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Archival Report

Sex-Dependent Shared and Nonshared 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 (G×S) interaction of risk for these disorders using 85,735 cases (33,403 SCZ, 19,924 BIP, and 32,408 MDD) and 109,946 controls from the PGC (Psychiatric Genomics Consortium) and iPSYCH.

RESULTS: Across disorders, genome-wide significant single nucleotide polymorphism–by-sex interaction was detected for a locus encompassing *NKAIN2* (rs117780815, $p = 3.2 \times 10^{-8}$), which interacts with sodium/potassium-transporting ATPase (adenosine triphosphatase) enzymes, implicating neuronal excitability. Three additional loci showed evidence ($p < 1 \times 10^{-6}$) for cross-disorder G×S 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 G×S 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 G×S interaction of genes regulating vascular endothelial growth factor receptor signaling in MDD (false discovery rate-corrected $p < .05$).

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CONCLUSIONS: In the largest genome-wide G×S 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 and immune and vascular functions across and within SCZ, BIP, and MDD at the variant, gene, and pathway levels.

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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). Prevalence of BIP is approximately similar, but age of onset, course, and prognosis vary considerably by sex (3,4), as they do in SCZ and MDD (5–7). In addition, 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 intrapair 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-to-hip ratio) (13,14). Apart 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 men with SCZ than in women with SCZ (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 it is 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 (33), suggesting potential mechanisms mediating sex differences in psychiatric disorders.

To test for sex differences in genetic risk, it is essential to have adequate power to test for interaction effects (34). Given sample size limitations, genome-wide association studies (GWASs) of psychiatric disorders have typically not examined genotype-by-sex (G×S) interactions. Here, we capitalized on a unique opportunity to utilize cohorts from the PGC (Psychiatric Genomics Consortium) 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 PGC dataset (35–37) included 43 SCZ (30,608 patients and 38,441 control subjects), 28 BIP (18,958 patients and 29,996 control subjects), and 26 MDD (15,970 patients and 24,984 control subjects) cohorts (Table S1 in Supplement 2). The iPSYCH cohort in Denmark (38) included 2795 patients with SCZ and 2436 control subjects, 966 patients with BIP and 551 control subjects, and 16,438 patients with MDD and 13,538 control subjects (Table S2 in Supplement 2). Primary analyses used the PGC and iPSYCH datasets. Secondary PGC-only analyses (see Supplement 1) were performed to facilitate comparison with other PGC studies and ensure that different diagnostic criteria in PGC and iPSYCH (DSM-IV and ICD-10, respectively) were not affecting results. All cohorts were of a European ancestry, except three East Asian SCZ cohorts.

Quality Controls and Analytics

Quality control and imputation to the 1000 Genomes Phase 3 reference panel were performed using PGC's Rapid Imputation for COnsortias PIpeLIne (39) and previously described filtering thresholds (35–37). An overview of subsequent quality control and analytic steps is provided in Figure S1 in Supplement 1. Identity-by-descent filtering is described in Supplemental Methods in Supplement 1. At a minor allele frequency of 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 (Table S3 in Supplement 2; Figure S2 in Supplement 1).

Sex-stratified GWAS summary statistics were obtained by logistic regression of men and women separately within each cohort using PLINK (40), followed by standard error–weighted meta-analysis across cohorts using METAL (41). Summary statistics were entered into linkage disequilibrium score regression (42,43) to estimate autosomal sex-specific single nucleotide polymorphism (SNP)-based heritability (h^2_{SNP}) for each disorder (Figure 1) and bivariate genetic correlations (r_g) within and across disorders.

PLINK (40) was used to perform a genome-wide G×S interaction analysis in each cohort, followed by standard error–weighted meta-analysis of G×S interactions using METAL (41). G×S interaction analyses were performed using linear regression with main effects for SNPs and sex and SNP-by-sex interaction terms, and using additive models for SNPs

(controlling for 10 ancestry principal components). Secondary regression models included additional controls using 10 SNP-by-principal component and 10 sex-by-principal component interaction terms (44). Adding too many covariates can destabilize the effect estimates, leading 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.

G×S 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. Because these assumptions often do not hold, model B assigned 0 or 1 copy to men.

An omnibus test with 3 degrees of freedom (45) was performed by summing χ^2 values for individual disorder G×S interaction meta-analyses to identify SNPs with opposing G×S effects across disorders (see Supplemental Methods in Supplement 1).

Linkage disequilibrium–independent SNPs ($r^2 < .1$) with suggestive or genome-wide significant G×S interactions ($p < 1\times10^{-6}$) were used as index SNPs for fine-mapping to obtain likely causal SNPs using FINEMAP (46) and CAVIAR (47) (see Supplemental Methods in Supplement 1). Regions for fine-mapping were defined as all SNPs in linkage disequilibrium ($r^2 > .6$) with the index SNP.

SCZ and cross-disorder analyses of autosomes and X chromosome were conducted with and without inclusion of East Asian cohorts to evaluate population effects. Findings were not significantly different, and therefore, all subsequent analyses utilized only European ancestry cohorts (see Supplemental Methods in Supplement 1).

