nature genetics

ARTICLES

https://doi.org/10.1038/s41588-021-00857-4

Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology

Bipolar disorder is a heritable mental illness with complex etiology. We performed a genome-wide association study of 41,917 bipolar disorder cases and 371,549 controls of European ancestry, which identified 64 associated genomic loci. Bipolar disorder risk alleles were enriched in genes in synaptic signaling pathways and brain-expressed genes, particularly those with high specificity of expression in neurons of the prefrontal cortex and hippocampus. Significant signal enrichment was found in genes encoding targets of antipsychotics, calcium channel blockers, antiepileptics and anesthetics. Integrating expression quantitative trait locus data implicated 15 genes robustly linked to bipolar disorder via gene expression, encoding druggable targets such as HTR6, MCHR1, DCLK3 and FURIN. Analyses of bipolar disorder subtypes indicated high but imperfect genetic correlation between bipolar disorder type I and II and identified additional associated loci. Together, these results advance our understanding of the biological etiology of bipolar disorder, identify novel therapeutic leads and prioritize genes for functional follow-up studies.

Bipolar disorder (BD) is a complex mental disorder characterized by recurrent episodes of (hypo)mania and depression. It is a common condition affecting an estimated 40 to 50 million people worldwide[1]. This, combined with the typical onset in young adulthood, an often chronic course and increased risk of suicide[2], makes BD a major public health concern and a major cause of global disability[1]. Clinically, BD is classified into two main subtypes: bipolar I disorder (BD I), in which manic episodes typically alternate with depressive episodes, and bipolar II disorder (BD II), characterized by the occurrence of at least one hypomanic and one depressive episode[3]. These subtypes have a lifetime prevalence of ~1% each in the population[4,5].

Family and molecular genetic studies provide convincing evidence that BD is a multifactorial disorder, with genetic and environmental factors contributing to its development[6]. On the basis of twin and family studies, the heritability of BD is estimated at 60–85%[7,8]. Genome-wide association studies (GWASs)[9–23] have led to valuable insights into the genetic etiology of BD. The largest such study has been conducted by the Psychiatric Genomics Consortium (PGC), in which genome-wide SNP data from 29,764 patients with BD and 169,118 controls were analyzed and 30 genome-wide significant loci were identified (PGC2)[24]. SNP-based heritability $\left(h^2_{\mathrm{SNP}}\right)$ estimation using the same data suggested that common genetic variants genome-wide explain ~20% of BD's phenotypic variance[24]. Polygenic risk scores (PRSs) generated from the results of this study explained ~4% of phenotypic variance in independent samples. Across the genome, genetic associations with BD converged on specific biological pathways including regulation of insulin secretion[25,26], retrograde endocannabinoid signaling[24], glutamate receptor signaling[27] and calcium channel activity[9].

Despite this considerable progress, only a fraction of the genetic etiology of BD has been identified, and the specific biological mechanisms underlying the development of the disorder are still unknown. In the present study, we report the results of the third GWAS meta-analysis of the PGC Bipolar Disorder Working Group, comprising 41,917 individuals with BD and 371,549 controls. These results confirm and expand on many previously reported findings, identify novel therapeutic leads and prioritize genes for functional follow-up studies[28,29]. Thus, our results further illuminate the biological etiology of BD.

Results

GWAS results. We conducted a GWAS meta-analysis of 57 BD cohorts collected in Europe, North America and Australia (Supplementary Table 1), totaling 41,917 individuals with BD (cases) and 371,549 controls of European descent (effective $n=101{,}962$, see Methods). For 52 cohorts, individual-level genotype and phenotype data were shared with the PGC and cases met international consensus criteria (DSM-IV, ICD-9 or ICD-10) for lifetime BD, established using structured diagnostic interviews, clinician-administered checklists or medical record review. BD GWAS summary statistics were received for five external cohorts (iPSYCH[30], deCODE genetics[31], Estonian Biobank[32], Trøndelag Health Study (HUNT)[33] and UK Biobank[34]), in which most cases were ascertained using ICD codes. The GWAS meta-analysis identified 64 independent loci associated with BD at genome-wide significance ($P<5\times10^{-8}$; Fig. 1, Table 1 and Supplementary Table 2). Using linkage disequilibrium score regression (LDSC)[35], the h^2_{SNP} of BD was estimated to be 18.6% (s.e.=0.008, $P=5.1\times10^{-132}$) on the liability scale, assuming a BD population prevalence of 2%, and 15.6% (s.e.=0.006, $P=5.0\times10^{-132}$) assuming a population prevalence of 1% (Supplementary Table 3). The genomic inflation factor (λ_{GC}) was 1.38 and the LDSC intercept was 1.04 (s.e.=0.01, $P=2.5\times10^{-4}$; Supplementary Fig. 1). While the intercept has frequently been used as an indicator of confounding from population stratification, it can rise above 1 with increased sample size and heritability. The attenuation ratio—(LDSC intercept−1)/(mean of association chi-square statistics−1)—which is not subject to these limitations, was 0.06 (s.e.=0.02), indicating that the majority of inflation of the GWAS test statistics was due to polygenicity[35,36]. Of the 64 genome-wide significant loci, 33 are novel discoveries (that is, loci not overlapping with any locus previously reported as genome-wide significant for BD). Novel loci include the major histocompatibility complex (MHC) and loci previously reaching genome-wide significance for other psychiatric disorders, including ten for schizophrenia, four for major depression and three for childhood-onset psychiatric disorders or problematic alcohol use (Table 1).

A full list of authors and their affiliations appears at the end of the paper.

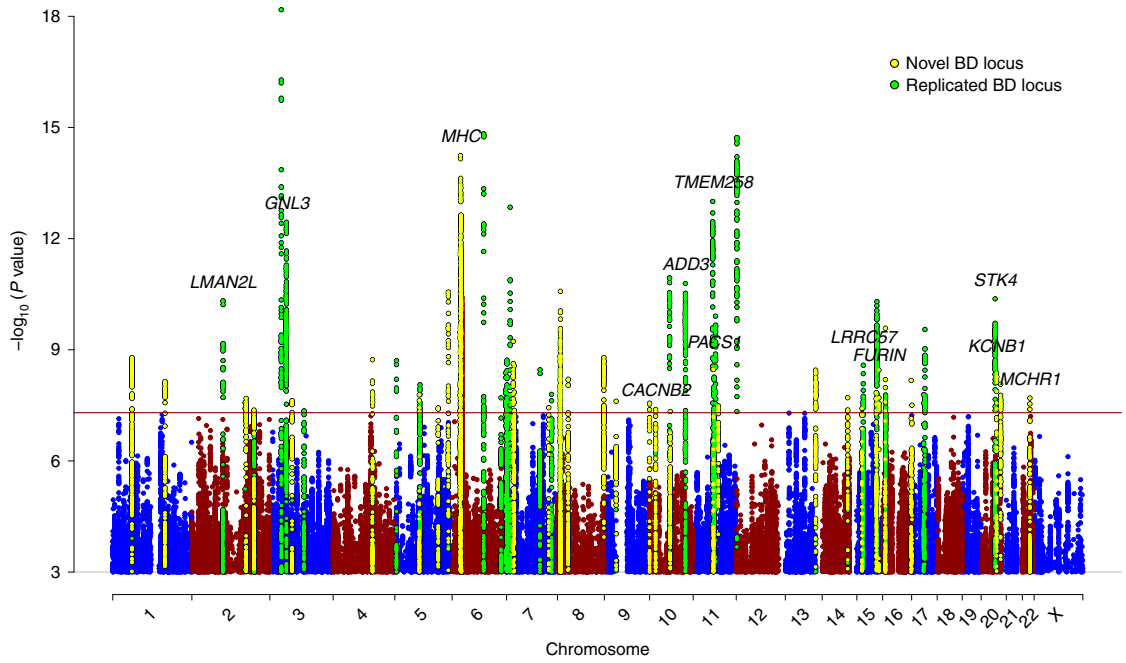

Fig. 1 | Manhattan plot of genome-wide association meta-analysis of 41,917 BD cases and 371,549 controls. The *x* axis shows genomic position (chromosomes 1–22 and X), and the *y* axis shows statistical significance as $-\log_{10}$[*P* value]. *P* values are two-sided and based on an inverse-variance-weighted fixed-effects meta-analysis. The red line shows the genome-wide significance threshold ($P < 5 \times 10^{-8}$). SNPs in genome-wide significant loci are colored green for loci previously associated with BD and yellow for novel associations from this study. The genes labeled are those prioritized by integrative eQTL analyses or notable genes in novel loci (MHC, *CACNB2* and *KCNB1*).

Enrichment analyses. Genome-wide analyses using MAGMA[37] indicated significant enrichment of BD associations in 161 genes (Supplementary Table 4) and 4 gene sets related to synaptic signaling (Supplementary Table 5). The BD association signal was enriched among genes expressed in different brain tissues (Supplementary Table 6), especially genes with high specificity of gene expression in neurons (both excitatory and inhibitory) versus other cell types, within cortical and subcortical brain regions in mice (Supplementary Fig. 2)[38]. In human brain samples, signal enrichment was also observed in hippocampal pyramidal neurons and interneurons of the prefrontal cortex and hippocampus, compared with other cell types (Supplementary Fig. 2).

In a gene-set analysis of the targets of individual drugs (from the Drug–Gene Interaction Database DGIdb v.2 (ref. [39]) and the Psychoactive Drug Screening Database Ki DB[40]), the targets of the calcium channel blockers mibefradil and nisoldipine were significantly enriched (Supplementary Table 7). Grouping drugs according to their anatomical therapeutic chemical classes[41], there was significant enrichment in the targets of four broad drug classes (Supplementary Table 8): psycholeptics (drugs with a calming effect on behavior; especially hypnotics and sedatives, antipsychotics and anxiolytics), calcium channel blockers, antiepileptics and (general) anesthetics (Supplementary Table 8).

Expression quantitative trait locus integrative analyses. We conducted a transcriptome-wide association study (TWAS) using FUSION[42] and expression quantitative trait locus (eQTL) data from the PsychENCODE Consortium (1,321 brain samples)[43]. BD-associated alleles significantly influenced expression of 77 genes in the brain (Supplementary Table 9 and Supplementary Fig. 3). These genes encompassed 40 distinct regions. We performed TWAS fine-mapping using FOCUS[44] to model the correlation among the TWAS signals and prioritize the most likely causal gene(s) in each region. Within the 90%-credible set, FOCUS prioritized 22 genes with a posterior inclusion probability (PIP) > 0.9 (encompassing 20 distinct regions) and 32 genes with a PIP > 0.7 (29 distinct regions; Supplementary Table 10).

We used summary-data-based Mendelian randomization (SMR)[45,46] to identify putative causal relationships between SNPs and BD via gene expression by integrating the BD GWAS results with brain eQTL summary statistics from the PsychENCODE[43] Consortium and blood eQTL summary statistics from the eQTLGen consortium (31,684 whole blood samples)[47]. The eQTLGen results represent the largest existing eQTL study and provide independent eQTL data. Of the 32 genes fine-mapped with PIP > 0.7, 15 were significantly associated with BD in the SMR analyses and passed the heterogeneity in dependent instruments (HEIDI) test[45,46], suggesting that their effect on BD is mediated via gene expression in the brain and/or blood (Supplementary Table 11). The genes located in genome-wide significant loci are labeled in Fig. 1. Other significant genes included *HTR6*, *DCLK3*, *HAPLN4* and *PACSIN2*.

MHC locus. Variants within and distal to the MHC locus were associated with BD at genome-wide significance. The most highly associated SNP was rs13195402, 3.2 megabases (Mb) distal to any *HLA* gene or the complement component 4 (*C4*) genes (Supplementary Fig. 4). Imputation of *C4* alleles using SNP data uncovered no association between the five most common structural forms of the *C4A*/*C4B* locus (BS, AL, AL–BS, AL–BL and AL–AL) and BD, either before or after conditioning on rs13195402 (Supplementary Fig. 5). While genetically predicted *C4A* expression initially showed a weak association with BD, this association was nonsignificant after controlling for rs13195402 (Supplementary Fig. 6).

Polygenic risk scoring. The performance of PRSs based on these GWAS results was assessed by excluding cohorts in turn from the meta-analysis to create independent test samples. PRSs explained ~4.57% of phenotypic variance in BD on the liability scale (at GWAS *P*-value threshold (GWAS P_T) < 0.1, BD population prevalence 2%), based on the weighted mean R^2 across cohorts (Fig. 2

Table 1 | Genome-wide significant loci for BD from meta-analysis of 41,917 cases and 371,549 controls

