Sex-Dependent Shared and Non-Shared Genetic Architecture

Across Mood and Psychotic Disorders

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Abstract

BACKGROUND: Sex differences in the incidence and/or presentation of schizophrenia (SCZ), major depressive disorder (MDD), and bipolar disorder (BIP) are pervasive. Previous evidence for shared genetic risk and sex differences in brain abnormalities across these disorders suggest possible shared sex-dependent genetic risk.

METHODS: We conducted the largest to date genome-wide genotype–by–sex (GxS) interaction analysis of risk for these disorders, using data from 85,735 cases (33,403 SCZ, 19,924 BIP, 32,408 MDD) and 109,946 controls from the Psychiatric Genomics Consortium (PGC) and iPSYCH.

RESULTS: Across disorders, genome-wide significant SNP-by-sex interaction was detected for a locus encompassing *NKAIN2* gene (rs117780815; p=3.2×10^{-8}), that interacts with sodium/potassium-transporting ATPase enzymes important for neuronal excitability. Three additional loci showed evidence (p<1×10^{-6}) for cross-disorder GxS interaction (rs7302529, p=1.6×10^{-7}; rs73033497, p=8.8×10^{-7}; rs7914279, p=6.4×10^{-7}) with various potential functions. Gene-based analyses identified GxS interaction across disorders (p=8.97×10^{-7}) with transcriptional inhibitor *SLTM*. Most significant in SCZ was a locus in the *MOCOS* gene (rs11665282; p=1.5×10^{-7}), implicating vascular endothelial cells. Secondary analysis of the SCZ PGC dataset detected a noteworthy interaction (rs13265509; p=1.1×10^{-7}) in a locus containing *IDO2*, a kynurenine pathway enzyme with an immunoregulatory function previously implicated in SCZ, BIP, and MDD. Pathway enrichment analysis detected significant GxS of genes regulating vascular endothelial growth factor (VEGF) receptor signaling in MDD (p_{FDR}<0.05).

CONCLUSIONS: In the largest genome-wide GxS analysis of mood and psychotic disorders to date, there was substantial genetic overlap between the sexes. However, significant sex-dependent effects were enriched for genes related to neuronal development, immune and

vascular functions across and within SCZ, BIP, and MDD at the variant, gene, and pathway enrichment levels.

Key words
sex differences; schizophrenia; bipolar disorder; major depressive disorder; genome-wide association study; genotype-by-sex interaction

Introduction

Sex differences are pervasive in psychiatric disorders, including major depressive disorder (MDD), schizophrenia (SCZ), and bipolar disorder (BIP). There is a significantly higher risk for MDD in females (1) and SCZ in males (2). BIP prevalence is approximately the same in both sexes, but age at onset, illness course, and prognosis vary considerably between the sexes (3, 4), as they do for SCZ and MDD (5-7). Additionally, certain brain regions share structural and functional abnormalities and dysregulated physiology across disorders that are sex-dependent (8, 9).

The majority of twin studies have not detected sex differences in heritability of these disorders (10) (and twin heritability includes sex chromosome effects), or differences in twin intra-pair correlations between same-sex and opposite-sex dizygotic twin pairs (11, 12). However, specific variants involved in disease etiology may not be the same in both sexes (i.e., "sex-specific" effects) or variants may have different effect sizes in each sex (i.e., "sex-dependent" effects). Sex-dependent modification of allelic effects on the autosomes and X chromosome may contribute to sex differences in disease prevalence, similar to what has been shown for several complex human traits (e.g., blood pressure, waist-hip ratio) (13, 14). Aside from sex-specific variants, incidence differences may result from a female protective effect, particularly for male-predominant neurodevelopmental disorders, whereby females may require a higher burden of genetic liability to cross the threshold to disease manifestation. This suggests quantitative differences (i.e., "sex-dependence") in genetic risk, a notion that is supported by an early observation that female SCZ cases were more likely to come from multiplex families (15), i.e. families with multiple affected individuals.

With regard to SCZ, there is a long history of examining sex differences in familial (and specifically, genetic) transmission (16), although few systematic and rigorous studies exist using advanced technologies of genomic assessment. This is true even in light of population and

clinical studies identifying significant sex differences in incidence, expression, neuroanatomical and functional brain abnormalities, and course of SCZ (17, 18). As a whole, family and twin studies, and recent genome-wide association studies (GWAS), support the presence of both sex-specific and sex-dependent genetic influences (16). In fact, recent work in large genetic cohorts of SCZ and autoimmune disorders identified sex differences in complement component 4 (C4) genes, with greater effects of C4 alleles in men with SCZ than women (19, 20).

Whereas the incidence of SCZ is significantly, although modestly, higher in males, there is a larger sex difference in the incidence of MDD, with a 2:1 female predominance. Although large-scale GWAS have provided little support for sex differences in genetic predisposition to broadly defined MDD (21-24), there is promise in studying recurrent MDD (rMDD) in the context of sex differences, based on greater disparity in prevalence by sex than single-episode MDD reported in some studies (25, 26), although not others (7, 27). Recently, there has been increased interest in examining sex differences in genetic contributions to psychiatric disorders and related phenotypes (21, 28-35). Transcriptomics studies are also beginning to provide insights into the mechanisms underlying sex differences that may influence disease risk. Notably, over 10% of autosomal genes exhibit sexually dimorphic gene expression in the brain, predominantly genes related to synaptic transmission, dopamine receptor signaling, and immune response (36), suggesting potential mechanisms mediating sex differences in psychiatric disorders. GxS studies like ours can serve to highlight genes worthy of deeper investigation regarding the underlying mechanisms of sexual brain differentiation in risk and presentation of psychiatric disorders, e.g. through transcriptomics and proteomics research.

In order to test for sex differences in genetic risk, it is essential to have adequate power to test for an interaction effect (37). Given sample size limitations, GWAS of psychiatric disorders have typically not examined GxS interactions at a genome-wide level. Here, we capitalized on a unique opportunity to utilize cohorts from the PGC and iPSYCH consortia (22, 38, 39) (total N =

195,681) to assess interactions between sex and genetic risk of MDD, SCZ and BIP individually and shared across disorders.

Methods and Materials

Subjects

The Psychiatric Genomics Consortium (PGC) dataset (22, 38, 39) included 43 SCZ cohorts (30,608 patients, 38,441 controls), 28 BIP cohorts (18,958 patients, 29,996 controls), and 26 MDD cohorts (15,970 patients, 24,984 controls; **Supplementary Table 1**). The iPSYCH cohort in Denmark (40) included 2,795 SCZ patients and 2,436 controls, 966 BIP patients and 551controls, and 16,438 MDD patients and 13,538 controls (**Supplementary Table 2**). Primary analyses used both the PGC and iPSYCH datasets. Secondary analyses of the PGC dataset alone (reported in **Supplementary Materials**) were performed to facilitate comparison to other PGC studies, and because the PGC and iPSYCH datasets use different diagnostic criteria (DSM-IV and ICD-10, respectively). All cohorts were of European ancestry, with the exception of 3 East Asian SCZ cohorts.

