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Sex-Dependent Shared and Non-Shared Genetic Architecture

Across Mood and Psychotic Disorders

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Abstract

BACKGROUND: Sex differences in 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 disorders suggest possible shared sex-dependent genetic risk.

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

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 women (1) and SCZ in men (2). BIP prevalence is approximately similar, but age at onset, course, and prognosis vary considerably by sex (3, 4), as they do in 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), or differences in twin intra-pair correlations between same-sex and opposite-sex dizygotic pairs (11, 12). However, specific disease risk variants 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 other complex human traits (e.g., blood pressure, waist-hip ratio) (13, 14). Aside from sex-specific variants, incidence differences may result from a female or male protective effect, whereby one sex may require a higher burden of genetic liability to cross the threshold to disease manifestation. This suggests quantitative risk differences (i.e., “sex-dependence”), a notion supported by an early observation that female SCZ cases were more likely to come from multiplex families (15).

Regarding SCZ, there is a long history of examining sex differences in familial/genetic transmission (16), given differences in incidence, brain abnormalities, and course (17, 18). Recently, large genetic cohorts of SCZ and autoimmune disorders identified greater effects of complement component 4 (C4) alleles in SCZ men than women (19, 20). Compared with SCZ, sex differences in incidence of MDD are greater, with a 2:1 female predominance, and there is some evidence for stronger sex differences in recurrent MDD (rMDD) compared with single-episode MDD, although inconsistent (7, 21-23). With increased interest in examining the

genetics of sex differences in psychiatric disorders and related phenotypes (24-32), transcriptomics studies are beginning to provide insights into mechanisms underlying sex differences in risk. Notably, >10% of autosomal genes exhibit sexually dimorphic gene expression in the brain, predominantly genes related to synaptic transmission, dopamine receptor signaling, and immune response, suggesting potential mechanisms mediating sex differences in psychiatric disorders.

In order to test for sex differences in genetic risk, it is essential to have adequate power to test for interaction effects (33). Given sample size limitations, genome-wide association studies (GWAS) of psychiatric disorders have typically not examined genotype-by-sex (GxS) interactions. Here, we capitalized on a unique opportunity to utilize cohorts from the PGC and iPSYCH consortia (n = 195,681) to assess interactions between sex and genetic risk of MDD, SCZ and BIP within and across disorders.

Methods and Materials

Participants

The Psychiatric Genomics Consortium (PGC) (34-36) included 43 SCZ (30,608 patients, 38,441 controls), 28 BIP (18,958 patients, 29,996 controls), and 26 MDD cohorts (15,970 patients, 24,984 controls; **Supplementary Table 1**). The iPSYCH cohort in Denmark (37) included 2,795 SCZ patients and 2,436 controls, 966 BIP and 551 controls, and 16,438 MDD and 13,538 controls (**Supplementary Table 2**). Primary analyses used the PGC and iPSYCH datasets. Secondary PGC-only analyses (see **Supplementary Materials**) were performed to facilitate comparison to other PGC studies and ensure that different diagnostic criteria in PGC and iPSYCH (DSM-IV and ICD-10, respectively) were not impacting results. All cohorts were European ancestry, except three East Asian SCZ cohorts.

Quality Controls and Analytics

Quality control (QC) and imputation to the 1000 Genomes Phase 3 reference panel were performed using PGC's Rapid Imputation for COnsortias PIpeLine (RICOPILI) (38) and previously described filtering thresholds (34-36). An overview of subsequent QC and analytic steps is provided in **Supplementary Figure 1**. Identity-by-descent (IBD) filtering is described in **Supplementary Methods**. At MAF=0.05, this study had 83%-99% (within-disorder) and 88% (cross-disorder) power to detect interaction effects at an odds ratio of ≥ 1.2 , and ≥ 1.1 , respectively (**Supplementary Table 3; Supplementary Figure 2**).

Sex-stratified GWAS summary statistics were obtained by logistic regression of men and women separately within each cohort using PLINK (39), followed by standard-error weighted meta-analysis across cohorts using METAL (40). Summary statistics were entered into Linkage Disequilibrium (LD) Score Regression (LDSC) (41, 42) to estimate autosomal sex-specific SNP-

based heritability (h_{SNP}^2) for each disorder (**Figure 1**) and bivariate genetic correlations (r_g) within and across disorders.

PLINK (39) was used to perform a genome-wide GxS interaction analysis in each study cohort, followed by standard-error weighted meta-analysis of GxS interactions using METAL (40). GxS interaction analyses were performed using linear regression with a main effect for each SNP, main effect of sex, and SNP-by-sex interaction terms, using an additive model for SNPs (controlling for 10 ancestry principal components [PC]). Secondary regression models included additional controls using 10 SNP-by-PC and 10 sex-by-PC interaction terms in addition to the above (43). Adding too many covariates can destabilize the effect estimates and lead to increased dropout of SNPs due to estimation problems, especially in smaller cohorts, thus the first model is our primary model. Secondary analytic model p -values are included in brackets.

GxS interactions with X-linked SNPs were tested using two models. Model A assumed complete and uniform X-inactivation in women and similar effect size between the sexes by assigning 0, 1, or 2 copies of an allele to women and 0 or 2 copies to men. As these assumptions often do not hold, Model B assigned 0 or 1 copy to men.

