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**Genome wide meta-analysis identifies genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders.**  
Cross-Disorder Group of the Psychiatric Genomics Consortium\*

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## **Summary**

Genetic influences on psychiatric disorders transcend diagnostic boundaries, suggesting substantial pleiotropy of contributing loci. However, the nature and mechanisms of these pleiotropic effects remain unclear. We performed a meta-analysis of 232,964 cases and 494,162 controls from genome-wide studies of anorexia nervosa, attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar disorder, major depression, obsessive-compulsive disorder, schizophrenia, and Tourette syndrome. Genetic correlation analyses revealed a meaningful structure within the eight disorders identifying three groups of inter-related disorders. We detected 109 loci associated with at least two psychiatric disorders, including 23 loci with pleiotropic effects on four or more disorders and 11 loci with antagonistic effects on multiple disorders. The pleiotropic loci are located within genes that are disproportionately expressed in the brain throughout the lifespan, beginning in the second trimester prenatally, and play prominent roles in a suite of neurodevelopmental processes. These findings have important implications for psychiatric nosology, drug development, and risk prediction.

## **Keywords**

Psychiatric genetics, cross-disorder genetics, psychiatric disorders, pleiotropy, neurodevelopment, GWAS, genetic correlation, gene expression

## Introduction

Psychiatric disorders affect more than 25% of the population in any given year and are a leading cause of worldwide disability (Disease et al., 2017; Kessler and Wang, 2008). The substantial influence of genetic variation on risk for a broad range of psychiatric disorders has been established by both twin and, more recently, large-scale genomic studies (Smoller et al., 2018). Psychiatric disorders are highly polygenic, with a large proportion of heritability contributed by common variation. Many risk loci have emerged from genome-wide association studies (GWAS) of, among others, schizophrenia (SCZ), bipolar disorder (BIP), major depression (MD), and attention-deficit/hyperactivity disorder (ADHD) from the Psychiatric Genomics Consortium (PGC) and other efforts (Sullivan et al., 2018). These studies have revealed a surprising degree of genetic overlap among psychiatric disorders (Brainstorm et al., 2018). Elucidating the extent and biological significance of cross-disorder genetic influences has implications for psychiatric nosology, drug development, and risk prediction. In addition, characterizing the functional genomics of cross-phenotype genetic effects may reveal fundamental properties of pleiotropic loci that differentiate them from disorder-specific loci, and help identify targets for diagnostics and therapeutics.

In 2013, analyses by the PGC's Cross-Disorder Workgroup identified loci with pleiotropic effects across five disorders: autism spectrum disorder (ASD), ADHD, SCZ, BIP, and MD in a sample comprising 33,332 cases and 27,888 controls (Smoller, 2013 #11061). In the current study, we examined pleiotropic effects in a greatly expanded dataset, encompassing 232,964 cases and 494,162 controls, that included three additional psychiatric disorders: Tourette syndrome (TS), obsessive-compulsive disorder (OCD), and anorexia nervosa (AN). We address four major questions regarding the shared genetic basis of these eight disorders: 1) Can we identify a shared etiologic structure within the broad range of these clinically distinct psychiatric disorders? 2) Can we detect additional loci associated with risk for multiple disorders (pleiotropic loci)? 3) Do some of these risk loci have opposite allelic effects across disorders? and 4) Can we identify functional features of the pleiotropic loci that could account for their broad effects on psychopathology?

## Results

We analyzed genome-wide single nucleotide polymorphism (SNP) data for eight neuropsychiatric disorders using a combined sample of 232,964 cases and 494,162 controls (**Table 1; Supplementary Table 1**). The eight disorders included AN (Duncan, 2017 #12578}, ASD (Grove et al., 2017), ADHD (Demontis et al., 2018), BIP (Stahl et al., 2018), MD (Wray et al., 2018), OCD (International Obsessive Compulsive Disorder Foundation Genetics and Studies, 2018), TS (Yu et al., In press.), and SCZ

(Schizophrenia Working Group of the Psychiatric Genomics, 2014). All study participants were of self-identified European ancestry, which was supported by principal component analysis of genome-wide data.

**Table 1. Summary of eight neuropsychiatric disorder datasets**

Disorder	Cases	Controls	Total Samples	Population prevalence (k)	Liability-based SNP heritability (SE)	References
<b>ADHD</b>	19,099	34,194	53,293	0.05	0.222 (0.014)	Demontis et al. 2018
<b>AN</b>	3,495	10,983	14,478	0.01	0.195 (0.029)	Duncan et al. 2017
<b>ASD</b>	18,381	27,969	46,350	0.01	0.113 (0.010)	Grove et al. 2017
<b>BIP</b>	20,352	31,358	51,710	0.01	0.182 (0.011)	Stahl et al. 2018
<b>MD</b>	130,664	330,470	461,134	0.15	0.085 (0.004)	Wray et al. 2018
<b>OCD</b>	2,688	7,037	9,725	0.025	0.280 (0.041)	IOCDF-GC and OCGAS
<b>SCZ</b>	33,640	43,456	77,096	0.01	0.222 (0.012)	Schizophrenia Working Group of PGC. 2014
<b>TS</b>	4,645	8,695	13,340	0.008	0.200 (0.026)	Yu et al. 2018
<b>Total</b>	<b>232,964</b>	<b>494,162</b>	<b>727,126</b>			

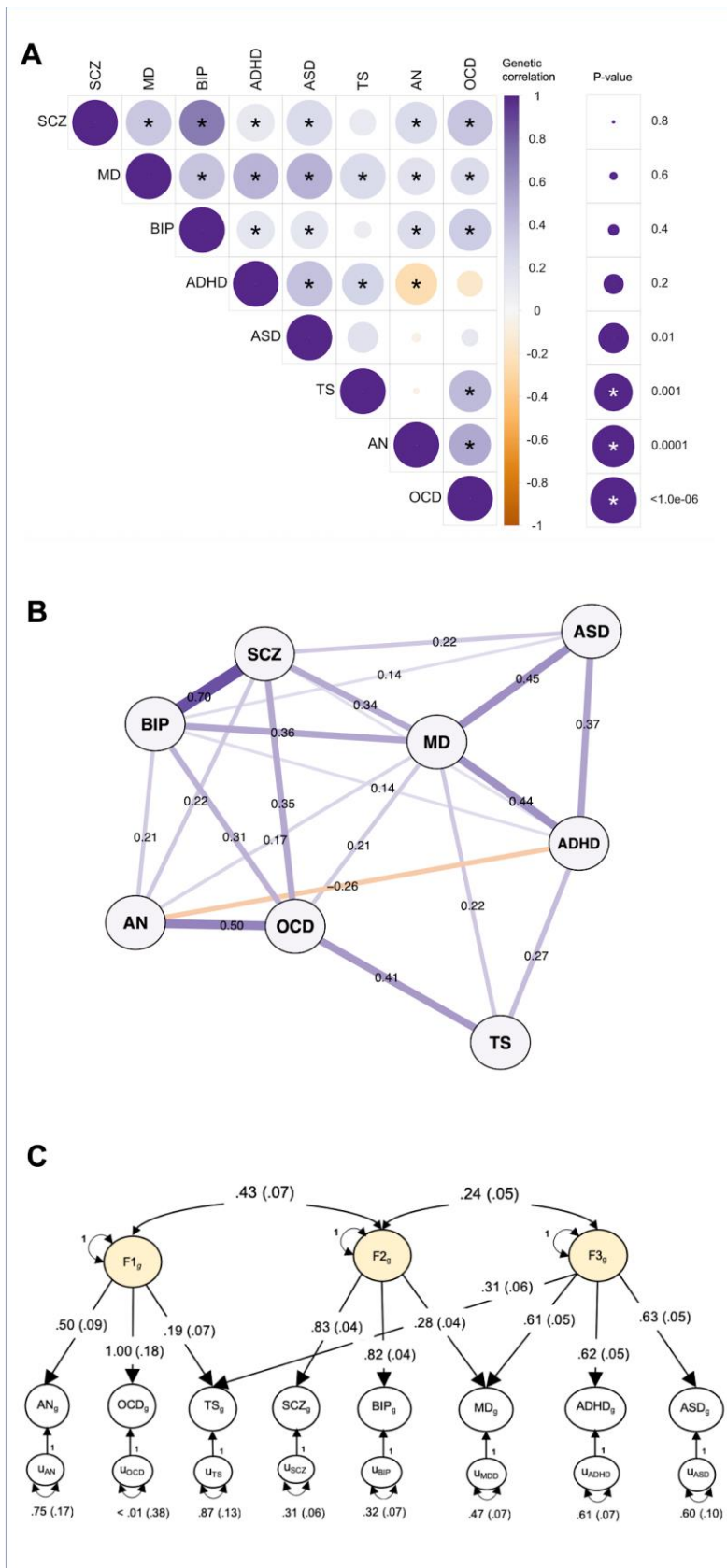
The number of cases and controls used in the meta-analysis of the present study. The numbers may differ from those reported in the original publications because our study included only European ancestry subjects to avoid potential confounding due to ancestral heterogeneity across distinct disorder studies. SNP heritability was estimated from the GWAS summary statistics using LD score regression.