Data Quality Controls and Analytic Approaches

Quality control (QC) and imputation to the 1000 Genomes Phase 1 reference panel were performed using the PGC's Rapid Imputation Consortium Pipeline (Ricopili) and previously described filtering thresholds (22, 38, 39). IBD filtering is described in the **Supplementary Methods**.

Sex-stratified GWAS summary statistics were obtained by logistic regression of males and females separately within each cohort using PLINK (41), followed by standard-error weighted meta-analysis across cohorts using METAL (42) (We provided the within-disorder meta-analysis summary statistics to a study by Martin et al, in submission). Summary statistics were entered into Linkage Disequilibrium (LD) Score Regression (LDSC) (43, 44) to estimate the autosomal sex-specific narrow sense SNP-based heritability (h^2_{SNP}) for each disorder (**Figure**

1) and autosomal sex-specific and cross-sex bivariate genetic correlations (r_g) within and across disorders.

PLINK (41) was used to perform a genome-wide GxS interaction analysis of each study cohort, followed by standard-error weighted meta-analysis of the GxS interaction results using METAL (42). GxS interaction analyses were performed using linear regression with a main effect for each SNP and SNP-by-sex interaction terms, using an additive model for each SNP (and controlling for 10 ancestry principal components).

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.

A three-degrees-of-freedom test omnibus test (45) was performed by summing the χ^2 values for each individual disease GxS interaction meta-analysis in order to identify SNPs with opposing effects across disorders (i.e., an allele is associated with increased risk of one disorder and decreased risk of another), which might eliminate each other in standard linear regression analyses. LD-independent SNPs ($r^2 < 0.1$) with suggestive or genome-wide significant GxS interactions ($p<1\times10^{-6}$) were used as index SNPs for fine-mapping to obtain credible SNPs, i.e. most likely to be causal, using FINEMAP (46) (v1.3) and CAVIAR (47) (-r 0.95, posterior probability; -c 2, maximum number of causal SNPs). The region for fine-mapping was defined as all SNPs in LD ($r^2 > 0.6$) with the index SNP.

SCZ and cross-disorder analyses of the autosomes and X chromosome were carried out with and without inclusion of the East Asian cohorts to evaluate population effects on GxS interaction. Subsequent analyses were limited to European ancestry given the gene- and

pathway-based analyses reported below require the application of an ancestry-specific reference panel.

Gene-based analyses were conducted using MAGMA (48) with an adjusted genome-wide significant *p*-value threshold of $p < 2.6\times10^{-6}$, accounting for 19,427 autosome and sex chromosome genes tested (see Supplementary Methods for details). Gene set enrichment tests were performed using MAGMA (48) to explore functional similarity of genes implicated by GxS interaction analyses. Hypothesis-free analyses were performed for 10,353 gene sets from the Molecular Signatures Database (MSigDB; **Supplementary Methods**). Data-driven enrichment analyses were performed for 9 gene sets/ pathways implicated in prior studies: three immune/neurotrophic, synaptic, and histone methylation gene sets reported to be enriched across the PGC SCZ, BIP, and MDD cohorts (49), and six central nervous system (CNS) pathways enriched in the CLOZUK+PGC SCZ cohort (50). The pathway enrichment *p*-values were FDR-corrected based on the number of pathways tested.

Gene expression and expression quantitative trait locus (eQTL) data from several publicly available resources were evaluated to validate and interpret SNPs with a GxS interaction *p*-value $< 1\times10^{-6}$ (see **Supplementary Methods** for details).

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 (29, 31, 35), ASD collection (30), 23andMe (21), and UK Biobank (32) (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) (51).

Results

Sex-stratified LD Score Regression

Within each disorder, the h^2_{SNP} for males and females (**Figure 1a**) was significantly greater than 0 (mean 0.20; all p < 0.001) (**Supplementary Table 3**), indicating that this study had adequate power to detect a broader polygenic signal. 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 3**). Heritability estimates were substantially different between the sexes for SCZ (p_{FDR} = 0.019; $h^2_M > h^2_F$) and MDD (p_{FDR} = 0.005; $h^2_F > h^2_M$), but not BIP (p_{FDR} = 0.381) (**Supplementary Table 3**). 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) (**Figure 1b; Supplementary Table 4a**). Additionally, we observed 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) (**Figure 1b; Supplementary Table 4b**).

Genome-wide SNP-by-Sex interaction for disease risk

Quantile-quantile plots indicated no systematic inflation of test statistics (**Supplementary Figure 4**). Genomic control lambda (λ_{GC}) revealed no significant evidence of population stratification in the meta-analysis of the cross-disorder European ancestry (λ_{GC}=0.9828), cross-disorder European + East Asian (λ_{GC}=0.9838), SCZ European ancestry (λ_{GC}=0.9991), SCZ European + East Asian (λ_{GC}=1.002), BIP (λ_{GC}=0.9879), or MDD (λ_{GC}=0.9833) cohorts.

Omnibus tests of autosomal SNP GxS effects across disorders revealed a genome-wide significant locus in the *NKAIN2* gene (rs117780815; p=3.2×10^{-8}; **Figure 2**) driven by BIP and SCZ. The effect was in opposite directions, with the minor allele increasing risk in BIP females and decreasing risk in BIP males, and vice versa in SCZ females and males (**Table 1**, **Supplementary Table 5**). The second strongest omnibus signal was for the *AMIGO1/GPR61* gene locus (rs12141273; p=4.16×10^{-7}), common to BIP and MDD, though in opposite directions. Of note, omnibus tests of the PGC dataset detected the second strongest signal (after *NKAIN2*) in the *IDO2/C8orf4* gene locus (rs13270586; p=1.55×10^{-7}), common to BIP and SCZ in opposite directions (**Supplementary Table 6**). As shown in **Supplementary Table 7-8**, omnibus tests of X chromosome SNPs detected no significant interactions (lowest p = 1.67×10^{-5}).