Gene-based analyses were conducted using MAGMA (48) (significant $p = 2.6 \times 10^{-6}$) (see Supplemental Methods in Supplement 1). Gene set enrichment tests (48) determined whether (near-)significant SNPs ($p < 1 \times 10^{-4}$) clustered into particular biological pathways characterizing functional similarity of genes implicated by G×S interactions. Hypothesis-free analyses were performed for 10,353 gene sets from the Molecular Signatures Database. Data-driven enrichment analyses were performed for nine gene sets/pathways implicated in previous studies (49,50).

Gene expression and expression quantitative trait locus (eQTL) data from several publicly available resources were evaluated to validate and interpret SNPs with G×S interaction p values $< 1 \times 10^{-6}$ (see Supplemental Methods in Supplement 1).

Finally, G×S interaction results were compared with previously reported sex-dependent or sex-specific effects on psychiatric risk ($p < 5 \times 10^{-8}$) (see Supplemental Methods in Supplement 1 and Supplemental Tables in Supplement 2).

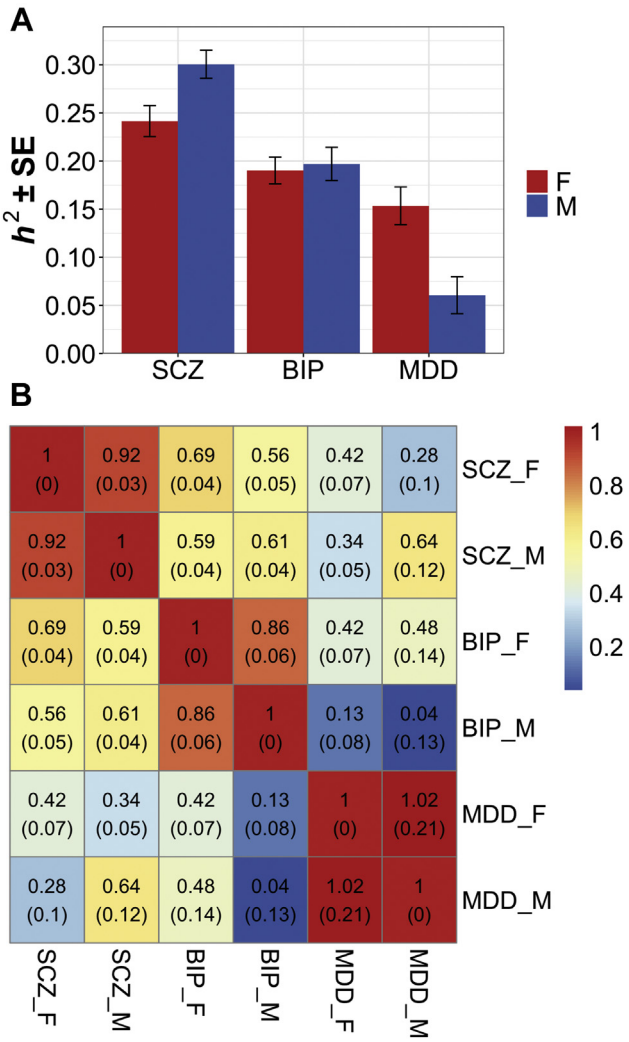

Figure 1. Linkage disequilibrium score regression estimates of sex-specific SNP-based **(A)** heritability, h^2 (±SE), and **(B)** genetic correlations, r_g (SE). This graph shows h^2 and r_g estimates for minor allele frequency > 0.01. **(A)** Heritability estimates were substantially different between the sexes for SCZ (p_{FDR} = .019) and MDD (p_{FDR} = .005), but not for BIP (p_{FDR} = .381). **(B)** SNP-based genetic correlations (r_g) between males and females within each disorder ranged between 0.86 and 1 and were significantly different from 1 for SCZ (p_{FDR} = .039) and BIP (p_{FDR} = .039), but not for MDD (p_{FDR} = .397). No significant differences were found in the cross-disorder genetic correlations between males and females, with the exception of r_g between BIP and MDD (r_{gF} = .42; r_{gM} = .04; p_{FDR} = .044). BIP, bipolar disorder; F, female; FDR, false discovery rate; M, male; MDD, major depressive disorder; SCZ, schizophrenia; SE, standard error; SNP, single nucleotide polymorphism.

RESULTS

Sex-Stratified GWAS

Sex-stratified GWAS analyses were performed to identify sex differences in heritability and genetic overlap between disorders, providing a reference point for interaction analyses. Manhattan plots (Figure S3 in Supplement 1) and scatter plots (Figure S4 in Supplement 1) showed considerable sex differences in the associations identified. Autosomal sex-specific SNP-based heritability (h^2_{SNP}) for each disorder and bivariate genetic correlations (r_g) within and across disorders were then estimated. Within each disorder, the h^2_{SNP} for men and women (Figure 1A) was significantly greater than 0 (mean 0.19; all $p <$ .001) (Table S4 in Supplement 2), indicating adequate power to detect broader polygenic signals. Estimates of h^2_{SNP} increased

