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## Sex-Dependent Shared and Nonshared Genetic Architecture Across Mood and Psychotic Disorders

Schizophrenia Working Group of the Psychiatric Genomics Consortium

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# Archival Report

## Sex-Dependent Shared and Nonshared Genetic Architecture Across Mood and Psychotic Disorders

Gabriëlla A.M. Blokland, Jakob Grove, Chia-Yen Chen, Chris Cotsapas, Stuart Tobet, Robert Handa, Schizophrenia Working Group of the Psychiatric Genomics Consortium, David St Clair, Todd Lencz, Bryan J. Mowry, Sathish Periyasamy, Murray J. Cairns, Paul A. Tooney, Jing Qin Wu, Brian Kelly, George Kirov, Patrick F. Sullivan, Aiden Corvin, Brien P. Riley, Tõnu Esko, Lili Milani, Erik G. Jönsson, Aarno Palotie, Hannelore Ehrenreich, Martin Begemann, Agnes Steixner-Kumar, Pak C. Sham, Nakao Iwata, Daniel R. Weinberger, Pablo V. Gejman, Alan R. Sanders, Joseph D. Buxbaum, Dan Rujescu, Ina Giegling, Bettina Konte, Annette M. Hartmann, Elvira Bramon, Robin M. Murray, Michele T. Pato, Jimmy Lee, Ingrid Melle, Espen Molden, Roel A. Ophoff, Andrew McQuillin, Nicholas J. Bass, Rolf Adolfsson, Anil K. Malhotra, Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, Nicholas G. Martin, Janice M. Fullerton, Philip B. Mitchell, Peter R. Schofield, Andreas J. Forstner, Franziska Degenhardt, Sabrina Schaupp, Ashley L. Comes, Manolis Kogevinas, José Guzman-Parra, Andreas Reif, Fabian Streit, Lea Sirignano, Sven Cichon, Maria Grigoriou-Serbanescu, Joanna Hauser, Jolanta Lissowska, Fermin Mayoral, Bertram Müller-Myhsok, Beata Świątkowska, Thomas G. Schulze, Markus M. Nöthen, Marcella Rietschel, John Kelsoe, Marion Leboyer, Stéphane Jamain, Bruno Etain, Frank Bellivier, John B. Vincent, Martin Alda, Claire O'Donovan, Pablo Cervantes, Joanna M. Biernacka, Mark Frye, Susan L. McElroy, Laura J. Scott, Eli A. Stahl, Mikael Landén, Marian L. Hamshere, Olav B. Smeland, Srdjan Djurovic, Arne E. Vaaler, Ole A. Andreassen, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Bernhard T. Baune, Tracy Air, Martin Preisig, Rudolf Uher, Douglas F. Levinson, Myrna M. Weissman, James B. Potash, Jianxin Shi, James A. Knowles, Roy H. Perlis, Susanne Lucae, Dorret I. Boomsma, Brenda W.J.H. Penninx, Jouke-Jan Hottenga, Eco J.C. de Geus, Gonneke Willemsen, Yuri Milaneschi, Henning Tiemeier, Hans J. Grabe, Alexander Teumer, Sandra Van der Auwera, Uwe Völker, Steven P. Hamilton, Patrik K.E. Magnusson, Alexander Viktorin, Divya Mehta, Niamh Mullins, Mark J. Adams, Gerome Breen, Andrew M. McIntosh, Cathryn M. Lewis, Sex Differences Cross-Disorder Analysis Group of the Psychiatric Genomics Consortium, iPSYCH, David M. Hougaard, Merete Nordentoft, Ole Mors, Preben B. Mortensen, Thomas Werge, Thomas D. Als, Anders D. Børglum, Tracey L. Petryshen, Jordan W. Smoller, and Jill M. Goldstein

### 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  $p < .05$ ).

**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 PLPeLine (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  $\geq 1.2$  and  $\geq 1.1$ , 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

## Sex-Dependent Genetic Architecture

(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  $\chi^2$  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 ( $p < 1 \times 10^{-6}$ ) 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).

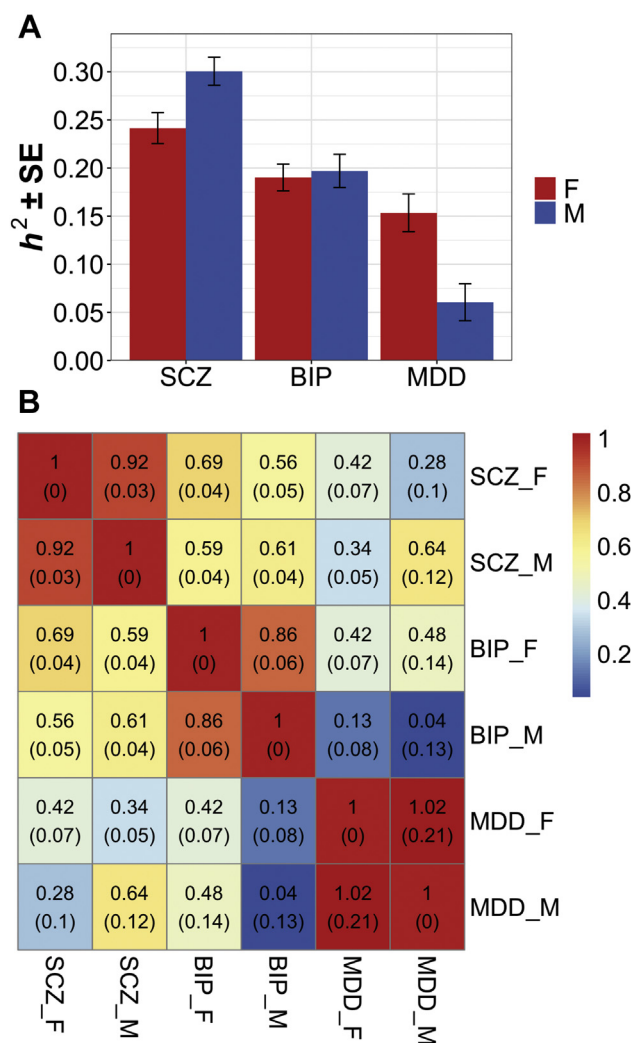
Gene expression and expression quantitative trait locus (eQTL) data from several publicly available resources were evaluated to validate and interpret SNPs with G×S interaction  $p$  values  $< 1 \times 10^{-6}$  (see Supplemental Methods in Supplement 1).

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).

## 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 1.** Linkage disequilibrium 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 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.