A three-degrees-of-freedom test omnibus test (44) was performed by summing the χ^2 values for individual disorder GxS interaction meta-analyses in order to identify SNPs with opposing GxS effects across disorders (see **Supplementary Methods** for details).

LD-independent SNPs ($r^2 < 0.1$) with suggestive or genome-wide significant GxS interactions ($p < 1 \times 10^{-6}$) were used as index SNPs for fine-mapping to obtain credible SNPs (i.e. likely causal) using FINEMAP (45) and CAVIAR (46) (see **Supplementary Methods**). Regions for fine-mapping were defined as all SNPs in LD ($r^2 > 0.6$) with the index SNP.

SCZ and cross-disorder analyses of autosomes and X chromosome were conducted with and without inclusion of the East Asian cohorts to evaluate population effects. Findings were not

significantly different and therefore all subsequent analyses utilized only European ancestry cohorts (see **Supplementary Methods**).

Gene-based analyses were conducted using MAGMA (47) (significant p -value= 2.6×10^{-6} ; see **Supplementary Methods**) Gene set enrichment tests were performed (47) to determine whether (near-)significant SNPs ($p < 1 \times 10^{-4}$) clustered into particular biological pathways, to explore functional similarity of genes implicated by GxS interactions. Hypothesis-free analyses were performed for 10,353 gene sets from the Molecular Signatures Database (MSigDB). Data-driven enrichment analyses were performed for nine gene sets/ pathways implicated in prior studies: immune/neurotrophic, synaptic, and histone methylation gene sets enriched across PGC SCZ, BIP, and MDD cohorts (48), and central nervous system (CNS) pathways enriched in the CLOZUK+PGC SCZ cohort (49). Pathway enrichment p -values were FDR-corrected based on 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 $< 1 \times 10^{-6}$ (see **Supplementary Methods** for details).

Finally, GxS interaction results were compared to previously reported sex-dependent or sex-specific effects on psychiatric risk ($p < 5 \times 10^{-8}$) (see **Supplementary Methods and Tables**).

Results

Sex-stratified LD Score Regression

Based on sex-stratified GWAS results displayed in **Supplementary Figure 3**, men and women h_{SNP}^2 were estimated. Within each disorder, the h_{SNP}^2 for men and women (**Figure 1a**) was significantly greater than 0 (mean 0.19; all $p < 0.001$) (**Supplementary Table 4**), indicating adequate power to detect broader polygenic signals. Estimates of h_{SNP}^2 increased minimally across a range of MAF cutoffs (MAF>1%, 2%, 5%), indicating rarer variants contributed little (**Supplementary Table 4**). Heritability estimates were substantially different between the sexes for SCZ ($p_{FDR} = 0.019$; $h_M^2 > h_F^2$) and MDD ($p_{FDR} = 0.005$; $h_F^2 > h_M^2$), but not BIP ($p_{FDR} = 0.381$) (**Supplementary Table 4**). Although correlations between male and female GWAS p -values were low (**Supplementary Figure 4**), SNP-based genetic correlations (r_g) between men and women within disorders 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 5a**). Additionally, we observed no significant differences in cross-disorder genetic correlations by sex, except r_g between BIP and MDD ($r_{gF} = 0.42$; $r_{gM} = 0.04$; $p_{FDR} = 0.044$) (**Figure 1b**; **Supplementary Table 5b**). However, within-sex, SCZ and BIP women were more highly correlated than SCZ with MDD women, and MDD women correlated similarly to both SCZ and BIP. In contrast, SCZ with BIP and MDD men correlated similarly, but MDD and BIP men were uncorrelated. Findings suggest there may be different within-sex genetic differences that need further understanding and raise the complexity of investigating the genetics of sex effects.

Genome-wide SNP-by-Sex Interactions

Quantile-quantile plots indicated no systematic inflation of test statistics (**Supplementary Figure 5**). Genomic control lambda (λ_{GC}) revealed no significant evidence of population stratification in the meta-analysis of the cross-disorder European ancestry ($\lambda_{GC}=0.9828$), cross-disorder European + East Asian ($\lambda_{GC}=0.9838$), SCZ European ancestry ($\lambda_{GC}=0.9991$), SCZ European + East Asian ($\lambda_{GC}=1.002$), BIP ($\lambda_{GC}=0.9879$), or MDD ($\lambda_{GC}=0.9833$) cohorts.