***Genetic correlations among eight neuropsychiatric disorders indicate three genetic factors.***

After standardized and uniform quality control, additive logistic regression analyses were performed on individual disorders (Online Methods). A total of 6,786,994 SNPs were common across all datasets and were retained for further study. Using the summary statistics of these SNPs, we first estimated pairwise genetic correlations among the eight disorders using linkage disequilibrium (LD) score regression analyses (Bulik-Sullivan, 2015 #12456) (Online Methods; **Fig. 1a**; **Supplementary Table 2**). The

results were broadly concordant with previous estimates (Brainstorm et al., 2018) (Cross-Disorder Group of the Psychiatric Genomics et al., 2013). The genetic correlation was highest between SCZ and BIP ( $r_g = 0.70 \pm 0.02$ ), followed by OCD and AN ( $r_g = 0.50 \pm 0.12$ ). Interestingly, based on genome-wide genetic correlations, MD was closely correlated with ASD ( $r_g = 0.45 \pm 0.04$ ) and ADHD ( $r_g = 0.44 \pm 0.03$ ), two childhood-onset disorders. Despite variation in magnitude, significant genetic correlations were apparent for most pairs of disorders, suggesting a complex, higher-order genetic structure underlying psychopathology (**Fig. 1b**).

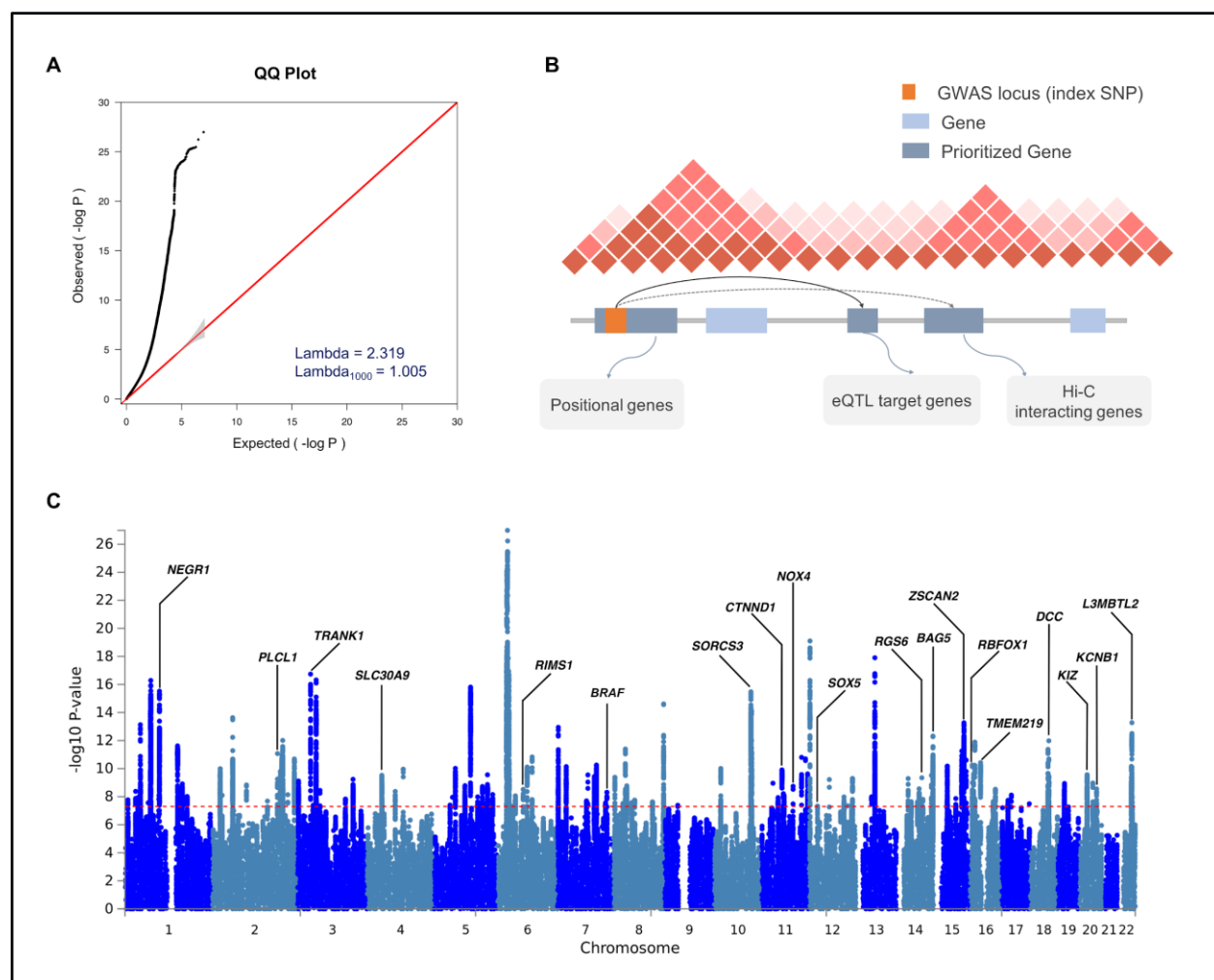
We modeled the genome-wide joint architecture of the eight neuropsychiatric disorders using an exploratory factor analysis (EFA) (Gorsuch, 1988), followed by genomic structural equation modeling (SEM) (Grotzinger et al., 2018) (Online Methods). EFA identified three correlated factors, which together explained 51% of the genetic variation in the eight neuropsychiatric disorders (**Supplementary Table 3**). The first factor consisted primarily of disorders characterized by compulsive behaviors, specifically AN, OCD, and, more weakly, TS. The second factor was characterized by mood and psychotic disorders (MD, BIP, and SCZ), and the third factor by three early-onset neurodevelopmental disorders (ASD, ADHD, TS) as well as MD. Similar to our EFA results, hierarchical clustering analyses also identified three sub-groups among the eight disorders (**Supplementary Fig. 1**).