Locus	CHR	BP	SNP	*P*	OR	s.e.	A1/A2	A1 freq in controls	Previous report[a] for BD (citation)	Name for novel locus[b]	Previous report[a] for psychiatric disorders
1	1	61105668	rs2126180	1.6×10^{-9}	1.058	0.009	A/G	0.457		*LINC01748*	
2	1	163745389	rs10737496	7.2×10^{-9}	1.056	0.009	C/T	0.444		*NUF2*	CDG
3[c]	2	97416153	rs4619651	4.8×10^{-11}	1.068	0.010	G/A	0.670	*LMAN2L* (PGC2)		CDG
4	2	166152389	rs17183814	2.7×10^{-8}	1.108	0.019	G/A	0.924	*SCN2A* (PGC2)		
5	2	169481837	rs13417268	2.1×10^{-8}	1.064	0.011	C/G	0.758		*CERS6*	
6	2	193738336	rs2011302	4.3×10^{-8}	1.055	0.010	A/T	0.377		*PCGEM1*	CDG
7	2	194437889	rs2719164	4.9×10^{-8}	1.053	0.010	A/G	0.564	Intergenic (PGC2)		CDG
8[c]	3	36856030	rs9834970	6.6×10^{-19}	1.087	0.009	C/T	0.481	*TRANK1* (PGC2)		SCZ, CDG
9[c]	3	52626443	rs2336147	3.6×10^{-13}	1.070	0.009	T/C	0.498	*ITIH1* (PGC2)		SCZ, CDG
10	3	70488788	rs115694474	2.4×10^{-8}	1.068	0.012	T/A	0.799		*MDFIC2*	
11	3	107757060	rs696366	4.5×10^{-8}	1.053	0.009	C/A	0.550	*CD47* (PGC2)		
12[c]	4	123076007	rs112481526	1.9×10^{-9}	1.065	0.011	G/A	0.256		*KIAA1109*	MD
13[c]	5	7542911	rs28565152	2.0×10^{-9}	1.070	0.011	A/G	0.238	*ADCY2* (PGC2)		
14[c]	5	78849505	rs6865469	1.7×10^{-8}	1.060	0.010	T/G	0.274		*HOMER1*	
15	5	80961069	rs6887473	8.8×10^{-9}	1.062	0.011	G/A	0.739	*SSBP2* (PGC2)		
16[c]	5	137712121	rs10043984	3.7×10^{-8}	1.062	0.011	T/C	0.236		*KDM3B*	CDG
17	5	169289206	rs10866641	2.8×10^{-11}	1.065	0.009	T/C	0.575		*DOCK2*	
18[c]	6	26463575	rs13195402	5.8×10^{-15}	1.146	0.018	G/T	0.919		MHC	MD, SCZ, CDG, MOOD
19[c]	6	98565211	rs1487445	1.5×10^{-15}	1.078	0.009	T/C	0.487	*POU3F2* (PGC2)		CDG
20	6	152793572	rs4331993	2.0×10^{-8}	1.056	0.010	A/T	0.382	*SYNE1* (Green et al. 2013)		
21[c]	6	166995260	rs10455979	4.2×10^{-9}	1.057	0.010	G/C	0.500	*RPS6KA2* (PGC2)		
22[c]	7	2020995	rs12668848	1.9×10^{-9}	1.059	0.010	G/A	0.575	*MAD1L1* (Hou et al. 2016, Ikeda et al. 2018)		MD, SCZ, CDG
23[c]	7	11871787	rs113779084	1.4×10^{-13}	1.079	0.010	A/G	0.299	*THSD7A* (PGC2)		
24[c]	7	21492589	rs6954854	5.9×10^{-10}	1.060	0.009	G/A	0.425		*SP4*	
25	7	24647222	rs12672003	2.7×10^{-9}	1.096	0.016	G/A	0.113		*MPP6*	SCZ, CDG, MOOD
26	7	105043229	rs11764361	3.5×10^{-9}	1.063	0.010	A/G	0.668	*SRPK2* (PGC2)		SCZ, ASD, CDG
27	7	131870597	rs6946056	3.7×10^{-8}	1.055	0.010	C/A	0.623		*PLXNA4*	
28	7	140676153	rs10255167	1.6×10^{-8}	1.068	0.012	A/G	0.778	*MRPS33* (PGC2)		CDG
29[c]	8	9763581	rs62489493	2.6×10^{-11}	1.094	0.014	G/C	0.128		*miR124-1*	SCZ, ALC, ASD
30[c]	8	10226355	rs3088186	2.1×10^{-8}	1.058	0.010	T/C	0.287		*MSRA*	SCZ, ALC, ASD
31	8	34152492	rs2953928	6.3×10^{-9}	1.124	0.020	A/G	0.067		*RP1-84O15.2* (lincRNA)	SCZ, ADHD, CDG
32[c]	8	144993377	rs6992333	1.6×10^{-9}	1.062	0.010	G/A	0.410		*PLEC*	
33	9	37090538	rs10973201	2.5×10^{-8}	1.101	0.017	C/T	0.110		*ZCCHC7*	MD, CDG, MOOD
34[c]	9	141066490	rs62581014	2.8×10^{-8}	1.067	0.012	T/C	0.366		*TUBBP5*	
35[c]	10	18751103	rs1998820	4.1×10^{-8}	1.087	0.015	T/A	0.886		*CACNB2*	SCZ, CDG
36[c]	10	62322034	rs10994415	1.1×10^{-11}	1.125	0.017	C/T	0.082	*ANK3* (PGC2)		
37	10	64525135	rs10761661	4.7×10^{-8}	1.053	0.009	T/C	0.472		*ADO*	

Continued

Table 1 | Genome-wide significant loci for BD from meta-analysis of 41,917 cases and 371,549 controls (Continued)

Locus	CHR	BP	SNP	*P*	OR	s.e.	A1/A2	A1 freq in controls	Previous report[a] for BD (citation)	Name for novel locus[b]	Previous report[a] for psychiatric disorders
38[c]	10	111648659	rs2273738	1.6×10^{-11}	1.096	0.014	T/C	0.135	*ADD3* (Charney et al. 2017, PGC2)		
39[c]	11	61618608	rs174592	9.9×10^{-14}	1.074	0.010	G/A	0.395	*FADS2* (PGC2)		MD, CDG, MOOD
40	11	64009879	rs4672	3.4×10^{-9}	1.107	0.017	A/G	0.083		*FKBP2*	
41[c]	11	65848738	rs475805	2.0×10^{-9}	1.070	0.011	A/G	0.767	*PACS1* (PGC2)		
42[c]	11	66324583	rs678397	5.5×10^{-9}	1.056	0.009	T/C	0.457	*PC* (PGC1, PGC2)		
43[c]	11	70517927	rs12575685	1.2×10^{-10}	1.067	0.010	A/G	0.327	*SHANK2* (PGC2)		MD
44	11	79092527	rs12289486	3.3×10^{-8}	1.086	0.015	T/C	0.115	*ODZ4* (PGC1)		
45[c]	12	2348844	rs11062170	1.9×10^{-15}	1.081	0.010	C/G	0.333	*CACNA1C* (PGC2)		SCZ, CDG, MOOD
46	13	113869045	rs35306827	3.6×10^{-9}	1.068	0.011	G/A	0.775		*CUL4A*	
47	14	99719219	rs2693698	2.0×10^{-8}	1.055	0.009	G/A	0.551		*BCL11B*	SCZ, CDG
48[c]	15	38973793	rs35958438	3.8×10^{-8}	1.066	0.012	G/A	0.772		*C15orf53*	CDG
49[c]	15	42904904	rs4447398	2.6×10^{-9}	1.086	0.014	A/C	0.131	*STARD9* (PGC2)		
50	15	83531774	rs62011709	1.4×10^{-8}	1.064	0.011	T/A	0.747		*HOMER2*	SCZ
51[c]	15	85149575	rs748455	5.0×10^{-11}	1.070	0.010	T/C	0.719	*ZNF592* (PGC2)		SCZ, CDG
52	15	91426560	rs4702	3.5×10^{-9}	1.059	0.010	G/A	0.446		*FURIN*	SCZ, CDG
53	16	9230816	rs28455634	2.6×10^{-10}	1.065	0.010	G/A	0.620		*C16orf72*	
54	16	9926348	rs7199910	1.7×10^{-8}	1.057	0.010	G/T	0.312	*GRIN2A* (PGC2)		SCZ, CDG
55	16	89632725	rs12932628	6.7×10^{-9}	1.058	0.010	T/G	0.487		*RPL13*	
56	17	1835482	rs4790841	3.1×10^{-8}	1.075	0.013	T/C	0.151		*RTN4RL1*	
57	17	38129841	rs11870683	2.8×10^{-8}	1.059	0.010	T/A	0.650	*ERBB2* (Hou et al. 2016)		
58	17	38220432	rs61554907	1.6×10^{-8}	1.091	0.015	T/G	0.124	*ERBB2* (Hou et al. 2016)		
59[c]	17	42191893	rs228768	2.8×10^{-10}	1.067	0.010	G/T	0.294	*HDAC5* (PGC2)		
60[c]	20	43682551	rs67712855	4.2×10^{-11}	1.070	0.010	T/G	0.687	*STK4* (PGC2)		
61[c]	20	43944323	rs6032110	1.0×10^{-9}	1.059	0.009	A/G	0.512	*WFDC12* (PGC2)		
62[c]	20	48033127	rs237460	4.3×10^{-9}	1.057	0.009	T/C	0.412		*KCNB1*	CDG
63	20	60865815	rs13044225	8.5×10^{-9}	1.056	0.010	G/A	0.440		*OSBPL2*	
64	22	41153879	rs5758064	2.0×10^{-8}	1.054	0.009	T/C	0.523		*SLC25A17*	MD, SCZ, CDG, MOOD

[a]Previous report refers to previous association of a SNP in the locus with the psychiatric disorder at genome-wide significance. PGC1, ref. [9]; PGC2, ref. [24]; Hou et al. 2016, ref. [17]; Ikeda et al. 2018, ref. [59]; Green et al. 2013, ref. [15]; Charney et al. 2017, ref. [11]. [b]Novel loci are named using the nearest gene to the index SNP. [c]Locus overlaps with a genome-wide significant locus for BD I. CHR, chromosome; BP, GRCh37 base-pair position; OR, odds ratio; A1, tested allele; A2, other allele; freq, frequency; CDG, cross-disorder GWAS of the PGC; MD, major depression; SCZ, schizophrenia; MOOD, mood disorders; ASD, autism spectrum disorder; ALC, alcohol use disorder or problematic alcohol use; ADHD, attention deficit/hyperactivity disorder. *P* values are two-sided and based on an inverse-variance-weighted fixed-effects meta-analysis.

and Supplementary Table 12). This corresponds to a weighted mean area under the curve of 65%. Results per cohort and per wave of recruitment to the PGC are in Supplementary Tables 12 and 13 and Supplementary Fig. 7. At GWAS $P_T < 0.1$, individuals in the top 10% of BD PRSs had an odds ratio of 3.5 (95% confidence interval (CI) 1.7–7.3) of being affected with the disorder compared with individuals in the middle decile (based on the weighted mean OR across PGC cohorts), and an odds ratio of 9.3 (95% CI 1.7–49.3) compared with individuals in the lowest decile. The generalizability of PRSs from this meta-analysis was examined in several non-European cohorts. PRSs explained up to 2.3% and 1.9% of variance in BD in two East Asian samples, and 1.2% and 0.4% in two admixed African American samples (Fig. 2 and Supplementary Table 14). The variance explained by the PRSs increased in every cohort with increasing sample size of the PGC BD European discovery sample (Supplementary Fig. 8 and Supplementary Table 14).

Genetic architecture of BD and other traits. The genome-wide genetic correlation (r_g) of BD with a range of diseases and traits was assessed on LD Hub[48]. After correction for multiple testing, BD showed significant r_g with 16 traits among 255 tested from published GWASs (Supplementary Table 15). Genetic correlation was positive with all psychiatric disorders assessed, particularly schizophrenia ($r_g = 0.68$) and major depression ($r_g = 0.44$), and to a lesser degree anorexia, attention deficit/hyperactivity disorder and autism spectrum disorder ($r_g \approx 0.2$). We found evidence of positive r_g between BD

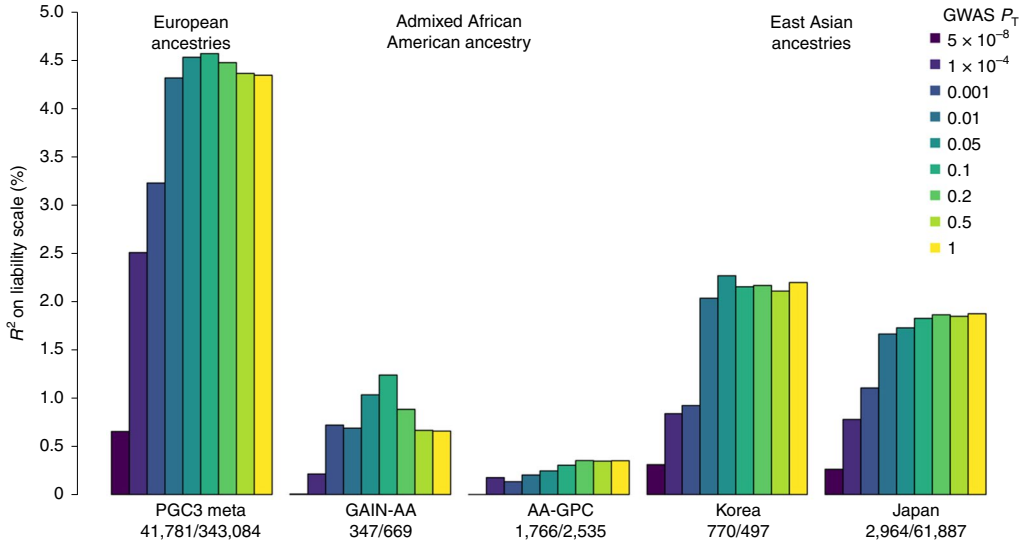

Fig. 2 | Phenotypic variance in BD explained by PRSs. Variance explained is presented on the liability scale, assuming a 2% population prevalence of BD. For European ancestries, the results shown are the weighted mean R^2 values across all 57 cohorts in the PGC3 meta-analysis, weighted by the effective *n* per cohort. The numbers of cases and controls are shown from left to right under the bar plot for each study. GWAS P_T, the color of the bars represents the *P*-value threshold used to select SNPs from the discovery GWAS; GAIN-AA, Genetic Association Information Network African American cohort; AA-GPC, African American Genomic Psychiatry Cohort.

and smoking initiation, cigarettes per day, problematic alcohol use and drinks per week (Fig. 3). BD was also positively genetically correlated with measures of sleep quality (daytime sleepiness, insomnia and sleep duration; Fig. 3). Among 514 traits measured in the general population of the UK Biobank, there was significant r_g between BD and many psychiatric-relevant traits or symptoms, dissatisfaction with interpersonal relationships, poorer overall health rating and feelings of loneliness or isolation (Supplementary Table 16).

Bivariate gaussian mixture models were applied to the GWAS summary statistics for BD and other complex traits using the MiXeR tool[49,50] to estimate the number of variants influencing each trait that explain 90% of h^2_{SNP} and their overlap between traits. MiXeR estimated that approximately 8,600 (s.e. = 200) variants influence BD, which is similar to the estimate for schizophrenia (9,700, s.e. = 200) and lower than that for major depression (12,300, s.e. = 600; Supplementary Table 17 and Supplementary Fig. 9). When considering the number of shared loci as a proportion of the total polygenicity of each trait, the vast majority of loci influencing BD were also estimated to influence major depression (97%) and schizophrenia (96%; Supplementary Table 17 and Supplementary Fig. 9). Interestingly, within these shared components, the variants that influenced both BD and schizophrenia had high concordance in direction of effect (80%, s.e. = 2%), while the portion of concordant variants between BD and major depressive disorder was only 69% (s.e. = 1%; Supplementary Table 17).

Genetic and causal relationships between BD and modifiable risk factors. Ten traits associated with BD from clinical and epidemiological studies were investigated in detail for genetic and potentially causal relationships with BD via LDSC[35], generalized summary statistics–based Mendelian randomization (GSMR)[51] and bivariate gaussian mixture modeling[49]. BD has been strongly linked with sleep disturbances[52], alcohol use[53], smoking[54], higher educational attainment[55,56] and mood instability[57]. Most of these traits had modest but significant genetic correlations with BD ($r_g = -0.05$ to 0.35; Fig. 3). Examining the effects of these traits on BD via GSMR, smoking initiation was associated with BD, corresponding to an OR of 1.49 (95% CI 1.38–1.61) for developing the disorder ($P = 1.74 \times 10^{-22}$; Fig. 3). Testing the effect of BD on the traits, we found that BD was significantly associated with reduced likelihood of being a morning person and increased number of drinks per week ($P < 1.47 \times 10^{-3}$; Fig. 3). Positive bidirectional relationships were identified between BD and longer sleep duration, problematic alcohol use, educational attainment and mood instability (Fig. 3). Notably, the instrumental variables for mood instability were selected from a GWAS conducted in the general population, excluding individuals with psychiatric disorders[58]. For all of the aforementioned BD–trait relationships, the effect size estimates from GSMR were consistent with those calculated using the inverse-variance-weighted regression method, and there was no evidence of bias from horizontal pleiotropy. Full MR results are in Supplementary Tables 18 and 19. Bivariate gaussian mixture modeling using MiXeR indicated large proportions of variants influencing both BD and all other traits tested, particularly educational attainment, where approximately 98% of variants influencing BD were estimated to also influence educational attainment. While cigarettes per day was a trait of interest, MiXeR could not model these data due to low polygenicity and heritability, and the effect of cigarettes per day on BD was inconsistent between MR methods, suggesting a violation of MR assumptions (Supplementary Tables 18–20).