Analyses within disorders did not detect genome-wide significant interactions for SCZ, BIP, or MDD, however suggestive evidence ($p < 1 \times 10^{-6}$) was obtained for several loci (**Table 1**, **Supplementary Table 8**). Overall, there was little overlap between the strongest interactions for each disorder (**Supplementary Figure 6**). The most significant results were obtained for SCZ for a locus in the 5' UTR of the *MOCOS* gene (rs11665282: $p=1.48 \times 10^{-7}$ [secondary model $p_{ext}=2.53 \times 10^{-5}$]; **Supplementary Figures 6-8**) and an intergenic locus near the non-coding RNA gene *LINC02181* (rs12445424: $p=3.52 \times 10^{-7}$ [$p_{ext}=2.28 \times 10^{-4}$]; **Supplementary Figures 6-8**). The top GxS interaction locus for BIP was located on chromosome 9 near the *TUSC1* gene (rs12341335: $p=2.29 \times 10^{-7}$ [$p_{ext}=7.91 \times 10^{-7}$]; **Supplementary Figures 6-8**). Suggestive evidence for GxS effects in MDD risk was detected for chromosome 1 locus in and around *SPAG17* (rs9428240: $p=1.64 \times 10^{-7}$ [$p_{ext}=3.31 \times 10^{-7}$]), which remained in rMDD ($p=1.40 \times 10^{-7}$ [$p_{ext}=1.05 \times 10^{-7}$]), and chromosome 17 locus spanning multiple genes including *ZNF385C* (rs147515485: $p=4.61 \times 10^{-7}$ [$p_{ext}=4.76 \times 10^{-6}$]; **Supplementary Figures 6-8**). Post-hoc analysis of rMDD did not reveal additional loci at $p < 1 \times 10^{-6}$. Secondary analyses of the PGC SCZ cohort identified a noteworthy locus in an intergenic region between the *IDO2* and *C8orf4* genes (rs13265509: $p=1.09 \times 10^{-7}$ [$p_{ext}=1.23 \times 10^{-6}$]; **Supplementary Table 15a**). Meta-analysis of GxS interactions across cohorts from all 3 disorders (in contrast to omnibus tests) revealed suggestive evidence for three additional intergenic loci ($p < 1 \times 10^{-6}$) (**Table 1**, **Supplementary Table 6f-i**).

Omnibus tests of autosomal SNP GxS effects across disorders revealed a significant locus in *NKAIN2* (rs117780815; $p=3.2\times 10^{-8}$ [$p_{ext}=4.67\times 10^{-7}$]; **Figure 2**) driven by BIP and SCZ (**Table 2, Supplementary Table 7**). The effect was in opposite directions, with the minor allele increasing risk in BIP women and decreasing risk in BIP men, and vice versa in SCZ women and men (see **Table 1, Supplementary Table 6a-e**, disorder-specific sex-stratified effects). The second strongest omnibus signal was for the *AMIGO1/GPR61* gene locus (rs12141273; $p=4.16\times 10^{-7}$ [$p_{ext}=1.95\times 10^{-6}$]), common to BIP and MDD, though in opposite directions. Of note, omnibus tests of the PGC dataset detected a second strong signal in the *IDO2/C8orf4* gene locus (rs13270586; $p=1.55\times 10^{-7}$ [$p_{ext}=4.62\times 10^{-7}$]), common to BIP and SCZ in opposite directions (**Supplementary Table 16**). Overall, all results from the secondary analytic model supported the primary model.

SNP-by-sex interactions of X chromosome SNPs using model A or B detected only modest effects within/across disorders (lowest $p=6.89\times 10^{-6}$; **Supplementary Table 8a,b**), similar regardless of model (**Supplementary Figure 8**). Omnibus tests of X chromosome SNPs detected no significant interactions (lowest $p=1.67\times 10^{-5}$; **Supplementary Table 9**).

Identification of credible SNPs

Loci displaying evidence for GxS interactions (index SNP $p<1\times 10^{-6}$) (**Tables 1-2, Supplementary Tables 6-9**) underwent fine-mapping to identify those SNPs most likely to be causal. Sixteen loci had a mean of 75 (± 68) SNPs. In ~50% 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 fine-mapping loci (**Table 3, Supplementary Table 10**) and highlight SNPs with likely causal effects in our disorders. Together, CAVIAR and FINEMAP indicated that genome-wide significant SNP rs117780815,

with posterior probability >0.90 (FINEMAP), was the most likely causal variant in the *NKAIN2* locus (see **Table 3**).

Gene- and pathway-based analyses

Gene-based tests within and across disorders detected near-significant GxS interaction of the SLTM gene within SCZ ($p=4.22\times 10^{-6}$ [$p_{ext}=7.28\times 10^{-6}$]; **Supplementary Figure 10a**) and genome-wide significant cross-disorder interaction (omnibus $p=8.97\times 10^{-7}$ [$p_{ext}=6.64\times 10^{-7}$]; **Supplementary Figure 10g-h**). No other results approached significance (**Supplementary Table 11; Supplementary Figure 10b-f**).

Gene set enrichment tests showed that within MDD, GxS SNPs were significantly enriched in genes regulating vascular endothelial growth factor (VEGF) receptor signaling ($p_{FDR}=3.90\times 10^{-4}$ [$p_{FDRext}=2.70\times 10^{-2}$]; **Supplementary Table 12c**). SNPs showing GxS interactions within SCZ or BIP were not significantly enriched for any MSigDB pathway (**Supplementary Table 12a,b**). Across disorders, the 'wang_barretts_esophagus_and_esophagus_cancer_dn' pathway showed enrichment ($p_{FDR}=0.035$ [$p_{FDRext}=0.065$]; **Supplementary Table 12f**).

Brain expression analysis

Brain expression data were examined for genes located adjacent to or encompassing SNPs with evidence for GxS interactions ($p<1\times 10^{-6}$). Most of these genes were expressed in multiple brain regions (**Supplementary Figure 11-13**), particularly prefrontal, anterior cingulate, pituitary, and hypothalamus (**Supplementary Figure 14**) from prenatal development (*C8orf4* [= *TCIM*], *CRSP2*, *GNAI2*, *MOCOS*, *SPAG17*), through puberty (*IDO2*) (**Supplementary Figure 12**), and through adulthood. **12-13**). Genes were expressed in various brain cell types (**Supplementary Figure 15**), with high relative expression of *NKAIN2* and *GNAI2* in oligodendrocytes, and *CSRP2*, *C8orf4* and *MOCOS* in endothelial cells.