1. Figure 1. Genetic relationships between eight psychiatric disorders.

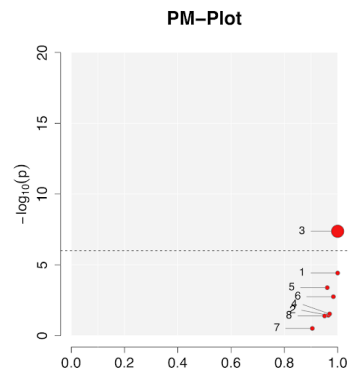
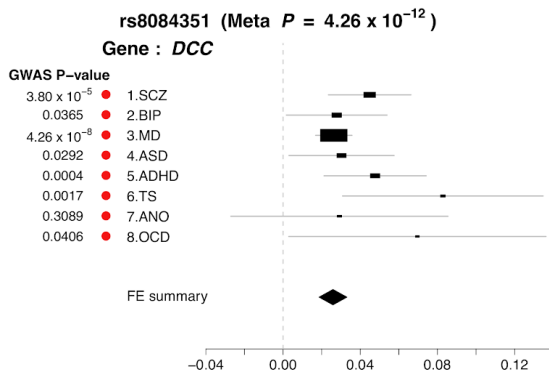
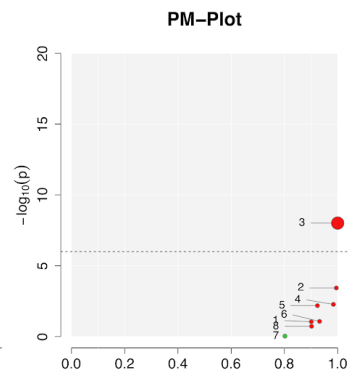
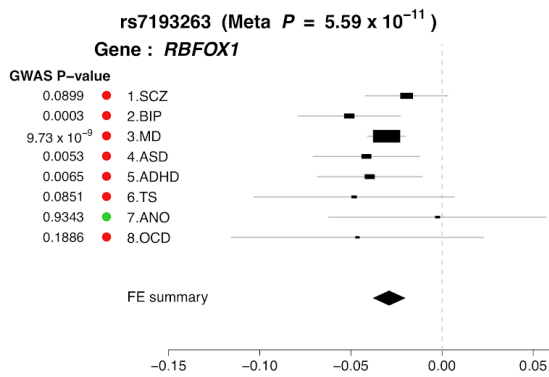
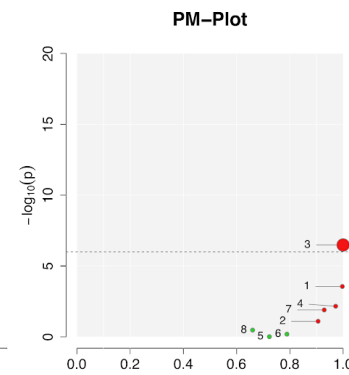
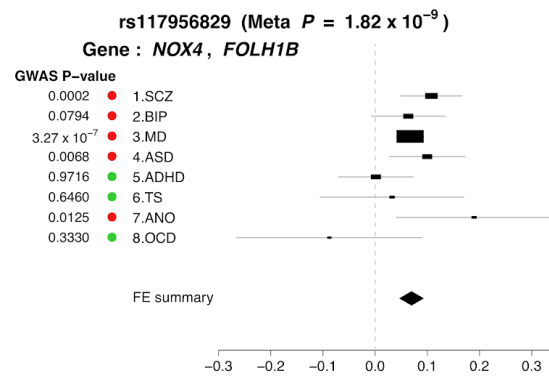
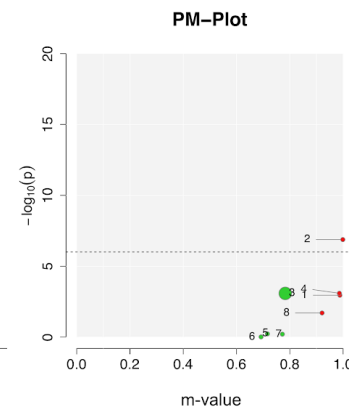
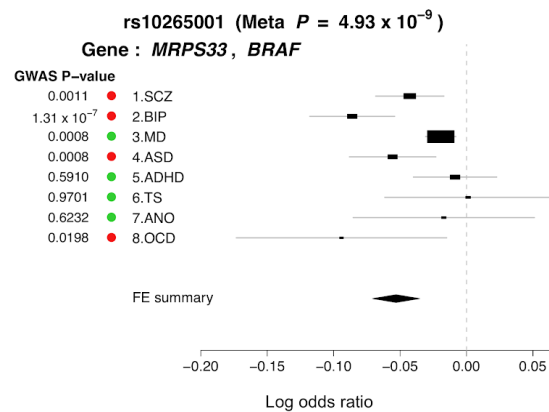
### Cross-disorder meta-analysis identifies 109 pleiotropic loci

The factor structure described above is based on average effects across the genome, but does not address more fine-grained cross-disorder effects at the level of genomic regions or individual loci. To identify genetic loci with shared risk, we performed a meta-analysis of the eight neuropsychiatric disorders using a fixed-effects-based method (Bhattacharjee et al., 2012) that accounts for the differences in sample sizes, existence of subset-specific effects, and overlapping subjects across datasets (Online Methods). There was no evidence of genomic inflation ( $\lambda_{1000} = 1.005$ ; **Fig. 2a**). Using the primary fixed-effects-based meta-analysis, we identified 136 LD-independent regions with genome-wide significant association ( $P_{\text{meta}} \leq 5 \times 10^{-8}$ ). Due to the known extensive LD at the major histocompatibility complex (MHC) region (chromosome 6 region at 25-35 Mb), we considered the multiple signals present there as one locus. 101 of the 136 (74.3%) significantly associated regions overlapped with previously reported genome-wide significant regions from at least one individual disorder, while 35 loci (25.7%) represented novel genome-wide significant associations.





**Figure 2. Results of cross-disorder meta-analysis and strategy for mapping loci to genes.**

**A****B****C****D**

**Figure 3. Profile of disorder associations for illustrative pleiotropic loci: (A) rs8084351 on 18q21.2; (B) rs7193263 on 16p13.3; (C) rs117956829 on 11q14.3; and (D) rs10265001 on 7q34.**

Within these 136 loci, multi-SNP-based conditional analysis (Yang et al., 2012) identified 10 additional SNPs with independent associations, resulting in a total of 146 independent lead SNPs (**Supplementary Table 4**). To provide a quantitative estimate of the best fit configuration of cross-disorder genotype-phenotype relationships, we estimated the posterior probability of association (referred to as the *m-value*) with each disorder using a Bayesian statistical framework<sup>17</sup> (Online Methods; **Supplementary Table 5**). As recommended<sup>17</sup>, an *m-value* threshold of 0.9 was used to predict with high confidence that a particular SNP was associated with a given disorder. Also, *m-values* of  $\leq 0.1$  were taken as strong evidence against association. Plots of the SNP *p*-value vs. *m-value* for all 146 lead SNPs are shown in **Supplementary Fig. 2**. Nearly 75% (N = 109/146) of the genome-wide significant SNPs were pleiotropic (i.e., associated with more than one disorder). As expected (**Supplementary Fig. 3**), configurations of disease association reflected the differences in the statistical power and genetic correlations between the samples. Of the 109 pleiotropic loci, 83% and 72% involved SCZ and BIP, respectively. MD, which had the largest case-control sample, was associated with 48% of the pleiotropic loci (N=52/109). Despite the relatively small sample size, ASD was implicated in 36% of the pleiotropic loci. Most of the ASD associations co-occurred with SCZ and BIP. The other disorders, ADHD, TS, OCD, and AN featured associations in 16%, 14%, 11%, and 7% of the pleiotropic loci, respectively. Of the single-disorder-specific loci, 81% and 16% were associated with SCZ and MD, respectively.

**Table 2** summarizes 23 pleiotropic loci associated with at least four of the disorders. Among these loci, heterogeneity of effect sizes was minimal (*p*-value of  $Q > 0.1$ ). Eleven of the 23 regions map to the intron of a protein-coding gene, and seven additional lead SNPs had at least one protein-coding gene within 100 kb. We used an array of functional genomics resources, including brain eQTL and Hi-C data to prioritize potential candidate genes to the identified regions (Online Methods; **Fig. 2b**). The Manhattan plot in **Fig. 2c** highlights the prioritized candidate genes.