minimally across a range of minor allele frequency cutoffs (minor allele frequency > 1%, 2%, 5%), indicating that rarer variants contributed little (Table S4 in Supplement 2). Heritability estimates were substantially different between the sexes for SCZ (false discovery rate-corrected p [p_{FDR}] = .019; $h^2_M > h^2_F$) and MDD (p_{FDR} = .005; $h^2_F > h^2_M$), but not for BIP (p_{FDR} = .381) (Table S4 in Supplement 2). Although correlations between male and female GWAS p values were low (Figure S4 in Supplement 1), 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} = .039) and BIP (p_{FDR} = .039), but not for MDD (p_{FDR} = .397) (Figure 1B; Table S5A in Supplement 2). In addition, we observed no significant differences in cross-disorder genetic correlations by sex, except r_g between BIP and MDD (r_{gF} = .42; r_{gM} = .04; p_{FDR} = .044) (Figure 1B; Table S5B in Supplement 2). However, within-sex analyses showed that women with SCZ and those with BIP were more highly genetically correlated than women with SCZ and those with MDD; women with MDD correlated similarly to both women with SCZ and those with BIP. In contrast, men with SCZ correlated similarly with men with BIP and those with MDD, but no genetic correlation was observed between men with MDD and those with BIP. Findings suggest that there may be different within-sex genetic differences that need further understanding and demonstrate the complexity of investigating sex differences in genetics.

Genome-wide SNP-by-Sex Interactions

To adequately test for sex effects, it is necessary to conduct SNP-by-sex interaction analyses. Quantile-quantile plots indicated no systematic inflation of test statistics (Figure S5 in Supplement 1). 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.

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; Table S8 in Supplement 2). Overall, there was little overlap between the strongest interactions for each disorder (Figure S6 in Supplement 1). The most significant results were obtained for SCZ for a locus in the 5′ untranslated region of the *MOCOS* gene (rs11665282: $p = 1.48 \times 10^{-7}$ [secondary model $p_{ext} = 2.53 \times 10^{-5}$]) (Figures S6–S8 in Supplement 1) and an intergenic locus near the noncoding RNA gene *LINC02181* (rs12445424: $p = 3.52 \times 10^{-7}$ [$p_{ext} = 2.28 \times 10^{-4}$]) (Figures S6–S8 in Supplement 1). The top G×S interaction locus for BIP was located on chromosome 9 near the *TUSC1* gene (rs12341335: $p = 2.29 \times 10^{-7}$ [$p_{ext} = 7.91 \times 10^{-7}$]) (Figures S6–S8 in Supplement 1). Suggestive evidence for G×S 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: $p = 4.61 \times 10^{-7}$ [$p_{ext} = 4.76 \times 10^{-6}$]) (Figures S6–S8 in Supplement 1). 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: $p = 1.09 \times 10^{-7}$ [$p_{ext} = 1.23 \times 10^{-6}$]) (Table S15A in Supplement 2). Meta-analysis of G×S interactions across cohorts from all three disorders (in contrast to omnibus tests) revealed suggestive evidence for three additional intergenic loci ($p < 1 \times 10^{-6}$) (Table 1; Table S6F–I in Supplement 2).

Omnibus tests of autosomal SNP G×S 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; Table S7 in Supplement 2). The effect was in opposite directions, with the minor allele increasing risk in women with BIP and decreasing risk in men with BIP, and vice versa in men and women with SCZ (see Table 1; Table S6A–E in Supplement 2) (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, although 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 (Table S16 in Supplement 2). 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 $p = 6.89 \times 10^{-6}$) (Table S8A, B in Supplement 2), similar regardless of model (Figure S8 in Supplement 1). Omnibus tests of X chromosome SNPs detected no significant interactions (lowest $p = 1.67 \times 10^{-5}$) (Table S9 in Supplement 2).

Fine-Mapping of SNP-by-Sex Interactions

Loci displaying evidence for G×S interactions (index SNP $p < 1 \times 10^{-6}$) (Tables 1 and 2; Tables S6–S9 in Supplement 2) underwent fine-mapping to identify those SNPs most likely to be causal. Sixteen loci had a mean of 75 (±68) SNPs. In approximately 50% of the loci, the index SNP was among the three most credible SNPs, and >70% of clumps had a simple model (≤ three causal variants). We summarize the posterior probabilities of all SNPs in fine-mapping loci (Table 3; Table S10 in Supplement 2) 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

To capture all potential risk-conferring variations and derive aggregate, gene-level p values, we conducted gene-based tests. Gene-based tests within/across disorders detected near-significant G×S interaction of the SLTM gene within SCZ ($p = 4.22 \times 10^{-6}$ [$p_{ext} = 7.28 \times 10^{-6}$]) (Figure S10A in Supplement 1) and genome-wide significant cross-disorder interaction (omnibus $p = 8.97 \times 10^{-7}$ [$p_{ext} = 6.64 \times 10^{-7}$]) (Figure S10G, H in Supplement 1). No other results