BD subtypes. We conducted GWAS meta-analyses of BD I (25,060 cases, 449,978 controls) and BD II (6,781 cases, 364,075 controls). The BD I analysis identified 44 genome-wide significant loci, 31 of which overlapped with genome-wide significant loci from the main BD GWAS (Table 1 and Supplementary Table 21). The remaining 13 genome-wide significant loci for BD I all had $P < 4.0 \times 10^{-5}$ in the main BD GWAS. One genome-wide significant locus was identified in the GWAS meta-analysis of BD II and had a $P < 1.1 \times 10^{-4}$ in the main GWAS of BD (Supplementary Table 21). The h^2_{SNP} estimates on the liability scale for BD I and BD II were 20.9% (s.e. = 0.009, $P = 1.0 \times 10^{-111}$) and 11.6% (s.e. = 0.01, $P = 3.9 \times 10^{-15}$), respectively, assuming a 1% population prevalence of each subtype. These heritability values are significantly different from each other ($P = 2.4 \times 10^{-25}$, block jackknife). The genetic correlation between BD I and BD II was 0.85

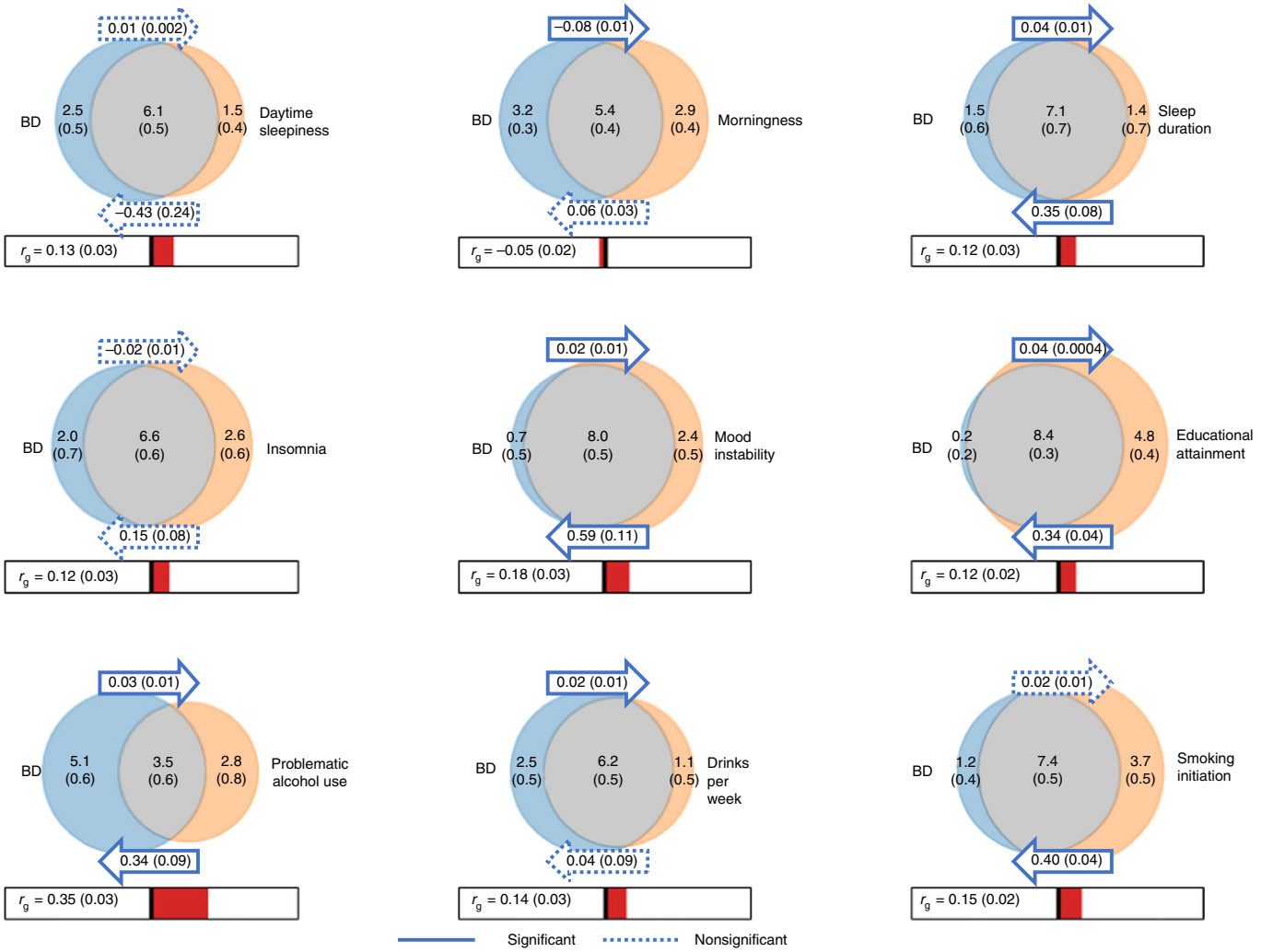

Fig. 3 | Relationships between BD and modifiable risk factors based on genetic correlations, GSMR and bivariate gaussian mixture modeling. The Venn diagrams depict MiXeR results of the estimated number of influencing variants shared between BD and each trait of interest (gray), unique to BD (blue) and unique to the trait of interest (orange). The number of influencing variants and standard error are shown in thousands. The size of the circles reflects the polygenicity of each trait, with larger circles corresponding to greater polygenicity. The estimated genetic correlation (r_g) between BD and each trait of interest and standard error from LDSC is shown below the corresponding Venn diagram, with an accompanying scale (−1 to +1). The arrows above and below the Venn diagrams indicate the results of GSMR of BD on the trait of interest, and the trait of interest on BD, respectively. The GSMR effect size and standard error is shown inside the corresponding arrow. Solid arrows indicate a significant relationship between the exposure and the outcome, after correction for multiple comparisons ($P < 1.47 \times 10^{-3}$), and dotted arrows indicate a nonsignificant relationship.

(s.e. = 0.05, $P = 2.88 \times 10^{-54}$), which is significantly different from 1 ($P = 1.6 \times 10^{-3}$). The genetic correlation of BD I with schizophrenia ($r_g = 0.66$, s.e. = 0.02) was higher than that of BD II ($r_g = 0.54$, s.e. = 0.05), whereas major depression was more strongly genetically correlated with BD II ($r_g = 0.66$, s.e. = 0.05) than with BD I ($r_g = 0.34$, s.e. = 0.03; Supplementary Table 22).

Discussion

In a GWAS of 41,917 BD cases, we identified 64 associated genomic loci, 33 of which are novel discoveries. With a 1.5-fold increase in effective sample size compared with the PGC2 BD GWAS, this study more than doubled the number of associated loci, representing an inflection point in the rate of risk variant discovery. We observed consistent replication of known BD loci, including 28/30 loci from the PGC2 GWAS[24] and several implicated by other BD GWAS[15–17], including a study of East Asian cases[59].

The 33 novel loci discovered here encompass genes of expected biological relevance to BD, such as the ion-channel-encoding genes *CACNB2* and *KCNB1*. Among the 64 BD loci, 17 have previously been implicated in GWAS of schizophrenia[60], and 7 in GWAS of major depression[61], representing the first overlap of genome-wide significant loci between the mood disorders. For these genome-wide significant loci shared across disorders, 17/17 and 5/7 of the BD index SNPs had the same direction of effect on schizophrenia and major depression, respectively (Supplementary Table 23). More generally, 50/64 and 62/64 BD loci had a consistent direction of effect on major depression and schizophrenia, respectively, considerably greater than chance ($P < 1 \times 10^{-5}$, binomial test). Bivariate gaussian mixture modeling estimated that across the entire genome, almost all variants influencing BD also influence schizophrenia and major depression, albeit with variable effects[62]. SNPs in and around the MHC locus reached genome-wide significance for BD for the first time. However, unlike in schizophrenia, we found no influence of *C4* structural alleles or gene expression[63]. Rather, the association was driven by variation outside the classical MHC locus, with the index SNP (rs13195402) being a missense

variant in *BTN2A1*, a brain-expressed gene[64] encoding a plasma membrane protein.

The genetic correlation of BD with other psychiatric disorders was consistent with previous reports[65,66]. Our results also corroborate previous genetic and clinical evidence of associations between BD and sleep disturbances[67], problematic alcohol use[68] and smoking[69]. While the genome-wide genetic correlations with these traits were modest ($r_g = -0.05$ to 0.35), MiXeR estimated that, for all traits, more than 55% of trait-influencing variants also influence BD (Fig. 3). Taken together, these results point to shared biology as one possible explanation for the high prevalence of substance use in BD. However, excluding genetic variants associated with both traits, MR analyses suggested that smoking is also a putatively 'causal' risk factor for BD, while BD has no effect on smoking, consistent with a previous report[70]. (We use the word 'causal' with caution here as we consider MR an exploratory analysis to identify potentially modifiable risk factors that warrant more detailed investigations to understand their complex relationship with BD.) In contrast, MR indicated that BD had bidirectional 'causal' relationships with problematic alcohol use, longer sleep duration and mood instability. Insights into the relationship of such behavioral correlates with BD may have future impact on clinical decision-making in the prophylaxis or management of the disorder. Higher educational attainment has previously been associated with BD in epidemiological studies[55,56], while lower educational attainment has been associated with schizophrenia and major depression[71,72]. Here, educational attainment had a significant positive effect on risk of BD and vice versa. Interestingly, MiXeR estimated that almost all variants that influence BD also influence educational attainment. The substantial genetic overlap observed between BD and the other phenotypes suggests that many variants likely influence multiple phenotypes, which may be differentiated by phenotype-specific effect size distributions among the shared influencing variants.

The integration of eQTL data with our GWAS results yielded 15 high-confidence genes for which there was converging evidence that their association with BD is mediated via gene expression. Among these were *HTR6*, encoding a serotonin receptor targeted by antipsychotics and antidepressants[73], and *MCHR1* (melanin-concentrating hormone receptor 1), encoding a target of the antipsychotic haloperidol[73]. We note that, for both of these genes, their top eQTLs have opposite directions of effect on gene expression in the brain and blood, possibly playing a role in the tissue-specific gene regulation influencing BD[74]. BD was associated with decreased expression of *FURIN*, a gene with a neurodevelopmental role that has already been the subject of functional genomics experiments in neuronal cells following its association with schizophrenia in GWAS[75]. The top association in our GWAS was in the *TRANK1* locus on chromosome 3, which has previously been implicated in BD[12,18,59]. Although BD-associated SNPs in this locus are known to regulate *TRANK1* expression[76], our eQTL analyses support a stronger but correlated regulation of *DCLK3*, located 87 kilobases (kb) upstream of *TRANK1* (refs. [43,77]). Both *FURIN* and *DCLK3* also encode druggable proteins (although they are not targets for any current psychiatric medications)[73,78]. These eQTL results provide promising BD candidate genes for functional follow-up experiments[29]. While several of these are in genome-wide significant loci, many are not the closest gene to the index SNP, highlighting the value of probing underlying molecular mechanisms to prioritize the most likely causal genes in the loci.

GWAS signals were enriched in the gene targets of existing BD pharmacological agents, such as antipsychotics, mood stabilizers and antiepileptics. However, enrichment was also found in the targets of calcium channel blockers used to treat hypertension and GABA-receptor-targeting anesthetics (Supplementary Table 8). Calcium channel antagonists have long been investigated for the treatment of BD, without becoming an established therapeutic approach, and there is evidence that some antiepileptics have calcium-channel-inhibiting effects[79,80]. These results underscore the opportunity for repurposing some classes of drugs, particularly calcium channel antagonists, as potential BD treatments[81].

BD associations were enriched in gene sets involving neuronal parts and synaptic signaling. Neuronal and synaptic pathways have been described in cross-disorder GWAS of multiple psychiatric disorders including BD[82–84]. Dysregulation of such pathways has also been suggested by previous functional and animal studies[85]. Analysis of single-cell gene expression data revealed enrichment in genes with high specificity of gene expression in neurons (both excitatory and inhibitory) of many brain regions, in particular the cortex and hippocampus. These findings are similar to those reported in GWAS data of schizophrenia[86] and major depressive disorder[38].

PRSs for BD explained on average 4.57% of phenotypic variance (liability scale) across European cohorts, although this varied in different waves of the BD GWAS, ranging from 6.6% in the PGC1 cohorts to 2.9% in the external biobank studies (Supplementary Fig. 7 and Supplementary Table 12). These results are in line with the h^2_{SNP} of BD per wave, which ranged from 24.6% (s.e. = 0.01) in PGC1 to 11.9% (s.e. = 0.01) in external studies (Supplementary Table 3). Some variability in h^2_{SNP} estimates may arise from the inclusion of cases from population biobanks, who may have more heterogeneous clinical presentations or less severe illness than patients with BD ascertained via inpatient or outpatient psychiatric clinics. Across the waves of clinically ascertained samples within the PGC, h^2_{SNP} and the R^2 of PRSs also varied, likely reflecting clinical and genetic heterogeneity in the type of BD cases ascertained; the PGC1 cohorts consisted mostly of BD I cases[9], known to be the most heritable of the BD subtypes[11,24], while later waves included more individuals with BD II[24]. Overall, the h^2_{SNP} of BD calculated from the meta-analysis summary statistics was 18% on the liability scale, a decrease of ~2% compared with the PGC2 GWAS[24], which may be due to the addition of cohorts with lower h^2_{SNP} estimates and heterogeneity between cohorts (Supplementary Table 3). However, despite differences in h^2_{SNP} and R^2 of PRSs per wave, the genetic correlation of BD between all waves was high (weighted mean $r_g = 0.94$, s.e. = 0.03), supporting our rationale for combining cases with different BD subtypes or ascertainment to increase power for discovery of risk variants. In Europeans, individuals in the top 10% of PRSs had an OR of 3.5 for BD, compared with individuals with average PRSs (middle decile), which translates into a modest absolute lifetime risk of the disorder (7% based on PRSs alone). While PRSs are invaluable tools in research settings, the current BD PRSs lack sufficient power to separate individuals into clinically meaningful risk categories, and therefore have no clinical utility at present[87,88]. PRSs from this European BD meta-analysis yield higher R^2 values in diverse ancestry samples than PRSs based on any currently available BD GWAS within the same ancestry[59]. However, performance still greatly lags behind that in Europeans, with ~2% variance explained in East Asian samples and substantially less in admixed African American samples, likely due to differences in allele frequencies and LD structures, consistent with previous studies[89,90]. There is a pressing need for more and larger studies in other ancestry groups to ensure that any future clinical utility is broadly applicable. Exploiting the differences in LD structure between diverse ancestry samples will also assist in the fine-mapping of risk loci for BD.