**Table 2. Summary of 23 loci with the broadest cross-disorder association**

SNP	CHR	BP	A1	A2	candidateGene (evidence)	ADHD	ANO	ASD	BIP	MDD	OCD	SCZ	TS	mDisorder_0.9
rs10149470	14	104017953	A	G	-	0.961(1.05)	0.905(1.03)	0.97(1.03)	0.965(1.03)	1(1.03)	0.951(1.07)	1(1.05)	0.984(1.09)	8
rs10265001	7	140665521	C	G	-	0.924(0.96)	0.802(1)	0.984(0.96)	0.995(0.95)	1(0.97)	0.902(0.95)	0.901(0.98)	0.932(0.95)	7
rs11570190	11	57560452	A	C	CTNND1(g);ORS5AK2(q);	0.908(0.96)	0.926(0.94)	0.992(0.94)	0.843(0.98)	1(0.96)	0.88(0.96)	0.929(0.97)	0.913(0.95)	6
rs11688767	2	57988194	A	T	BCL11A(h);	0.963(1.06)	0.165(0.91)	0.999(1.06)	0.972(1.04)	1(1.03)	0.574(0.98)	1(1.05)	0.963(1.08)	6
rs117956829	11	89339666	A	G	TRIM64B(ha);GRM5(hf);TRIM77(hf);TYR(hf)	0.905(1.03)	0.938(1.07)	0.976(1.04)	0.984(1.04)	0.993(1.02)	0.897(1.04)	1(1.07)	0.892(1.03)	6
rs12129573	1	73768366	A	C	-	0.987(0.92)	0.954(0.92)	0.992(0.95)	0.985(0.96)	1(0.96)	0.854(0.98)	1(0.94)	0.886(0.97)	6
rs12658451	5	103904037	T	C	-	0.74(0.99)	0.949(0.93)	0.963(0.97)	0.785(0.98)	1(0.96)	0.858(0.97)	0.973(0.97)	0.921(0.96)	5
rs1484144	4	80217597	T	C	-	0.97(1.07)	0.884(1.03)	0.973(1.03)	0.98(1.04)	1(1.02)	0.84(1.01)	0.998(1.04)	0.85(1.01)	5
rs1518367	2	198807015	A	T	PLCL1(g);5F3B1(q)	0.836(1.02)	0.827(1.02)	0.987(1.05)	0.93(1.03)	0.999(1.02)	0.917(1.07)	1(1.05)	0.729(0.99)	5
rs2332700	14	72417326	C	G	RGS6(g);	0.944(1.05)	0.855(1.02)	0.972(1.03)	0.877(1.02)	1(1.03)	0.853(1.02)	0.999(1.04)	0.963(1.07)	5
rs34215985	4	42047778	C	G	SLC30A9(g);SLC30A9(q);	0.927(0.95)	0.79(0.99)	0.97(0.96)	0.58(1)	1(0.98)	0.916(0.93)	1(0.95)	0.832(0.98)	5
rs5758265	22	41617897	A	G	L3MBTL2(g);CHADL(g);	0.723(1)	0.929(1.21)	0.972(1.1)	0.906(1.07)	1(1.07)	0.66(0.92)	0.997(1.11)	0.789(1.03)	5
rs6125656	20	48090779	A	G	KCNB1(g);	0.844(0.98)	0.833(0.99)	0.998(0.95)	0.979(0.97)	1(0.97)	0.868(0.98)	0.997(0.96)	0.97(0.93)	5
rs61867293	10	106563924	T	C	SORCS3(g);	0.929(1.05)	0.835(1.03)	0.894(1.03)	0.948(1.03)	1(1.04)	0.85(1.04)	1(1.07)	0.539(0.98)	4
rs6969410	7	110069015	T	C	-	0.845(0.98)	0.899(0.96)	0.929(0.97)	0.983(0.96)	1(0.97)	0.849(0.97)	1(1.03)	0.698(1)	4
rs7193263	16	6315880	A	G	RBFOX1(g);	0.897(0.96)	0.783(0.99)	0.913(0.97)	0.991(0.95)	1(0.97)	0.674(1.03)	1(0.94)	0.865(0.97)	4
rs7405404	16	13749859	T	C	-	0.716(0.99)	0.772(0.98)	0.986(0.95)	0.999(0.92)	0.783(0.98)	0.921(0.91)	0.988(0.96)	0.692(1)	4
rs7531118	1	72837239	T	C	-	0.865(1.04)	0.854(1.04)	0.966(1.05)	0.999(1.1)	1(1.04)	0.734(0.97)	0.999(1.07)	0.798(1.01)	4
rs78337797	12	23987925	T	G	SOX5(g);	0.849(1.03)	0.797(1.1)	0.97(1.06)	0.954(1.05)	1(1.04)	0.831(1.02)	0.996(1.06)	0.885(1.05)	4
rs79879286	7	24826589	C	G	-	0.755(1)	0.884(1.04)	0.951(1.03)	0.948(1.03)	0.999(1.03)	0.885(1.05)	1(1.08)	0.817(1.01)	4
rs8084351	18	50726559	A	G	DCC(g);DCC(q);	0.763(1.02)	0.765(1.02)	0.99(1.06)	0.939(1.04)	1(1.03)	0.726(1)	1(1.08)	0.562(0.98)	4
rs9360557	6	73132745	C	G	KCNQ5(ha);KCNQ5(hf);KCNQ5-IT1(hf);	0.768(1.01)	0.885(1.06)	0.986(1.06)	0.995(1.07)	0.985(1.02)	0.731(0.98)	0.999(1.07)	0.707(0.99)	4
rs9787523	10	106460460	T	C	SORCS3(g);	0.735(1)	0.885(1.04)	0.89(1.02)	0.885(1.02)	1(1.03)	0.913(1.07)	1(1.08)	0.978(1.09)	4

nearestGene: evidences for assigning index SNP to candidate genes were coded as: (g) genic SNP; (q) cis-eQTL target; (h) hi-C interacting gene based on FUMA; (hf) hi-C interacting in fetal brain based on Won et al. (2016); (ha) hi-C interact

Table 2: SNP ID, location, prioritized candidate gene, disorder-specific m-values and Odds ratios for 23 most pleiotropic loci. The number of disorders with high confidence association (mDisorder\_0.9) is shown in the last column.

<https://drive.google.com/open?id=18qFWLO7HdXf80zNqLBLJ4auXTrA101R8>

Of the 109 risk loci with shared effects, the 18q21.2 region surrounding SNP rs8084351 at the netrin 1 receptor gene *DCC* featured the most pleiotropic association ( $P_{meta} = 4.26 \times 10^{-12}$ ; **Fig. 3a**). This region showed association with all eight psychiatric disorders, and has been previously associated with both MD and neuroticism (Wray et al. 2018; Turley et al. 2018 PMID 29292387). The product of *DCC* plays a key role in guiding axonal growth during neurodevelopment and serves as a master regulator of midline crossing and white matter projections (Bendriem, 2017). Gene expression data indicate that *DCC* expression peaks during early prenatal development (**Supplementary Fig. 4a**).

The second most pleiotropic locus in our analysis was identified in an intron of *RBFOX1* (RNA Binding Fox-1 Homolog 1) on 16p13.3 (lead SNP rs7193263;  $P_{meta} = 5.59 \times 10^{-11}$ ). The lead SNP showed association with all of the disorders except AN (**Fig. 3b**). *RBFOX1* (also called *A2BP1*) encodes a splicing regulator mainly expressed in neurons and known to target several genes important to neuronal development, including *NMDA* receptor 1 and voltage-gated calcium channels (Hamada N, 2015). Knock-down and silencing of *RBFOX1* during mouse corticogenesis impairs neuronal migration and synapse formation (Hamada N, 2015, 2016), implying its pivotal role in early cortical maturation. In contrast to *DCC*, however, developmental gene-expression of *RBFOX1* showed gradually increasing gene expression throughout the prenatal period (**Supplementary Fig. 4b**). Animal models and association studies have implicated *RBFOX1* in aggressive behaviors, a trait observed in several of the disorders in our analysis (Fernandez-Castillo, 2017 #12870).

Of the 109 pleiotropic loci, 76 were identified in the GWAS of individual disorders, while the remaining 33 are novel. The most pleiotropic among these novel loci was a region downstream of *NOX4* (NADPH Oxidase 4) that was associated with SCZ, BIP, MD, ASD, and AN (rs117956829;  $P_{\text{meta}} = 1.82 \times 10^{-9}$ ; **Fig. 3c**). Brain Hi-C data (Won, 2016, Wang et al. Science) detected a direct interaction of the cross-disorder association region with *NOX4* in both adult and fetal brains (interaction  $p=3.2 \times 10^{-16}$  and  $9.324 \times 10^{-6}$ , respectively). As a member of the family of *NOX* genes that encode subunits of NADPH oxidase, *NOX4* is a major source of superoxide production in human brain and a promoter of neural stem cell growth (Topchiy, 2013 #12882; Kuroda, 2014 #12881).