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)	Cases, *n* (% Female)	Controls, *n* (% Female)	$Beta_{G\times S}$ (SE)	$p_{G\times S}$ (p_{ext})	$Beta_F$ (SE)	p_F	$Beta_M$ (SE)	p_M	z_{FM}	p_{FM}
SCZ (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)	1.48×10^{-7} (2.53×10^{-5})	−0.081 (0.023)	3.98×10^{-4}	0.072 (0.019)	2.16×10^{-4}	−5.09	3.50×10^{-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)	3.52×10^{-7} (2.28×10^{-4})	0.097 (0.021)	5.80×10^{-6}	−0.050 (0.018)	4.67×10^{-3}	5.30	1.19×10^{-7}
SCZ (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)	3.74×10^{-7} (4.46×10^{-5})	−0.077 (0.023)	6.74×10^{-4}	0.070 (0.019)	2.53×10^{-4}	−4.96	6.89×10^{-7}
BIP																
rs12341335	9	25649145	T/C	0.90/0.10	Intergenic	*TUSC1* (27.2)	7730 (57.72%)	13,635 (51.28%)	0.373 (0.072)	2.29×10^{-7} (7.91×10^{-7})	0.176 (0.048)	2.59×10^{-4}	−0.201 (0.054)	2.11×10^{-4}	5.20	2.03×10^{-7}
rs17651437	2	106055684	T/C	0.52/0.48	Upstream	*FHL2*	16,365 (60.18%)	28,140 (50.75%)	0.155 (0.031)	3.72×10^{-7} (1.04×10^{-5})	0.079 (0.020)	9.97×10^{-5}	−0.069 (0.023)	3.08×10^{-3}	4.79	1.63×10^{-6}
MDD																
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)	1.64×10^{-7} (3.31×10^{-7})	−0.087 (0.022)	6.41×10^{-5}	0.094 (0.028)	8.41×10^{-4}	−5.08	3.70×10^{-7}
rs147515485	17	40182099	T/C	0.02/0.02	Intronic	*ZNF385C*	31,149 (61.17%)	35,385 (50.89%)	−0.472 (0.094)	4.61×10^{-7} (4.76×10^{-6})	−0.190 (0.060)	1.55×10^{-3}	0.303 (0.074)	4.39×10^{-5}	−5.17	2.39×10^{-7}
Recurrent MDD																
rs61138090	1	118832069	D/I2	0.59/0.41	Intergenic	*SPAG17* (104.2)	7685 (70.59%)	15,976 (51.71%)	−0.240 (0.046)	1.40×10^{-7} (−)	−0.109 (0.028)	1.03×10^{-4}	0.142 (0.038)	2.08×10^{-4}	−5.28	1.30×10^{-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)	1.60×10^{-7} (5.35×10^{-7})	0.087 (0.019)	5.09×10^{-6}	−0.051 (0.020)	1.15×10^{-2}	4.98	6.51×10^{-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)	8.82×10^{-7} (2.24×10^{-6})	0.116 (0.036)	1.09×10^{-3}	−0.128 (0.035)	2.69×10^{-4}	4.89	1.03×10^{-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)	6.39×10^{-7} (4.78×10^{-6})	0.064 (0.020)	1.86×10^{-3}	−0.077 (0.021)	2.27×10^{-4}	4.82	1.43×10^{-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)	8.82×10^{-7} (2.24×10^{-6})	0.116 (0.036)	1.09×10^{-3}	−0.128 (0.035)	2.69×10^{-4}	4.89	1.03×10^{-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)	9.37×10^{-7} (2.69×10^{-6})	0.082 (0.019)	1.35×10^{-5}	−0.044 (0.020)	2.37×10^{-2}	4.64	3.51×10^{-6}
Cross-Disorder SCZ-BIP-Recurrent MDD (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)	6.22×10^{-7} (2.22×10^{-6})	0.142 (0.039)	2.55×10^{-4}	−0.129 (0.037)	4.89×10^{-4}	5.05	4.37×10^{-7}

Table 1. Continued

SNP	CHR	BP	A1/A2	Freq1/MAF	Compartment	Gene (Distance in kb)	Cases, *n* (% Female)	Controls, *n* (% Female)	$Beta_{G\times S}$ (SE)	$p_{G\times S}$ (p_{ext})	$Beta_F$ (SE)	p_F	$Beta_M$ (SE)	p_M	z_{FM}	p_{FM}
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)	7.43×10^{-7} (2.32×10^{-6})	0.094 (0.020)	4.48×10^{-6}	−0.048 (0.021)	2.13×10^{-2}	4.86	1.18×10^{-6}
Cross-Disorder SCZ-BIP-Recurrent MDD (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)	3.90×10^{-7} (8.25×10^{-7})	0.084 (0.026)	1.18×10^{-3}	−0.093 (0.025)	2.18×10^{-4}	4.89	9.90×10^{-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)	6.22×10^{-7} (2.22×10^{-6})	0.142 (0.039)	2.55×10^{-4}	−0.129 (0.037)	4.89×10^{-4}	5.05	4.37×10^{-7}

Within-disorder and cross-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, (recurrent) 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 Table S6 in Supplement 2.