Analyses within disorders did not detect genome-wide significant interactions for SCZ, BIP, or MDD, however suggestive evidence (p<1×10^{-6}) was obtained for several loci (**Table 2, Supplementary Tables 9-10**). Overall, there was little overlap between the strongest interactions for each disorder (**Supplementary Figure 2)**. The most significant results were obtained for SCZ for a locus in the 5' UTR of the *MOCOS* gene (rs11665282: p=1.48×10^{-7}) and an intergenic locus near the non-coding RNA gene *LINC02181* (rs12445424: p=3.52×10^{-7}). The top GxS interaction locus for BIP was located on chromosome 9 near the *TUSC1* gene (rs12341335: p=2.29×10^{-7}). Suggestive evidence for GxS effects in MDD risk was detected for a chromosome 1 locus in and around *SPAG17* (rs9428240: p=1.64×10^{-7}), which remained in rMDD (p=1.40×10^{-7}), and a chromosome 17 locus spanning multiple genes including *ZNF385C* (rs147515485: p=4.61×10^{-7}). Post-hoc analysis of rMDD did not reveal additional loci at p < 1×10^{-6}. Secondary analyses of the PGC SCZ dataset (without iPSYCH) identified a noteworthy locus in an intergenic region between the *IDO2* and *C8orf4* genes (rs13265509: p=1.09×10^{-7}; **Supplementary Table 10e**).

Meta-analysis of GxS interaction results across cohorts from all 3 disorders (in contrast to omnibus tests) did not reveal additional genome-wide significant interactions across the three disorders. However, three independent loci, all intergenic, exhibited at least suggestive evidence ($p<1\times10^{-6}$) for different effects on cross-disorder risk in males and females (**Table 2, Supplementary Table 9a-d**).

SNP-by-sex interaction analyses of X chromosome SNPs under model A or model B detected only modest interactions within and across disorders (lowest $p = 6.89\times10^{-6}$; **Supplementary Table 11a,b).** Results from the two models did not differ substantially, as indicated by scatter plots showing substantial correlation between *p*-values (**Supplementary Figure 12**).

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 for SNP-by-sex interaction GWAS loci.

The loci displaying suggestive evidence for GxS interactions ($p<1\times10^{-6}$) in the SNP-by-sex analyses (**Tables 1-2, Supplementary Tables 5, 6, 9, 10**) underwent fine-mapping using index SNPs to identify credible SNPs (i.e., those most likely to be causal). These 16 loci had a mean of 75 (± 68) SNPs. In approximately half of the loci, the index SNP was among the three most credible SNPs, and >70% of clumps had a “simple” model (<=3 causal variants). We summarize the posterior probabilities of all SNPs in the fine-mapping loci (**Supplementary Tables 13-14**) and highlight SNPs that are most likely to have a causal effect on mood and psychotic disorders. In many loci, CAVIAR and FINEMAP were in partial agreement. There

were multiple SNPs, including rs117780815 (*NKAIN2*), with posterior probability higher than 0.90. These SNPs are the most likely variants to have a causal effect on mood and psychotic disorders.

Gene- and pathway-based analyses

Gene-based tests across and within each disorder detected genome-wide significant GxS interaction of the SLTM gene across disorders (p=8.97×10^{-7}; Bonferroni-corrected threshold: p<2.6×10^{-6}) and near significant interaction within SCZ (p=4.22×10^{-6}). No other results approached significance (**Supplementary Tables 15-16)**.

Gene set enrichment tests were performed to determine whether SNPs exhibiting some degree of GxS interaction (p<1×10^{-4}) clustered into particular biological pathways. Across disorders (regular meta-analysis), the 'wang_barretts_esophagus_and_esophagus_cancer_dn' pathway showed enrichment (p_{FDR} = 0.035) (**Supplementary Table 17d)**. Within MDD, the SNPs were significantly enriched in genes involved in regulation of vascular endothelial growth factor (VEGF) receptor signaling (p_{FDR} = 0.3.9×10^{-4}) (**Supplementary Table 17g)**. SNPs from GxS interaction analyses within SCZ or BIP were not significantly enriched for any particular MSigDB pathway (all p_{FDR} > 0.05) (**Supplementary Table 17-18)**.

Brain expression analysis

Brain expression data were examined for genes located adjacent to SNPs with suggestive evidence for GxS interactions (p<1×10^{-6}; **Tables 1-2)**. Most of the genes examined were expressed in multiple brain regions at several stages from prenatal neurodevelopment through adulthood (**Supplementary Figures 20-23)**. However, some of the genes are predominantly expressed prenatally in one or more regions (*CRSP2*, *MOCOS*, C8orf4, *SPAG17*) or, in the case of *IDO2*, at the beginning of puberty (8-12 years) in prefrontal and orbitofrontal cortex

(**Supplementary Figure 22**). 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**). Among seven brain cell types, the genes examined are expressed in various cell types, with no preponderance of expression in a particular type (**Supplementary Figure 24**).

eQTL overlap with GxS loci

Examination of eQTL data for SNPs with suggestive evidence for GxS interactions ($p<1\times10^{-6}$; **Tables 1-2)** found that the top omnibus cross-disorder SNP (rs117780815) in *NKAIN2* was not an eQTL according to any database, while the second most significant SNP genome-wide (rs12141273), intergenic between *AMIGO1* and *GPR61*, is a cis-eQTL for AMIGO1 in non-brain tissues and is associated with expression of the glutathione-S-transferase genes GSTM1 and GSTM5, and the microtubule regulator gene PSRC1, in DLPFC (**Table 1**). The most significant cross-disorder SNP (rs7302529) (regular meta-analysis) was an eQTL for the nearest gene, *CSRP2*, in several brain regions (**Table 2**). The most significant SCZ SNP (rs11665282) in *MOCOS* was a cis-eQTL in several brain regions (**Table 2**) and is associated with cerebellar and DLPFC expression of the *ELP2* gene, which functions in transcriptional elongation and potentially chromatin remodeling.

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 (21), two SNPs exhibited nominally significant GxS interactions in our analyses (**Supplementary Table 21)** 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 (29-31, 35, 52) or UK Biobank psychiatric phenotypes (32) 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 (51), 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 (51), was among our top cross-disorder GxS results (regular meta-analysis). However, the most significant SNP in each analysis differed.

Discussion

Sex differences in incidence, age of onset, presentation of symptoms, and/or brain abnormalities and physiology in SCZ, BIP, and MDD are pervasive (1-7). Previous work has demonstrated the impact of gonadal hormones on some of these phenotypic sex differences. Here, we hypothesized these sex differences may, in part, be due to differences in genetic variation, either sex-specific or sex-dependent, and that these risk variants may be shared across the disorders.

Heritability estimates were significantly different between the sexes for SCZ and MDD, but not BIP. In contrast, SNP-based genetic correlations between males and females ranged between 0.86 (BIP) and 1 (MDD) and were significantly different from 1 for SCZ and BIP, but not MDD, suggesting modest genetic architecture differences between males and females. Taken together, these results indicate that, although the vast majority of common variant genetic effects are shared by men and women, it is likely there are sex-specific and sex-dependent effects on disorder risks, although modest in effect sizes (31).