(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;  $h_M^2 > h_F^2$ ) and MDD ( $p_{FDR}$  = .005;  $h_F^2 > h_M^2$ ), 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 ( $\lambda_{GC}$ ) 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; 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 ( $\pm 68$ ) 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 ( $\leq$  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. Continued

SNP	CHR	BP	A1/A2	Freq1/MAF	Compartment	Gene (Distance in kb)	Cases, n (% Female)	Controls, n (% Female)	Beta <sub>G×S</sub> (SE)	p <sub>G×S</sub> (p <sub>ext</sub> )	Beta <sub>F</sub> (SE)	p <sub>F</sub>	Beta <sub>M</sub> (SE)	p <sub>M</sub>	Z <sub>FM</sub>	p <sub>FM</sub>
rs7302529	12	77321581	T/C	0.26/0.26	Intergenic	CSRP2 (48.8); EFZ7 (93.4)	31,541 (49.75%)	31,377 (50.42%)	0.144 (0.029)	7.43 × 10 <sup>-7</sup> (2.32 × 10 <sup>-6</sup> )	0.094 (0.020)	4.48 × 10 <sup>-6</sup>	-0.048 (0.021)	2.13 × 10 <sup>-2</sup>	4.86	1.18 × 10 <sup>-6</sup>
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 <sup>-7</sup> (8.25 × 10 <sup>-7</sup> )	0.084 (0.026)	1.18 × 10 <sup>-3</sup>	-0.093 (0.025)	2.18 × 10 <sup>-4</sup>	4.89	9.90 × 10 <sup>-7</sup>
rs73033497	7	2910659	A/T	0.86/0.14	Intergenic	GNA12 (26.7); CARD11 (95.0)	13,497 (47.22%)	14,619 (48.26%)	0.267 (0.054)	6.22 × 10 <sup>-7</sup> (2.22 × 10 <sup>-6</sup> )	0.142 (0.039)	2.55 × 10 <sup>-4</sup>	-0.129 (0.037)	4.89 × 10 <sup>-4</sup>	5.05	4.37 × 10 <sup>-7</sup>

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 -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<sub>G×S</sub>, beta for female-stratified association; beta<sub>F</sub>, beta for male-stratified association; beta<sub>M</sub>, 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<sub>F</sub>,  $p$  value for female-stratified association; p<sub>FM</sub>,  $p$  value for female-stratified association; PGC, Psychiatric Genomics Consortium; p<sub>G×S</sub>,  $p$  value for G×S interaction in combined PGC+IPSYCH datasets ( $p$  value for secondary extended model, with p<sub>ext</sub> in parentheses); p<sub>M</sub>,  $p$  value for male-stratified association; SCZ, schizophrenia; SE, standard error; SNP, single nucleotide polymorphism (variant rs ID); UTR, untranslated region; Z<sub>FM</sub>, 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 ( $p_{\text{FDR}} = 3.90 \times 10^{-4}$  [ $p_{\text{FDRext}} = 2.70 \times 10^{-2}$ ]) (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 ( $p_{\text{FDR}} = .035$  [ $p_{\text{FDRext}} = .065$ ]) (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 *CRSP2*, *C8orf4*, and *MOCOS* in endothelial cells (Supplemental Results in Supplement 1 report other genes).

### eQTL Overlap With G×S Loci

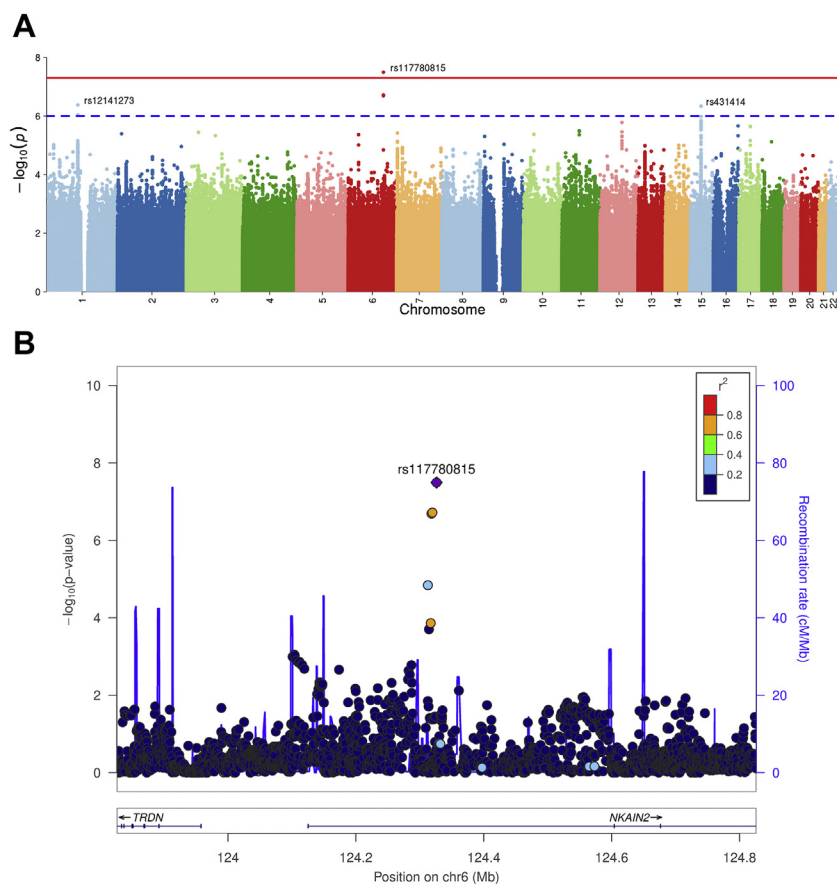
Examination of eQTL data for SNPs with evidence for G×S interactions ( $p < 1 \times 10^{-6}$ ) (Tables S6 and S7 in Supplement 2) found that the highly significant SCZ *MOCOS* SNP (rs11665282) was a *cis*-eQTL in several brain regions (Table S6A in Supplement 2) associated with transcriptional elongation 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

## Sex-Dependent Genetic Architecture



**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  $G \times S$  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,  $G \times S$  interaction tests are ultimately necessary to identify significant

sex differences, and sex-stratified analyses may fail to detect or spuriously report differences.