**Figure 3d** illustrates another novel psychiatric risk locus associated with SCZ, BIP, ASD, and OCD ( $P_{\text{meta}} = 3.58 \times 10^{-8}$ ). The lead SNP rs10265001 resides between *MRPS33* (Mitochondrial Ribosomal Protein S33) and *BRAF* (B-Raf Proto-Oncogene, Serine/Threonine Kinase) on 7q34. The brain Hi-C data indicated interaction of the associated region with the promoters of two nearby genes: *BRAF*, which contributes to the MAP kinase signal transduction pathway and plays a role in postsynaptic responses of hippocampal neurons (Grantyn, 1973), and *KDM7A* (encoding Lysine Demethylase 7A), which plays a central role in the nervous system and midbrain development (Horton, 2010; Qi, 2010; Tsukada, 2010).

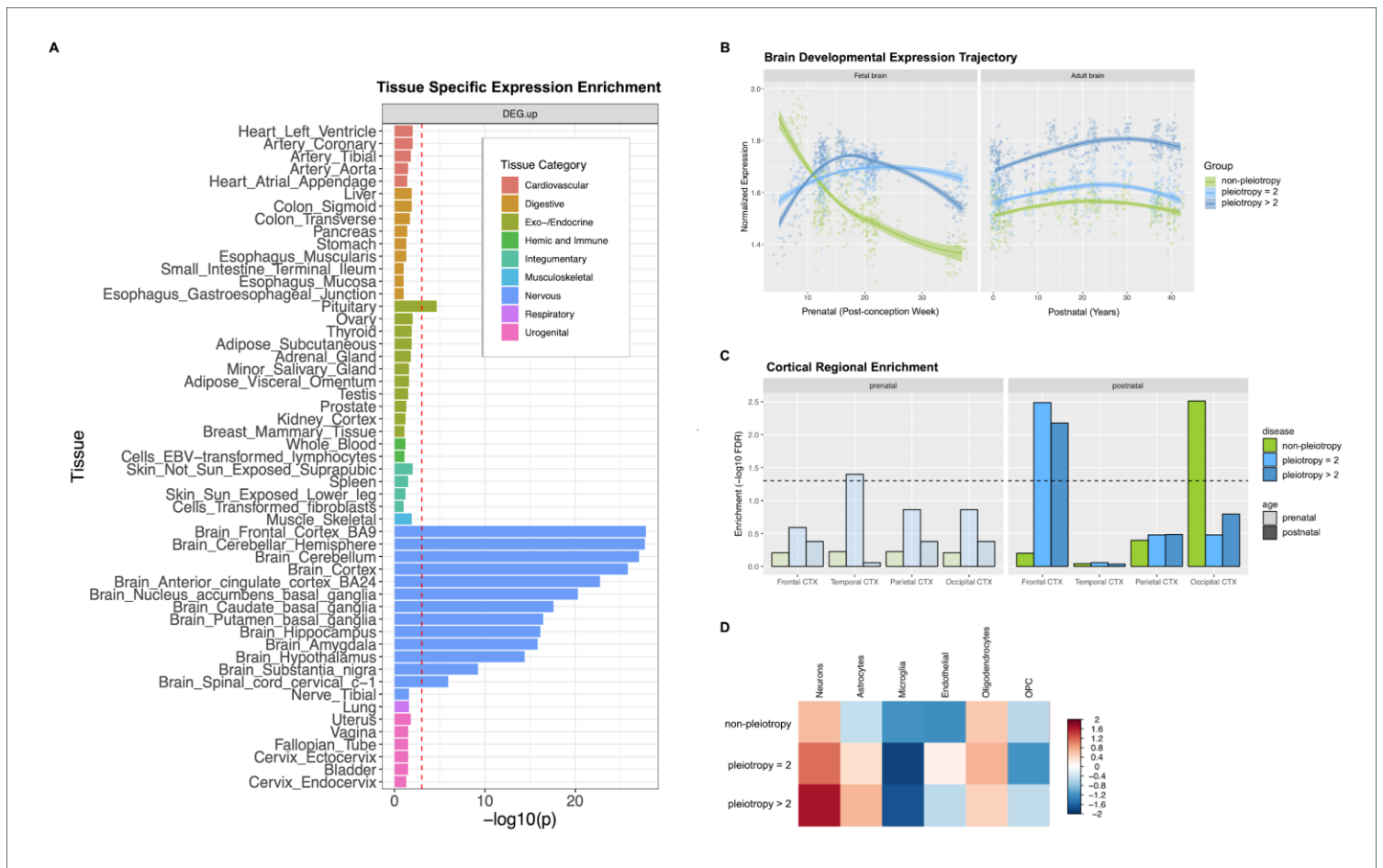
Our prior cross-disorder meta-analysis of five psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) found no evidence of SNPs with antagonistic effects on two or more disorders. Here, we examined whether any variants with meta-analysis  $p \leq 1 \times 10^{-6}$  had opposite directional effects between disorders (Online Methods). After adjusting for having examined 206 loci across eight disorders ( $q < 0.001$ ), we identified 11 loci with evidence of opposite directional effects on two or more disorders (**Fig. 4; Supplementary Table. 6**). The disorder configuration of opposite directional effects varied for the 11 loci, including three loci with opposite directional effects on SCZ and MD (rs301805, rs1933802, rs3806843), two loci between SCZ and ASD (rs9329221, rs2921036), and one locus (rs75595651) with opposite directional effects on the two mood disorders, BIP and MD. Notably, all of the six loci involving SCZ and BIP exhibited the same directional effect on the two disorders ( $P_{\text{binom}} < 0.05$ ), in line with their strong genome-wide genetic correlation.

**Figure 4. Eleven loci with opposite directional effects (could't include in the google doc)** - Dotted circle indicates where disease-association is assumed ( $q < 0.001$ ).

<https://www.dropbox.com/s/ro9bowc7756z9yd/Figure.4.antagonistic.pdf?dl=0>

## Functional characterization of pleiotropic risk loci

We conducted a series of bioinformatic analyses that examined whether loci with shared risk effects on multiple neuropsychiatric disorders had characteristic features that distinguished them from non-pleiotropic risk loci. First, we annotated the functional characteristics of 146 lead SNPs using various public data sources (Online Methods; **Supplementary Table 7-9**). Overall, they showed significant enrichment of genes expressed in the brain ( $\beta=0.123$ ,  $SE=0.0109$ , enrichment  $p = 1.22 \times 10^{-29}$ ) and pituitary ( $\beta=0.0916$ ,  $SE=0.0136$ ,  $p = 8.74 \times 10^{-12}$ ), but not in the other Genotype-Tissue Expression (GTEx) tissues. (**Supplementary Table 10; Fig. 5a**). A separate analysis of 109 pleiotropic risk loci also showed specific enrichment of genes expressed in multiple brain tissues ( $p = 1.55 \times 10^{-5}$ ; **Supplementary Table 11**), while disorder-specific loci showed nominally enriched brain gene expression in the cortex ( $p = 2.14 \times 10^{-2}$ ; **Supplementary Table 12**).



## Figure 5. Results of functional genomics data analysis for pleiotropic vs. disorder-specific loci.

Gene-set enrichment analyses using Gene Ontology data suggested involvement of pleiotropic risk loci in neurodevelopmental processes (**Supplementary Table 13,14**). The 109 pleiotropic risk loci were enriched for genes involved in neurogenesis (gene-set enrichment  $p = 9.67 \times 10^{-6}$ ), regulation of nervous system development ( $p = 3.41 \times 10^{-5}$ ), and neuron differentiation ( $p = 3.30 \times 10^{-5}$ ), while enrichment of these gene-sets was not seen for disorder-specific risk loci (adjusted enrichment  $p > 0.05$ ). Pleiotropic risk loci also showed enrichment of genes involved in specific neurotransmitter-related pathways -- glutamate receptor signaling ( $p = 2.45 \times 10^{-6}$ ) and voltage-gated calcium channel complex ( $p = 5.72 \times 10^{-4}$ ) -- while non-pleiotropic risk loci, which were predominantly SCZ-associated, were over-represented among acetylcholine receptor genes ( $p = 7.25 \times 10^{-8}$ ). Analysis of cortical gene expression data also suggested enrichment of pleiotropic risk genes in cortical glutamatergic neurons through layers 2-6 (**Supplementary Table 15**), further supporting the shared role of glutamate receptor signaling in the pathogenesis of diverse neuropsychiatric disorders.

