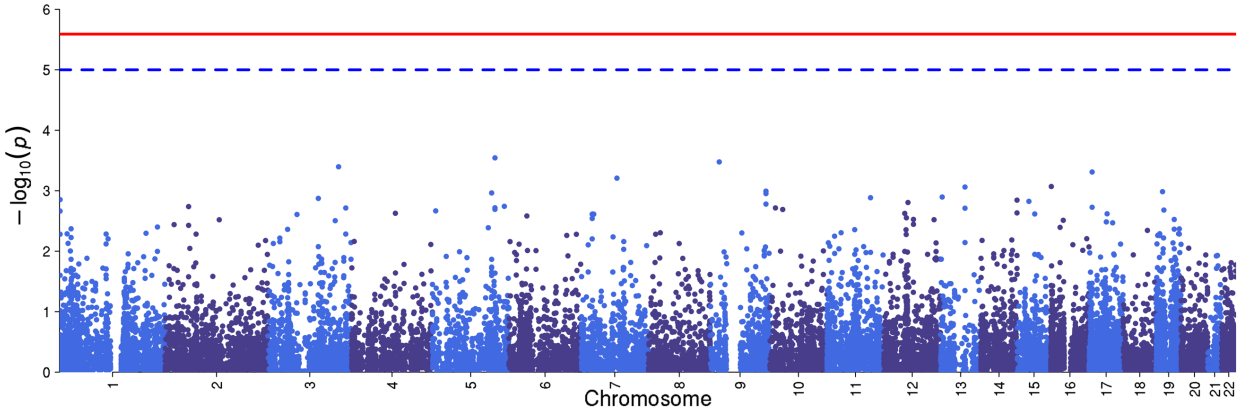
Abbreviations: BIP = Bipolar Disorder; (r)MDD = (recurrent) Major Depressive Disorder; SCZ = Schizophrenia; SLTM = SAFB Like Transcription Modulator