Significant sex effects, including sex-stratified associations, have been reported in GWAS studies of other psychiatric disorders (21, 22, 29-35). *Sex-stratified* statistics, calculated within-disorder as part of our study in the PGC-only samples, were extended in a recent set of analyses (Martin et al., in submission), which aimed to evaluate sex differences in heritability estimates and genetic correlations of multiple psychiatric disorders and relevant quantitative phenotypes. Mechanisms implicated across multiple sex-stratified studies of divergent methodologies and statistical approaches included CNS-related or neurodevelopmental mechanisms and immune pathways (21, 30, 31, 33), supporting findings here and suggesting some degree of consistency of sex-dependent genetic effects despite diverse samples and phenotypes.

With regard to neurodevelopmental mechanisms, omnibus tests across the disorders detected genome-wide significant evidence for GxS interaction emanating from the *NKAIN2* gene, which is specifically expressed in brain and interacts with potassium sodium ATPases that regulate neuron membrane potential, transmembrane fluxes of Ca^{2+} and excitatory neurotransmitters, and CNS differentiation (53). *NKAIN2* has previously been associated with general cognitive ability (54) and risk for schizophrenia (55, 56). The second most significant omnibus GxS result was a SNP adjacent to *AMIGO1*, which regulates activity of the Kv2.1 voltage-dependent potassium channel (57), again important for regulating neuronal excitability in brain (58). Other support for GxS interaction was obtained from gene-based analyses across disorders that detected a genome-wide significant GxS interaction with the *SLTM* gene, a general inhibitor of transcription that is highly expressed in cerebellum and putamen, among other regions. Taken together, these findings suggest a sex-dependent genetic contribution to the balance between excitatory and inhibitory regulation of neuronal development and functioning, a hypothesis worthy of further functional "omics" investigations.

In fact, the strongest locus identified in our secondary GxS interaction analyses for SCZ (using the PGC dataset) (rs13270586; $p=1.55\times10^{-7}$) was near *C8orf4* (aka *TCIM*), which functions as a positive regulator of the Wnt/ß-catenin signaling pathway that has a central role in fundamental neuronal processes—including synaptogenesis, axon guidance, and dendrite development (59)—and a pathway previously implicated in SCZ, BIP, and MDD (60-63). Interestingly, recent transcriptomic work identified female-biased genes enriched for expression in Cajal-Retzius cells, an early form of neuron that plays a major role in neural migration, whereas male-biased genes were enriched for neural progenitor cells (64), suggesting sex differences at the level of neuron development. This is consistent with our earlier work in mice with impaired GABA-B receptor signaling and demonstrating sex differences in developmental

migration of neurons containing estrogen receptor (ER)-α into the paraventricular nucleus of the hypothalamus (PVN) and impact on depressive-associated behaviors, particularly in females (65).

Several of the strongest omnibus results had opposite effects on risk of the disorders by sex. For example, the *NKAIN2* GxS interaction effect was opposite in SCZ and BIP, with the minor allele increasing risk in SCZ females and showing a trend towards decreased risk in SCZ males, and opposite effects on risk in BIP females and males. Similarly, the *AMIGO1/GPR61* GxS effect was opposite in BIP and MDD, with the minor allele having a stronger effect in females in BIP and weaker effect in females in MDD versus males. Opposite effects on disease risk were also recently reported in a GWAS across eight psychiatric disorders, though this concerned the main additive effect of the SNP (51), not GxS effects. While opposite GxS effects have not previously been reported across multiple psychiatric or somatic diseases, opposite gene effects in males and females have been reported within disorders, e.g. in association with asthma (66), and on transcription in MDD (67). Sex-by-diagnosis interactions were seen in the rearrangement of brain transcriptional patterns in MDD (67), an effect also seen in stressed mice (68). In MDD, cell type–specific analyses revealed men with MDD exhibited transcriptional increases in oligodendrocyte- and microglia-related genes, while women with MDD had transcriptional decreases in markers of these cell types (67).

Several mechanisms could account for opposite direction interactions by disorder, including balancing selection due to antagonistic pleiotropic effects on the disorders (69). Our analysis implies that variants with opposite effects on different diseases may facilitate the maintenance of common susceptibility alleles in human populations. Opposing effects suggest the potential presence of a ‘genetic switch’ for progression to either one of the diseases, in addition to shared genetic risk factors. Results in autism (70) and SCZ support the idea in (71)

that these disorders may be opposite extremes of a single gradient of mental disorders or could be due to diametric gene-dosage deviations caused by disrupted genomic imprinting (70) or copy number variants. Further, “sexual antagonism” occurs when genetically correlated traits have opposite effects on male and female fitness (72). This could play an important role in maintaining genetic variation in the population. These results underscore the complexity of GxS relationships among related disorders and suggest that overall sex-specific and sex-dependent genetic correlations may obscure a more complex set of genetic relationships at the level of specific loci, brain regions, and pathways (51).

A number of identified genes in our study are expressed in immune cells, not surprising given the substantial sex differences in development and functioning of immune cells and autoimmunity (73, 74). In fact, among the strongest results for MDD was a locus spanning *ZNF385C*, which is implicated in transcriptional regulation (75) and immune-related phenotypes via enhancers (i.e. transcription factors) (76, 77). Further, it may play a role in cognition, since its paralogs *ZNF385B* and *ZNF385D*, were associated with intelligence (78), general cognitive ability, mathematical ability and educational attainment (79). It is possible that genes associated with cognitive abnormalities may be shared across disorders, given that the two strongest GxS interaction loci for BIP located near *TUSC1* and *FHL2* have been associated with depression, educational attainment, and other cognitive phenotypes (79, 80).

Our findings on sex-biased genes implicating immune mechanisms at the population level complement recent transcriptomic work in healthy brain development (81) and MDD (discussed above) (67), and human population work in SCZ (19). Consistent with this, animal studies have demonstrated sex differences in microglia density and morphology in key brain regions beginning early in prenatal development (e.g. hypothalamic preoptic area (POA), hippocampus, amygdala), the latter of which was investigated in human postmortem work in (67). For example, in males *in utero*, microglia morphology in the POA is ameboid, representing

the activated state in which increased inflammatory cytokines and prostaglandins are produced. Heightened *in utero* activation of microglia in males may create a priming effect leading to sex-dependent vulnerability for neurodevelopmental disorders such as SCZ (82).