(**Supplementary Results** reports other genes.)

eQTL overlap with GxS loci

Examination of eQTL data for SNPs with evidence for GxS interactions ($p < 1 \times 10^{-6}$; **Supplementary Tables 6-7**) found the highly significant SCZ SNP (rs11665282) in *MOCOS* was a cis-eQTL in several brain regions (**Supplementary Table 6a**) associated with transcriptional elongation and chromatin remodeling in the *ELP2* gene in cerebellum and DLPFC. The most significant cross-disorder SNP (rs7302529) was an eQTL for *CSRP2* (**Supplementary Table 6f**), although the top omnibus cross-disorder SNP (rs117780815) in *NKAIN2* was not an eQTL. Finally, genome-wide SNP rs12141273, intergenic between *AMIGO1* and *GPR61*, is a cis-eQTL for *AMIGO1* in non-brain tissues and associated with expression of glutathione-S-transferase genes *GSTM1* and *GSTM5* and microtubule regulator gene *PSRC1*, in DLPFC (**Supplementary Table 7**).

Overall, consistency of our significant GxS effects with previous GWAS of sex differences in MDD, BIP, and SCZ is described in **Supplementary Results, Table 14**.

Discussion

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

Heritability estimates were significantly different between the sexes for SCZ and MDD, but not BIP, partly reflecting significant sex differences in incidence for SCZ and MDD, but not BIP. Male-female SNP-based genetic correlations ranged between 0.86 (BIP) and 1 (MDD), significantly <1 for SCZ and BIP but not MDD, with by-sex cross-disorder correlation differences suggesting further complexity. Thus, although the majority of common variant genetic effects were shared between the sexes, there were sex-specific and sex-dependent effects on risks, with modest effect sizes (27).

Significant sex effects, primarily sex-stratified associations, were reported previously in GWAS studies (25-32, 34), implicating neurodevelopmental mechanisms and immune pathways (26-28, 30). However, sex-stratified analyses are only equivalent to GxS interaction tests when there are no interactions between covariates and sex, and the trait variances are equivalent in the two sexes. As this is unlikely, GxS interaction tests are ultimately necessary to identify significant sex differences, and sex-stratified analyses may fail to detect or spuriously report differences.

GxS interaction findings in our study implicate neuronal excitability and inhibitory regulation of brain development and functioning and immune and vascular pathways. Omnibus tests across disorders detected genome-wide significant evidence for GxS emanating from the *NKAIN2* gene, expressed in brain implicating potassium sodium ATPases regulating neuron membrane potential, transmembrane fluxes of Ca^{2+} and excitatory neurotransmitters, and CNS

differentiation (50). *NKAIN2* has previously been associated with cognitive ability (51) and SCZ risk (52, 53). The second most significant omnibus GxS result was a SNP adjacent to *AMIGO1*, which regulates activity of the Kv2.1 voltage-dependent potassium channel (54), again important for regulating neuronal excitability in brain (55). 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, 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 GxS analyses for SCZ (PGC-only; rs13270586) was near *C8orf4* (aka *TCIM*), which functions as a positive regulator of the Wnt/ β -catenin signaling pathway with a central role in fundamental neuronal processes—including synaptogenesis, axon guidance, and dendrite development (56)—and a pathway implicated previously in SCZ, BIP, and MDD (57-60). Interestingly, recent transcriptomic work identified female-biased genes enriched for expression in Cajal-Retzius cells that play a major role in neural migration, whereas male-biased genes were enriched for neural progenitor cells (61). 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 hypothalamus paraventricular nucleus that impacted depressive-like behaviors, particularly in females (62).

Several genes that implicated neuronal excitability and immune functions had opposite effects on disorder risk by sex. For example, the *NKAIN2* SNP GxS effect was opposite in SCZ and BIP, with the minor allele increasing risk in SCZ women and decreasing risk in SCZ men,

and opposite effects on risk in BIP women and men. Similarly, the *AMIGO1/GPR61* GxS effect was opposite in BIP and MDD, with the minor allele having stronger effects in BIP women and weaker effect in MDD women versus men.

Immune pathway dysregulation, shared across disorders, also demonstrated some evidence of opposite genetic effects by sex. The strongest GxS interaction for SCZ was in a locus between *IDO2* and *C8orf4* (rs13270586; $p=1.55 \times 10^{-7}$), with opposite risk effects by sex. *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 (63, 64) and postmortem brains (65, 66) in SCZ and BIP, while reduced plasma levels were associated with depressive symptoms (63). Given recent evidence implicating the kynurenine pathway as a link between brain immune activation and disorder risk (67, 68) and sex differences in immune mechanisms (69), it is plausible that *IDO2* has different effects on SCZ risk in men and women through differential KYNA expression between the sexes. This is consistent with recent findings implicating the complement system (C4) as a source of sexual dimorphisms in vulnerability to SCZ and autoimmune disorders (20). Further, among the strongest results for MDD was a locus spanning *ZNF385C*, associated with transcriptional regulation (70) and immune-related phenotypes via transcriptional enhancers (71, 72).

Our sex-biased genes implicating immune mechanisms at the population level complement recent transcriptomic work in healthy brain development (73), population work in SCZ (19), and MDD (74). Sex-by-diagnosis interactions were seen in the rearrangement of brain transcriptional patterns in MDD (74), an effect also seen in stressed mice (75). In MDD, cell type-specific analyses revealed MDD men exhibited transcriptional increases and MDD women transcriptional decreases in oligodendrocyte- and microglia-related genes (74).