$G \times S$  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  $G \times S$  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  $G \times S$  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  $G \times S$  interaction was obtained from gene-based analyses across disorders that detected a genome-wide significant  $G \times S$  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	<i>NKAIN2</i>	$3.19 \times 10^{-8}$ ( $4.67 \times 10^{-7}$ )	BIP	SCZ	$1.34 \times 10^{-7}$	$1.12 \times 10^{-2}$	2.0 (1.52–2.51)	0.79 (0.65–0.95)	$8.10 \times 10^{-2}$	1.12 (1.11–1.13)
rs12141273	1	110079143	A/G	0.067	Intergenic	<i>AMIGO1</i> (26.8); <i>GPR61</i> (3.3)	$4.16 \times 10^{-7}$ ( $1.95 \times 10^{-6}$ )	BIP	MDD	$1.60 \times 10^{-4}$	$1.40 \times 10^{-4}$	1.3 (1.14–1.50)	0.81 (0.73–0.90)	$2.03 \times 10^{-1}$	0.96 (0.95–0.96)
rs431414	15	59147800	T/C	0.181	UTR3	<i>MINDY2</i>	$4.60 \times 10^{-7}$ ( $4.36 \times 10^{-7}$ )	SCZ	BIP	$1.62 \times 10^{-7}$	$1.53 \times 10^{-1}$	1.2 (1.14–1.34)	0.91 (0.80–1.04)	$1.67 \times 10^{-2}$	1.07 (1.07–1.07)
SCZ-BIP-MDD (European+East Asian)															
rs117780815	6	124326227	T/A	0.036	Intronic	<i>NKAIN2</i>	$2.84 \times 10^{-8}$ ( $5.90 \times 10^{-7}$ )	BIP	SCZ	$1.34 \times 10^{-7}$	$9.89 \times 10^{-3}$	2.0 (1.52–2.51)	0.79 (0.65–0.94)	$9.46 \times 10^{-2}$	1.11 (1.10–1.12)
rs12141273	1	110079143	A/G	0.067	Intergenic	<i>AMIGO1</i> (26.8); <i>GPR61</i> (3.3)	$4.16 \times 10^{-7}$ ( $1.95 \times 10^{-6}$ )	BIP	MDD	$1.60 \times 10^{-4}$	$1.40 \times 10^{-4}$	1.3 (1.14–1.50)	0.81 (0.73–0.90)	$2.03 \times 10^{-1}$	0.96 (0.95–0.96)
rs35477914	15	59197669	T/A	0.193	Intronic	<i>SLTM</i>	$8.54 \times 10^{-7}$ ( $1.73 \times 10^{-6}$ )	BIP; MDD	SCZ	$1.30 \times 10^{-2}$	$3.60 \times 10^{-6}$	1.1 (1.01–1.14)	0.86 (0.80–0.92)	$4.84 \times 10^{-1}$	0.99 (0.98–0.99)
SCZ-BIP-Recurrent MDD (European Only)															
rs117780815	6	124326227	T/A	0.036	Intronic	<i>NKAIN2</i>	$3.17 \times 10^{-8}$ ( $1.69 \times 10^{-7}$ )	BIP	SCZ	$1.33 \times 10^{-7}$	$1.12 \times 10^{-2}$	2.0 (1.52–2.51)	0.79 (0.65–0.95)	$1.58 \times 10^{-1}$	1.10 (1.09–1.11)
rs431414	15	59147800	T/C	0.182	UTR3	<i>MINDY2</i>	$4.58 \times 10^{-7}$ ( $4.34 \times 10^{-7}$ )	SCZ	BIP	$1.62 \times 10^{-7}$	$1.53 \times 10^{-1}$	1.2 (1.14–1.34)	0.91 (0.80–1.04)	$7.27 \times 10^{-3}$	1.08 (1.08–1.09)
SCZ-BIP-Recurrent MDD (European+East Asian)															
rs117780815	6	124326227	T/A	0.036	Intronic	<i>NKAIN2</i>	$2.82 \times 10^{-8}$ ( $2.14 \times 10^{-7}$ )	BIP	SCZ	$1.33 \times 10^{-7}$	$9.88 \times 10^{-3}$	2.0 (1.52–2.51)	0.79 (0.65–0.94)	$1.81 \times 10^{-1}$	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 <sub>ext</sub> )	CAVIAR: PP causal (PP <sub>ext</sub> )	Compartment	Gene	CHR	BP	A1/A2	MAF	Beta	SE	z
rs117780815	rs117780815	1 (1)	0.83 (0.88)	Intronic	<i>NKAIN2</i>	6	124326227	T/A	0.04	0.670	0.127	5.27
rs117780815	rs4574657	1 (1)	$5.9 \times 10^{-3}$ ( $7.2 \times 10^{-3}$ )	Intronic	<i>NKAIN2</i>	6	124319710	A/G	0.04	0.283	0.089	3.17
rs117780815	rs4895382	1 (1)	$8.0 \times 10^{-2}$ ( $7.8 \times 10^{-3}$ )	Intronic	<i>NKAIN2</i>	6	124312658	G/A	0.02	0.736	0.171	4.29
rs117780815	rs73557075	1 (1)	$1.4 \times 10^{-2}$ ( $5.6 \times 10^{-3}$ )	Intronic	<i>NKAIN2</i>	6	124313730	A/G	0.04	0.195	0.114	1.71
rs117780815	rs7748718	$6.7 \times 10^{-2}$ ( $3.5 \times 10^{-2}$ )	$8.8 \times 10^{-3}$ ( $1.6 \times 10^{-2}$ )	Intronic	<i>NKAIN2</i>	6	124317132	C/A	0.05	0.358	0.108	3.33
rs117780815	rs7754419	$2.9 \times 10^{-2}$ ( $5.4 \times 10^{-1}$ )	$6.1 \times 10^{-2}$ ( $1.6 \times 10^{-1}$ )	Intronic	<i>NKAIN2</i>	6	124318348	G/A	0.04	0.541	0.118	4.58
rs117780815	rs7761506	$3.7 \times 10^{-2}$ ( $4.8 \times 10^{-5}$ )	$6.8 \times 10^{-3}$ ( $7.2 \times 10^{-3}$ )	Intronic	<i>NKAIN2</i>	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<sub>(ext)</sub>, 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/β-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<sub>B</sub> (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<sub>B</sub> 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

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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

From the Department of Psychiatry and Neuropsychology (GAMB), School for Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht; University Medical Center Utrecht (RAO), Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, Utrecht; Department of Biological Psychology/Netherlands Twin Register (DIB, J-JH, EJCG, GW), Vrije Universiteit Amsterdam; Amsterdam Public Health Research Institute (DIB, J-JH, EJCG, GW), Amsterdam UMC; Department of Psychiatry (BWJHP, YM), Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam; and Child and Adolescent Psychiatry (HT), Erasmus Medical Center, Rotterdam, the Netherlands; Psychiatric and Neurodevelopmental Genetics Unit (GAMB, C-YC, AP, RHP, TLP, JWS), Department of Psychiatry and Center for Genomic Medicine, Massachusetts General Hospital; Department of Psychiatry (GAMB, RHP, TLP, JWS), Harvard Medical School, Boston; Stanley Center for Psychiatric Research (GAMB, CC, TE, AP, RHP, TLP, JWS), Broad Institute of MIT and Harvard, Cambridge; Biogen Inc. (C-YC), Cambridge; and Innovation Center on Sex Differences in Medicine (ICON) (ST, RH, JMG), Massachusetts General Hospital, Boston; Broad Institute of MIT and Harvard (TE, LM), Cambridge; Medical and Population Genetics (TE, EAS), Broad Institute of MIT and Harvard, Cambridge; Concert Pharmaceuticals, Inc. (TLP), Lexington; Department of Psychiatry and Vincent Department of Obstetrics, Gynecology & Reproductive Biology (JMG), Massachusetts General Hospital, Boston; MGH-MIT-HMS Athinoula A. Martinos Center for Biomedical Imaging (JMG), Charlestown; Departments of Psychiatry and Medicine (JMG), Harvard Medical School, Boston, Massachusetts; Departments of Neurology and Genetics (CC), Yale School of Medicine, New Haven, Connecticut; Department of Biomedical Sciences (ST, RH), Colorado State University, Fort Collins, Colorado; The Feinstein Institute for Medical Research (TL, AKM), Manhasset; The Zucker School of Medicine at Hofstra/Northwell (TL, AKM), Hempstead; The Zucker Hillside Hospital (TL, AKM), Glen Oaks; Departments of Human Genetics and Neuroscience (JDB),