In fact, immune pathway dysregulation was shared across our disorders of interest here. In our secondary analyses of the PGC dataset alone the strongest GxS interaction for SCZ was in a locus between *IDO2* and *C8orf4* (rs13270586; p=1.55×10^{-7}), with opposite effects on disease risk in males and females. *IDO2* is involved in catabolism of tryptophan in the kynurenine pathway. An end metabolite of the kynurenine pathway, kynurenic acid (KYNA), is elevated in the cerebrospinal fluid (83, 84) and postmortem brains (85, 86) of patients with SCZ or BIP with psychotic symptoms, while reduced plasma levels were associated with depressive symptoms (83). Given recent evidence implicating the kynurenine pathway as a link between brain immune activation and risk of psychiatric disorders (e.g. (87, 88)), and sex differences in immune mechanisms (89), it is plausible that *IDO2* has different effects on SCZ risk in males and females through differential KYNA expression between the sexes. This is consistent with the most recent findings implicating the complement system (C4) as a source of sexual dimorphisms in vulnerability to SCZ and autoimmune disorders (20).

Our findings also identified genes associated with vascular development, which is interesting in light of the link between the vasculature, risk and expression of cardiovascular disease (CVD), and comorbidity of CVD with disorders like MDD (i.e., comorbidity higher in women) (90). Genes involved in regulation of VEGF signaling were enriched among GxS loci for MDD in our analyses. Sex differences have been observed in serum VEGF levels throughout life (91), and brain expression of VEGF has been associated with cognitive aging and Alzheimer's disease (92, 93). Further, the strongest GxS interaction was detected for SCZ in the 5' UTR of *MOCOS* (rs11665282; p=1.48×10^{-7}), which, based on evaluation of brain expression datasets, is highly expressed in endothelial cells lining blood vessels (**Supplementary Figure**

24). Interestingly, our previous work on sex differences in the positioning of cells containing ERα in the PVN associated with impaired GABA-B signaling (65) also was significantly associated with sex differences in vascular development, being more severe in females and associated with depression-related behaviors (94). These previous studies suggest potentially shared genetic risks across these disorders with vascular dysfunctions and may explain high comorbidity of disorders like MDD and SCZ with CVD (90). In fact, a recent meta-analysis of 22 available gene expression microarrays across multiple organs and tissues cited areas of the brain (i.e., anterior cingulate cortex, implicated in MDD, SCZ and BIP) with the most substantial sex differences in gene expression, followed by the heart (95).

Although it seems intuitive that genes located on sex chromosomes would be involved in sex differences in disease risk, our analyses did not detect evidence for GxS interactions involving X chromosome SNPs (lowest *p*-value = 1.67×10^{-5} for omnibus test and 6.89×10^{-6} for the regular meta-analyses). A lack of significant results could be due to insensitive quantitative modeling of the X chromosome by sex. Development of more refined models that allow for variability in X inactivation patterns across genes and individuals, and incorporate the Y chromosome, will be important for clarifying the role of sex chromosome genes in disease risk.

Nevertheless, our results of GxS interactions for autosomal genes are consistent with transcriptomics data demonstrating sexually dimorphic expression in the brain of a substantial proportion of autosomal genes related to fundamental neural functions (36, 64, 67, 96) and data enriched for tissue-related functions and diseases, such as neurodegenerative disease risk genes in brain tissue (97). Thus, sexual dimorphisms in the transcriptome may contribute to understanding sex differences in incidence and prevalence of diseases (98). With regard to sex differences in the epigenome, Van Dongen et al. (99) found genetic and environmental influences interacting with sex (and age) to shape the methylome, which may in part, implicate

the gonadal hormone regulation of gene expression and sex differences in disease risk. Further, our findings related to synaptic transmission and immune response are among the gene sets showing the strongest sexually dimorphic brain expression (36), again suggesting potential mechanisms mediating sex differences in psychiatric disorders. Taken together, our findings underscore the utility of studies like ours on sex differences in genetic architecture (i.e. testing for interaction effects), that highlight genes worthy of deeper mechanistic investigations using transcriptomics and proteomics research and animal models.

Here, we report the largest genome-wide analysis of GxS interactions for psychiatric disorders to date. The analyses determined whether effect sizes were statistically different between the sexes, after which sex-stratified analyses were performed to characterize the effect size itself and the direction of effect within sex. In contrast, many studies initially perform a sex-stratified analysis followed by Z difference test. However, this is only equivalent to a formal GxS interaction test when there are no interactions between covariates and the sexes, and the trait variances are equivalent in the two sexes. As this is typically not the case, sex-stratified analyses may fail to detect significant sex differences.

A limitation of this study is the relatively low sex-stratified SNP heritability, for MDD males in particular (mean h^2_{SNP} = 0.2). Nevertheless, all heritability estimates were greater than zero and had very good precision (i.e., small standard errors), indicating the ability of this study to detect common variant effects. Genetic correlations between the sexes were high and only differed significantly for SCZ and BIP. In the latest PGC SCZ GWAS (manuscript in preparation), the cross-sex r_g did not significantly differ from zero, which may, in part, be due to an increased SCZ sample size and different meta-analysis composition. While genetic correlations between the sexes within-disorder were high, most striking were the differences in genetic correlations by disorder by sex. For example, high genetic correlations were observed

between MDD (both sexes) and BIP-females (0.42, 0.48), but much weaker with MDD (both sexes) and BIP-males (0.13, 0.04). A recent study suggested that this may reflect study recruitment bias or misclassification (100). This is less likely for our study presented here, given that men and women were recruited in different numbers across all three disorders (given their prevalences), but we showed no genetic correlations by sex among SCZ compared with high genetic correlations among MDD and BIP. Misclassification of cases is always a possibility, although clinical diagnoses were based on extensive DSM-IV or ICD-10 interviews, limiting the likelihood of this explanation. Further, if there were bias, it would require similar bias across multiple international institutions in substantial numbers.

Indeed, the lack of detailed clinical data prevented examination of important questions related to symptom type, severity, age at onset, and cognitive deficits. These limitations emphasize the need for larger, deeply-phenotyped datasets to fully characterize sex differences in genetic and *clinical* characteristics of these disorders, as highlighted by e.g. Khramtsova et al (31). As mentioned, there is a lack of adequate models in the field for testing sex chromosome effects. Notably, X inactivation is assumed to be entirely random and complete in the models tested here, whereas recent data suggest tissue-specific patterns of X inactivation (101).

Conclusions. In the largest genome-wide GxS analysis of mood and psychotic disorders to date, we find substantial genetic overlap between males and females for each disorder (i.e. high r_g). However, we also find several loci that showed significant GxS interactions across and within SCZ, BIP, and MDD – *NKAIN2* at the variant level, *SLTM* at the gene level, and *VEGF* at pathway level. Functional genomics suggests that all of the genes examined are expressed in at least one brain region during prenatal development through adulthood, with most genes expressed in multiple brain regions at several developmental stages implicating mood/anxiety and cognition, and sex-specific expression of several genes and eQTL status in some brain regions.