A1, allele 1; A2, allele 2; BP, base pair position; $beta_{G\times S}$, beta for G×S interaction; $beta_F$, beta for female-stratified association; $beta_M$, beta for male-stratified association; BIP, bipolar disorder; CHR, chromosome; eQTL, expression quantitative trait locus; Freq1, frequency of allele 1; G×S; genotype-by-sex; MAF, minor allele frequency; MDD, major depressive disorder; p_F, *p* value for female-stratified association; p_{FM}, *p* value heterogeneity females-males; PGC, Psychiatric Genomics Consortium; $p_{G\times S}$, *p* value for G×S interaction in combined PGC+iPSYCH datasets (*p* value for secondary extended model, with p_{ext}, in parentheses); p_M, *p* value for male-stratified association; SCZ, schizophrenia; SE, standard error; SNP, single nucleotide polymorphism (variant rs ID); UTR, untranslated region; z_{FM}, *z* score heterogeneity females-males.

approached significance (Table S11 in Supplement 2; Figure S10B–F in Supplement 1).

To identify the functional significance of sex-dependent loci, pathway-based analyses were conducted. Gene set enrichment tests showed that within MDD, G×S SNPs were significantly enriched in genes regulating vascular endothelial growth factor (VEGF) receptor signaling ($p_{FDR} = 3.90 \times 10^{-4}$ [$p_{FDRext} = 2.70 \times 10^{-2}$]) (Table S12C in Supplement 2). SNPs showing G×S interactions within SCZ or BIP were not significantly enriched for any Molecular Signatures Database pathway (Table S12A, B in Supplement 2). Across disorders, the "wang_barretts_esophagus_and_esophagus_cancer_dn" pathway showed enrichment ($p_{FDR} = .035$ [$p_{FDRext} = .065$]) (Table S12F in Supplement 2).

Brain Expression Analysis

To further validate the identified sex-dependent variants functionally, brain expression data were examined for genes located adjacent to or encompassing SNPs with evidence for G×S interactions ($p < 1 \times 10^{-6}$). Most of these genes were expressed in multiple brain regions (Figure S11–S13 in Supplement 1), particularly prefrontal, anterior cingulate, pituitary, and hypothalamus (Figure S14 in Supplement 1) from prenatal development (*C8orf4* [= *TCIM*], *CRSP2*, *GNA12*, *MOCOS*, *SPAG17*), through puberty (*IDO2)* (Figure S12 in Supplement 1), and through adulthood (Figures S12 and S13 in Supplement 1). Genes were expressed in various brain cell types (Figure S15 in Supplement 1), with high relative expression of *NKAIN2* and *GNA12* in oligodendrocytes, and *CSRP2*, *C8orf4*, and *MOCOS* in endothelial cells (Supplemental Results in Supplement 1 report other genes).

eQTL Overlap With G×S Loci

Examination of eQTL data for SNPs with evidence for G×S interactions ($p < 1 \times 10^{-6}$) (Tables S6 and S7 in Supplement 2) found that the highly significant SCZ *MOCOS* SNP (rs11665282) was a *cis*-eQTL in several brain regions (Table S6A in Supplement 2) associated with transcriptional elongation and chromatin remodeling in the *ELP2* gene in the cerebellum and dorsolateral prefrontal cortex. The most significant cross-disorder SNP (rs7302529) was an eQTL for *CSRP2* (Table S6F in Supplement 2), 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 nonbrain tissues and is associated with expression of glutathione-S-transferase genes *GSTM1* and *GSTM5* and microtubule regulator gene *PSRC1*, in the dorsolateral prefrontal cortex (Table S7 in Supplement 2).

Overall, consistency of our significant G×S effects with previous GWAS of sex differences in MDD, BIP, and SCZ is described in Supplemental Results in Supplement 1 and Table S14 in Supplement 2.

DISCUSSION

Sex differences in incidence, symptomatology, 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