Our analyses confirmed that BD is a highly polygenic disorder, with an estimated 8,600 variants explaining 90% of its h^2_{SNP}. Hence, many more SNPs than those identified here are expected to account for the common variant architecture underlying BD. This GWAS marks an inflection point in risk variant discovery, and we expect that, from this point forward, the addition of more samples will lead to a dramatic increase in genetic findings. Nevertheless, fewer genome-wide significant loci have been identified in BD than in a schizophrenia GWASs of comparable sample size[60]. This may be due to the clinical and genetic heterogeneity that exists in BD.

Our GWAS of subtypes BD I and BD II identified additional associated loci. Consistent with previous findings[24], our analysis showed that the two subtypes were highly but imperfectly genetically correlated ($r_g = 0.85$), and that BD I is more genetically correlated with schizophrenia, while BD II has stronger genetic correlation with major depression. The subtypes are sufficiently similar to justify joint analysis as BD, but are not identical in their genetic composition, and as such contribute to the genetic heterogeneity of BD[91]. We identified 13 loci passing genome-wide significance for BD I, and one for BD II, which did not reach significance in the main BD GWAS, further illustrating the partially differing genetic composition of the two subtypes. Understanding the shared and distinct genetic components of BD subtypes and symptoms requires detailed phenotyping efforts in large cohorts and is an important area for future psychiatric genetics research.

In summary, these new data advance our understanding of the biological etiology of BD and prioritize a set of candidate genes for functional follow-up experiments. Several lines of evidence converge on the involvement of calcium channel signaling, providing a promising avenue for future therapeutic development.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41588-021-00857-4.

Received: 2 September 2020; Accepted: 25 March 2021;
Published online: 17 May 2021

References

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **390**, 1211–1259 (2017).
2. Plans, L. et al. Association between completed suicide and bipolar disorder: a systematic review of the literature. *J. Affect. Disord.* **242**, 111–122 (2019).
3. American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders* 5th edn (American Psychiatric Association Publishing, 2013).
4. Merikangas, K. R. et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Arch. Gen. Psychiatry* **64**, 543–552 (2007).
5. Merikangas, K. R. et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch. Gen. Psychiatry* **68**, 241–251 (2011).
6. Craddock, N. & Sklar, P. Genetics of bipolar disorder. *Lancet* **381**, 1654–1662 (2013).
7. Song, J. et al. Bipolar disorder and its relation to major psychiatric disorders: a family-based study in the Swedish population. *Bipolar Disord.* **17**, 184–193 (2015).
8. Bienvenu, O. J., Davydow, D. S. & Kendler, K. S. Psychiatric 'diseases' versus behavioral disorders and degree of genetic influence. *Psychol. Med.* **41**, 33–40 (2011).
9. Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near *ODZ4*. *Nat. Genet.* **43**, 977–983 (2011).
10. Baum, A. E. et al. A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Mol. Psychiatry* **13**, 197–207 (2008).
11. Charney, A. W. et al. Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder. *Transl. Psychiatry* **7**, e993 (2017).
12. Chen, D. T. et al. Genome-wide association study meta-analysis of European and Asian-ancestry samples identifies three novel loci associated with bipolar disorder. *Mol. Psychiatry* **18**, 195–205 (2013).
13. Cichon, S. et al. Genome-wide association study identifies genetic variation in neurocan as a susceptibility factor for bipolar disorder. *Am. J. Hum. Genet.* **88**, 372–381 (2011).
14. Ferreira, M. A. R. et al. Collaborative genome-wide association analysis supports a role for *ANK3* and *CACNA1C* in bipolar disorder. *Nat. Genet.* **40**, 1056–1058 (2008).
15. Green, E. K. et al. Association at *SYNE1* in both bipolar disorder and recurrent major depression. *Mol. Psychiatry* **18**, 614–617 (2013).
16. Green, E. K. et al. Replication of bipolar disorder susceptibility alleles and identification of two novel genome-wide significant associations in a new bipolar disorder case–control sample. *Mol. Psychiatry* **18**, 1302–1307 (2013).
17. Hou, L. et al. Genome-wide association study of 40,000 individuals identifies two novel loci associated with bipolar disorder. *Hum. Mol. Genet.* **25**, 3383–3394 (2016).
18. Mühleisen, T. W. et al. Genome-wide association study reveals two new risk loci for bipolar disorder. *Nat. Commun.* **5**, 3339 (2014).
19. Schulze, T. G. et al. Two variants in Ankyrin 3 (*ANK3*) are independent genetic risk factors for bipolar disorder. *Mol. Psychiatry* **14**, 487–491 (2009).
20. Scott, L. J. et al. Genome-wide association and meta-analysis of bipolar disorder in individuals of European ancestry. *Proc. Natl Acad. Sci. USA* **106**, 7501–7506 (2009).
21. Sklar, P. et al. Whole-genome association study of bipolar disorder. *Mol. Psychiatry* **13**, 558–569 (2008).
22. Smith, E. N. et al. Genome-wide association study of bipolar disorder in European American and African American individuals. *Mol. Psychiatry* **14**, 755–763 (2009).
23. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661–678 (2007).
24. Stahl, E. A. et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat. Genet.* **51**, 793–803 (2019).
25. Lee, S.-H., Zabolotny, J. M., Huang, H., Lee, H. & Kim, Y.-B. Insulin in the nervous system and the mind: functions in metabolism, memory, and mood. *Mol. Metab.* **5**, 589–601 (2016).
26. McIntyre, R. S. et al. A randomized, double-blind, controlled trial evaluating the effect of intranasal insulin on neurocognitive function in euthymic patients with bipolar disorder. *Bipolar Disord.* **14**, 697–706 (2012).
27. Nurnberger, J. I. Jr et al. Identification of pathways for bipolar disorder: a meta-analysis. *JAMA Psychiatry* **71**, 657–664 (2014).
28. Gordovez, F. J. A. & McMahon, F. J. The genetics of bipolar disorder. *Mol. Psychiatry* **25**, 544–559 (2020).
29. Zhang, C., Xiao, X., Li, T. & Li, M. Translational genomics and beyond in bipolar disorder. *Mol. Psychiatry* **26**, 186–202 (2021).
30. Pedersen, C. B. et al. The iPSYCH2012 case–cohort sample: new directions for unravelling genetic and environmental architectures of severe mental disorders. *Mol. Psychiatry* **1**, 6–14 (2018).
31. Gudbjartsson, D. F. et al. Large-scale whole-genome sequencing of the Icelandic population. *Nat. Genet.* **47**, 435–444 (2015).
32. Leitsalu, L. et al. Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. *Int. J. Epidemiol.* **44**, 1137–1147 (2015).
33. Krokstad, S. et al. Cohort Profile: the HUNT Study, Norway. *Int. J. Epidemiol.* **42**, 968–977 (2013).
34. Sudlow, C. et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* **12**, e1001779 (2015).
35. Bulik-Sullivan, B. K. et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).
36. Loh, P.-R., Kichaev, G., Gazal, S., Schoech, A. P. & Price, A. L. Mixed-model association for biobank-scale datasets. *Nat. Genet.* **50**, 906–908 (2018).
37. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).
38. Bryois, J. et al. Genetic identification of cell types underlying brain complex traits yields insights into the etiology of Parkinson's disease. *Nat. Genet.* **52**, 482–493 (2020).
39. Wagner, A. H. et al. DGIdb 2.0: mining clinically relevant drug–gene interactions. *Nucleic Acids Res.* **44**, D1036–D1044 (2016).
40. Roth, B. L., Lopez, E., Patel, S. & Kroeze, W. K. The multiplicity of serotonin receptors: uselessly diverse molecules or an embarrassment of riches? *Neuroscientist* **6**, 252–262 (2000).
41. Gaspar, H. A. & Breen, G. Drug enrichment and discovery from schizophrenia genome-wide association results: an analysis and visualisation approach. *Sci. Rep.* **7**, 12460 (2017).
42. Gusev, A. et al. Integrative approaches for large-scale transcriptome-wide association studies. *Nat. Genet.* **48**, 245–252 (2016).
43. Gandal, M. J. et al. Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. *Science* **362**, eaat8127 (2018).
44. Mancuso, N. et al. Probabilistic fine-mapping of transcriptome-wide association studies. *Nat. Genet.* **51**, 675–682 (2019).
45. Zhu, Z. et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48**, 481–487 (2016).
46. Wu, Y. et al. Integrative analysis of omics summary data reveals putative mechanisms underlying complex traits. *Nat. Commun.* **9**, 918 (2018).

47. Võsa, U. et al. Unraveling the polygenic architecture of complex traits using blood eQTL metaanalysis. Preprint at *bioRxiv* https://doi.org/10.1101/447367 (2018).
48. Zheng, J. et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics* **33**, 272–279 (2017).
49. Frei, O. et al. Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation. *Nat. Commun.* **10**, 2417 (2019).
50. Holland, D. et al. Beyond SNP heritability: polygenicity and discoverability of phenotypes estimated with a univariate Gaussian mixture model. *PLoS Genet.* **16**, e1008612 (2020).
51. Zhu, Z. et al. Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat. Commun.* **9**, 224 (2018).
52. Steardo, L. Jr et al. Sleep disturbance in bipolar disorder: neuroglia and circadian rhythms. *Front. Psychiatry* **10**, 501 (2019).
53. Hunt, G. E., Malhi, G. S., Cleary, M., Lai, H. M. X. & Sitharthan, T. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990–2015: systematic review and meta-analysis. *J. Affect. Disord.* **206**, 331–349 (2016).
54. Heffner, J. L., Strawn, J. R., DelBello, M. P., Strakowski, S. M. & Anthenelli, R. M. The co-occurrence of cigarette smoking and bipolar disorder: phenomenology and treatment considerations. *Bipolar Disord.* **13**, 439–453 (2011).
55. Vreeker, A. et al. High educational performance is a distinctive feature of bipolar disorder: a study on cognition in bipolar disorder, schizophrenia patients, relatives and controls. *Psychol. Med.* **46**, 807–818 (2016).
56. MacCabe, J. H. et al. Excellent school performance at age 16 and risk of adult bipolar disorder: national cohort study. *Br. J. Psychiatry* **196**, 109–115 (2010).
57. Broome, M. R., Saunders, K. E. A., Harrison, P. J. & Marwaha, S. Mood instability: significance, definition and measurement. *Br. J. Psychiatry* **207**, 283–285 (2015).
58. Ward, J. et al. The genomic basis of mood instability: identification of 46 loci in 363,705 UK Biobank participants, genetic correlation with psychiatric disorders, and association with gene expression and function. *Mol. Psychiatry* **25**, 3091–3099 (2020).
59. Ikeda, M. et al. A genome-wide association study identifies two novel susceptibility loci and trans population polygenicity associated with bipolar disorder. *Mol. Psychiatry* **23**, 639–647 (2018).
60. Pardiñas, A. F. et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat. Genet.* **50**, 381–389 (2018).
61. Howard, D. M. et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat. Neurosci.* **22**, 343–352 (2019).
62. Smeland, O. B., Frei, O., Dale, A. M. & Andreassen, O. A. The polygenic architecture of schizophrenia – rethinking pathogenesis and nosology. *Nat. Rev. Neurol.* **16**, 366–379 (2020).
63. Sekar, A. et al. Schizophrenia risk from complex variation of complement component 4. *Nature* **530**, 177–183 (2016).
64. GTEx Consortium et al. Genetic effects on gene expression across human tissues. *Nature* **550**, 204–213 (2017).
65. Brainstorm Consortium et al. Analysis of shared heritability in common disorders of the brain. *Science* **360**, eaap8757 (2018).
66. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell* **179**, 1469–1482 (2019).
67. Lewis, K. J. S. et al. Comparison of genetic liability for sleep traits among individuals with bipolar disorder I or II and control participants. *JAMA Psychiatry* **77**, 303–310 (2020).
68. Zhou, H. et al. Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. *Nat. Neurosci.* **23**, 809–818 (2020).
69. Okbay, A. et al. Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* **533**, 539–542 (2016).
70. Vermeulen, J. M. et al. Smoking and the risk for bipolar disorder: evidence from a bidirectional Mendelian randomisation study. *Br. J. Psychiatry* **218**, 88–94 (2021).
71. Peyrot, W. J. et al. The association between lower educational attainment and depression owing to shared genetic effects? Results in ~25 000 subjects. *Mol. Psychiatry* **20**, 735–743 (2015).
72. Swanson, C. L. Jr, Gur, R. C., Bilker, W., Petty, R. G. & Gur, R. E. Premorbid educational attainment in schizophrenia: association with symptoms, functioning, and neurobehavioral measures. *Biol. Psychiatry* **44**, 739–747 (1998).
73. Wishart, D. S. et al. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res.* **46**, D1074–D1082 (2018).
74. Mizuno, A. & Okada, Y. Biological characterization of expression quantitative trait loci (eQTLs) showing tissue-specific opposite directional effects. *Eur. J. Hum. Genet.* **27**, 1745–1756 (2019).
75. Schrode, N. et al. Synergistic effects of common schizophrenia risk variants. *Nat. Genet.* **51**, 1475–1485 (2019).
76. Jiang, X. et al. Sodium valproate rescues expression of *TRANK1* in iPSC-derived neural cells that carry a genetic variant associated with serious mental illness. *Mol. Psychiatry* **24**, 613–624 (2019).
77. Huckins, L. M. et al. Transcriptomic imputation of bipolar disorder and bipolar subtypes reveals 29 novel associated genes. Preprint at *bioRxiv* https://doi.org/10.1101/222786 (2017).
78. Finan, C. et al. The druggable genome and support for target identification and validation in drug development. *Sci. Transl. Med.* **9**, eaag1166 (2017).
79. von Wegerer, J., Hesslinger, B., Berger, M. & Walden, J. A calcium antagonistic effect of the new antiepileptic drug lamotrigine. *Eur. Neuropsychopharmacol.* **7**, 77–81 (1997).
80. Cipriani, A. et al. A systematic review of calcium channel antagonists in bipolar disorder and some considerations for their future development. *Mol. Psychiatry* **21**, 1324–1332 (2016).
81. Harrison, P. J., Tunbridge, E. M., Dolphin, A. C. & Hall, J. Voltage-gated calcium channel blockers for psychiatric disorders: genomic reappraisal. *Br. J. Psychiatry* **216**, 250–253 (2020).
82. Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat. Neurosci.* **18**, 199–209 (2015).
83. Forstner, A. J. et al. Identification of shared risk loci and pathways for bipolar disorder and schizophrenia. *PLoS ONE* **12**, e0171595 (2017).
84. Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. *Cell* **173**, 1705–1715 (2018).
85. Lee, Y., Zhang, Y., Kim, S. & Han, K. Excitatory and inhibitory synaptic dysfunction in mania: an emerging hypothesis from animal model studies. *Exp. Mol. Med.* **50**, 1–11 (2018).
86. Skene, N. G. et al. Genetic identification of brain cell types underlying schizophrenia. *Nat. Genet.* **50**, 825–833 (2018).
87. Lewis, C. M. & Vassos, E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med.* **12**, 44 (2020).
88. Torkamani, A., Wineinger, N. E. & Topol, E. J. The personal and clinical utility of polygenic risk scores. *Nat. Rev. Genet.* **19**, 581–590 (2018).
89. Duncan, L. et al. Analysis of polygenic risk score usage and performance in diverse human populations. *Nat. Commun.* **10**, 3328 (2019).
90. Martin, A. R. et al. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat. Genet.* **51**, 584–591 (2019).
91. Coleman, J. R. I. et al. The genetics of the mood disorder spectrum: genome-wide association analyses of more than 185,000 cases and 439,000 controls. *Biol. Psychiatry* **88**, 169–184 (2020).