Our results suggest that the risk for SCZ, MDD and BIP is impacted by the interactions of genotype with sex, beyond the impact of gonadal steroid hormones. Though specific mechanisms remain unknown, our study underscores the importance of designing large-scale genetic studies to include an examination of sex differences in genetic risk. Further investigation of specific loci exhibiting SNP-by-sex interactions within and across disorders will be important for dissecting the impact of sex, genes, and pathophysiology to identify potential targets for sex-dependent or sex-specific therapeutic interventions.

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Disclosures

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Figure Legends

Figure 1. LD Score Regression estimates of SNP-based **(a)** heritability, h^2(±SE), and **(b)** genetic correlations, r_g (SE).

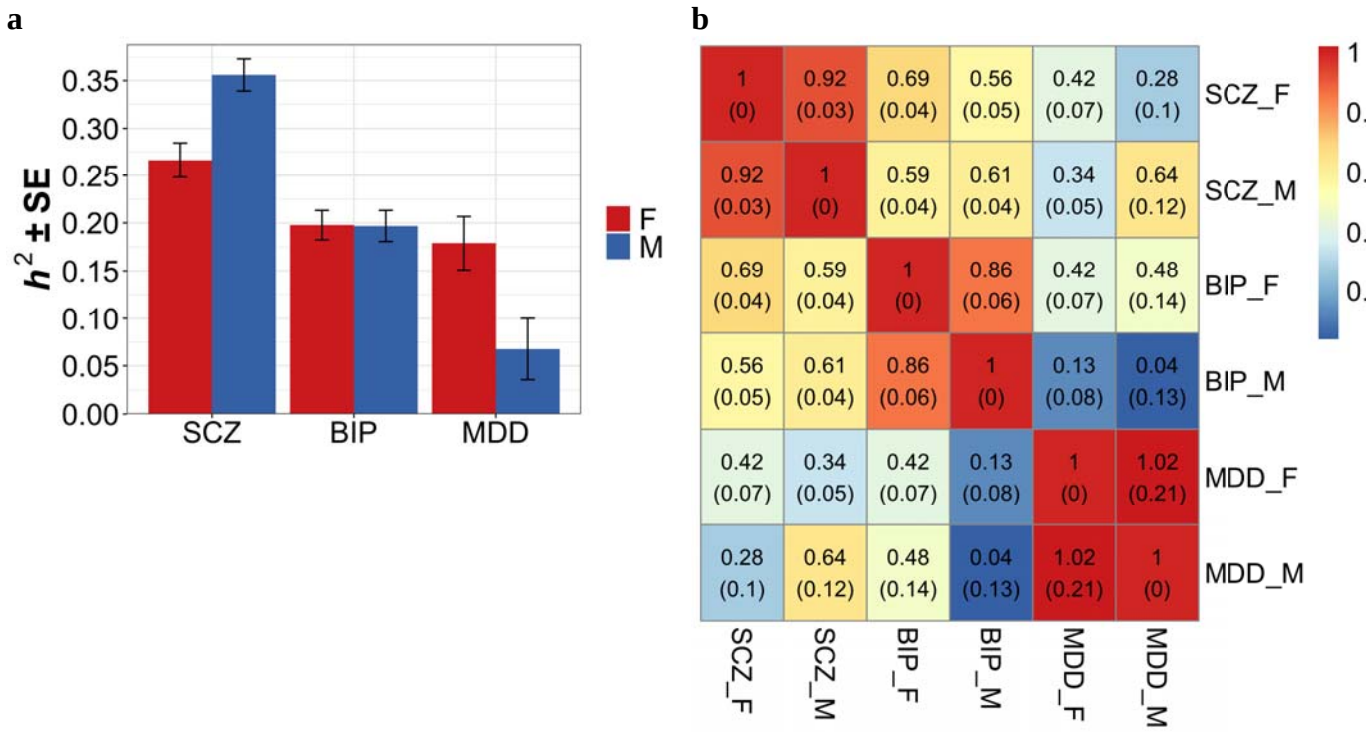
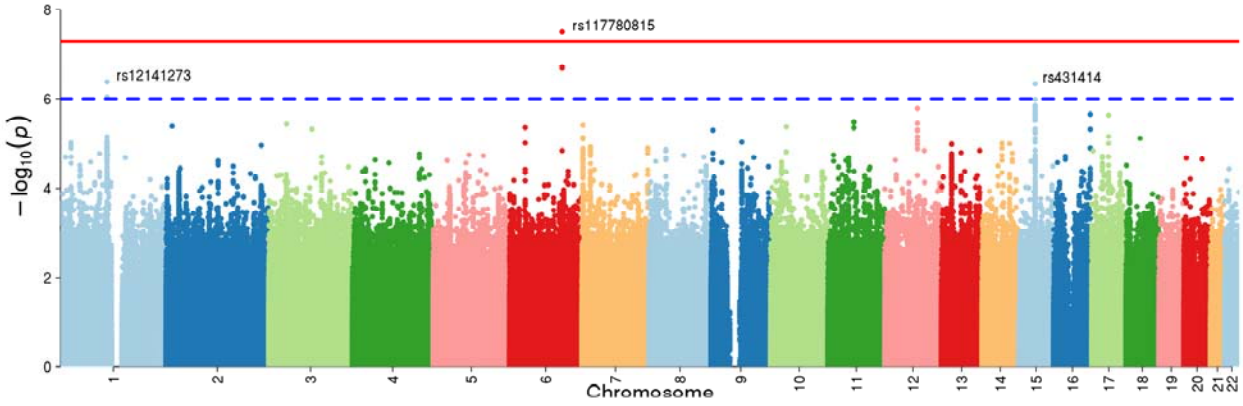


Figure 2. Cross-disorder Manhattan plot of SNP-by-sex interaction p-values **(a)** and locus zoom plot for the NKAIN2 locus exhibiting a significant SNP-by-sex interaction effect on cross-disorder risk **(b)**.