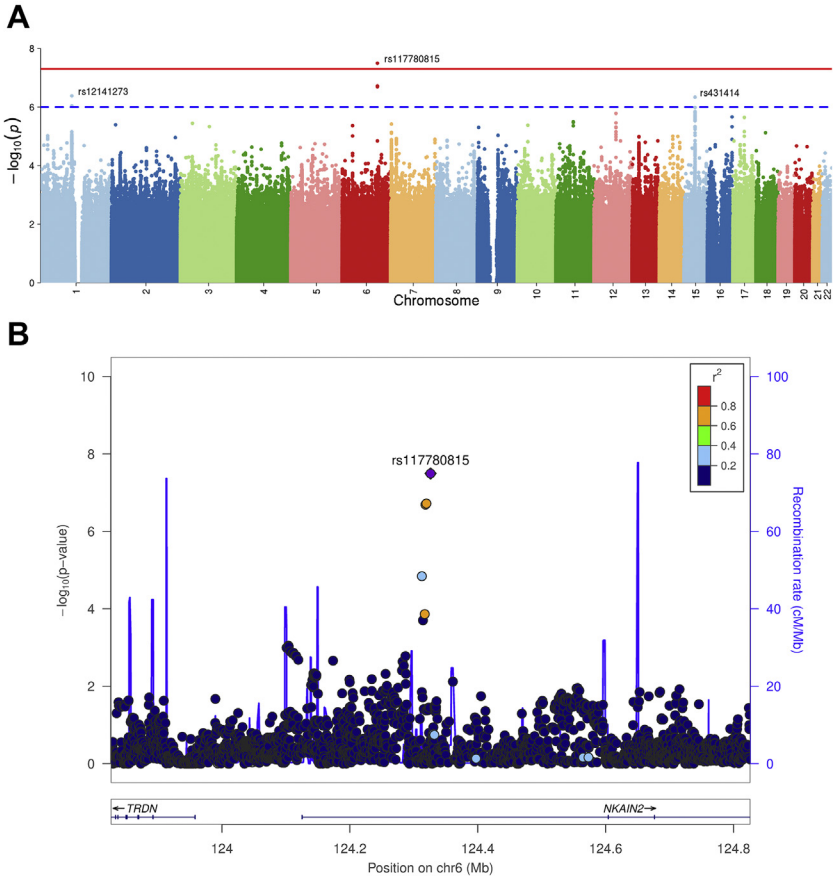

Figure 2. Cross-disorder Manhattan plot of SNP-by-sex interaction *p* values **(A)** and LocusZoom plot for the *NKAIN2* gene locus exhibiting a significant SNP-by-sex interaction effect on cross-disorder risk **(B)**. This graph shows the genome-wide significant result from the cross-disorder omnibus test in ASSET (primary model). Negative $\log_{10}$-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 genotype-by-sex interaction was found for SNP rs117780815 on chromosome 6 ($p = 3.2 \times 10^{-8}$) driven by bipolar disorder and schizophrenia. The effect was in opposite directions, with the minor allele increasing risk in women with bipolar disorder and decreasing risk in men with bipolar disorder, and vice versa in men and women with schizophrenia (Table 2; Table S7 in Supplement 2). r^2 indicates the linkage disequilibrium level. chr, chromosome; SNP, single nucleotide polymorphism.

hypothesized that sex differences may be due in part 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 for BIP, partly reflecting significant sex differences in incidence for SCZ and MDD, but not for BIP. Male-female SNP-based genetic correlations ranged between 0.86 (BIP) and 1 (MDD), significantly <1 for SCZ and BIP but not for 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 GWASs (25–32,35), implicating neurodevelopmental mechanisms and immune pathways (26–28,30). However, sex-stratified analyses are only equivalent to G×S interaction tests when there are no interactions between covariates and sex, and the trait variances are equivalent in the two sexes. Because this is unlikely, G×S interaction tests are ultimately necessary to identify significant sex differences, and sex-stratified analyses may fail to detect or spuriously report differences.

G×S 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 G×S emanating from the *NKAIN2* gene, expressed in the brain, implicating potassium sodium ATPases (adenosine triphosphatases) regulating neuron membrane potential, transmembrane fluxes of Ca^{2+} and excitatory neurotransmitters, and central nervous system differentiation (51). *NKAIN2* has previously been associated with cognitive ability (52) and SCZ risk (53,54). The second most significant omnibus G×S result was an SNP adjacent to *AMIGO1*, which regulates activity of the Kv2.1 voltage-dependent potassium channel (55), again important for regulating neuronal excitability in the brain (56). Other support for G×S interaction was obtained from gene-based analyses across disorders that detected a genome-wide significant G×S interaction with the *SLTM* gene, a general inhibitor of transcription highly expressed in the cerebellum and putamen, among others. Taken together, these