In contrast to the differences in neuronal development and neuronal signaling pathways, pleiotropic and non-pleiotropic risk loci shared several characteristics related to genomic function. For instance, gene-set enrichment analyses indicated that both pleiotropic and non-pleiotropic risk loci were enriched for genes involved in the regulation of synaptic plasticity, neurotransmission, and synaptic cellular components.

More than 41% of the genes associated with our genome-wide significant loci, both pleiotropic and non-pleiotropic, were intolerant of loss of function mutations (pLI score  $\geq 0.9$ ); this is highly unlikely to occur by chance (Fisher's exact  $p=4.90 \times 10^{-8}$ ). This finding was consistent when examining pleiotropic ( $p=2.85 \times 10^{-11}$ ) and non-pleiotropic risk loci ( $p=1.56 \times 10^{-3}$ ) separately.

Next, we compared spatio-temporal gene-expression patterns for the 109 pleiotropic risk loci and the 37 disorder-specific loci using post-mortem brain data. On average, disorder-specific and pleiotropic risk loci showed a similar level of gene expression in both prenatal and postnatal development after multiple testing correction (t-test  $p > 0.025 \times 10^{-2}$ ; **Supplementary Fig. 5**). During prenatal development, non-pleiotropic loci (mainly SCZ-associated) showed peak expression in the first trimester, after which expression rapidly decreased, while pleiotropic genes associated with only 2 disorders ("*pleiotropy*=2"; 60 loci) and those associated with more than 2 ("*pleiotropy*>2", 49 loci)

showed peak expression around the second trimester (**Fig. 5b**). After birth, all three groups showed gradually increasing gene expression until adulthood. Expression levels were associated with the degree of pleiotropy, with the *pleiotropy*>2 group showing higher gene expression than either the *pleiotropy*=2 group (t-test  $p < 2.10 \times 10^{-4}$ ) or non-pleiotropic risk loci (t-test  $p < 2.2 \times 10^{-16}$ ).

Enrichment analyses using the genes preferentially expressed in specific cortical regions suggested that pleiotropic loci were over-represented among genes expressed in the frontal cortex, while non-pleiotropic loci were enriched in the occipital cortex (FDR  $q < 0.05$ ; **Fig. 5c**). Cell-type-specific analysis indicated that genes implicated in pleiotropic loci were mainly expressed in neurons (FDR  $q < 0.05$ ) but not in glial cell types. Further, enrichment of pleiotropic loci in neuronal cells was also associated with the degree of pleiotropy, as highlighted in **Fig. 5d**.

Previous studies of model organisms using gene knock-out experiments suggested that pleiotropic risk loci may undergo stronger selection than non-pleiotropic loci (Hill, 2012). However, we found no evidence that pleiotropic risk variants are under stronger evolutionary constraints (**Supplementary Table 16**). Various comparative genomics resources, including PhyloP (Pollard, 2010), PhastCons (Siepel, 2005), and GERP++ (Davydov, 2010), showed our top loci to have similar properties regardless of the extent of pleiotropy. Neither did we find differences between disorder-specific lead SNPs and pleiotropic SNPs with respect to their minor allele frequencies, average heterozygosity, or predicted allele ages (Kiezun, 2013). Pleiotropic and non-pleiotropic SNPs also did not differ in terms of the distance to nearest genes, distance to splicing sites, chromosome compositions, and predicted functional consequences of non-coding regulatory elements.

### ***Relationship between cross-disorder genetic risk and other brain-related traits and diseases***

To explore the genetic relationship of cross-disorder genetic risk with other traits, we treated this 8-disorder GWAS meta-analysis as a single “cross-disorder phenotype.” We applied LDSC to estimate SNP heritability ( $h^2_{\text{SNP}}$ ) and genetic correlations with other phenotypes, using block jackknife-based standard errors to estimate statistical significance. The estimated  $h^2_{\text{SNP}}$  of the cross-disorder phenotype was 0.146 (SE 0.0058; observed scale). Using data for 28 brain-related traits selected from LDHub (Zheng et al., 2017), we found significant genetic correlations of the cross-disorder phenotype with seven traits (at a Bonferroni-corrected p-value threshold 0.002): never/ever smoking status, years of education, neuroticism, subjective well-being, and three sleep-related phenotypes (chronotype, insomnia, and excessive daytime sleepiness) (**Supplementary Table 17**).



GWAS catalog data for the 109 pleiotropic risk loci showed enrichment of implicated genes in a range of brain-related traits (**Supplementary Table 18**). As expected, the associated traits included previous studies of neuropsychiatric disorders including SCZ, BIP, and ASD. In addition, they were enriched among genes previously associated with neuroticism (corrected enrichment  $p= 5.28 \times 10^{-6}$ ; *GRIK3, CTNND1, DRD2, RGS6, RBFOX1, ZNF804A, L3MBTL2, CHADL, RANGAP1, RSRC1, GRM3*) and cognitive ability (corrected  $p= 7.15 \times 10^{-5}$ ; *PTPRF, NEGR1, ELOVL3, SORCS3, DCC, CACNA1I*), and night sleep phenotypes (corrected  $p= 1.86 \times 10^{-2}$ ; *PBX1, NPAS3, RGS6, GRIN2A, MYO18A, TIAF1, CNTN4, PPP2R2B, TENM2, CSMD1*). We also found significant enrichment of pleiotropic risk genes in multiple measures of body mass index (BMI), supporting previous studies suggesting a shared etiologic basis between a range of neuropsychiatric disorders and obesity (Hartwig et al. 2016; Rajan and Menon 2017; Guenzel and Schober 2017).

## DISCUSSION

In the largest cross-disorder GWAS meta-analysis of neuropsychiatric disorders to date, comprising more than 725,000 cases and controls across eight disorders, we identified 146 LD-independent lead SNPs associated with at least one disorder, including 35 novel loci. Of these, 109 loci were found to affect two or more disorders, although characterisation of this pleiotropy is partly dependent on per-disorder sample size. Our results provide four major insights into the shared genetic basis of psychiatric disorders.

First, modeling of genetic correlations among the eight disorders using two different methods (EFA and hierarchical clustering) identified three groups of disorders based on shared genomics: one comprising disorders characterized by compulsive behaviors (AN, OCD and TS), a second comprising mood and psychotic disorders (MD, BIP and SCZ), and a third comprising two early-onset neurodevelopmental disorders (ASD and ADHD) and one disorder each from the first two factors (TS and MD). The loading of MD on two factors may reflect biological heterogeneity within MD, consistent with recent evidence showing that early-onset depression is associated with genetic risk for ADHD and with neurodevelopmental phenotypes 'Rice, 2018 #12873}. Overall, these results indicate a substantial pairwise genetic correlation between multiple disorders along with a higher-level genetic structure that underlies psychopathology. These findings are at odds with the classical, categorical classification of mental illness.

Second, variant-level analyses support the existence of substantial pleiotropy, with nearly 75% of the 146 genome-wide significant SNPs influencing more than one of the eight examined disorders. We also identified a set of 23 loci with particularly extensive pleiotropic profiles, affecting four or more disorders. The most highly pleiotropic locus, in our analyses, with evidence of association with all eight disorders, maps within *DCC*, a gene fundamental to the early development of white matter connections in the brain

(Bendriem and Ross, 2017). Prior studies showed that *DCC* is a master regulator of axon guidance (through its interactions with netrin-1 and draxin (Liu et al., 2018). Loss of function mutations in *DCC* cause severe neurodevelopmental syndromes involving loss of midline commissural tracts and diffuse disorganization of white matter tracts (Bendriem and Ross, 2017; Jamuar et al., 2017; Marsh et al., 2017). A highly pleiotropic effect of variation in *DCC* on diverse psychiatric disorders with childhood and adolescent onset would be consistent with its role in both early organization of neuronal circuits and the maturation of mesolimbic dopaminergic connections to the prefrontal cortex during adolescence (Hoops and Flores, 2017; Reynolds et al., 2018; Vosberg et al., 2018).