a



b

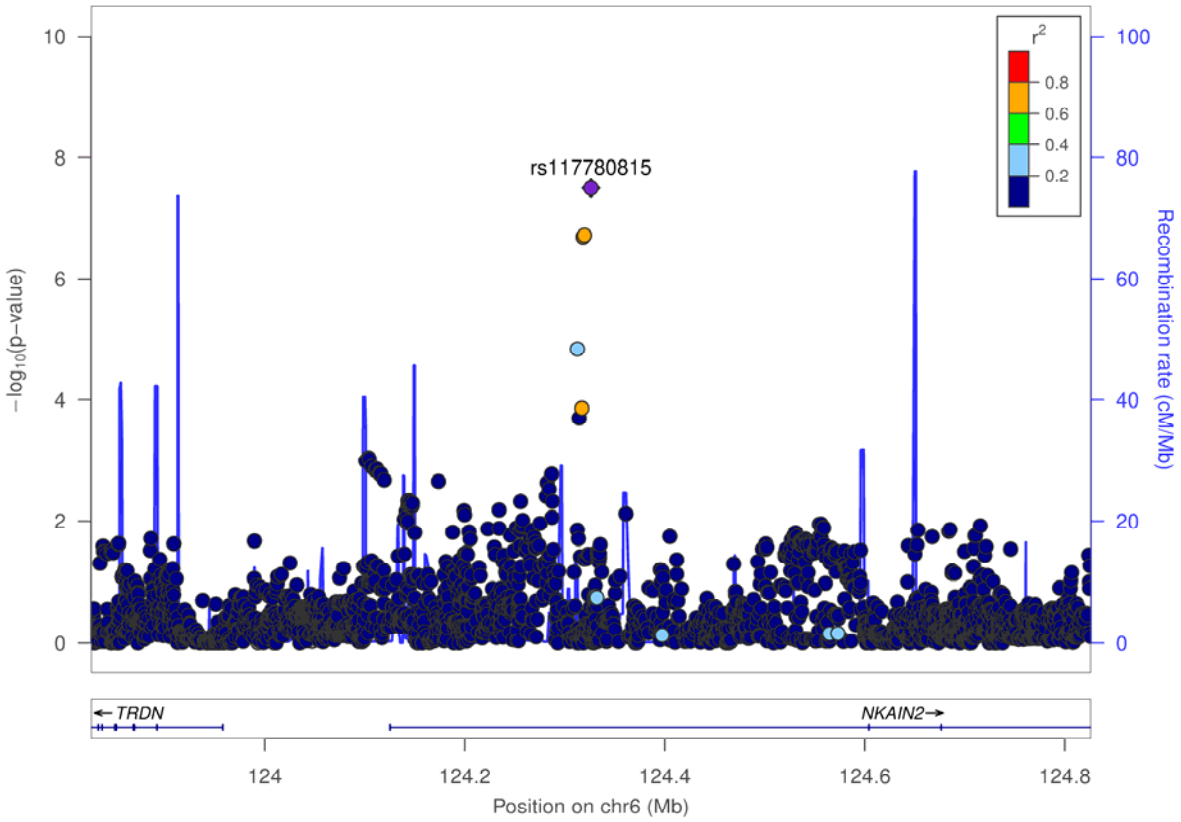


Table Legends

Table 1. Cross-Disorder Omnibus tests.

Listed are 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: SNP, Variant ID; A1/A2, Allele 1 (reference allele)/Allele 2; CHR, Chromosome; BP, Base Pair Position; P, Omnibus p-value in combined PGC+iPSYCH datasets; Pheno.1, Phenotype(s) associated in direction 1; Pheno.2, Phenotype(s) associated in direction 2; P.1, Phenotype(s) 1 p-value; P.2, Phenotype(s) 2 p-value; OR.1 (CI), Phenotype(s) 1 Odds Ratio (Confidence Interval); OR.2 (CI), Phenotype(s) 2 Odds Ratio (Confidence Interval); Meta.Pvalue, Basic Meta-Analysis P value; Meta.OR (CI), Basic Meta-Analysis Odds Ratio (Confidence Interval)

Table 2. Single-disorder and Cross-disorder Autosomal SNP-by-sex interaction results.

Listed are 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: SNP, Variant rs ID; P_{GxS}; *p*-value for GxS interaction in combined PGC + iPSYCH datasets; CHR, Chromosome; BP, Base Pair Position; A1/A2, Allele 1/Allele 2; Freq1, Frequency of Allele 1; MAF, Minor Allele Frequency; $Beta_{GxS}$, Beta (Standard Error) for GxS interaction; $Beta_F$ (SE), Beta (Standard Error) for female-stratified association; P_F, *p*-value for female-stratified association; $Beta_M$, Beta (Standard Error) for male-stratified association; P_M, *p*-value for male-stratified association; Z_{FM}, Z-score heterogeneity females-males; P_{FM}, *p*-value heterogeneity females-males

Table 1. Cross-Disorder Omnibus tests of SNP-by-sex interactions

SNP	CHR	BP	A1/ A2	MAF	Compart-ment	Gene (Distance in kb)	P	Pheno.1	Pheno.2	P.1	P.2	OR.1 (CI)	OR.2 (CI)	Meta P	Meta OR (CI)
SCZ-BIP-MDD (European only)															
rs117780815	6	124326227	T/A	0.036	intronic	NKAIN2	3.19E-08	BIP	SCZ	1.34E-07	1.12E-02	2.0 (1.52, 2.51)	0.79 (0.65, 0.95)	8.10E-02	1.12 (1.11, 1.13)
rs12141273	1	110079143	A/G	0.067	intergenic	AMIGO1 (26.8); GPR61 (3.3)	4.16E-07	BIP	MDD	1.60E-04	1.40E-04	1.3 (1.14, 1.50)	0.81 (0.73, 0.90)	2.03E-01	0.96 (0.95, 0.96)
rs431414	15	59147800	T/C	0.181	UTR3	MINDY2	4.60E-07	SCZ	BIP	1.62E-07	1.53E-01	1.2 (1.14, 1.34)	0.91 (0.80, 1.04)	1.67E-02	1.07 (1.07, 1.07)
SCZ-BIP-MDD (European + East Asian)															
rs117780815	6	124326227	T/A	0.036	intronic	NKAIN2	2.84E-08	BIP	SCZ	1.34E-07	9.89E-03	2.0 (1.52, 2.51)	0.79 (0.65, 0.94)	9.46E-02	1.11 (1.10, 1.12)
rs12141273	1	110079143	A/G	0.067	intergenic	AMIGO1 (26.8); GPR61 (3.3)	4.16E-07	BIP	MDD	1.60E-04	1.40E-04	1.3 (1.14, 1.50)	0.81 (0.73, 0.90)	2.03E-01	0.96 (0.95, 0.96)
rs35477914	15	59197669	T/A	0.193	intronic	SLTM	8.54E-07	BIP; MDD	SCZ	0.01329	3.60E-06	1.1 (1.01, 1.14)	0.86 (0.80, 0.92)	4.84E-01	0.99 (0.98, 0.99)
SCZ-BIP-rMDD (European only)															
rs117780815	6	124326227	T/A	0.036	intronic	NKAIN2	3.17E-08	BIP	SCZ	1.33E-07	1.12E-02	2.0 (1.52, 2.51)	0.79 (0.65, 0.95)	1.58E-01	1.10 (1.09, 1.11)
rs431414	15	59147800	T/C	0.182	UTR3	MINDY2	4.58E-07	SCZ	BIP	1.62E-07	1.53E-01	1.2 (1.14, 1.34)	0.91 (0.80, 1.04)	7.27E-03	1.08 (1.08, 1.09)
SCZ-BIP-rMDD (European + East Asian)															
rs117780815	6	124326227	T/A	0.036	intronic	NKAIN2	2.82E-08	BIP	SCZ	1.33E-07	9.88E-03	2.0 (1.52, 2.51)	0.79 (0.65, 0.94)	1.81E-01	1.10 (1.09, 1.11)

Table 2. Single-disorder and Cross-disorder Autosomal SNP-by-sex interaction results.