Table 2. Cross-Disorder Omnibus Tests of SNP-by-Sex Interactions

SNP	CHR	BP	A1/A2	MAF	Compartment	Gene (Distance in kb)	p (p_{ext})	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*	3.19×10^{-8} (4.67×10^{-7})	BIP	SCZ	1.34×10^{-7}	1.12×10^{-2}	2.0 (1.52–2.51)	0.79 (0.65–0.95)	8.10×10^{-2}	1.12 (1.11–1.13)
rs12141273	1	110079143	A/G	0.067	Intergenic	*AMIGO1* (26.8); *GPR61* (3.3)	4.16×10^{-7} (1.95×10^{-6})	BIP	MDD	1.60×10^{-4}	1.40×10^{-4}	1.3 (1.14–1.50)	0.81 (0.73–0.90)	2.03×10^{-1}	0.96 (0.95–0.96)
rs431414	15	59147800	T/C	0.181	UTR3	*MINDY2*	4.60×10^{-7} (4.36×10^{-7})	SCZ	BIP	1.62×10^{-7}	1.53×10^{-1}	1.2 (1.14–1.34)	0.91 (0.80–1.04)	1.67×10^{-2}	1.07 (1.07–1.07)
SCZ-BIP-MDD (European+East Asian)															
rs117780815	6	124326227	T/A	0.036	Intronic	*NKAIN2*	2.84×10^{-8} (5.90×10^{-7})	BIP	SCZ	1.34×10^{-7}	9.89×10^{-3}	2.0 (1.52–2.51)	0.79 (0.65–0.94)	9.46×10^{-2}	1.11 (1.10–1.12)
rs12141273	1	110079143	A/G	0.067	Intergenic	*AMIGO1* (26.8); *GPR61* (3.3)	4.16×10^{-7} (1.95×10^{-6})	BIP	MDD	1.60×10^{-4}	1.40×10^{-4}	1.3 (1.14–1.50)	0.81 (0.73–0.90)	2.03×10^{-1}	0.96 (0.95–0.96)
rs35477914	15	59197669	T/A	0.193	Intronic	*SLTM*	8.54×10^{-7} (1.73×10^{-6})	BIP; MDD	SCZ	1.30×10^{-2}	3.60×10^{-6}	1.1 (1.01–1.14)	0.86 (0.80–0.92)	4.84×10^{-1}	0.99 (0.98–0.99)
SCZ-BIP-Recurrent MDD (European Only)															
rs117780815	6	124326227	T/A	0.036	Intronic	*NKAIN2*	3.17×10^{-8} (1.69×10^{-7})	BIP	SCZ	1.33×10^{-7}	1.12×10^{-2}	2.0 (1.52–2.51)	0.79 (0.65–0.95)	1.58×10^{-1}	1.10 (1.09–1.11)
rs431414	15	59147800	T/C	0.182	UTR3	*MINDY2*	4.58×10^{-7} (4.34×10^{-7})	SCZ	BIP	1.62×10^{-7}	1.53×10^{-1}	1.2 (1.14–1.34)	0.91 (0.80–1.04)	7.27×10^{-3}	1.08 (1.08–1.09)
SCZ-BIP-Recurrent MDD (European+East Asian)															
rs117780815	6	124326227	T/A	0.036	Intronic	*NKAIN2*	2.82×10^{-8} (2.14×10^{-7})	BIP	SCZ	1.33×10^{-7}	9.88×10^{-3}	2.0 (1.52–2.51)	0.79 (0.65–0.94)	1.81×10^{-1}	1.10 (1.09–1.11)

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 Table S7 in Supplement 2.

A1, allele 1 (reference allele); A2, allele 2; BIP, bipolar disorder; BP, base pair position; CHR, chromosome; CI, confidence interval; eQTL, expression quantitative trait locus; MAF, minor allele frequency; MDD, major depressive disorder; meta OR, basic meta-analysis odds ratio; meta p, basic meta-analysis p value; OR.1, phenotype(s) 1 odds ratio; OR.2, phenotype(s) 2 odds ratio; p, omnibus p value in combined PGC+iPSYCH datasets (p value for secondary extended model, p_{ext}, in parentheses); p.1, phenotype(s) 1 p value; p.2, phenotype(s) 2 p value; PGC, Psychiatric Genomics Consortium; Pheno.1, phenotype(s) associated in direction 1; Pheno.2, phenotype(s) associated in direction 2; SCZ, schizophrenia; SNP, single nucleotide polymorphism (variant rs ID); UTR, untranslated region.

Table 3. Credible SNP Results for Genome-wide Significant *NKAIN2* Locus

Index SNP	SNP	FINEMAP: PP causal (PP_{ext})	CAVIAR: PP causal (PP_{ext})	Compartment	Gene	CHR	BP	A1/A2	MAF	Beta	SE	*z*
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)	5.9×10^{-3} (7.2×10^{-3})	Intronic	*NKAIN2*	6	124319710	A/G	0.04	0.283	0.089	3.17
rs117780815	rs4895382	1 (1)	8.0×10^{-2} (7.8×10^{-3})	Intronic	*NKAIN2*	6	124312658	G/A	0.02	0.736	0.171	4.29
rs117780815	rs73557075	1 (1)	1.4×10^{-2} (5.6×10^{-3})	Intronic	*NKAIN2*	6	124313730	A/G	0.04	0.195	0.114	1.71
rs117780815	rs7748718	6.7×10^{-2} (3.5×10^{-2})	8.8×10^{-3} (1.6×10^{-2})	Intronic	*NKAIN2*	6	124317132	C/A	0.05	0.358	0.108	3.33
rs117780815	rs7754419	2.9×10^{-2} (5.4×10^{-1})	6.1×10^{-2} (1.6×10^{-1})	Intronic	*NKAIN2*	6	124318348	G/A	0.04	0.541	0.118	4.58
rs117780815	rs7761506	3.7×10^{-2} (4.8×10^{-5})	6.8×10^{-3} (7.2×10^{-3})	Intronic	*NKAIN2*	6	124314413	G/A	0.02	0.493	0.159	3.09

CAVIAR and FINEMAP results for the genome-wide significant locus observed in the omnibus test of schizophrenia, bipolar disorder, and major depressive disorder (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.

A1, allele 1 (reference allele); A2, allele 2; BP, base pair position; CHR, chromosome; MAF, minor allele frequency; $PP_{(ext)}$, posterior probability (extended secondary model); SE, standard error; SNP, single nucleotide polymorphism (index SNP indicates genome-wide significant SNP in locus, and SNP refers to all SNPs in locus).