We also identified a set of loci that have opposite effects on risk of psychiatric disorders. Notably, these included loci with opposing effects on pairs of disorders that are genetically correlated and have common clinical features. For example, a SNP within *MRSA* was associated with opposing effects on two neurodevelopmental disorders (ASD and SCZ), and a variant within *KIAA1109* had opposite directional effects on major mood disorders (BIP and MD) (Table 3). These results underscore the complexity of genetic relationships among related disorders and suggest that overall genetic correlations may obscure antagonistic biological mechanisms that operate at the level of component loci and pathways as seen in immune-mediated diseases (Baurecht et al., 2015; Lettre and Rioux, 2008; Schmitt et al., 2016). This heterogeneity of effects between genetically correlated disorders is also consistent with a recent analysis that revealed loci contributing to biological differences between BIP and SCZ and found polygenic risk score associations with specific symptom dimensions (Bipolar et al., 2018).

Third, we found extensive evidence that neurodevelopmental effects underlie the cross-disorder genetics of mental illness. In addition to *DCC*, a link between pleiotropy and genetic effects on neurodevelopment was also seen for other top loci in our analysis, including *RBFOX1*, *BRAF*, and *KDM7A*, all of which have been shown in prior research to influence aspects of nervous system development. Gene enrichment analyses showed that pleiotropic loci were distinguished from disorder-specific loci by their involvement in neurodevelopmental pathways including neurogenesis, regulation of nervous system development, and neuron differentiation. These results are consistent with those of a smaller recent analysis in the population-based Danish iPSYCH cohort (comprising 46,008 cases and 19,526 controls across six neuropsychiatric disorders) (Schork et al., 2017). In that analysis, consistent with the present findings, functional genomic characterization of cross-disorder loci implicated fetal neurodevelopmental processes, with greater prenatal than postnatal expression. However, the specific loci, cell types, and pathways implicated in the iPSYCH analysis differed from those identified in our study. Of note, however, *SORCS3* emerged as a genome-wide significant cross-disorder locus in both studies.

Fourth, our analyses of spatiotemporal gene expression profiles revealed that pleiotropic loci are enriched among genes expressed in neuronal cell types, particularly in frontal or prefrontal regions. They also demonstrated a distinctive feature of genes related to pleiotropic loci: compared with disorder-specific loci, they are on average expressed at higher levels both prenatally and postnatally (Figure 4). More specifically, single-disorder (mainly SCZ) loci were related to genes that were preferentially expressed in the first fetal trimester followed by a decline over the prenatal period and then relatively stable levels postnatally. In contrast, expression of genes related to pleiotropic loci peaked in the second trimester and remained overexpressed throughout the lifespan. When dividing the pleiotropic loci into bins of those associated with two disorders (mainly SCZ and BIP) vs. three or more disorders, we observed a consistent gradient of greater expression associated with broader pleiotropy.

Taken together, our results suggest that pleiotropic loci appear to be distinguished by both their differential importance in neurodevelopmental processes and their heightened brain expression after the first trimester. Apart from this, however, pleiotropic loci were similar to non-pleiotropic loci across a range of other functional features, including intolerance to loss-of-function mutations, evidence of selection, minor allele frequencies, and genomic position relative to functional elements.

Overall, our results identify a range of pleiotropic effects among loci associated with psychiatric disorders. Consistent with prior research (Brainstorm et al., 2018) (Cross-Disorder Group of the Psychiatric Genomics et al., 2013), we found substantial pairwise genetic correlations across child- and adult-onset disorders and extended these findings by demonstrating clusters of genetically-related disorders. These results augment a substantial body of research demonstrating that genetic influences on psychopathology do not map cleanly onto the clinical nosology instantiated in the DSM or ICD (Smoller et al., 2018). Using a range of bioinformatic and functional genomic analyses, we find that loci with pleiotropic effects are distinguished by their involvement in early neurodevelopment and increased expression beginning in the second trimester of fetal development and persisting throughout adulthood. Taken together, the analyses presented here suggest that genetic influences on psychiatric disorders comprise at least two general classes of loci. The first comprises a set of genes that confer relatively broad liability to psychiatric disorders by acting on early neurodevelopment and the establishment of brain circuitry. These pleiotropic genes begin to come online by the second trimester of fetal development and exhibit differentially high expression thereafter. Such loci may underlie a latent general psychopathology factor (the “p” factor) (Caspi et al., 2014) that has been identified in developmental studies of mental disorders, comprising transdiagnostic symptom clusters (internalizing, externalizing, and psychotic) (Caspi et al., 2014). The expression and differentiation of this generalized genetic risk into discrete psychiatric syndromes (e.g., ASD, BIP, AN) may then involve

direct and/or interactive effects of additional sets of loci and environmental factors, possibly mediated by epigenetic effects, that shape phenotypic expression via effects on brain structure/function and behavior. Further research will be needed to clarify the nature of such effects.

Our results should be interpreted in light of several limitations. First, while our dataset is the largest genome-wide cross-disorder analysis to date, data available for individual disorders varied substantially—from a minimum of 9725 cases and controls for OCD to 461,134 cases and controls for MD. This imbalance of sample size may have limited our power to detect pleiotropic effects on underrepresented disorders. Second, it is possible that comorbidity among disorders contributed to apparent pleiotropy; however we found that less than 2% of cases overlapped between disorder datasets (excluding 23andMe data) and we adjusted for overlap in meta-analysis. Second, the method we applied to detect cross-phenotype association, which combines an all-subsets fixed-effects GWAS meta-analysis with a Bayesian method for evaluating the best-fit configuration of genotype-phenotype associations, is one of several approaches (Solovieff et al., 2013). However, we have previously shown that this method outperforms a range of alternatives for detecting pleiotropy. (Zhu et al., 2018) Third, our designation of loci as pleiotropic vs. non-pleiotropic loci refers only to their observed effects on the eight target brain disorders. Thus, some of the “non-pleiotropic” loci may have additional effects on psychiatric phenotypes that were not included in our meta-analysis and/or on non-psychiatric phenotypes. Fourth, our functional genomic analyses were constrained by the limitations of existing resources (e.g. spatiotemporal gene expression data resources). Our work underscores the need for more comprehensive functional data including single cell transcriptomic and epigenomic profiles across development and brain tissues. Fifth, we included only individuals of European ancestry to avoid potential confounding due to ancestral heterogeneity across distinct disorder studies. Similar efforts are needed to examine these questions in other populations.

In sum, in a large-scale cross-disorder genome-wide meta-analysis, we identified three genetic factors underlying the genetic basis of eight psychiatric disorders. We also identified 109 genomic loci with pleiotropic effects, of which 33 have not previously been associated with any of the individual disorders. In addition, we identified 11 loci with opposing directional effects on two or more psychiatric disorders. These results highlight disparities between our clinically-defined classification of psychiatric disorders and underlying biology. Finally, we found that genes associated with multiple psychiatric disorders are disproportionately associated with biological pathways related to neurodevelopment and exhibit distinctive gene expression patterns, with enhanced expression beginning in the second prenatal trimester and persistently elevated expression relative to less pleiotropic genes. Therapeutic modulation of pleiotropic gene products could have broad-spectrum effects on psychopathology.



## STAR\* METHODS

(link to this file: <https://drive.google.com/open?id=1r7NI4Kt4pg0rzoqfkAgbKAlfExcj9s0v>)  
Detailed methods are provided in the online version of this paper and include the following:

- [KEY RESOURCES TABLE](#)
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- [EXPERIMENTAL MODEL AND SUBJECT DETAILS](#)
  - Genotyped sample description
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- [QUANTIFICATION AND STATISTICAL ANALYSIS](#)
  - Genome-wide SNP-heritability estimation
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  - Summary-data-based meta-analysis
  - Disease-association modeling
  - Candidate-gene mapping
  -
- [DATA AND SOFTWARE AVAILABILITY](#)

## SUPPLEMENTAL INFORMATION

Supplemental Information includes 5 figures, 18 tables, and a list of consortium author affiliations and can be found with this article online at XXX.