Niamh Mullins[1,2,235] ✉, Andreas J. Forstner[3,4,5,235], Kevin S. O'Connell[6,7], Brandon Coombes[8], Jonathan R. I. Coleman[9,10], Zhen Qiao[11], Thomas D. Als[12,13,14], Tim B. Bigdeli[15,16], Sigrid Børte[17,18,19], Julien Bryois[20], Alexander W. Charney[2], Ole Kristian Drange[21,22], Michael J. Gandal[23], Saskia P. Hagenaars[9,10], Masashi Ikeda[24], Nolan Kamitaki[25,26], Minsoo Kim[23], Kristi Krebs[27], Georgia Panagiotaropoulou[28], Brian M. Schilder[1,29,30,31], Laura G. Sloofman[1], Stacy Steinberg[32], Vassily Trubetskoy[28], Bendik S. Winsvold[19,33], Hong-Hee Won[34], Liliya Abramova[35], Kristina Adorjan[36,37], Esben Agerbo[14,38,39], Mariam Al Eissa[40], Diego Albani[41], Ney Alliey-Rodriguez[42,43],

Adebayo Anjorin[44], Verneri Antilla[45], Anastasia Antoniou[46], Swapnil Awasthi[28], Ji Hyun Baek[47], Marie Bækvad-Hansen[14,48], Nicholas Bass[40], Michael Bauer[49], Eva C. Beins[3], Sarah E. Bergen[20], Armin Birner[50], Carsten Bøcker Pedersen[14,38,39], Erlend Bøen[51], Marco P. Boks[52], Rosa Bosch[53,54,55,56], Murielle Brum[57], Ben M. Brumpton[19], Nathalie Brunkhorst-Kanaan[57], Monika Budde[36], Jonas Bybjerg-Grauholm[14,48], William Byerley[58], Murray Cairns[59], Miquel Casas[53,54,55,56], Pablo Cervantes[60], Toni-Kim Clarke[61], Cristiana Cruceanu[60,62], Alfredo Cuellar-Barboza[63,64], Julie Cunningham[65], David Curtis[66,67], Piotr M. Czerski[68], Anders M. Dale[69], Nina Dalkner[50], Friederike S. David[3], Franziska Degenhardt[3,70], Srdjan Djurovic[71,72], Amanda L. Dobbyn[1,2], Athanassios Douzenis[46], Torbjørn Elvsåshagen[18,73,74], Valentina Escott-Price[75], I. Nicol Ferrier[76], Alessia Fiorentino[40], Tatiana M. Foroud[77], Liz Forty[75], Josef Frank[78], Oleksandr Frei[6,18], Nelson B. Freimer[23,79], Louise Frisén[80], Katrin Gade[36,81], Julie Garnham[82], Joel Gelernter[83,84,85], Marianne Giørtz Pedersen[14,38,39], Ian R. Gizer[86], Scott D. Gordon[87], Katherine Gordon-Smith[88], Tiffany A. Greenwood[89], Jakob Grove[12,13,14,90], José Guzman-Parra[91], Kyooseob Ha[92], Magnus Haraldsson[93], Martin Hautzinger[94], Urs Heilbronner[36], Dennis Hellgren[20], Stefan Herms[3,95,96], Per Hoffmann[3,95,96], Peter A. Holmans[75], Laura Huckins[1,2], Stéphane Jamain[97,98], Jessica S. Johnson[1,2], Janos L. Kalman[36,37,99], Yoichiro Kamatani[100,101], James L. Kennedy[102,103,104,105], Sarah Kittel-Schneider[57,106], James A. Knowles[107,108], Manolis Kogevinas[109], Maria Koromina[110], Thorsten M. Kranz[57], Henry R. Kranzler[111,112], Michiaki Kubo[113], Ralph Kupka[114,115,116], Steven A. Kushner[117], Catharina Lavebratt[118,119], Jacob Lawrence[120], Markus Leber[121], Heon-Jeong Lee[122], Phil H. Lee[123], Shawn E. Levy[124], Catrin Lewis[75], Calwing Liao[125,126], Susanne Lucae[62], Martin Lundberg[118,119], Donald J. MacIntyre[127], Sigurdur H. Magnusson[32], Wolfgang Maier[128], Adam Maihofer[89], Dolores Malaspina[1,2], Eirini Maratou[129], Lina Martinsson[80], Manuel Mattheisen[12,13,14,106,130], Steven A. McCarroll[25,26], Nathaniel W. McGregor[131], Peter McGuffin[9], James D. McKay[132], Helena Medeiros[108], Sarah E. Medland[87], Vincent Millischer[118,119], Grant W. Montgomery[11], Jennifer L. Moran[25,133], Derek W. Morris[134], Thomas W. Mühleisen[4,95], Niamh O'Brien[40], Claire O'Donovan[82], Loes M. Olde Loohuis[23,79], Lilijana Oruc[135], Sergi Papiol[36,37], Antonio F. Pardiñas[75], Amy Perry[88], Andrea Pfennig[49], Evgenia Porichi[46], James B. Potash[136], Digby Quested[137,138], Towfique Raj[1,29,30,31], Mark H. Rapaport[139], J. Raymond DePaulo[136], Eline J. Regeer[140], John P. Rice[141], Fabio Rivas[91], Margarita Rivera[142,143], Julian Roth[106], Panos Roussos[1,2,29], Douglas M. Ruderfer[144], Cristina Sánchez-Mora[53,54,56,145], Eva C. Schulte[36,37], Fanny Senner[36,37], Sally Sharp[40], Paul D. Shilling[89], Engilbert Sigurdsson[93,146], Lea Sirignano[78], Claire Slaney[82], Olav B. Smeland[6,7], Daniel J. Smith[147], Janet L. Sobell[148], Christine Søholm Hansen[14,48], Maria Soler Artigas[53,54,56,145], Anne T. Spijker[149], Dan J. Stein[150], John S. Strauss[102], Beata Świątkowska[151], Chikashi Terao[101], Thorgeir E. Thorgeirsson[32], Claudio Toma[152,153,154], Paul Tooney[59], Evangelia-Eirini Tsermpini[110], Marquis P. Vawter[155], Helmut Vedder[156], James T. R. Walters[75], Stephanie H. Witt[78], Simon Xi[157], Wei Xu[158], Jessica Mei Kay Yang[75], Allan H. Young[159,160], Hannah Young[1], Peter P. Zandi[136], Hang Zhou[83,84], Lea Zillich[78], HUNT All-In Psychiatry*, Rolf Adolfsson[161], Ingrid Agartz[51,130,162], Martin Alda[82,163], Lars Alfredsson[164], Gulja Babadjanova[165], Lena Backlund[118,119], Bernhard T. Baune[166,167,168], Frank Bellivier[169,170], Susanne Bengesser[50], Wade H. Berrettini[171], Douglas H. R. Blackwood[61], Michael Boehnke[172], Anders D. Børglum[14,173,174], Gerome Breen[9,10], Vaughan J. Carr[175], Stanley Catts[176], Aiden Corvin[177], Nicholas Craddock[75], Udo Dannlowski[166], Dimitris Dikeos[178], Tõnu Esko[26,27,179,180], Bruno Etain[169,170], Panagiotis Ferentinos[9,46], Mark Frye[64], Janice M. Fullerton[152,153], Micha Gawlik[106], Elliot S. Gershon[42,181],

Fernando S. Goes[136], Melissa J. Green[152,175], Maria Grigoroiu-Serbanescu[182], Joanna Hauser[68], Frans Henskens[59], Jan Hillert[80], Kyung Sue Hong[47], David M. Hougaard[14,48], Christina M. Hultman[20], Kristian Hveem[19,183], Nakao Iwata[24], Assen V. Jablensky[184], Ian Jones[75], Lisa A. Jones[88], René S. Kahn[2,52], John R. Kelsoe[89], George Kirov[75], Mikael Landén[20,185], Marion Leboyer[97,98,186], Cathryn M. Lewis[9,10,187], Qingqin S. Li[188], Jolanta Lissowska[189], Christine Lochner[190], Carmel Loughland[59], Nicholas G. Martin[87,191], Carol A. Mathews[192], Fermin Mayoral[91], Susan L. McElroy[193], Andrew M. McIntosh[127,194], Francis J. McMahon[195], Ingrid Melle[6,196], Patricia Michie[59], Lili Milani[27], Philip B. Mitchell[175], Gunnar Morken[21,197], Ole Mors[14,198], Preben Bo Mortensen[12,14,38,39], Bryan Mowry[176], Bertram Müller-Myhsok[62,199,200], Richard M. Myers[124], Benjamin M. Neale[25,45,179], Caroline M. Nievergelt[89,201], Merete Nordentoft[14,202], Markus M. Nöthen[3], Michael C. O'Donovan[75], Ketil J. Oedegaard[203,204], Tomas Olsson[205], Michael J. Owen[75], Sara A. Paciga[206], Chris Pantelis[207], Carlos Pato[108], Michele T. Pato[108], George P. Patrinos[110,208,209], Roy H. Perlis[210,211], Danielle Posthuma[212,213], Josep Antoni Ramos-Quiroga[53,54,55,56], Andreas Reif[57], Eva Z. Reininghaus[50], Marta Ribasés[53,54,56,145], Marcella Rietschel[78], Stephan Ripke[25,28,45], Guy A. Rouleau[126,214], Takeo Saito[24], Ulrich Schall[59], Martin Schalling[118,119], Peter R. Schofield[152,153], Thomas G. Schulze[36,78,81,136,215], Laura J. Scott[172], Rodney J. Scott[59], Alessandro Serretti[216], Cynthia Shannon Weickert[152,175,217], Jordan W. Smoller[25,133,218], Hreinn Stefansson[32], Kari Stefansson[32,219], Eystein Stordal[220,221], Fabian Streit[78], Patrick F. Sullivan[20,222,223], Gustavo Turecki[224], Arne E. Vaaler[225], Eduard Vieta[226], John B. Vincent[102], Irwin D. Waldman[227], Thomas W. Weickert[152,175,217], Thomas Werge[14,228,229,230], Naomi R. Wray[11,231], John-Anker Zwart[18,19,33], Joanna M. Biernacka[8,64], John I. Nurnberger[232], Sven Cichon[3,4,95,96], Howard J. Edenberg[77,233], Eli A. Stahl[1,2,179,236], Andrew McQuillin[40,236], Arianna Di Florio[75,223,236], Roel A. Ophoff[23,79,117,234,236] and Ole A. Andreassen[6,7,236] ✉

[1]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [2]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [3]Institute of Human Genetics, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany. [4]Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany. [5]Centre for Human Genetics, University of Marburg, Marburg, Germany. [6]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. [7]NORMENT, University of Oslo, Oslo, Norway. [8]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA. [9]Social, Genetic and Developmental Psychiatry Centre, King's College London, London, UK. [10]NIHR Maudsley BRC, King's College London, London, UK. [11]Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, Australia. [12]iSEQ, Center for Integrative Sequencing, Aarhus University, Aarhus, Denmark. [13]Department of Biomedicine - Human Genetics, Aarhus University, Aarhus, Denmark. [14]iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark. [15]Department of Psychiatry and Behavioral Sciences, SUNY Downstate Health Sciences University, Brooklyn, NY, USA. [16]VA NY Harbor Healthcare System, Brooklyn, NY, USA. [17]Research and Communication Unit for Musculoskeletal Health, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway. [18]Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [19]K. G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. [20]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [21]Department of Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. [22]Department of Østmarka, Division of Mental Health Care, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. [23]Department of Psychiatry and Biobehavioral Science, Semel Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA. [24]Department of Psychiatry, School of Medicine, Fujita Health University, Toyoake, Japan. [25]Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, USA. [26]Department of Genetics, Harvard Medical School, Boston, MA, USA. [27]Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia. [28]Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, Germany. [29]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [30]Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [31]Estelle and Daniel Maggin Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [32]deCODE Genetics/Amgen, Reykjavik, Iceland. [33]Department of Research, Innovation and Education, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway. [34]Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea. [35]Russian Academy of Medical Sciences, Mental Health Research Center, Moscow, Russian Federation. [36]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany. [37]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany. [38]National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark. [39]Centre for Integrated Register-Based Research, Aarhus University, Aarhus, Denmark. [40]Division of Psychiatry, University College London, London, UK. [41]Department of Neuroscience, Istituto Di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy. [42]Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA. [43]Northwestern University, Chicago, IL, USA. [44]Psychiatry, Berkshire Healthcare NHS Foundation Trust, Bracknell, UK. [45]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. [46]2nd Department of Psychiatry, Attikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece. [47]Department of Psychiatry, Samsung Medical Center, School of Medicine, Sungkyunkwan University, Seoul, South Korea. [48]Center for Neonatal Screening, Department for Congenital