Department of Psychiatry (JDB, EAS, NM), Department of Genetics and Genomic Sciences (EAS, NM), and Friedman Brain Institute (JDB), Icahn School of Medicine at Mount Sinai, New York; Institute for Genomic Health (MTP), SUNY Downstate Medical Center College of Medicine, Brooklyn; Department of Psychiatry and Behavioral Sciences (TGS), SUNY Upstate Medical University, Syracuse; Department of Psychiatry (MMW), Columbia University College of Physicians and Surgeons, New York; and Division of Translational Epidemiology (MMW), New York State Psychiatric Institute, New York, New York; Departments of Genetics and Psychiatry (PFS), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Virginia Institute for Psychiatric and Behavioral Genetics (BPR), Departments of Psychiatry and Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia; Lieber Institute for Brain Development (DRW), Baltimore; Departments of Psychiatry, Neurology, Neuroscience and Institute of Genetic Medicine (DRW), and Department of Psychiatry and Behavioral Sciences (TGS), Johns Hopkins University School of Medicine, Baltimore; and Division of Cancer Epidemiology and Genetics (JS), National Cancer Institute, Bethesda, Maryland; Department of Psychiatry and Behavioral Neuroscience (PVG, ARS), University of Chicago, Chicago; and Department of Psychiatry and Behavioral Sciences (PVG, ARS), North Shore University Health System, Evanston, Illinois; Department of Psychiatry and Zilkha Neurogenetics Institute (MTP), Keck School of Medicine at University of Southern California, Los Angeles; Department of Human Genetics (RAO), David Geffen School of Medicine, and Center for Neurobehavioral Genetics (RAO), Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles; Department of Psychiatry (JK), University of California San Diego, La Jolla; Psychiatry & Behavioral Sciences (DLF), Stanford University, Stanford; Psychiatry & The Behavioral Sciences (JAK), University of Southern California, Los Angeles; and Kaiser Permanente Northern California (SPH), San Francisco, California; Department of Health Sciences Research (JMB) and Department of Psychiatry & Psychology (MF), Mayo Clinic, Rochester, Minnesota; Research Institute (SLM), Lindner Center of HOPE, Mason, Ohio; Center for Statistical Genetics and Department of Biostatistics (LJS), University of Michigan, Ann Arbor, Michigan; Department of Psychiatry (JBP), University of Iowa, Iowa City, Iowa; Department of Biomedicine (JG, TDA, ADB), Centre for Integrative Sequencing (iSEQ) (PBMo), National Centre for Register-Based Research (NCCR) (PBMo), and Centre for Integrated Register-based Research (CIRRAU) (PBMo), Aarhus University, Aarhus; The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) (JG, DMH, MN, OM, PBMo, TDA, ADB), Copenhagen; Center for Genome Analysis and Personalized Medicine (JG, TDA, ADB), Aarhus; Bioinformatics Research Centre (BIRC) (JG), Aarhus; Center for Neonatal Screening (DMH), Department for Congenital Disorders, Statens Serum Institut, Copenhagen; Copenhagen Mental Health Center (MN), Mental Health Services Capital Region of Denmark Copenhagen, Copenhagen; Department of Clinical Medicine (MN, TW), Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen; Psychosis Research Unit (OM), Aarhus University Hospital, Risskov; and Institute of Biological Psychiatry (TW), Mental Health Center Sct. Hans, Mental Health Services Copenhagen, Roskilde, Denmark; University of Aberdeen (DSC), Institute of Medical Sciences, Aberdeen; MRC Centre for Neuropsychiatric Genetics and Genomics (GK, MLH), Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff; Mental Health Neuroscience Research Department (EB), Division of Psychiatry, Faculty of Brain Sciences, University College London, London; Institute of Psychiatry (RMM), Social, Genetic and Developmental Psychiatry Centre (NM), NIHR Maudsley Biomedical Research Centre (GB), and Department of Medical & Molecular Genetics (CML), King's College London, London; Molecular Psychiatry Laboratory (AM, NJB), Division of Psychiatry, University College London, London; University of Liverpool (BM-M), Liverpool; Centre for Affective Disorders (BE), Institute of Psychiatry, Psychology and Neuroscience, London; and Division of Psychiatry (MJA, AMM) and Centre for Cognitive Ageing and Cognitive Epidemiology (AMM), University of Edinburgh, Edinburgh, United Kingdom; Queensland Brain Institute (BJM, SP), Queensland Centre for Mental Health Research (BJM), and School of Psychology (NGM), University of Queensland, Brisbane; Genetics and Computational Biology (NGM), QIMR Berghofer Medical Research Institute, Brisbane; School of Psychology and Counseling (DM), Queensland University of Technology, Brisbane; Queensland Centre for Mental Health