## CONSORTIA

**Cell format: All consortia author names without affiliation information**

Note: 23andme will be included as author, here.

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## AUTHOR CONTRIBUTIONS

*Writing Group:* P.H.L., Y.A.F., V.A., S.V.F., B.M.N., K.S.M., L.T., S.R., N.W., M.N., G.B., J.W., J.S., H.E., J.G., O.A., M.B.S., C.A.M., A.F., S.S., M.M., A.Z., A.B., K.S.K., J.W.S.

(Chair). *Analysis Group*: P.H.L., H.W., Y.A.F, D.H.G., J.R, V.A., A.D.G, E.T-D., M.G.N., and Z.Z., D.P. Disorder-specific data collection, analysis, and identification of duplicate subjects were conducted by S.R., E.S., R.A., D.Y., R.W., D.M., M.M., A.B., 23andme, and L.E.D. *Editorial Revisions Group*: J.I.N., others **TBD** The remaining authors contributed to the recruitment, genotyping, or data processing for the contributing components of the study. All other authors saw, had the opportunity to comment on, and approved the final draft.

## **DECLARATION OF INTERESTS**

J.W.S. is an unpaid member of the Bipolar/Depression Research Community Advisory Panel of 23andMe. The other authors declare no competing interests. → Need to be checked

HRK (**Henry R. Kranzler**) is a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last three years by AbbVie, Alkermes, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, Pfizer, Arbor, and Amygdala Neurosciences. HRK and JG (**Joel Gelernter**) are named as inventors on PCT patent application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018.

BMN (Benjamin M Neale) is a member of the Deep Genomics Scientific Advisory Board, a consultant for Camp4 Therapeutics Corporation, a consultant for Merck & Co., a consultant for Avanir Pharmaceuticals, Inc, and a consultant for Takeda Pharmaceutical.

KMV (Kirsten Müller-Vahl) has nonfinancial competing interests as a member of the TAA medical advisory board, the scientific advisory board of the German Tourette Association TGD, the board of directors of the German (ACM) and the International (IACM) Association for Cannabinoid Medicines, and the committee of experts for narcotic drugs at the federal opium bureau of the Federal Institute for Drugs and Medical Devices (BfArM) in Germany; has received financial or material research support from the EU (FP7-HEALTH-2011 No. 278367, FP7-PEOPLE-2012-ITN No. 316978), the German Research Foundation (DFG: GZ MU 1527/3-1), the German Ministry of Education and Research (BMBF: 01KG1421), the National Institute of Mental Health (NIMH), the Tourette Gesellschaft Deutschland e.V., the Else-Kroner-Fresenius-Stiftung, and GW, Almirall, Abide Therapeutics, and Therapix Biosciences; has served as a guest editor for *Frontiers in Neurology* on the research topic "The neurobiology and genetics of Gilles de la Tourette syndrome: new avenues through large-scale collaborative projects", is an associate editor for "Cannabis and Cannabinoid Research" and an Editorial Board Member of "Medical Cannabis and Cannabinoids"; has received consultant's honoraria from Abide Therapeutics, Fundacion Canna, Therapix Biosciences

and Wayland Group, speaker's fees from Tilray, and royalties from Medizinisch Wissenschaftliche Verlagsgesellschaft Berlin, and is a consultant for Zynerba Pharmaceuticals.

JIN has been an investigator for Assurex and is currently an investigator for Janssen.

BF has received educational speaking fees from Medice and Shire.



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## Figure Legends

**Figure 1. Genetic relationship between eight neuropsychiatric disorders.** (A) SNP-based genetic correlations ( $r_g$ ) were estimated between eight neuropsychiatric disorders using LDSC. The size of the circles scales with the significance of the p-values. The darker the color, the larger the magnitude of  $r_g$ . Star sign (\*) indicates statistical significance after Bonferroni correction. ADHD: attention-deficit/hyperactivity disorder; AN: anorexia nervosa; ASD: autism spectrum disorder; BIP: bipolar disorder; OCD: obsessive compulsive disorder; SCZ: schizophrenia. (B) SNP-based genetic correlations between eight disorders were depicted using an undirected graph to reveal complex genetic relationships than pairwise. Only significant genetic correlations in (A) were displayed. Each node represents a particular disorder, with edges indicating the strength of the pairwise correlations. The width of the edges increases, while the length decreases, with the absolute values of  $r_g$ . (C) Based on results of an exploratory factor analysis of the genetic correlation matrix, a confirmatory factor model with three correlated genetic factors was specified using Genomic SEM and estimated with the weighted least squares algorithm. Two-headed arrows connecting the three factors to one another represent their correlations. Two-headed arrows connecting the genetic components of the individual psychiatric disorders to themselves represent residual genetic variances, and correspond to the proportion of heritable variation in liability to each individual psychiatric disorder that is unexplained by the three factors. Standardized parameters are depicted with their standard errors in parentheses. Paths labeled 1 with no standard errors reported are fixed parameters, which are used for scaling.

**Figure 2. Results of cross-disorder meta-analysis and candidate gene mapping.**

(A) Quantile-quantile (QQ) plot displaying the observed meta-analysis statistics vs. the expected ones under the null model of no associations in the  $-\log_{10}(\text{p-value})$  scale. Although a marked departure is notable between the two statistics, the estimated  $\lambda_{1000}$  and the estimated LD Score regression intercept indicate that the observed inflation is mainly due to polygenic signals rather than major confounding factors including population stratification. (B) Gene prioritization strategies for associated locus. Candidate genes were mapped on each locus if index SNP and credible SNPs reside within a protein-coding gene, are eQTL markers of the gene in the brain tissue, or interact with promoter regions of the gene based on brain Hi-C data. (C) Manhattan plot displaying the cross-disorder meta-analysis results highlighted with candidate genes mapped to top pleiotropic regions.

**Figure 3. Prediction of disorder-specific associations for illustrative pleiotropic loci: (A) rs8084351 on 18q21.2; (B) rs7193263 on 16p13.3; (C) rs117956829 on 11q14.3; and (D) rs10265001 on 7q34.**

Results are presented for the two most pleiotropic loci (A, B) and two highly pleiotropic novel loci (C, D). For each locus, disorder-specific effects of the index SNP were presented using ForestPMPlot. The first panel is the forest plot, displaying disorder-specific association p-value, log odds ratio (OR), and standard errors of the SNP. The meta-analysis p-value and the corresponding summary statistic are displayed on the top and the bottom of the forest plot, respectively. The second panel is the PM-plot, in which the X-axis represents the m-value, the posterior probability that the effect exists in each disorder, and the Y-axis represents the disorder-specific association p-value as  $-\log_{10}(\text{p-value})$ . Disorders are depicted as a dot, of which the size represents the sample size of an individual GWAS. Disorders with an estimated m-value  $\geq 0.9$  are colored in red, while those with an m-value  $< 0.9$  are marked in green.

**Figure 4. Eleven loci with opposite directional effects.** The radius of each wedge corresponds to the absolute values of the Z-scores ( $\log(\text{Odds ratio})/\text{S.E}$ ) obtained from association tests of the SNP for eight disorders. The color indicates whether the examined SNP carries risk (red) or protective effects (green) for each disorder.

**Figure 5. Results of functional genomics data analysis for pleiotropic vs.**

**disorder-specific loci.** (A) GTEX tissue-specific enrichment results for 109 pleiotropic risk loci. (B) Average gene-expression in brain cortical regions is depicted based on the pleiotropy level of the associated genes. The 147 genome-wide significant loci from the cross-disorder meta analysis were clustered into three groups based on predicted disorder-specific associations: (1) no-pleiotropy, (2) pleiotropy=2, and (3) pleiotropy>2. The “no-pleiotropy” group included 37 loci that showed a single-disorder-specific

association, while the “pleiotropy=2” and “pleiotropy>2” groups included 60 and 49 loci that are associated with two and more than two disorders, respectively. (C) Brain developmental expression trajectory displayed for the three groups of genes based on the BrainSpan data. (D) Cortical regional enrichments calculated for the three gene groups. (E) Cell-type specific enrichment analysis results.

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