Disorders, Statens Serum Institut, Copenhagen, Denmark. [49]Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. [50]Department of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz, Graz, Austria. [51]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway. [52]Psychiatry, Brain Center UMC Utrecht, Utrecht, the Netherlands. [53]Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health (CIBERSAM), Madrid, Spain. [54]Department of Psychiatry, Hospital Universitari Vall d´Hebron, Barcelona, Spain. [55]Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain. [56]Psychiatric Genetics Unit, Group of Psychiatry Mental Health and Addictions, Vall d´Hebron Research Institut (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain. [57]Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany. [58]Psychiatry, University of California San Francisco, San Francisco, CA, USA. [59]University of Newcastle, Newcastle, New South Wales, Australia. [60]Mood Disorders Program, Department of Psychiatry, McGill University Health Center, Montreal, Quebec, Canada. [61]Division of Psychiatry, University of Edinburgh, Edinburgh, UK. [62]Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany. [63]Department of Psychiatry, Universidad Autonoma de Nuevo Leon, Monterrey, Mexico. [64]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA. [65]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. [66]Centre for Psychiatry, Queen Mary University of London, London, UK. [67]UCL Genetics Institute, University College London, London, UK. [68]Department of Psychiatry, Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland. [69]Center for Multimodal Imaging and Genetics, Departments of Neurosciences, Radiology, and Psychiatry, University of California, San Diego, CA, USA. [70]Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Essen, University of Duisburg-Essen, Duisburg, Germany. [71]Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. [72]NORMENT, Department of Clinical Science, University of Bergen, Bergen, Norway. [73]Department of Neurology, Oslo University Hospital, Oslo, Norway. [74]NORMENT, KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, Norway. [75]Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK. [76]Academic Psychiatry, Newcastle University, Newcastle upon Tyne, UK. [77]Department of Medical and Molecular Genetics, Indiana University, Indianapolis, IN, USA. [78]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. [79]Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA, USA. [80]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. [81]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany. [82]Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada. [83]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA. [84]Veterans Affairs Connecticut Healthcare System, West Haven, CT, USA. [85]Departments of Genetics and Neuroscience, Yale University School of Medicine, New Haven, CT, USA. [86]Department of Psychological Sciences, University of Missouri, Columbia, MO, USA. [87]Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. [88]Psychological Medicine, University of Worcester, Worcester, UK. [89]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA. [90]Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark. [91]Mental Health Department, University Regional Hospital, Biomedicine Institute (IBIMA), Málaga, Spain. [92]Department of Psychiatry, Seoul National University College of Medicine, Seoul, South Korea. [93]Landspitali University Hospital, Reykjavik, Iceland. [94]Department of Psychology, Eberhard Karls Universität Tübingen, Tübingen, Germany. [95]Department of Biomedicine, University of Basel, Basel, Switzerland. [96]Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland. [97]Neuropsychiatrie Translationnelle, Inserm U955, Créteil, France. [98]Faculté de Santé, Université Paris Est, Créteil, France. [99]International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany. [100]Laboratory of Complex Trait Genomics, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan. [101]Laboratory for Statistical and Translational Genetics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. [102]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. [103]Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. [104]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada. [105]Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada. [106]Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg, Würzburg, Germany. [107]Cell Biology, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA. [108]Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA. [109]ISGlobal, Barcelona, Spain. [110]Laboratory of Pharmacogenomics and Individualized Therapy, Department of Pharmacy, School of Health Sciences, University of Patras, Patras, Greece. [111]Mental Illness Research, Education and Clinical Center, Crescenz VAMC, Philadelphia, PA, USA. [112]Center for Studies of Addiction, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. [113]RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. [114]Psychiatry, Altrecht, Utrecht, the Netherlands. [115]Psychiatry, GGZ inGeest, Amsterdam, the Netherlands. [116]Psychiatry, VU Medisch Centrum, Amsterdam, the Netherlands. [117]Department of Psychiatry, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands. [118]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden. [119]Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden. [120]Psychiatry, North East London NHS Foundation Trust, Ilford, UK. [121]Clinic for Psychiatry and Psychotherapy, University Hospital Cologne, Cologne, Germany. [122]Department of Psychiatry, Korea University College of Medicine, Seoul, South Korea. [123]Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. [124]HudsonAlpha Institute for Biotechnology, Huntsville, AL, USA. [125]Department of Human Genetics, McGill University, Montréal, Quebec, Canada. [126]Montreal Neurological Institute and Hospital, McGill University, Montréal, Quebec, Canada. [127]Division of Psychiatry, Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, UK. [128]Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany. [129]Clinical Biochemistry Laboratory, Attikon General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece. [130]Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden. [131]Systems Genetics Working Group, Department of Genetics, Stellenbosch University, Stellenbosch, South Africa. [132]Genetic Cancer Susceptibility Group, International Agency for Research on Cancer, Lyon, France. [133]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA. [134]Centre for Neuroimaging and Cognitive Genomics (NICOG), National University of Ireland Galway, Galway, Ireland. [135]Medical Faculty, School of Science and Technology, University Sarajevo, Sarajevo, Bosnia and Herzegovina. [136]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [137]Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK. [138]Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK. [139]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA. [140]Outpatient Clinic for Bipolar Disorder, Altrecht, Utrecht, the Netherlands. [141]Department of Psychiatry, Washington University in Saint Louis, Saint Louis, MO, USA. [142]Department of Biochemistry and Molecular Biology II, Faculty of Pharmacy, University of Granada, Granada, Spain. [143]Institute of Neurosciences, Biomedical Research Center (CIBM), University of Granada, Granada, Spain. [144]Medicine, Psychiatry, Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA. [145]Department of Genetics, Microbiology and Statistics, Faculty of Biology, Universitat de Barcelona, Barcelona, Spain. [146]Faculty of Medicine, Department of Psychiatry, School of Health Sciences, University of Iceland, Reykjavik, Iceland. [147]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK. [148]Psychiatry and the Behavioral Sciences, University of Southern California, Los Angeles, CA, USA. [149]Mood Disorders, PsyQ, Rotterdam, the Netherlands. [150]SAMRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa. [151]Department of Environmental Epidemiology, Nofer Institute of Occupational Medicine, Lodz, Poland. [152]Neuroscience Research Australia, Sydney, New South Wales, Australia. [153]School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia. [154]Centro de Biología Molecular Severo Ochoa, Universidad Autónoma de Madrid and CSIC, Madrid, Spain.

[155]Department of Psychiatry and Human Behavior, School of Medicine, University of California, Irvine, Irvine, CA, USA. [156]Psychiatry, Psychiatrisches Zentrum Nordbaden, Wiesloch, Germany. [157]Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, USA. [158]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada. [159]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [160]South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Beckenham, UK. [161]Department of Clinical Sciences, Psychiatry, Umeå University Medical Faculty, Umeå, Sweden. [162]NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Institute of Clinical Medicine and Diakonhjemmet Hospital, University of Oslo, Oslo, Norway. [163]National Institute of Mental Health, Klecany, Czech Republic. [164]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [165]Institute of Pulmonology, Russian State Medical University, Moscow, Russian Federation. [166]Department of Psychiatry, University of Münster, Münster, Germany. [167]Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, Victoria, Australia. [168]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Victoria, Australia. [169]Université de Paris, INSERM, Optimisation Thérapeutique en Neuropsychopharmacologie, UMRS 1144, Paris, France. [170]APHP Nord, DMU Neurosciences, Département de Psychiatrie et de Médecine Addictologique, GHU Saint Louis-Lariboisière-Fernand Widal, Paris, France. [171]Psychiatry, University of Pennsylvania, Philadelphia, PA, USA. [172]Center for Statistical Genetics and Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA. [173]Department of Biomedicine and the iSEQ Center, Aarhus University, Aarhus, Denmark. [174]Center for Genomics and Personalized Medicine, CGPM, Aarhus, Denmark. [175]School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia. [176]University of Queensland, Brisbane, Queensland, Australia. [177]Neuropsychiatric Genetics Research Group, Department of Psychiatry and Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland. [178]1st Department of Psychiatry, Eginition Hospital, National and Kapodistrian University of Athens, Athens, Greece. [179]Medical and Population Genetics, Broad Institute, Cambridge, MA, USA. [180]Division of Endocrinology, Children's Hospital Boston, Boston, MA, USA. [181]Department of Human Genetics, University of Chicago, Chicago, IL, USA. [182]Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania. [183]HUNT Research Center, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. [184]University of Western Australia, Nedlands, Western Australia, Australia. [185]Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden. [186]Department of Psychiatry and Addiction Medicine, Assistance Publique - Hôpitaux de Paris, Paris, France. [187]Department of Medical and Molecular Genetics, King's College London, London, UK. [188]Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, USA. [189]Cancer Epidemiology and Prevention, M. Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland. [190]SA MRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry, Stellenbosch University, Stellenbosch, South Africa. [191]School of Psychology, The University of Queensland, Brisbane, Queensland, Australia. [192]Department of Psychiatry and Genetics Institute, University of Florida, Gainesville, FL, USA. [193]Research Institute, Lindner Center of HOPE, Mason, OH, USA. [194]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK. [195]Human Genetics Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA. [196]Division of Mental Health and Addiction, University of Oslo, Institute of Clinical Medicine, Oslo, Norway. [197]Psychiatry, St Olavs University Hospital, Trondheim, Norway. [198]Psychosis Research Unit, Aarhus University Hospital - Psychiatry, Risskov, Denmark. [199]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. [200]University of Liverpool, Liverpool, UK. [201]Research/Psychiatry, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA. [202]Mental Health Services in the Capital Region of Denmark, Mental Health Center Copenhagen, University of Copenhagen, Copenhagen, Denmark. [203]Division of Psychiatry, Haukeland Universitetssjukehus, Bergen, Norway. [204]Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway. [205]Department of Clinical Neuroscience and Center for Molecular Medicine, Karolinska Institutet at Karolinska University Hospital, Solna, Sweden. [206]Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, USA. [207]University of Melbourne, Melbourne, Victoria, Australia. [208]Department of Pathology, College of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates. [209]Zayed Center of Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates. [210]Psychiatry, Harvard Medical School, Boston, MA, USA. [211]Division of Clinical Research, Massachusetts General Hospital, Boston, MA, USA. [212]Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands. [213]Department of Clinical Genetics, Amsterdam Neuroscience, Vrije Universiteit Medical Center, Amsterdam, the Netherlands. [214]Department of Neurology and Neurosurgery, Faculty of Medicine, McGill University, Montreal, Quebec, Canada. [215]Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA. [216]Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy. [217]Department of Neuroscience, SUNY Upstate Medical University, Syracuse, NY, USA. [218]Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, USA. [219]Faculty of Medicine, University of Iceland, Reykjavik, Iceland. [220]Department of Psychiatry, Hospital Namsos, Namsos, Norway. [221]Department of Neuroscience, Norges Teknisk Naturvitenskapelige Universitet Fakultet for Naturvitenskap og Teknologi, Trondheim, Norway. [222]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [223]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [224]Department of Psychiatry, McGill University, Montreal, Quebec, Canada. [225]Department of Psychiatry, Sankt Olavs Hospital Universitetssykehuset i Trondheim, Trondheim, Norway. [226]Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain. [227]Department of Psychology, Emory University, Atlanta, GA, USA. [228]Institute of Biological Psychiatry, Mental Health Services, Copenhagen University Hospital, Copenhagen, Denmark. [229]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. [230]Center for GeoGenetics, GLOBE Institute, University of Copenhagen, Copenhagen, Denmark. [231]Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia. [232]Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA. [233]Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, USA. [234]Department of Human Genetics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA. [235]These authors contributed equally: Niamh Mullins, Andreas J. Forstner. [236]These authors jointly supervised this work: Eli A. Stahl, Andrew McQuillin, Arianna Di Florio, Roel A. Ophoff, Ole A. Andreassen. *A list of authors and their affiliations appears at the end of the paper. ✉e-mail: niamh.mullins@mssm.edu; ole.andreassen@medisin.uio.no

HUNT All-In Psychiatry

Bendik S. Winsvold[19,33], Eystein Stordal[220,221], Gunnar Morken[21,197], John-Anker Zwart[18,19,33], Ole Kristian Drange[21,22] and Sigrid Børte[17,18,19]

A list of members and their affiliations appears in the Supplementary Information.

Methods

Sample description. The meta-analysis sample comprises 57 cohorts collected in Europe, North America and Australia, totaling 41,917 BD cases and 371,549 controls of European descent (Supplementary Table 1). The total effective *n*, equivalent to an equal number of cases and controls in each cohort ($4\times n_{cases}\times n_{controls}/(n_{cases}+n_{controls})$), is 101,962. For 52 cohorts, individual-level genotype and phenotype data were shared with the PGC. Cohorts have been added to the PGC in five waves (PGC1 (ref. [9]), PGC2 (ref. [24]), PGC PsychChip, PGC3 and External studies); all cohorts from previous PGC BD GWASs were included. The source and inclusion/exclusion criteria for cases and controls for each cohort are described in the Supplementary Note. Cases were required to meet international consensus criteria (DSM-IV, ICD-9 or ICD-10) for a lifetime diagnosis of BD, established using structured diagnostic instruments from assessments by trained interviewers, clinician-administered checklists or medical record review. In most cohorts, controls were screened for the absence of lifetime psychiatric disorders and randomly selected from the population. For five cohorts (iPSYCH[30], deCODE genetics[31], Estonian Biobank[32], HUNT[33] and UK Biobank[34]), GWAS summary statistics for BD were shared with the PGC. In these cohorts, BD cases were ascertained using ICD codes or self-report during a nurse interview, and the majority of controls were screened for the absence of psychiatric disorders via ICD codes. Follow-up analyses included four non-European BD case–control cohorts, two from East Asia (Japan[59] and Korea[92]) and two admixed African American cohorts[22,93], providing a total of 5,847 cases and 65,588 controls. These BD cases were ascertained using international consensus criteria (DSM-IV)[22,93] through psychiatric interviews (Supplementary Note).

Genotyping, quality control and imputation. For 52 cohorts internal to the PGC, genotyping was performed following local protocols and genotypes were called using standard genotype calling software from commercial sources (Affymetrix and Illumina). Subsequently, standardized quality control, imputation and statistical analyses were performed centrally using Rapid Imputation for Consortias Pipeline (RICOPILI; version 2018_Nov_23.001)[94], separately for each cohort. Briefly, the quality control parameters for retaining SNPs and subjects were: SNP missingness < 0.05 (before sample removal), subject missingness < 0.02, autosomal heterozygosity deviation (F_{het} < 0.2), SNP missingness < 0.02 (after sample removal), difference in SNP missingness between cases and controls < 0.02, SNP Hardy–Weinberg equilibrium ($P > 10\times10^{-10}$ in psychiatric cases and $P > 10\times10^{-6}$ in controls). Relatedness was calculated across cohorts using identity by descent and one of each pair of related individuals (pi_hat > 0.2) was excluded. Principal components (PCs) were generated using genotyped SNPs in each cohort separately using EIGENSTRAT v6.1.4 (ref. [95]). On the basis of visual inspection of plots of PCs for each dataset (which were all of European descent according to self-report/clinical data), we excluded samples to obtain more clearly homogeneous datasets. Genotype imputation was performed using the prephasing/imputation stepwise approach implemented in Eagle v2.3.5 (ref. [96]) and Minimac3 (ref. [97]) to the Haplotype Reference Consortium (HRC) reference panel v1.0 (ref. [98]). Data on the X chromosome were available for 50 cohorts internal to the PGC and one external cohort (HUNT), and the X chromosome was imputed to the HRC reference panel in males and females separately within each cohort. The five external cohorts were processed by the collaborating research teams using comparable procedures and imputed to the HRC or a custom reference panel as appropriate. Full details of the genotyping, quality control and imputation for each of these cohorts are available in the Supplementary Note. Identical individuals between PGC cohorts and the Estonian Biobank and UK Biobank cohorts were detected using genotype-based checksums (https://personal.broadinstitute.org/sripke/share_links/zpXkV8INxUg9bayDpLToG4g58TMtjN_PGC_SCZ_w3.0718d.76) and removed from PGC cohorts.

GWAS. For PGC cohorts, GWASs were conducted within each cohort using an additive logistic regression model in PLINK v1.90 (ref. [99]), covarying for PCs 1–5 and any others as required. Association analyses of the X chromosome were conducted in males and females separately using the same procedures, with males coded as 0 or 2 for 0 or 1 copies of the reference allele. Results from males and females were then meta-analyzed within each cohort. For external cohorts, GWASs were conducted by the collaborating research teams using comparable procedures (Supplementary Note). To control test statistic inflation at SNPs with low minor allele frequency (MAF) in small cohorts, SNPs were retained only if cohort MAF was >1% and minor allele count was >10 in either cases or controls (whichever had smaller *n*). There was no evidence of stratification artifacts or uncontrolled inflation of test statistics in the results from any cohort (λ_{GC} = 0.97–1.05; Supplementary Table 1). Meta-analysis of GWAS summary statistics was conducted using an inverse-variance-weighted fixed-effects model in METAL (version 2011-03-25)[100] across 57 cohorts for the autosomes (41,917 BD cases and 371,549 controls) and 51 cohorts for the X chromosome (35,691 BD cases and 96,731 controls). A genome-wide significant locus was defined as the region around a SNP with $P < 5\times10^{-8}$, with LD $r^2 > 0.1$, within a 3,000-kb window. Regional association plots and forest plots of the index SNPs for all genome-wide significant loci are presented in Supplementary Data 1 and 2, respectively.