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 G×S analyses for SCZ (PGC-only; rs13270586) was near *C8orf4* (aka *TCIM*), which functions as a positive regulator of the Wnt/ß-catenin signaling pathway, implicated previously in SCZ, BIP, and MDD (57–60), with a central role in fundamental neuronal processes, including synaptogenesis, axon guidance, and dendrite development (61). 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 (62). This is consistent with our earlier work in mice with impaired $GABA_B$ (gamma-aminobutyric acid B) receptor signaling and demonstrating sex differences in developmental migration of neurons containing estrogen receptor ER-α into the hypothalamus paraventricular nucleus that affected depressive-like behaviors, particularly in females (63).

Several genes that implicated neuronal excitability and immune functions had opposite effects on disorder risk by sex. The *NKAIN2* SNP G×S effect was opposite in SCZ and BIP, with the minor allele increasing risk in women with SCZ and decreasing risk in men with SCZ, and opposite effects on risk in men and women with BIP. Similarly, the *AMIGO1/GPR61* G×S effect was opposite in BIP and MDD, with the minor allele having stronger effects in women with BIP and weaker effect in women with MDD versus men with MDD.

Immune pathway dysregulation, shared across disorders, also demonstrated some evidence of opposite genetic effects by sex. The strongest G×S 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, is elevated in the cerebrospinal fluid (64,65) and postmortem brains (66,67) in SCZ and BIP, while reduced plasma levels were associated with depressive symptoms (64). Given recent evidence implicating the kynurenine pathway as a link between brain immune activation and disorder risk (68,69) and sex differences in immune mechanisms (70), it is plausible that *IDO2* has different effects on SCZ risk in men and women through differential kynurenic acid 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). Furthermore, among the strongest results for MDD was a locus spanning *ZNF385C*, associated with transcriptional regulation (71) and immune-related phenotypes via transcriptional enhancers (72,73).

Our sex-biased genes implicating immune mechanisms at the population level complement recent transcriptomic work in healthy brain development (74), population work in SCZ (19), and MDD (75). Sex-by-diagnosis interactions were seen in the rearrangement of brain transcriptional patterns in MDD (75), an effect also seen in stressed mice (76). In MDD, cell type–specific analyses revealed that men with MDD exhibited transcriptional increases, and women with MDD exhibited transcriptional decreases in oligodendrocyte- and microglia-related genes (75).

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, hippocampus, amygdala). In males in utero, there is heightened activation of preoptic area microglia that may result in a priming effect leading to sex-dependent vulnerability for disorders such as SCZ (77). 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 (77), a critical period analogous to human sexual brain differentiation (second and third trimesters). This suggests that timing is critical in identifying G×S effects, which may have opposing effects at different developmental periods, a fact that must be

considered in transcription studies of brain regions across the life span. In fact, sex differences in the expression of *IDO2* were identified as also critical during puberty, with postpuberty 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 (78), which 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 (79) and SCZ (80) 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 (79) or copy number variants. Opposing effects were most likely to be significant because they generally have the largest effect sizes and thus greatest statistical power to detect. The majority of common SNPs likely have disease risk interaction effect sizes of odds ratio <1.1. Nevertheless, 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 (81) 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 cardiovascular disease with MDD (higher in women) (82) and SCZ. Results demonstrated that genes involved in regulation of VEGF signaling were enriched among G×S loci for MDD. Sex differences were reported in VEGF levels (83), and brain expression of VEGF has been associated with cognitive aging and Alzheimer's disease (84,85). Furthermore, the strongest G×S 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 $GABA_B$ receptor signaling (63) was also significantly associated with sex differences in hypothalamic neurovascular development, being more severe in females and associated with depression-related behaviors (86). 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 (87).

Finally, G×S effects had implications for cognitive functions, which is not surprising, given the brain regions implicated by some of the significant loci in this study. For example, *ZNF385C* in MDD may play a role in cognition because its paralogs *ZNF385B* and *ZNF385D* have been associated with intelligence (88), general cognition, mathematical ability, and educational attainment (89). It is possible that genes associated with cognitive abnormalities may be shared across disorders, given that the two strongest G×S interaction loci for BIP located near *TUSC1* and *FHL2* have been associated with educational attainment, other cognitive phenotypes, and depression (89,90).

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 G×S 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 (91). Nevertheless, our results of G×S 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 (33,61,74,92) and data enriched for tissue-related diseases (33). These findings underscore the utility of studies such as ours, with statistical power to test for interaction effects and 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 men with MDD (mean h^2_{SNP} = 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 be due in part 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 women with BIP (0.42, 0.48), but much weaker with MDD (both sexes) and men with BIP (0.13, 0.04). Although some have argued that 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 prevalence) and no genetic correlations by sex among SCZ subjects compared with high correlations among MDD and BIP subjects. 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. Furthermore, 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 of 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). Furthermore, alternative explanations for sex differences in incidence, presentation, and course include genotype-by-environment interactions, e.g., implicating gonadal hormone regulation of genes, which 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 G×S 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 G×S 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 life span, 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 affected 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.

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

JMG is on the scientific advisory board for and has equity in Cala Health, a neuromodulation company, although this is unrelated to the topic in this study; TLP is an employee of Concert Pharmaceuticals, also unrelated to this study. JWS is an unpaid member of the Bipolar/Depression Research Community Advisory Panel of 23andMe. All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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