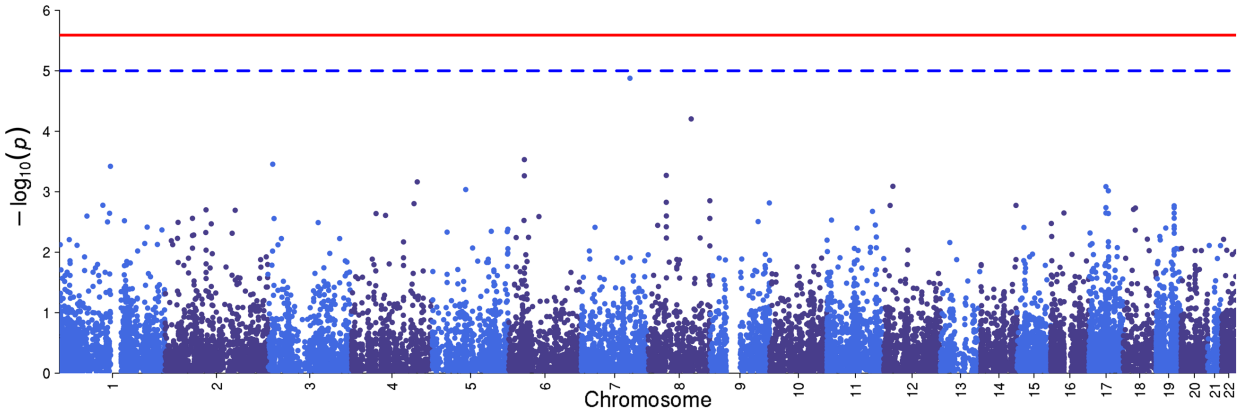
c) Major Depressive Disorder



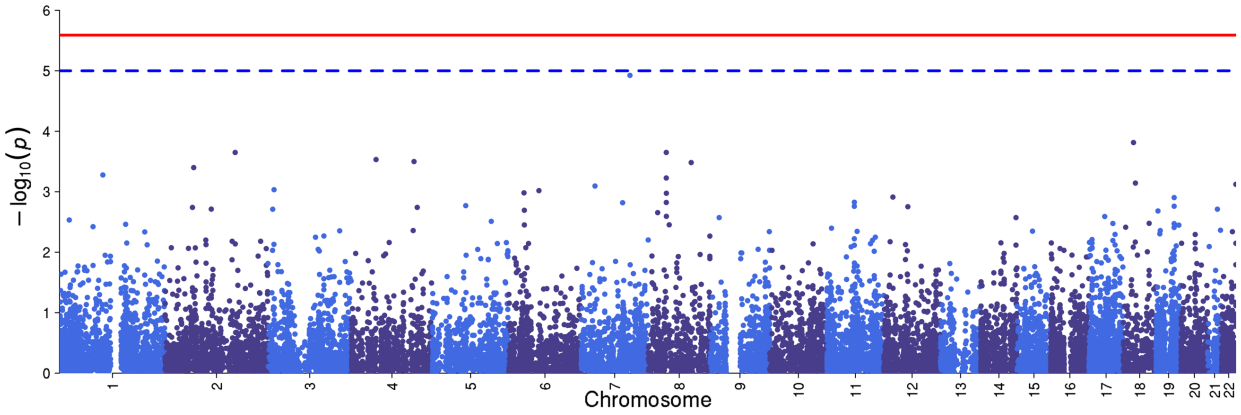
d) Recurrent Major Depressive Disorder



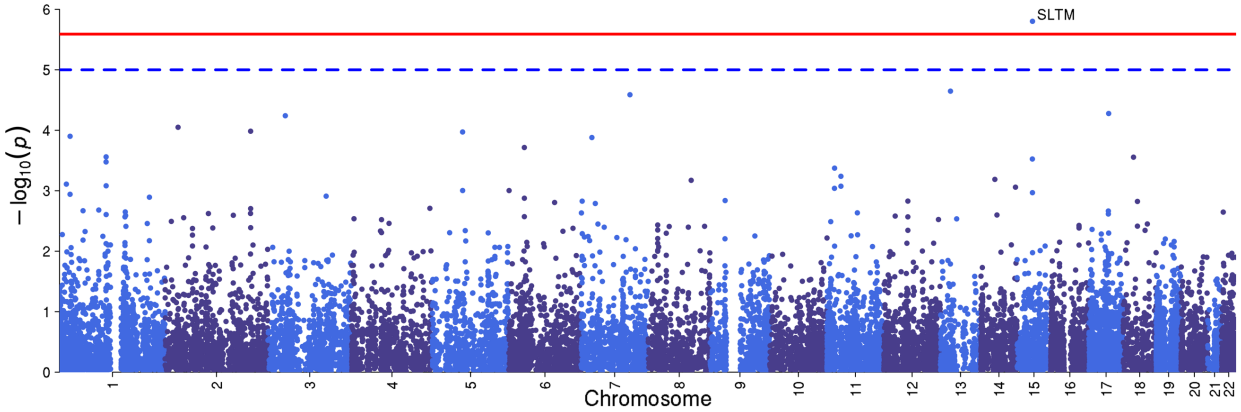
e) Cross-Disorder SCZ-BIP-MDD



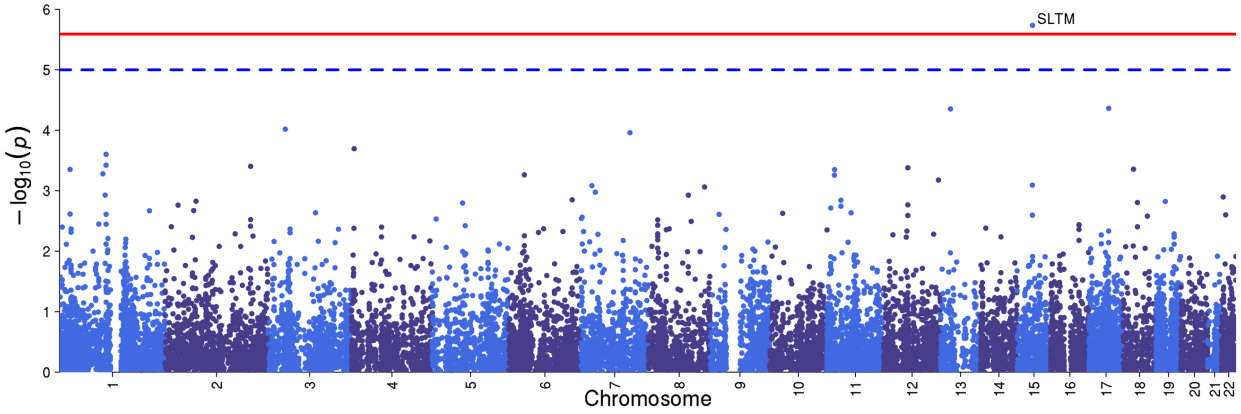
f) Cross-Disorder SCZ-BIP-rMDD



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.

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