Overlap of loci with other psychiatric disorders. Genome-wide significant loci for BD were assessed for overlap with genome-wide significant loci for other psychiatric disorders, using the largest available GWAS results for major depression[61], schizophrenia[60], attention deficit/hyperactivity disorder[101], post-traumatic stress disorder[102], lifetime anxiety disorder[103], Tourette's syndrome[104], anorexia nervosa[105], alcohol use disorder or problematic alcohol use[68], autism spectrum disorder[106], mood disorders[91] and the cross-disorder GWAS of the PGC[66]. The boundaries of the genome-wide significant loci were calculated in the original publications. Overlap of loci was calculated using bedtools v2.29.2 (ref. [107]).

Enrichment analyses. *P* values quantifying the degree of association of genes and gene sets with BD were calculated using MAGMA v1.08 (ref. [37]), implemented in FUMA v1.3.6a (refs. [64,108]). Gene-based tests were performed for 19,576 genes (Bonferroni-corrected *P*-value threshold = 2.55×10^{-6}). A total of 11,858 curated gene sets including at least 10 genes from MSigDB V7.0 were tested for association with BD (Bonferroni-corrected *P*-value threshold = 4.22×10^{-6}). Competitive gene-set tests were conducted correcting for gene size, variant density and LD within and between genes. Tissue-set enrichment analyses were also performed using MAGMA implemented in FUMA, to test for enrichment of association signal in genes expressed in 54 tissue types from GTEx V8 (Bonferroni-corrected *P*-value threshold = 9.26×10^{-4})[64,108].

For single-cell enrichment analyses, publicly available single-cell RNA-sequencing data were compiled from five studies of the adult human and mouse brain[86,109–112]. The mean expression for each gene in each cell type was computed from the single-cell expression data (if not provided). For the Zeisel dataset[109], we used the mean expression at level 4 (39 cell types from 19 regions for the mouse nervous system). For the Saunders dataset[110], we computed the mean expression of the different classes in each of the 9 different brain regions sampled (88 cell types in total). We filtered out any genes with nonunique names, genes not expressed in any cell types, non-protein-coding genes and, for mouse datasets, genes that had no expert-curated 1:1 orthologs between mouse and human (Mouse Genome Informatics, The Jackson Laboratory, version 11/22/2016, http://www.informatics.jax.org/downloads/reports/index.html#homology), resulting in 16,472 genes. Gene expression was then scaled to a total of 1 million unique molecular identifiers (or transcripts per million) for each cell type/tissue. Using a previously described method[38], a metric of gene expression specificity was calculated by dividing the expression of each gene in each cell type by the total expression of that gene in all cell types, leading to values ranging from 0 to 1 for each gene (0 meaning that the gene is not expressed in that cell type and 1 meaning that all of the expression of the gene is in that cell type). We then selected the top 10% most specific genes for each cell type/tissue for enrichment analysis. MAGMA v1.08 (ref. [37]) was used to test gene-set enrichment using GWAS summary statistics, covarying for gene size, gene density, mean sample size for tested SNPs per gene, the inverse of the minor allele counts per gene and the log of these metrics. We excluded any SNPs with INFO score < 0.6, with MAF < 1% or with estimated odds ratio > 25 or smaller than 1/25, as well as SNPs located in the MHC region (chr6:25–34 Mb). We set a window of 35 kb upstream to 10 kb downstream of the gene coordinates to compute gene-level association statistics and used the European reference panel from phase 3 of the 1000 Genomes Project as the reference population[113]. We then used MAGMA to test whether the 10% most specific genes (with an expression of at least 1 transcript per million or 1 unique molecular identifier per million) for each cell type/tissue were associated with BD. The *P*-value threshold for significance was $P < 9.1\times10^{-3}$, representing a 5% false discovery rate across datasets.

Further gene-set analyses were performed restricted to genes targeted by drugs, assessing individual drugs and grouping drugs with similar actions. This approach has been described previously[41]. Gene-level and gene-set analyses were performed in MAGMA v1.08 (ref. [37]). Gene boundaries were defined using build 37 reference data from the National Center for Biotechnology Information, available on the MAGMA website (https://ctg.cncr.nl/software/magma), extended 35 kb upstream and 10 kb downstream to include regulatory regions outside the transcribed region. Gene-level association statistics were defined as the aggregate of the mean and the lowest variant-level *P* value within the gene boundary, converted to a *Z* value. Gene sets were defined comprising the targets of each drug in the Drug–Gene Interaction database DGIdb v.2 (ref. [39]) and in the Psychoactive Drug Screening Database Ki DB[40], both downloaded in June 2016[41]. Analyses were performed using competitive gene-set analyses in MAGMA. Results from the drug-set analysis were then grouped according to the Anatomical Therapeutic Chemical class of the drug[41]. Only drug classes with at least ten valid drug gene sets within them were analyzed. Drug-class analysis was performed using enrichment curves. All drug gene sets were ranked by their association in the drug-set analysis, and then for a given drug class an enrichment curve was drawn scoring a 'hit' if the drug gene set was within the class, or a 'miss' if it was outside the class. The area under the curve was calculated, and a *P* value for this was calculated using the Wilcoxon Mann–Whitney test comparing drug gene sets within the class to drug gene sets outside the class[41]. Multiple testing was controlled using a Bonferroni-corrected significance threshold of $P < 5.60\times10^{-5}$ for drug-set analysis and $P < 7.93\times10^{-4}$ for drug-class analysis, accounting for 893 drug sets and 63 drug classes tested.

eQTL integrative analysis. A TWAS was conducted using the precomputed gene expression weights from PsychENCODE data (1,321 brain samples)[43], available online with the FUSION software[42]. For genes with significant *cis*-SNP heritability (13,435 genes), FUSION software (vOct 1, 2019) was used to test whether SNPs influencing gene expression are also associated with BD (Bonferroni-corrected *P*-value threshold $< 3.72\times10^{-6}$). For regions including a TWAS-significant gene, TWAS fine-mapping of the region was conducted using FOCUS (fine-mapping of causal gene sets, v0.6.10)[44]. Regions were defined using the correlation matrix of predicted effects on gene expression around TWAS-significant genes[44]. A PIP was assigned to each gene for being causal for the observed TWAS association signal. Based on the PIP of each gene and a null model, whereby no gene in the region is causal for the TWAS signal, the 90%-credible gene set for each region was computed[44].

SMR (v1.03)[45,46] was applied to further investigate putative causal relationships between SNPs and BD via gene expression. SMR was performed using eQTL summary statistics from the eQTLGen (31,684 blood samples)[47] and PsychENCODE[43] consortia. SMR analysis is limited to transcripts with at least one significant *cis*-eQTL ($P < 5\times10^{-8}$) in each dataset (15,610 in eQTLGen; 10,871 in PsychENCODE). The Bonferroni-corrected significance threshold was $P < 3.20\times10^{-6}$ and $P < 4.60\times10^{-6}$ for eQTLGen and PsychENCODE, respectively. The significance threshold for the HEIDI test was $P_{HEIDI} \geq 0.01$ (ref. [46]). While the results of TWAS and SMR indicate an association between BD and gene expression, a nonsignificant HEIDI test additionally indicates either a direct causal role or a pleiotropic effect of the BD-associated SNPs on gene expression.

***C4* imputation.** To investigate the MHC (chr6:24–34 Mb on hg19), the alleles of *C4* genes (*C4A* and *C4B*) were imputed in 47 PGC cohorts for which individual-level genotype data were accessible, totaling 32,749 BD cases and 53,370 controls. The imputation reference panel comprised 2,530 reference haplotypes of MHC SNPs and *C4* alleles, generated using a sample of 1,265 individuals with whole-genome sequence data, from the Genomic Psychiatry cohort[114]. Briefly, imputation of *C4* as a multiallelic variant was performed using Beagle v4.1 (refs. [115,116]), using SNPs from the MHC region that were also in the haplotype reference panel. Within the Beagle pipeline, the reference panel was first converted to bref format. We used the conform-gt tool to perform strand-flipping and filtering of specific SNPs for which the strand remained ambiguous. Beagle was run using default parameters with two key exceptions: we used the GRCh37 PLINK recombination map, and we set the output to include genotype probability (that is, GP field in VCF) for correct downstream probabilistic estimation of *C4A* and *C4B* joint dosages. The output consisted of dosage estimates for each of the common *C4* structural haplotypes for each individual. The five most common structural forms of the *C4A*/*C4B* locus (BS, AL, AL–BS, AL–BL and AL–AL) could be inferred with reasonably high accuracy (generally $0.70 < r^2 < 1.00$). The imputed *C4* alleles were tested for association with BD in a joint logistic regression that included terms for dosages of the five most common *C4* structural haplotypes (AL–BS, AL–BL, AL–AL, BS and AL), rs13195402 genotype (top lead SNP in the MHC) and PCs as per the GWAS. The genetically regulated expression of *C4A* was predicted from the imputed *C4* alleles using a model previously described[63]. Predicted *C4A* expression was tested for association with BD in a joint logistic regression that included predicted *C4A* expression, rs13195402 genotype (top lead SNP in the MHC) and PCs as per the GWAS.

Polygenic risk scoring. PRSs from our GWAS meta-analysis were tested for association with BD in individual cohorts, using a discovery GWAS where the target cohort was left out of the meta-analysis. Briefly, the GWAS results from each discovery GWAS were pruned for LD using the *P*-value-informed clumping method in PLINK v1.90 (ref. [99]; r^2 0.1 within a 500-kb window) based on the LD structure of the HRC reference panel[98]. Subsets of SNPs were selected from the results below nine increasingly liberal *P*-value thresholds (GWAS P_T; 5×10^{-8}, 1×10^{-4}, 1×10^{-3}, 0.01, 0.05, 0.1, 0.2, 0.5, 1). Sets of alleles, weighted by their log odds ratios from the discovery GWAS, were summed into PRSs for each individual in the target datasets, using PLINK v1.90 implemented via RICOPILI[94,99]. PRSs were tested for association with BD in the target dataset using logistic regression, covarying for PCs as per the GWAS in each cohort. PRSs were tested in the external cohorts by the collaborating research teams using comparable procedures. The variance explained by the PRSs (R^2) was converted to the liability scale to account for the proportion of cases in each target dataset, using a BD population prevalence of 2% and 1%[117]. The weighted average R^2 values were calculated using the effective *n* for each cohort. The odds ratios for BD for individuals in the top decile of PRSs compared with those in the lowest decile and middle decile were calculated in the 52 datasets internal to the PGC. To assess cross-ancestry performance, PRSs generated from the meta-analysis results were tested for association with BD using similar methods in a Japanese sample[59], a Korean sample[92] and two admixed African American samples. Full details of the QC, imputation and analysis of these samples are in the Supplementary Note.

LDSC. LDSC[35] was used to estimate the h^2_{SNP} of BD from GWAS summary statistics. h^2_{SNP} was converted to the liability scale, using a lifetime BD prevalence of 2% and 1%. LDSC bivariate genetic correlations attributable to genome-wide SNPs (r_g) were estimated with 255 human diseases and traits from published GWASs and 514 GWASs of phenotypes in the UK Biobank from LD Hub[48]. Adjusting for the number of traits tested, the Bonferroni-corrected *P*-value thresholds were $P < 1.96\times10^{-4}$ and $P < 9.73\times10^{-5}$, respectively.

MiXeR. We applied causal mixture models[49,50] to the GWAS summary statistics, using MiXeR v1.3. MiXeR provides univariate estimates of the proportion of non-null SNPs ('polygenicity') and the variance of effect sizes of non-null SNPs ('discoverability') in each phenotype. For each SNP, *i*, univariate MiXeR models its additive genetic effect of allele substitution, β_i, as a point-normal mixture, $\beta_i = (1-\pi_1)\,N(0,0) + \pi_1 N(0, \sigma^2_\beta)$, where π_1 represents the proportion of non-null SNPs ('polygenicity') and σ^2_β represents variance of effect sizes of non-null SNPs ('discoverability'). Then, for each SNP, *j*, MiXeR incorporates LD information and allele frequencies for $M = 9{,}997{,}231$ SNPs extracted from 1000 Genomes phase 3 data to estimate the expected probability distribution of the signed test statistic, $z_j = \delta_j + \varepsilon_j = N\sum_i \sqrt{H_i} r_{ij}\beta_i + \varepsilon_j$, where *N* is sample size, H_i indicates heterozygosity of the *i*th SNP, r_{ij} indicates allelic correlation between the *i*th and *j*th SNPs and $\varepsilon_j \sim N(0, \sigma^2_0)$ is the residual variance. Further, the three parameters, π_1, σ^2_β and σ^2_0, are fitted by direct maximization of the likelihood function. The optimization is based on a set of approximately 600,000 SNPs, obtained by selecting a random set of 2,000,000 SNPs with MAF of 5% or higher, followed by LD pruning at LD $r^2 = 0.8$ threshold. The random SNP selection and full optimization procedure are repeated 20 times to obtain the means and standard errors of model parameters. The log-likelihood figures show individual curves for each of the 20 runs, each shifted vertically so that the best log-likelihood point is shown at the zero ordinate.

The total number of trait-influencing variants is estimated as $M\pi_1$, where $M = 9{,}997{,}231$ gives the number of SNPs in the reference panel. MiXeR Venn diagrams report the effective number of influencing variants, $\eta M\pi_1$, where η is a fixed number, $\eta = 0.319$, which gives the fraction of influencing variants contributing to 90% of the trait's heritability (with rationale for this adjustment being that the remaining 68.1% of influencing variants are small and cumulatively explain only 10% of the trait's heritability). Phenotypic variance explained on average by an influencing genetic variant is calculated as $\underline{H}\sigma^2_\beta$, where $\underline{H} = \frac{1}{M}\sum_i H_i = 0.2075$ is the average heterozygosity across SNPs in the reference panel. Under the assumptions of the MiXeR model, SNP heritability is then calculated as $h^2_{SNP} = M\pi_1 \times \underline{H}\sigma^2_\beta$.

In the cross-trait analysis, MiXeR models additive genetic effects as a mixture of four components, representing null SNPs in both traits (π_0); SNPs with a specific effect on the first and on the second trait (π_1 and π_2, respectively); and SNPs with nonzero effect on both traits (π_{12}). In the last component, MiXeR models the variance–covariance matrix as $\Sigma_{12} = \begin{bmatrix} \sigma^2_1 & \rho_{12}\sigma_1\sigma_2 \\ \rho_{12}\sigma_1\sigma_2 & \sigma^2_2 \end{bmatrix}$, where ρ_{12} indicates correlation of effect sizes within the shared component, and σ^2_1 and σ^2_2 correspond to the discoverability parameter estimated in the univariate analysis of the two traits. These components are then plotted in Venn diagrams. After fitting parameters of the model, the Dice coefficient of polygenic overlap is then calculated as $\frac{2\pi_{12}}{\pi_1+2\pi_{12}+\pi_2}$, and genetic correlation is calculated as $r_g = \frac{\rho_{12}\pi_{12}}{\sqrt{(\pi_1+\pi_{12})(\pi_2+\pi_{12})}}$. The fraction of influencing variants with concordant effect direction is calculated as twice the multivariate normal cumulative distribution function at point (0, 0) for the bivariate normal distribution with zero mean and variance–covariance matrix Σ_{12}. All code is available online (https://github.com/precimed/mixer).