Research (SP), The Park - Centre for Mental Health, Wacol, Queensland; Schizophrenia Research Institute (MJC), Sydney; School of Biomedical Sciences and Pharmacy (MJC, PAT, JQW), University of Newcastle, Callaghan; Priority Centre for Translational Neuroscience and Mental Health (MJC, PAT, BKe), University of Newcastle, Newcastle; Schizophrenia Research Institute (PAT, JQW), Sydney; Neuroscience Research Australia (JMF, PRS), Sydney; School of Medical Sciences (JMF, PRS) and School of Psychiatry (PBMi), University of New South Wales, Sydney, New South Wales; Department of Psychiatry (BTB), Melbourne Medical School, University of Melbourne, Melbourne; Florey Institute for Neuroscience and Mental Health (BTB), University of Melbourne, Parkville, Victoria; and Discipline of Psychiatry (TA), The University of Adelaide, Adelaide, South Australia, Australia; Department of Medical Epidemiology and Biostatistics (PFS, MLa, PKEM, AV), Karolinska Institutet, Stockholm; Department of Clinical Neuroscience (EGJ), Psychiatry Section, Karolinska Institutet, Stockholm; Department of Clinical Sciences (RA), Psychiatry, Umeå University Medical Faculty, Umeå; and Institute of Neuroscience and Physiology (MLa), the Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden; Neuropsychiatric Genetics Research Group (AC), Department of Psychiatry, Trinity College Dublin, Dublin, Ireland; Institute of Genomics (TE, LM), University of Tartu, Tartu, Estonia; Norwegian Centre for Mental Disorders Research (NORMENT) (EGJ), KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo; Norwegian Centre for Mental Disorders Research (NORMENT) (IM, OBS, OAA), Institute of Clinical Medicine, University of Oslo and Division of Mental Health and Addiction, Oslo University Hospital, Oslo; Center for Psychopharmacology (EM), Diakonhjemmet Hospital, Oslo; Department of Pharmaceutical Biosciences (EM), School of Pharmacy, University of Oslo, Oslo; Department of Medical Genetics (SD), Oslo University Hospital, Oslo; NORMENT Centre (SD), Department of Clinical Science, University of Bergen, Bergen; Department of Mental Health (AEV), Norwegian University of Science and Technology - NTNU, Trondheim; and Department of Psychiatry (AEV), St Olavs' University Hospital, Trondheim, Norway; Institute for Molecular Medicine Finland (FIMM) (AP), University of Helsinki, Helsinki, Finland; Department of Clinical Neuroscience (HE, MB, AS-K), Max Planck Institute of Experimental Medicine, Göttingen; Department of Psychiatry (DR, IG, BKO, AMH), University of Halle, Halle; Department of Psychiatry (DR, IG), University of Munich, Munich; Centre for Human Genetics (AJF), University of Marburg, Marburg; Institute of Human Genetics (AJF, FD, SC, MMN), University of Bonn, School of Medicine & University Hospital Bonn, Bonn; Department of Child and Adolescent Psychiatry (FD), Psychosomatics and Psychotherapy, University Hospital Essen, University of Duisburg-Essen, Duisburg; Institute of Psychiatric Phenomics and Genomics (IPPG) (SS, ALC, TGS), University Hospital, LMU Munich, Munich; International Max Planck Research School for Translational Psychiatry (IMPRS-TP) (ALC), Munich; Department of Psychiatry (AR), Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main; Department of Genetic Epidemiology in Psychiatry (FL, LS, TGS, MR), Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim; Institute of Neuroscience and Medicine (INM-1) (SC), Research Centre Jülich, Jülich; Department of Translational Research in Psychiatry (BM-M, SL), Max Planck Institute of Psychiatry, Munich; Munich Cluster for Systems Neurology (SyNergy) (BM-M), Munich; Department of Psychiatry and Psychotherapy (TGS), University Medical Center Göttingen, Göttingen; Department of Psychiatry (BTB), University of Münster, Münster; Max Planck Institute of Psychiatry (SL), Munich; and Department of Psychiatry and Psychotherapy (HJG, SVA), Institute of Community Medicine (AT), and Interfaculty Institute for Genetics and Functional Genomics (UV), University Medicine Greifswald, Greifswald, Germany; Department of Psychiatry (PCS) and State Key Laboratory for Brain and Cognitive Sciences (PCS), Li Ka Shing Faculty of Medicine, and Centre for Genetic Sciences (PCS), The University of Hong Kong, Hong Kong, SAR China; Department of Psychiatry (NI), Fujita Health University School of Medicine, Toyooka, Aichi, Japan; Research Division and Department of General Psychiatry (JLe), Institute of Mental Health, Singapore; Duke-National University of Singapore Graduate Medical School (JLe), Singapore; ISGlobal (MK), Barcelona; and Mental Health Department (JG-P, FM), University Regional Hospital, Biomedical Research Institute of Málaga (IBIMA), Málaga, Spain; Department of Biomedicine (SC), University of Basel, Basel; Institute of Medical Genetics and Pathology (SC), University Hospital

Basel, Basel; and Department of Psychiatry (MP), Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; Biometric Psychiatric Genetics Research Unit (MG-S), Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania; Department of Psychiatry (JH), Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan; Cancer Epidemiology and Prevention (JLI), M. Skłodowska-Curie National Research Institute of Oncology, Warsaw; and Department of Environmental Epidemiology (BS), Nofer Institute of Occupational Medicine, Lodz, Poland; Faculté de Médecine (MLE, SJ), Université Paris Est, Créteil; Department of Psychiatry and Addiction Medicine (MLE, BE, FB), Assistance Publique - Hôpitaux de Paris, Paris; Institut national de la santé et de la recherche médicale (INSERM) (MLE), Paris; INSERM U955 (SJ), Psychiatrie Translationnelle, Créteil; UMR-S1144 Team 1 Biomarkers of relapse and therapeutic response in addiction and mood disorders (BE, FB), INSERM, Paris; Psychiatry (BE, FB), Université Paris Diderot, Paris; and Paris Bipolar and TRD Expert Centres (FB), FondaMental Foundation, Paris, France; Centre for Addiction and Mental Health (JBV), Toronto, Ontario; Department of Psychiatry (MA, CO, RU), Dalhousie University, Halifax, Nova Scotia; and Department of Psychiatry (PC), Mood Disorders Program, McGill University Health Center, Montréal, Québec, Canada; and National Institute of Mental Health (MA), Klecany, Czech Republic.

See below for a full membership list and [Supplement 1](#) for member affiliations of Psychiatric Genomics Consortium and iPSYCH.

**Schizophrenia Working Group of the Psychiatric Genomics Consortium:** Stephan Ripke, Benjamin M. Neale, Aiden Corvin, James T.R. Walters, Kai-How Farh, Peter A. Holmans, Phil Lee, Brendan Bulik-Sullivan, David A. Collier, Hailiang Huang, Tune H. Pers, Ingrid Agartz, Esben Agerbo, Margot Albus, Madeline Alexander, Farooq Amin, Silviu A. Bacanu, Martin Begemann, Richard A. Belliveau Jr, Judit Bene, Sarah E. Bergen, Elizabeth Bevilacqua, Tim B. Bigdeli, Donald W. Black, Richard Bruggeman, Nancy G. Buccola, Randy L. Buckner, William Byerley, Wiepke Cahn, Guiqing Cai, Dominique Campion, Rita M. Cantor, Vaughan J. Carr, Noa Carrera, Stanley V. Catts, Kimberly D. Chambert, Raymond C.K. Chan, Ronald Y.L. Chen, Eric Y.H. Chen, Wei Cheng, Eric F.C. Cheung, Siow Ann Chong, C. Robert Cloninger, David Cohen, Nadine Cohen, Paul Cormican, Nick Craddock, James J. Crowley, David Curtis, Michael Davidson, Kenneth L. Davis, Franziska Degenhardt, Jurgen Del Favero, Ditte Demontis, Dimitris Dikeos, Timothy Dinan, Srđjan Djurovic, Gary Donohoe, Elodie Drøge, Jubao Duan, Frank Dudbridge, Naser Durmishi, Peter Eichhammer, Johan Eriksson, Valentina Escott-Price, Laurent Essioux, Ayman H. Fanous, Marttila S. Farrell, Josef Frank, Lude Franke, Robert Freedman, Nelson B. Freimer, Marion Friedl, Joseph I. Friedman, Menachem Fromer, Giulio Genovese, Lyudmila Georgieva, Ina Giegling, Paola Giusti-Rodríguez, Stephanie Godard, Jacqueline I. Goldstein, Vera Golimbet, Srihari Gopal, Jacob Gratten, Lieuwe de Haan, Christian Hammer, Marian L. Hamshere, Mark Hansen, Juha Karjalainen, Vahram Haroutunian, Annette M. Hartmann, Frans A. Henskens, Stefan Herms, Joel N. Hirschhorn, Per Hoffmann, Andrea Hofman, Mads V. Hollegaard, David M. Hougaard, Masashi Ikeda, Inge Joa, Antonio Juliá, René S. Kahn, Luba Kalaydjieva, Sena Karachanak-Yankova, Juha Karjalainen, David Kavanagh, Matthew K. Keller, James L. Kennedy, Andrey Khrunin, Yunjung Kim, Janis Klovins, James A. Knowles, Bettina Konte, Vaidutis Kucinskas, Zita Ausrele Kucinskiene, Hana Kuzelova-Ptackova, Anna K. Kähler, Claudine Laurent, Jimmy Lee Chee Keong, S. Hong Lee, Sophie E. Legge, Bernard Lerer, Miaoxin Li, Tao Li, Kung-Yee Liang, Jeffrey Lieberman, Svetlana Limborska, Carmel M. Loughland, Jan Lubinski, Jouko Lönnqvist, Milan Macek Jr, Patrik K.E. Magnusson, Brion S. Maher, Wolfgang Maier, Jacques Mallet, Sara Marsal, Manuel Mattheisen, Morten Matingsdal, Robert W. McCauley, Colm McDonald, Andrew M. McIntosh, Sandra Meier, Carin J. Meijer, Bela Meleg, Ingrid Melle, Raquelle I. Meshulam-Gately, Andres Metspalu, Patricia T. Michie, Lili Milani, Viha Milanova, Younes Mokrab, Derek W. Morris, Ole Mors, Kieran C. Murphy, Robin M. Murray, Inez Myin-Germeys, Bertram Müller-Myhsok, Mari Nelis, Igor Nenadic, Deborah A. Nertney, Gerald Nestadt, Kristin K. Nicodemus, Liene Nikitina-Zake, Laura Nisenbaum, Annelie Nordin, Eadhbhard O'Callaghan, Colm O'Dushlaine, F. Anthony O'Neill, Sang-Yun Oh, Ann Olincy, Line Olsen, Jim Van Os, Psychosis Endophenotypes International Consortium, Christos Pantelis, George N. Papadimitriou, Sergi Papiol, Elena Parkhomenko, Michele T. Pato, Tiina Paunio, Milica Pejovic-Milovancevic, Diana O. Perkins, Olli Pietiläinen, Jonathan Pimm, Andrew J. Pocklington, John