Consistent with this, animal studies demonstrated sex differences in microglia density and morphology in key brain regions beginning in prenatal development (e.g., hypothalamic

preoptic area (POA), hippocampus, amygdala). In males *in utero*, there is heightened activation of POA microglia that may result in a priming effect leading to sex-dependent vulnerability for disorders such as SCZ (76). In contrast, while males appear to have a prolonged period of enhanced immune sensitivity *in utero* in *preclinical* studies, the period of immune sensitivity for females is shifted toward the end of prenatal development continuing into early postnatal life in rodents (76), a critical period analogous to human sexual brain differentiation (2nd and 3rd trimesters). This suggests that timing is critical in identifying sex-by-gene effects, which may have opposing effects at different developmental periods, a fact that must be considered in transcription studies of brain regions across the lifespan. In fact, sex differences in expression of IDO2 was identified as also critical during puberty, with post-puberty being the emergence of sex differences in MDD and SCZ.

Other mechanisms that might account for opposing sex interaction effects, include balancing selection due to antagonistic pleiotropic effects (77), that could play a role in maintaining common susceptibility alleles in the population. 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 (78) and SCZ (79) support the idea that these disorders may be opposite extremes of a single gradient of mental disorders or due to diametric gene-dosage deviations caused by disrupted genomic imprinting (78) or copy number variants. Findings 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 (80), and that timing of mechanisms implicated in sex effects is critical.

Our findings also identified genes associated with vascular development, interesting in light of the comorbidity of CVD with MDD (higher in women) (81) and SCZ. Results demonstrated genes involved in regulation of VEGF signaling were enriched among GxS loci for MDD. Sex differences were reported in VEGF levels (82), and brain expression of VEGF has

been associated with cognitive aging and Alzheimer's disease (83, 84). Further, the strongest GxS interaction was detected for SCZ in a locus in the *MOCOS* gene most highly expressed in endothelial cells lining blood vessels. Interestingly, our previous work on sex differences in neuronal migration due to impaired GABA-B signaling (62) was also significantly associated with sex differences in hypothalamic neurovascular development, being more severe in females and associated with depression-related behaviors (85). 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 (86).

Finally, sex-by-gene effects had implications for cognitive functions, not surprising given brain regions implicated by some of the significant loci in this study. For example, *ZNF385C* in MDD may play a role in cognition, since its paralogs *ZNF385B* and *ZNF385D*, have been associated with intelligence (87), general cognition, mathematical ability and educational attainment (88). 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 educational attainment, other cognitive phenotypes, and depression (88, 89).

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 significant GxS interactions involving X chromosome SNPs. Lack of significance could be due to insensitive X chromosome modeling by sex, thus necessitating more refined models allowing for variability in X inactivation patterns and incorporation of the Y chromosome to clarify the role of sex chromosomes in disease risk. Recent data suggest tissue-specific patterns of X inactivation (90). 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 (61, 74, 91, 92) and data enriched for tissue-related diseases (92). These findings underscore the utility of studies like ours, with statistical power to test for interaction effects, that highlight genes worthy of deeper mechanistic investigations using transcriptomics and proteomics research and animal models.

A limitation of this study is the relatively low sex-stratified SNP heritability, in particular for MDD men (mean $h_{SNP}^2 = 0.2$). Nevertheless, all heritability estimates were greater than zero with 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 (93), 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. High genetic correlations were observed between MDD (both sexes) and BIP women (0.42, 0.48), but much weaker with MDD (both sexes) and BIP men (0.13, 0.04). Although some have argued this may reflect study recruitment bias or misclassification (94), this is less likely for our study, given varying sample sizes across disorders (due to differing prevalences), and no genetic correlations by sex among SCZ compared with high 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. Further, if there were bias, it would require similar and substantial bias across multiple international institutions.

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 recently in (27). Further, alternative

explanations for sex differences in incidence, presentation, and course, include genotype-by-environment interactions, e.g., implicating gonadal hormone regulation of genes, that we know from clinical and animal studies are sex-dependent. Finally, additional replication samples would significantly strengthen these findings.

Conclusions. In the largest genome-wide GxS analysis of mood and psychotic disorders to date, we found substantial genetic overlap between men and women for SCZ, BIP, and MDD. However, we also found several loci with significant GxS interaction effects across and within disorder – *NKAIN2* at the variant level, *SLTM* at the gene level, and *VEGF* at pathway level. Functional genomics suggests that all genes were expressed in at least one brain region at some period across the lifespan, with most genes expressed in multiple brain regions associated with mood/anxiety and cognition.

Our results demonstrate that the risk for SCZ, MDD and BIP is impacted by 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 that have the statistical power to test for interactions with sex. Dissecting the impact of sex, genes, and pathophysiology will identify potential targets for sex-dependent or sex-specific therapeutic interventions.

Resources

Summary statistics are available for download from <https://www.med.unc.edu/pgc/> upon publication.

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Figure Legends

Figure 1. LD Score Regression estimates of sex-specific SNP-based **(a)** heritability, h^2 (\pm SE), and **(b)** genetic correlations, r_g (SE). This graph shows h^2 and r_g estimates for MAF > 0.01.