SNP	CHR	BP	A1/ A2	Freq1 MAF	Compartment	Gene (Distance in kb)	N Cases (%Female)	N Controls (%Female)	$Beta_{GxS}$ (SE)	P_{GxS}	$Beta_F$ (SE)	P_F	$Beta_M$ (SE)	P_M	Z_{FM}	P_{FM}
Cross-Disorder SCZ-BIP-MDD (European only)																
rs7302529	12	77321581	T/C	0.26 0.26	intergenic	CSRP2 (48.8); E2F7 (93.4)	34,638 (51.36%)	34.696 (50.15%)	0.145 (0.028)	1.60E-7	0.087 (0.019)	5.09E-6	-0.051 (0.020)	1.15E-2	4.98	6.51E-7
rs73033497	7	2910659	A/T	0.86 0.14	intergenic	GNA12 (26.7); CARD11 (35.0)	14,916 (49.21%)	17,547 (47.81%)	0.246 (0.050)	8.82E-7	0.116 (0.036)	1.09E-3	-0.128 (0.035)	2.69E-4	4.89	1.03E-6
Cross-Disorder SCZ-BIP-MDD (European + East Asian)																
rs7914279	10	122161890	T/G	0.89 0.11	intergenic	MIR4682 (44.3); PLPP4 (54.6)	78,640 (49.95%)	71.790 (49.70%)	0.146 (0.029)	6.39E-7	0.064 (0.020)	1.86E-3	-0.077 (0.021)	2.27E-4	4.82	1.43E-6
rs73033497	7	2910659	A/T	0.86 0.14	intergenic	GNA12 (26.7); CARD11 (35.0)	14,916 (49.21%)	17,547 (47.81%)	0.246 (0.050)	8.82E-7	0.116 (0.036)	1.09E-3	-0.128 (0.035)	2.69E-4	4.89	1.03E-6
rs7302529	12	77321581	T/C	0.25 0.25	intergenic	CSRP2 (48.8); E2F7 (93.4)	35,114 (50.69%)	36,707 (50.72%)	0.133 (0.027)	9.37E-7	0.082 (0.019)	1.35E-5	-0.044 (0.020)	2.37E-2	4.64	3.51E-6
Cross-Disorder SCZ-BIP-rMDD (European only)																
rs73033497	7	2910659	A/T	0.86 0.14	intergenic	GNA12 (26.7); CARD11 (35.0)	13,497 (47.22%)	14,619 (48.26%)	0.267 (0.054)	6.22E-7	0.142 (0.039)	2.55E-4	-0.129 (0.037)	4.89E-4	5.05	4.37E-7
rs7302529	12	77321581	T/C	0.26 0.26	intergenic	CSRP2 (48.8); E2F7 (93.4)	31,541 (49.75%)	31,377 (50.42%)	0.144 (0.029)	7.43E-7	0.094 (0.020)	4.48E-6	-0.048 (0.021)	2.13E-2	4.86	1.18E-6
Cross-Disorder SCZ-BIP-rMDD (European + East Asian)																
rs8040598	15	71857368	A/G	0.86 0.14	intronic	THSD4	41,001 (45.92%)	43,732 (50.94%)	0.183 (0.036)	3.90E-7	0.084 (0.026)	1.18E-3	-0.093 (0.025)	2.18E-4	4.89	9.90E-7
rs73033497	7	2910659	A/T	0.86 0.14	intergenic	GNA12 (26.7); CARD11 (35.0)	13,497 (47.22%)	14,619 (48.26%)	0.267 (0.054)	6.22E-7	0.142 (0.039)	2.55E-4	-0.129 (0.037)	4.89E-4	5.05	4.37E-7
Schizophrenia (European only)																
rs11665282	18	33767479	A/G	0.69 0.31	UTR5	MOCOS	21,581 (35.18%)	24,250 (48.62%)	-0.156 (0.030)	1.48E-7	-0.081 (0.023)	3.98E-4	0.072 (0.019)	2.16E-4	-5.09	3.50E-7
rs12445424	16	87063374	A/G	0.26 0.26	intergenic	LINC02188 (291.9); LINC02181 (280.2)	29,467 (36.04%)	34,519 (48.33%)	0.140 (0.028)	3.52E-7	0.097 (0.021)	5.80E-6	-0.050 (0.018)	4.67E-3	5.30	1.19E-7
Schizophrenia (European + East Asian)																
rs11665282	18	33767479	A/G	0.69 0.31	UTR5	MOCOS	22,060 (35.39%)	24,674 (48.26%)	-0.149 (0.03)	3.74E-7	-0.077 (0.023)	6.74E-4	0.070 (0.019)	2.53E-4	-4.96	6.89E-7
Bipolar Disorder																
rs12341335	9	25649145	T/C	0.90 0.10	intergenic	TUSC1 (27.2)	7,730 (57.72%)	13,635 (51.28%)	0.373 (0.072)	2.29E-7	0.176 (0.048)	2.59E-4	-0.201 (0.054)	2.11E-4	5.20	2.03E-7
rs17651437	2	106055684	T/C	0.52 0.48	upstream	FHL2	16,365 (60.18%)	28,140 (50.75%)	0.155 (0.031)	3.72E-7	0.079 (0.020)	9.97E-5	-0.069 (0.023)	3.08E-3	4.79	1.63E-6
Major Depressive Disorder																
rs9428240	1	118831676	T/C	0.59 0.41	intergenic	SPAG17 (103.8)	14,232 (68.63%)	21,846 (50.63%)	-0.181 (0.035)	1.64E-7	-0.087 (0.022)	6.41E-5	0.094 (0.028)	8.41E-4	-5.08	3.70E-7
rs147515485	17	40182099	T/C	0.02 0.02	intronic	ZNF385C	31,149 (61.17%)	35,385 (50.89%)	-0.472 (0.094)	4.61E-7	-0.190 (0.060)	1.55E-3	0.303 (0.074)	4.39E-5	-5.17	2.39E-7
Recurrent Major Depressive Disorder																
rs61138090	1	118832069	D/I2	0.59 0.41	intergenic	SPAG17 (104.2)	7,685 (70.59%)	15,976 (51.71%)	-0.240 (0.046)	1.40E-7	-0.109 (0.028)	1.03E-4	0.142 (0.038)	2.08E-4	-5.28	1.30E-7