## Sex-Dependent Genetic Architecture

Powell, Alkes Price, Ann E. Pulver, Shaun M. Purcell, Digby Quedsted, Henrik B. Rasmussen, Abraham Reichenberg, Mark A. Reimers, Alexander L. Richards, Joshua L. Roffman, Panos Roussos, Douglas M. Ruderfer, Veikko Salomaa, Alan R. Sanders, Ulrich Schall, Christian R. Schubert, Thomas G. Schulze, Sibylle G. Schwab, Edward M. Scolnick, Rodney J. Scott, Larry J. Seidman†, Jianxin Shi, Engilbert Sigurdsson, Teimuraz Silagadze, Jeremy M. Silverman, Kang Sim, Petr Slominsky, Jordan W. Smoller, Hon-Cheong So, Chris C.A. Spencer, Eli A. Stahl, Hreinn Stefansson, Stacy Steinberg, Elisabeth Stogmann, Richard E. Straub, Eric Strengman, Jana Strohmaier, T. Scott Stroup, Mythily Subramaniam, Jaana Suvisaari, Dragan M. Svrakic, Jin P. Szatkiewicz, Erik Söderman, Srinivas Thirumalai, Draga Toncheva, Sarah Tosato, Juha Veijola, John Waddington, Dermot Walsh, Dai Wang, Qiang Wang, Bradley T. Webb, Mark Weiser, Dieter B. Wildenauer, Nigel M. Williams, Stephanie Williams, Stephanie H. Witt, Aaron R. Wolen, Emily H.M. Wong, Brandon K. Wormley, Hualin Simon Xi, Clement C. Zai, Xuebin Zheng, Fritz Zimprich, Naomi R. Wray, Kari Stefansson, Peter M. Visscher, Wellcome Trust Case-Control Consortium, Rolf Adolfsson, Ole A. Andreassen, Douglas H.R. Blackwood, Elvira Bramon, Joseph D. Buxbaum, Anders D. Børglum, Sven Cichon, Ariel Darvasi†, Enrico Domenici, Hannelore Ehrenreich, Tõnu Esko, Pablo V. Gejman, Michael Gill, Hugh Gurling, Christina M. Hultman, Nakao Iwata, Assen V. Jablensky, Erik G. Jönsson, Kenneth S. Kendler, George Kirov, Jo Knight, Todd Lencz, Douglas F. Levinson, Qingqin S. Li, Jianjun Liu, Anil K. Malhotra, Steven A. McCarroll, Andrew McQuillin, Jennifer L. Moran, Preben B. Mortensen, Sathish Periyasamy, Murray J. Cairns, Paul A. Tooney, Jing Qin Wu, Brian Kelly, Bryan J. Mowry, Markus M. Nöthen, Rolf A. Ophoff, Michael J. Owen, Aarno Palotie, Carlos N. Pato, Tracey L. Petryshen, Danielle Posthuma, Marcella Rietschel, Brien P. Riley, Dan Rujescu, Pak C. Sham, Pamela Sklar, David St Clair, Daniel R. Weinberger, Jens R. Wendland, Thomas Werge, Mark J. Daly, Patrick F. Sullivan, Michael C. O'Donovan.

Wellcome Trust Case-Control Consortium: *Management Committee*: Peter Donnelly, Ines Barroso, Jenefer M. Blackwell, Elvira Bramon, Matthew A. Brown, Juan P. Casas, Aiden Corvin, Panos Deloukas, Audrey Duncanson, Janusz Jankowski, Hugh S. Markus, Christopher G. Mathew, Colin N.A. Palmer, Robert Plomin, Anna Rautanen, Stephen J. Sawcer, Richard C. Trembath, Ananth C. Viswanathan, Nicholas W. Wood. *Data and Analysis Group*: Chris C.A. Spencer, Gavin Band, Céline Bellenguez, Peter Donnelly, Colin Freeman, Eleni Giannoulatou, Garrett Hellenthal, Richard Pearson, Matti Pirinen, Amy Strange, Zhan Su, Damjan Vukcevic. *DNA, Genotyping, Data QC, and Informatics*: Cordelia Langford, Ines Barroso, Hannah Blackburn, Suzannah J. Bumpstead, Panos Deloukas, Serge Dronov, Sarah Edkins, Matthew Gillman, Emma Gray, Rhian Gwilliam, Naomi Hammond, Sarah E. Hunt, Alagurevathi Jayakumar, Jennifer Liddle, Owen T. McCann, Simon C. Potter, Radhi Ravindrarajah, Michelle Ricketts, Avazeh Tashakkori-Ghanbaria, Matthew Waller, Paul Weston, Pamela Whittaker, Sara Widaa. *Publications Committee*: Christopher G. Mathew, Jenefer M. Blackwell, Matthew A. Brown, Aiden Corvin, Mark I. McCarthy, Chris C.A. Spencer.

Psychosis Endophenotype International Consortium: Maria J. Arranz, Steven Bakker, Stephan Bender, Elvira Bramon, David A. Collier, Benedicto Crespo-Facorro, Jeremy Hall, Conrad Iyegbe, Assen V. Jablensky, René S. Kahn, Luba Kalaydjieva, Stephen Lawrie, Cathryn M. Lewis, Kuang Lin, Don H. Linszen, Ignacio Mata, Andrew M. McIntosh, Robin M. Murray, Roel A. Ophoff, Jim Van Os, John Powell, Dan Rujescu, Muriel Walshe, Matthias Weisbrod, Durk Wiersma.