- Heritability estimates were substantially different between the sexes for SCZ ($p_{\text{FDR}} = 0.019$) and MDD ($p_{\text{FDR}} = 0.005$), but not BIP ($p_{\text{FDR}} = 0.381$).
- 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 ($p_{\text{FDR}} = 0.039$) and BIP ($p_{\text{FDR}} = 0.039$), but not MDD ($p_{\text{FDR}} = 0.397$). No significant differences in the cross-disorder genetic correlations between males and females, with the exception of r_g between BIP and MDD ($r_{gF} = 0.42$; $r_{gM} = 0.04$; $p_{\text{FDR}} = 0.044$).

Abbreviations: BIP = bipolar disorder; MDD = major depressive disorder; SCZ = schizophrenia; F = females; M = males; LD = linkage disequilibrium; SE = standard error.

Figure 2. Cross-disorder Manhattan plot of SNP-by-sex interaction p-values **(a)** and LocusZoom plot for the *NKAIN2* gene locus exhibiting a significant SNP-by-sex interaction effect on cross-disorder risk **(b)**. This graph shows the genome-wide significant result from the cross-disorder omnibus test in ASSET (primary model). Negative log10-transformed p-values for each variant (each dot) (y-axis) are plotted by chromosomal position (x-axis). The red and blue lines represent the thresholds for genome-wide significant association ($p = 5 \times 10^{-8}$) and suggestive association ($p = 1 \times 10^{-6}$), respectively. The strongest GxS interaction was found for SNP rs117780815 on chromosome 6 ($p = 3.2 \times 10^{-8}$) driven by BIP and SCZ. The effect was in opposite directions, with the minor allele increasing risk in BIP women and decreasing risk in BIP men, and vice versa in SCZ women and men (**Table 2, Supplementary Table 7**). Abbreviations: chr = chromosome; cM = centimorgans; Mb = megabases; r^2 = linkage disequilibrium level; *NKAIN2* = Sodium/Potassium Transporting ATPase Interacting 2

Table Legends

Table 1. Single-disorder and Cross-disorder Autosomal SNP-by-sex interaction results.

Cross-disorder and within-disorder meta-analyses were carried out using METAL, incorporating cohort-level summary statistics from PLINK. Listed are SNPs with interaction p -values $< 1 \times 10^{-6}$ in SCZ, BIP, (r)MDD, and cross-disorder. Loci were clumped using ‘plink --bfile 1kgp_ref_file --clump metal_output --clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.6 --clump-kb 3000’. Extended results ($p < 1 \times 10^{-4}$), including eQTL data for the variants highlighted in this table, and including secondary extended model statistics, are available in **Supplementary Table 6**. Abbreviations: SNP, Variant rs ID; $p_{G \times S}$, p -value for GxS interaction in combined PGC + iPSYCH datasets (p -value for secondary extended model, p_{ext} , in parentheses); CHR, Chromosome; BP, Base Pair Position; A1/A2, Allele 1/Allele 2; Freq1, Frequency of Allele 1; MAF, Minor Allele Frequency; Beta $_{G \times S}$, 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 2. Cross-Disorder Omnibus tests.

Omnibus tests were carried out using ASSET, incorporating the within-disorder meta-analysis summary statistics from METAL. Listed are SNPs with cross-disorder interaction p -values $< 1 \times 10^{-6}$. Loci were clumped using ‘plink --bfile 1kgp_ref_file --clump asset_output --clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.6 --clump-kb 3000’. Extended results ($p < 1 \times 10^{-4}$), including eQTL data for the variants highlighted in this table, and including secondary extended model statistics, are available in **Supplementary Table 7**.

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 (p -value for secondary extended model, p_{ext} , in parentheses); 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 p , Basic Meta-Analysis p -value; Meta OR (CI), Basic Meta-Analysis Odds Ratio (Confidence Interval)

Table 3. Credible SNP results for genome-wide significant locus *NKAIN2*.

CAVIAR and FINEMAP results for the genome-wide significant locus observed in the omnibus test of SCZ, BIP, and MDD (European ancestry). There were four SNPs, including genome-wide significant *NKAIN2* SNP rs117780815, with posterior probability higher than 0.90. These SNPs are the most likely variants to have a causal effect on mood and psychotic disorders from that locus.

Abbreviations: Index SNP, genome-wide significant SNP; SNP, all SNPs in locus; A1/A2, Allele 1 (reference allele)/Allele 2; CHR, Chromosome; BP, Base Pair Position; MAF, Minor Allele Frequency; PP($_{ext}$), posterior probability (extended secondary model); SE, Standard Error

Table 1. Single-disorder and Cross-disorder Autosomal SNP-by-sex interaction results.

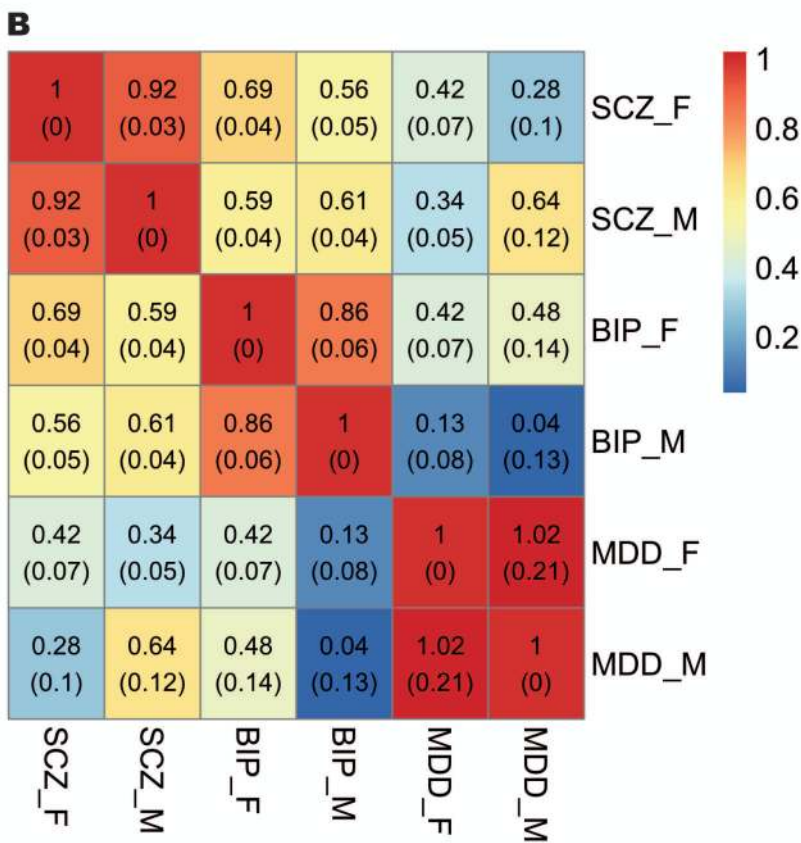
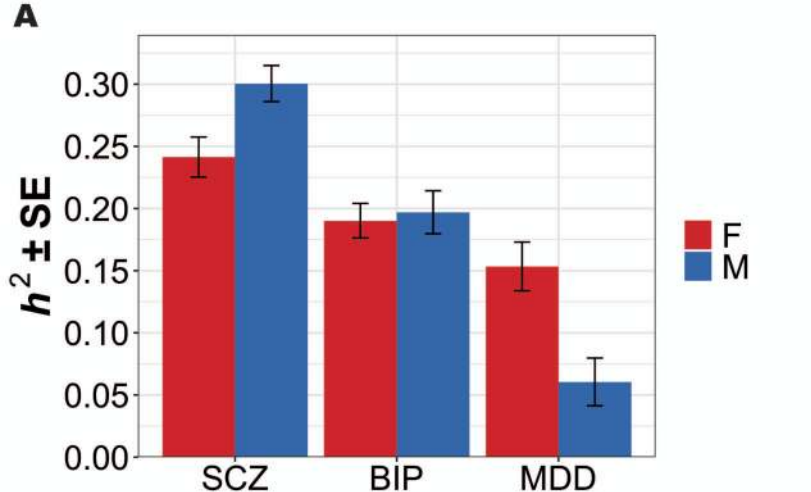
SNP	CHR	BP	A1/ A2	Freq1 MAF	Compartment	Gene (Distance in kb)	N Cases (%Female)	N Controls (%Female)	Beta _{GxS} (SE)	p _{GxS} (p _{ext})	Beta _F (SE)	p _F	Beta _M (SE)	p _M	Z _{FM}	p _{FM}
Schizophrenia (European only)																
rs11665282	18	33767479	A/G	0.69 0.31	UTR5	MOCOS	21,581 (35.18%)	24,250 (48.62%)	-0.156 (0.030)	1.48E-7 (2.53E-5)	-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 (2.28E-4)	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 (4.46E-5)	-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 (7.91E-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 (1.04E-5)	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 (3.31E-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 (4.76E-6)	-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
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 (5.35E-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 (2.24E-6)	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 (4.78E-6)	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 (2.24E-6)	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 (2.69E-6)	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 (2.22E-6)	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 (2.32E-6)	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 (8.25E-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 (2.22E-6)	0.142 (0.039)	2.55E-4	-0.129 (0.037)	4.89E-4	5.05	4.37E-7

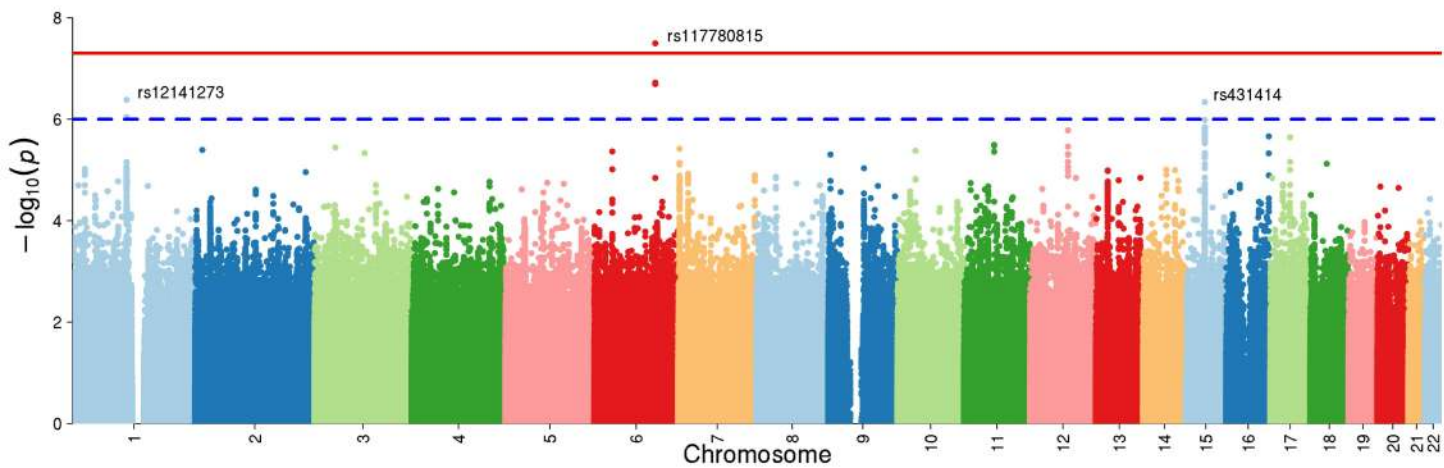
Table 2. Cross-Disorder Omnibus tests of SNP-by-sex interactions