**Bipolar Disorder Working Group of the Psychiatric Genomics Consortium**: Eli A. Stahl, Jerome Breen, Andreas J. Forstner, Andrew McQuillin, Stephan Ripke, Vassily Trubetskoy, Manuel Mattheisen, Yungpeng Wang, Jonathan R.I. Coleman, Hélène A. Gaspar, Christiaan A. de Leeuw, Stacy Steinberg, Jennifer M. Whitehead Pavlides, Maciej Trzaskowski, Enda M. Byrne, Tune H. Pers, Peter A. Holmans, Alexander L. Richards, Liam Abbott, Esben Agerbo, Huda Akil, Diego Albani, Ney Alliey-Rodriguez, Thomas D. Als, Adebayo Anjorin, Verner Antilla, Swapnil Awasthi, Judith A. Badner, Marie Bækvad-Hansen, Jack D. Barchas, Nicholas Bass, Michael Bauer, Richard Belliveau, Sarah E. Bergen, Carsten Bøcker Pedersen, Erlend Bøen, Marco P. Boks, James Boocock, Monika Budde, William Bunney, Margit Burmeister, Jonas Bybjerg-Grauholm, William Byerley, Miquel Casas, Felicia Cerrato, Pablo Cervantes, Kimberly Chambert, Alexander W. Charney, Danfeng Chen, Claire Churchhouse, Toni-Kim Clarke, William Coryell, David

W. Craig, Cristiana Cruceanu, David Curtis, Piotr M. Czerski, Anders M. Dale, Simone de Jong, Franziska Degenhardt, Jurgen Del-Favero, J. Raymond DePaulo, Srdjan Djurovic, Amanda L. Dobbyn, Ashley Dumont, Torbjørn Elvsåshagen, Valentina Escott-Price, Chun Chieh Fan, Sascha B. Fischer, Matthew Flickinger, Tatiana M. Foroud, Liz Forty, Josef Frank, Christine Fraser, Nelson B. Freimer, Katrin Gade, Diane Gage, Julie Garnham, Claudia Giambartolomei, Marianne Giørtz Pedersen, Jaqueline Goldstein, Scott D. Gordon, Katherine Gordon-Smith, Elaine K. Green, Melissa J. Green, Tiffany A. Greenwood, Jakob Grove, Weihua Guan, José Guzman-Parra, Marian L. Hamshere, Martin Hautzinger, Urs Heilbronner, Stefan Herms, Maria Hipolito, Per Hoffmann, Dominic Holland, Laura Huckins, Stéphane Jamain, Jessica S. Johnson, Radhika Kandaswamy, Robert Karlsson, James L. Kennedy, Sarah Kittel-Schneider, James A. Knowles, Manolis Kogevinas, Anna C. Koller, Ralph Kupka, Catharina Lavebratt, Jacob Lawrence, William B. Lawson, Markus Leber, Phil H. Lee, Shawn E. Levy, Jun Z. Li, Chunyu Liu, Susanne Lucae, Anna Maaser, Donald J. MacIntyre, Pamela B. Mahon, Wolfgang Maier, Lina Martinsson, Steve McCarroll, Peter McGuffin, Melvin G. McInnis, James D. McKay, Helena Medeiros, Sarah E. Medland, Fan Meng, Lili Milani, Grant W. Montgomery, Derek W. Morris, Thomas W. Mühleisen, Niamh Mullins, Hoang Nguyen, Caroline M. Nievergelt, Annelie Nordin Adolfsson, Evaristus A. Nwulia, Claire O'Donovan, Loes M. Olde Loohuis, Anil P.S. Ori, Lijijana Oruc, Urban Ösby, Roy H. Perlis, Amy Perry, Andrea Pfennig, James B. Potash, Shaun M. Purcell, Eline J. Regeer, Andreas Reif, Céline S. Reinbold, John P. Rice, Fabio Rivas, Margarita Rivera, Panos Roussos, Douglas M. Ruderfer, Euijung Ryu, Cristina Sánchez-Mora, Alan F. Schatzberg, William A. Scheftner, Nicholas J. Schork, Cynthia Shannon Weickert, Tatyana Shekhtman, Paul D. Shilling, Engilbert Sigurdsson, Claire Slaney, Olav B. Smeland, Janet L. Sobell, Christine Søholm Hansen, Anne T. Spijker, David St Clair, Michael Steffens, John S. Strauss, Fabian Streit, Jana Strohmaier, Szabolcs Szeinger, Robert C. Thompson, Thorgeir E. Thorgeirsson, Jens Treutlein, Helmut Vedder, Weiqing Wang, Stanley J. Watson, Thomas W. Weickert, Stephanie H. Witt, Simon Xi, Wei Xu, Allan H. Young, Peter Zandi, Peng Zhang, Sebastian Zöllner, eQTLGen Consortium, BIOS Consortium, Rolf Adolfsson, Ingrid Agartz, Martin Alda, Lena Backlund, Bernhard T. Baune, Frank Bellivier, Wade H. Berrettini, Joanna M. Biernacka, Douglas H.R. Blackwood, Michael Boehnke, Anders D. Børglum, Aiden Corvin, Nicholas Craddock, Mark J. Daly, Udo Dannlowski, Tõnu Esko, Bruno Etain, Mark Frye, Janice M. Fullerton, Elliot S. Gershon, Michael Gill, Fernando Goes, Maria Grigoriou-Serbanescu, Joanna Hauser, David M. Hougaard, Christina M. Hultman, Ian Jones, Lisa A. Jones, René S. Kahn, George Kirov, Mikael Landén, Marion Leboyer, Cathryn M. Lewis, Qingqin S. Li, Jolanta Lissowska, Nicholas G. Martin, Fermin Mayoral, Susan L. McElroy, Andrew M. McIntosh, Francis J. McMahon, Ingrid Melle, Andres Metspalu, Philip B. Mitchell, Gunnar Morken, Ole Mors, Preben B. Mortensen, Bertram Müller-Myhsok, Richard M. Myers, Benjamin M. Neale, Vishwajit Nimgaonkar, Merete Nordentoft, Markus M. Nöthen, Michael C. O'Donovan, Ketil J. Oedegaard, Michael J. Owen, Sara A. Paciga, Carlos Pato, Michele T. Pato, Danielle Posthuma, Josep Antoni Ramos-Quiroga, Marta Ribasés, Marcella Rietschel, Guy A. Rouleau, Martin Schalling, Peter R. Schofield, Thomas G. Schulze, Alessandro Serretti, Jordan W. Smoller, Hreinn Stefansson, Kari Stefansson, Eystein Stordal, Patrick F. Sullivan, Gustavo Turecki, Arne E. Vaaler, Eduard Vieta, John B. Vincent, Thomas Werge, John I. Nurnberger, Naomi R. Wray, Arianna Di Florio, Howard J. Edenberg, Sven Cichon, Roel A. Ophoff, Laura J. Scott, Ole A. Andreassen, John Kelsoe, Pamela Sklar†.

**Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium**: Naomi R. Wray, Stephan Ripke, Manuel Mattheisen, Maciej Trzaskowski, Enda M. Byrne, Abdel Abdellaoui, Mark J. Adams, Esben Agerbo, Tracy M. Air, Till F.M. Andlauer, Silviu-Alin Bacanu, Marie Bækvad-Hansen, Aartjan T.F. Beekman, Tim B. Bigdeli, Elisabeth B. Binder, Julien Bryois, Henriette N. Buttenshön, Jonas Bybjerg-Grauholm, Na Cai, Enrique Castela, Jane Hvarregaard Christensen, Toni-Kim Clarke, Jonathan R.I. Coleman, Lucia Colodro-Conde, Baptiste Couvy-Duchesne, Nick Craddock, Gregory E. Crawford, Gail Davies, Ian J. Deary, Franziska Degenhardt, Eske M. Derks, Nese Direk, Connor V. Dolan, Erin C. Dunn, Thalia C. Eley, Valentina Escott-Price, Farnush Farhadi Hassan Kia-deh, Hilary K. Finucane, Jerome C. Foo, Andreas J. Forstner, Josef Frank, Hélène A. Gaspar, Michael Gill, Fernando S. Goes, Scott D. Gordon, Jakob Grove, Lynsey S. Hall, Christine Søholm Hansen, Thomas F. Hansen, Stefan

Herns, Ian B. Hickie, Per Hoffmann, Georg Homuth, Carsten Horn, Jouke-Jan Hottenga, David M. Hougaard, David M. Howard, Marcus Ising, Rick Jansen, Ian Jones, Lisa A. Jones, Eric Jorgenson, James A. Knowles, Isaac S. Kohane, Julia Kraft, Warren W. Kretschmar, Zoltán Kutalik, Yihan Li, Penelope A. Lind, Donald J. MacIntyre, Dean F. MacKinnon, Robert M. Maier, Wolfgang Maier, Jonathan Marchini, Hamdi Mbarek, Patrick McGrath, Peter McGuffin, Sarah E. Medland, Divya Mehta, Christel M. Middeldorp, Evelin Mihailov, Yuri Milaneshi, Lili Milani, Francis M. Mondimore, Grant W. Montgomery, Sara Mostafavi, Niamh Mullins, Matthias Nauck, Bernard Ng, Michel G. Nivard, Dale R. Nyholt, Paul F. O'Reilly, Hogni Oskarsson, Michael J. Owen, Jodie N. Painter, Carsten Bøcker Pedersen, Marianne Giørtz Pedersen, Roseann E. Peterson, Wouter J. Peyrot, Giorgio Pistis, Danielle Posthuma, Jorge A. Quiroz, Per Qvist, John P. Rice, Brien P. Riley, Margarita Rivera, Saira Saeed Mirza, Robert Schoevers, Eva C. Schulte, Ling Shen, Jianxin Shi, Stanley I. Shyn, Engilbert Sigurdsson, Grant C.B. Sinnamon, Johannes H. Smit, Daniel J. Smith, Hreinn Stefansson, Stacy Steinberg, Fabian Streit, Jana Strohmaier, Katherine E. Tansey, Henning Teismann, Alexander Teumer, Wesley Thompson, Pippa A. Thomson, Thorgerir E. Thorgeirsson, Matthew Traylor, Jens Treutlein, Vassily Trubetsky, André G. Uitterlinden, Daniel Umrbricht, Sandra Van der Auwera, Albert M. van Hemert, Alexander Viktorin, Peter M. Visscher, Yunpeng Wang, Bradley T. Webb, Shantel Marie Weinsheimer, Jürgen Wellmann, Gonneke Willemsen, Stephanie H. Witt, Yang Wu, Hualin S. Xi, Jian Yang, Futao Zhang, Volker Aroitt, Bernhard T. Baune, Klaus Berger, Dorret I. Boomsma, Sven Cichon, Udo Dannlowski, Eco J.C. de Geus, J. Raymond DePaulo, Enrico Domenici, Katharina Domschke, Tõnu Esko, Hans J. Grabe, Steven P. Hamilton, Caroline Hayward, Andrew C. Heath, Kenneth S. Kendler, Stefan Kloiber, Glyn Lewis, Qingqin S. Li, Susanne Lucae, Pamela AF Madden, Patrik K. Magnusson, Nicholas G. Martin, Andrew M. McIntosh, Andres Metspalu, Ole Mors, Preben Bo Mortensen, Bertram Müller-Myhsok, Merete Nordentoft, Markus M. Nöthen, Michael C. O'Donovan, Sara A. Paciga, Nancy L. Pedersen, Brenda W.J.H. Penninx, Roy H. Perlis, David J. Porteous, James B. Potash, Martin Preisig, Marcella Rietschel, Catherine Schaefer, Thomas G. Schulze, Jordan W. Smoller, Kari Stefansson, Henning Tiemeier, Rudolf Uher, Henry Völzke, Myrna M. Weissman, Thomas Werge, Cathryn M. Lewis, Douglas F. Levinson, Gerome Breen, Anders D. Børglum, Patrick F. Sullivan.

† Deceased

**Sex Differences Cross-Disorder Analysis Group of the Psychiatric Genomics Consortium:** Martin Alda, Gabriëlla A.M. Blokland, Anders D. Børglum, Marco Bortolato, Janita Bralten, Gerome Breen, Cynthia M. Bulik, Christie L. Burton, Enda M. Byrne, Caitlin E. Carey, Jonathan R.I. Coleman, Lea K. Davis, Ditte Demontis, Laramie E. Duncan, Howard J. Edenberg, Lauren Erdman, Stephen V. Faraone, Jill M. Goldstein, Slavina B. Goleva, Jakob Grove, Wei Guo, Christopher Hübel, Laura M. Huckins, Ekaterina A. Khrantsova, Phil H. Lee, Joanna Martin, Carol A. Mathews, Manuel Mattheisen, Benjamin M. Neale, Roseann E. Peterson, Tracey L. Petryshen, Elise Robinson, Jordan W. Smoller, Eli Stahl, Barbara E. Stranger, Michela Traglia, Raymond K. Walters, Lauren A. Weiss, Thomas Werge, Stacey J. Winham, Naomi R. Wray, Yin Yao.

**iPSYCH: Management Group:** Anders D. Børglum, David M. Hougaard, Merete Nordentoft, Ole Mors, Preben Bo Mortensen, Thomas Werge, Kristjar Skajaa. *Advisory Board:* Markus Nöthen, Michael Owen, Robert H. Yolken, Niels Plath, Jonathan Mill, Daniel Geschwind.

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Work for this study by GAMB, C-YC, and TLP was primarily conducted at the Department of Psychiatry and Center for Genomic Medicine, Massachusetts General Hospital, Boston, Massachusetts (GAMB, C-YC, and TLP) and the Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands (GAMB).

Address correspondence to Gabriëlla A.M. Blokland, Ph.D., at [gamb.blokland@maastrichtuniversity.nl](mailto:gamb.blokland@maastrichtuniversity.nl), or Jill M. Goldstein, Ph.D., at [jill\\_goldstein@hms.harvard.edu](mailto:jill_goldstein@hms.harvard.edu).

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