SNP	CHR	BP	A1/ A2	MAF	Compartment	Gene (Distance in kb)	p (p _{test})	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-8 (4.67E-7)	BIP	SCZ	1.34E-7	1.12E-2	2.0 (1.52, 2.51)	0.79 (0.65, 0.95)	8.10E-2	1.12 (1.11, 1.13)
rs12141273	1	110079143	A/G	0.067	intergenic	AMIGO1 (26.8); GPR61 (3.3)	4.16E-7 (1.95E-6)	BIP	MDD	1.60E-4	1.40E-4	1.3 (1.14, 1.50)	0.81 (0.73, 0.90)	2.03E-1	0.96 (0.95, 0.96)
rs431414	15	59147800	T/C	0.181	UTR3	MINDY2	4.60E-7 (4.36E-7)	SCZ	BIP	1.62E-7	1.53E-1	1.2 (1.14, 1.34)	0.91 (0.80, 1.04)	1.67E-2	1.07 (1.07, 1.07)
SCZ-BIP-MDD (European + East Asian)															
rs117780815	6	124326227	T/A	0.036	intronic	NKAIN2	2.84E-8 (5.90E-7)	BIP	SCZ	1.34E-7	9.89E-3	2.0 (1.52, 2.51)	0.79 (0.65, 0.94)	9.46E-2	1.11 (1.10, 1.12)
rs12141273	1	110079143	A/G	0.067	intergenic	AMIGO1 (26.8); GPR61 (3.3)	4.16E-7 (1.95E-6)	BIP	MDD	1.60E-4	1.40E-4	1.3 (1.14, 1.50)	0.81 (0.73, 0.90)	2.03E-1	0.96 (0.95, 0.96)
rs35477914	15	59197669	T/A	0.193	intronic	SLTM	8.54E-7 (1.73E-6)	BIP; MDD	SCZ	1.30E-2	3.60E-6	1.1 (1.01, 1.14)	0.86 (0.80, 0.92)	4.84E-1	0.99 (0.98, 0.99)
SCZ-BIP-rMDD (European only)															
rs117780815	6	124326227	T/A	0.036	intronic	NKAIN2	3.17E-8 (1.69E-7)	BIP	SCZ	1.33E-7	1.12E-2	2.0 (1.52, 2.51)	0.79 (0.65, 0.95)	1.58E-1	1.10 (1.09, 1.11)
rs431414	15	59147800	T/C	0.182	UTR3	MINDY2	4.58E-7 (4.34E-7)	SCZ	BIP	1.62E-7	1.53E-1	1.2 (1.14, 1.34)	0.91 (0.80, 1.04)	7.27E-3	1.08 (1.08, 1.09)
SCZ-BIP-rMDD (European + East Asian)															
rs117780815	6	124326227	T/A	0.036	intronic	NKAIN2	2.82E-8 (2.14E-7)	BIP	SCZ	1.33E-7	9.88E-3	2.0 (1.52, 2.51)	0.79 (0.65, 0.94)	1.81E-1	1.10 (1.09, 1.11)

Table 3. Credible SNP results for genome-wide significant *NKAIN2* locus.

Index SNP	SNP	FINEMAP	CAVIAR	Compartment	Gene	CHR	BP	A1/A2	MAF	Beta	SE	Z
		PP causal (PPext)	PP causal (PPext)									
rs117780815	rs117780815	1 (1)	0.83 (0.88)	intronic	NKAIN2	6	124326227	T/A	0.04	0.670	0.127	5.27
rs117780815	rs4574657	1 (1)	5.9E-03 (7.2E-03)	intronic	NKAIN2	6	124319710	A/G	0.04	0.283	0.089	3.17
rs117780815	rs4895382	1 (1)	8.0E-02 (7.8E-03)	intronic	NKAIN2	6	124312658	G/A	0.02	0.736	0.171	4.29
rs117780815	rs73557075	1 (1)	1.4E-02 (5.6E-03)	intronic	NKAIN2	6	124313730	A/G	0.04	0.195	0.114	1.71
rs117780815	rs7748718	6.7E-02 (3.5E-02)	8.8E-03 (1.6E-02)	intronic	NKAIN2	6	124317132	C/A	0.05	0.358	0.108	3.33
rs117780815	rs7754419	2.9E-02 (5.4E-01)	6.1E-02 (1.6E-01)	intronic	NKAIN2	6	124318348	G/A	0.04	0.541	0.118	4.58
rs117780815	rs7761506	3.7E-02 (4.8E-05)	6.8E-03 (7.2E-03)	intronic	NKAIN2	6	124314413	G/A	0.02	0.493	0.159	3.09



A**B**