MR. We selected 17 traits associated with BD in clinical or epidemiological studies for MR to dissect their relationship with BD (Supplementary Note). Bidirectional GSMR[51] analyses were performed between BD and the traits of interest using GWAS summary statistics, implemented in GCTA software (v1.93.1f beta). The instrumental variables were selected by a clumping procedure internal to the GSMR software with parameters: --gwas-thresh 5×10^{-8} --clump-r2 0.01. Traits with fewer than 10 instrumental variables available were excluded from the GSMR analyses to avoid conducting underpowered tests[51], resulting in 10 traits tested (Bonferroni-corrected *P*-value threshold $< 2.5\times10^{-3}$). The HEIDI-outlier test was applied to test for horizontal pleiotropy ($P_{HEIDI} < 0.01$)[51]. For comparison, the MR analyses were also performed using the inverse-variance-weighted regression method, implemented via the TwoSampleMR R package, using the instrumental variables selected by GSMR[118,119]. To further investigate horizontal pleiotropy, the MR Egger intercept test was conducted using the TwoSampleMR package[118,119] and MR-PRESSO software was used to perform the global test and the distortion test[120].

BD subtypes. GWAS meta-analyses were conducted for BD I (25,060 cases, 449,978 controls from 55 cohorts, effective $n = 64{,}802$) and BD II (6,781 cases, 364,075 controls from 31 cohorts, effective $n = 22{,}560$; Supplementary Table 1) using the same procedures described for the main GWAS. BD subtypes were defined based on international consensus criteria (DSM-IV, ICD-9 or ICD-10), established using structured diagnostic instruments from assessments by

trained interviewers, clinician-administered checklists or medical record review. In the external biobank cohorts, BD subtypes were defined using ICD codes (Supplementary Note). LDSC[35] was used to estimate the h^2_{SNP} of each subtype, and the genetic correlation between the subtypes. The difference between the LDSC h^2_{SNP} estimates for BD I and BD II was tested for deviation from 0 using the block jackknife[121]. The LDSC genetic correlation (r_g) was tested for difference from 1 by calculating a chi-square statistic corresponding to the estimated r_g as $((r_g-1)/\text{s.e.})^2$.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

GWAS summary statistics are publicly available on the PGC website (https://www.med.unc.edu/pgc/results-and-downloads). Individual-level data are accessible through collaborative analysis proposals to the Bipolar Disorder Working Group of the PGC (https://www.med.unc.edu/pgc/shared-methods/how-to/). This study included some publicly available datasets accessed through dbGaP (PGC bundle phs001254) and the HRC reference panel v1.0 (http://www.haplotype-reference-consortium.org/home). Databases used: Drug–Gene Interaction Database DGIdb v.2 (https://www.dgidb.org); Psychoactive Drug Screening Database Ki DB (https://pdsp.unc.edu/databases/kidb.php); DrugBank 5.0 (https://www.drugbank.ca); LD Hub (http://ldsc.broadinstitute.org); FUMA (https://fuma.ctglab.nl).

Code availability

All software used is publicly available at the URLs or references cited.

References

92. Moon, S. et al. The Korea Biobank Array: design and identification of coding variants associated with blood biochemical traits. *Sci. Rep.* **9**, 1382 (2019).
93. Bigdeli, T. B. et al. Contributions of common genetic variants to risk of schizophrenia among individuals of African and Latino ancestry. *Mol. Psychiatry* **25**, 2455–2467 (2020).
94. Lam, M. et al. RICOPILI: Rapid Imputation for COnsortias PIpeLIne. *Bioinformatics* **36**, 930–933 (2020).
95. Price, A. L. et al. Principal components analysis corrects for stratification in genome-wide association studies. *Nat. Genet.* **38**, 904–909 (2006).
96. Loh, P.-R. et al. Reference-based phasing using the haplotype reference consortium panel. *Nat. Genet.* **48**, 1443–1448 (2016).
97. Das, S. et al. Next-generation genotype imputation service and methods. *Nat. Genet.* **48**, 1284–1287 (2016).
98. McCarthy, S. et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–1283 (2016).
99. Chang, C. C. et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).
100. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190–2191 (2010).
101. Demontis, D. et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat. Genet.* **51**, 63–75 (2019).
102. Nievergelt, C. M. et al. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. *Nat. Commun.* **10**, 4558 (2019).
103. Purves, K. L. et al. A major role for common genetic variation in anxiety disorders. *Mol. Psychiatry* **25**, 3292–3303 (2020).
104. Yu, D. et al. Interrogating the genetic determinants of Tourette's syndrome and other tic disorders through genome-wide association studies. *Am. J. Psychiatry* **176**, 217–227 (2019).
105. Watson, H. J. et al. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat. Genet.* **51**, 1207–1214 (2019).
106. Grove, J. et al. Identification of common genetic risk variants for autism spectrum disorder. *Nat. Genet.* **51**, 431–444 (2019).
107. Quinlan, A. R. & Hall, I. M. BEDTools: a flexible suite of utilities for comparing genomic features. *Bioinformatics* **26**, 841–842 (2010).
108. Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. *Nat. Commun.* **8**, 1826 (2017).
109. Zeisel, A. et al. Molecular architecture of the mouse nervous system. *Cell* **174**, 999–1014 (2018).
110. Saunders, A. et al. Molecular diversity and specializations among the cells of the adult mouse brain. *Cell* **174**, 1015–1030 (2018).
111. Habib, N. et al. Massively parallel single-nucleus RNA-seq with DroNc-seq. *Nat. Methods* **14**, 955–958 (2017).
112. Lake, B. B. et al. Integrative single-cell analysis of transcriptional and epigenetic states in the human adult brain. *Nat. Biotechnol.* **36**, 70–80 (2018).
113. 1000 Genomes Project Consortium. et al. A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).
114. Kamitaki, N. et al. Complement genes contribute sex-biased vulnerability in diverse disorders. *Nature* **582**, 577–581 (2020).
115. Browning, S. R. & Browning, B. L. Rapid and accurate haplotype phasing and missing-data inference for whole-genome association studies by use of localized haplotype clustering. *Am. J. Hum. Genet.* **81**, 1084–1097 (2007).
116. Browning, B. L. & Browning, S. R. Genotype imputation with millions of reference samples. *Am. J. Hum. Genet.* **98**, 116–126 (2016).
117. Lee, S. H., Goddard, M. E., Wray, N. R. & Visscher, P. M. A better coefficient of determination for genetic profile analysis. *Genet. Epidemiol.* **36**, 214–224 (2012).
118. Hemani, G., Tilling, K. & Davey Smith, G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet.* **13**, e1007081 (2017).
119. Hemani, G. et al. The MR-Base platform supports systematic causal inference across the human phenome. *Elife* **7**, e34408 (2018).
120. Verbanck, M., Chen, C.-Y., Neale, B. & Do, R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat. Genet.* **50**, 693–698 (2018).
121. Hübel, C. et al. Genomics of body fat percentage may contribute to sex bias in anorexia nervosa. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **180**, 428–438 (2019).

Acknowledgements

We thank the participants who donated their time, life experiences and DNA to this research and the clinical and scientific teams that worked with them. We are deeply indebted to the investigators who make up the PGC. The PGC has received major funding from the US National Institute of Mental Health (PGC3: U01 MH109528; PGC2: U01 MH094421; PGC1: U01 MH085520). Statistical analyses were carried out on the NL Genetic Cluster Computer (http://www.geneticcluster.org) hosted by SURFsara and the Mount Sinai high-performance computing cluster (http://hpc.mssm.edu), which is supported by the Office of Research Infrastructure of the National Institutes of Health under award numbers S10OD018522 and S10OD026880. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Full acknowledgements are included in the Supplementary Note.

Author contributions

Writing group: N.M., A.J.F., K.S.O'C., B.C., J.R.I.C., J.M.B., J.I.N., S. Cichon, H.J.E., E.A.S., A. McQuillin, A.D.F., R.A.O., O.A.A. PGC BD PI group: A.J.F., M.I., H.-H.W., D.C., R.A., I.A., M.A., L. Alfredsson, G. Babadjanova, L.B., B.T.B., F.B., S. Bengesser, W.H.B., D.H.R.B., M. Boehnke, A.D.B., G. Breen, V.J.C., S. Catts, A.C., N.C., U.D., D.D., T. Esko, B.E., P.F., M.F., J.M.F., M.G., E.S.G., F.S.G., M. J. Green, M.G.-S., J. Hauser, F.H., J. Hillert, K.S.H., D.M.H., C.M.H., K. Hveem, N.I., A.V.J., I.J., L.A.J., R.S.K., J.R.K., G.K., M. Landén, M. Leboyer, C.M.L., Q.S.L., J. Lissowska, C. Lochner, C. Loughland, N.G.M., C.A.M., F.M., S.L.M., A.M.M., F.J.M., I.M., P. Michie, L. Milani, P. B. Mitchell, G.M., O.M., P. B. Mortensen, B.M., B.M.-M., R.M.M., B.M.N., C.M.N., M.N., M.M.N., M.C.O'D., K.J.O., T.O., M.J.O., S.A.P., C. Pantelis, C. Pato, M.T.P., G.P.P., R.H.P., D.P., J.A.R.-Q., A.R., E.Z.R., M. Ribasés, M. Rietschel, S.R., G.A.R., T.S., U.S., M.S., P.R.S., T.G.S., L.J.S., R.J.S., A.S., C.S.W., J.W.S., H.S., K.S., E. Stordal, F. Streit, P.F.S., G.T., A.E.V., E.V., J.B.V., I.D.W., T.W.W., T.W., N.R.W., J.-A.Z., J.M.B., J.I.N., S. Cichon, H.J.E., E.A.S., A. McQuillin, A.D.F., R.A.O., O.A.A. Bioinformatics: N.M., A.J.F., J.R.I.C., S. Børte, M.J. Gandal, M. Kim, B.M.S., L.G.S., B.S.W., H.-H.W., N.A.-R., S.E.B., B.M.B., V.E.-P., S.H., P.A.H., Y.K., M. Koromina, M. Kubo, M. Leber, P.H.L., C. Liao, L.M.O.L., T.R., P.R., P.D.S., M.S.A., C. Terao, T.E.T., S.X., H.Y., P.P.Z., S. Bengesser, G. Breen, P.F., E.S.G., Q.S.L., G.A.R., H.S., T.W., E.A.S. Clinical: O.K.D., M.I., L. Abramova, K.A., E.A., N.A.-R., A. Anjorin, A. Antoniou, J.H.B., N.B., M. Bauer, A.B., C.B.P., E.B., M.P.B., R.B., M. Brum, N.B.-K., M. Budde, W.B., M. Cairns, M. Casas, P.C., A.C.-B., D.C., P.M.C., N.D., A.D., T. Elvsåshagen, L. Forty, L. Frisén, K.G., J. Garnham, M.G.P., I.R.G., K.G.-S., J. Grove, J.G.-P., K. Ha, M. Haraldsson, M. Hautzinger, U.H., D.H., J. L. Kalman, J. L. Kennedy, S.K.-S., M. Kogevinas, T.M.K., R.K., S.A.K., J. Lawrence, H.-J.L., C. Lewis, S.L., M. Lundberg, D.J.M., W.M., D.M., L. Martinsson, M.M., P. McGuffin, H.M., V.M., C.O'D., L.O., S.P., A. Perry, A. Pfennig, E.P., J.B.P., D.Q., M.H.R., J.R.D., E.J.R., J.P.R., F.R., J.R., E.C.S., F. Senner, E. Sigurdsson, L.S., C.S., O.B.S., D. J. Smith, J.L.S., A.T.S., J.S.S., B.Ś., P.T., M.P.V., H.V., A.H.Y., L.Z., HUNT All-In Psychiatry, R.A., I.A., M.A., G. Babadjanova, L.B., B.T.B., F.B., S. Bengesser, D.H.R.B., A.D.B., A.C., N.C., U.D., D.D., B.E., P.F., M.F., M.G., E.S.G., F.S.G., M. J. Green, M.G.-S., J. Hauser, K.S.H., N.I., I.J., L.A.J., R.S.K., G.K., M. Landén, C.M.L., J. Lissowska, N.G.M., C.A.M., F.M., S.L.M., A.M.M., I.M., P. B. Mitchell, G.M., O.M., P. B. Mortensen, M.C.O'D., K.J.O., M.J.O., C. Pato, M.T.P., R.H.P., J.A.R.-Q., A.R., E.Z.R., M. Rietschel, T.S., T.G.S., A.S., C.S.W., J.W.S., E. Stordal, F. Streit, A.E.V., E.V., J.B.V., I.D.W., T.W.W., T.W., J.I.N., A. McQuillin, A.D.F. Genomic assays/data generation: A.J.F., M.I., E.A., M.A.E., D.A., M.B.-H., E.C.B., C.B.P., J.B.-G., M. Cairns, T.-K.C., C.C., J.C., F.S.D., F.D., S.D., A.F., J.F., N.B.F., J. Gelernter, M.G.P., P.H., S.J., Y.K., H.R.K., M. Kubo, S.E.L., C. Liao, E.M., N.W.M., J.D.M., G.W.M., J.L.M., D.W.M., T.W.M., N.O'B., M. Rivera, C.S.-M., S. Sharp, C.S.H., C. Terao, C. Toma, E.-E.T., S.H.W., HUNT All-In Psychiatry, G. Breen, A.C., T. Esko, J.M.F., E.S.G., D.M.H., N.I., F.J.M., L. Milani,

R.M.M., M.M.N., M. Ribasés, G.A.R., T.S., G.T., S. Cichon. Obtained funding for BD samples: M.I., M. Cairns, I.N.F., L. Frisén, S.J., Y.K., J.A.K., M. Kubo, C. Lavebratt, S.L., D.M., P. McGuffin, G.W.M., J.B.P., M.H.R., J.R.D., D. J. Stein, J.S.S., C. Terao, A.H.Y., P.P.Z., M.A., L. Alfredsson, L.B., B.T.B., F.B., W.H.B., M. Boehnke, A.D.B., G. Breen, A.C., N.C., B.E., M.F., J.M.F., E.S.G., M. J. Green, M.G.-S., K.S.H., K. Hveem, N.I., I.J., L.A.J., M. Landén, M. Leboyer, N.G.M., F.J.M., P. B. Mitchell, O.M., P. B. Mortensen, B.M.N., M.N., M.M.N., M.C.O'D., T.O., M.J.O., C. Pato, M.T.P., G.P.P., M. Rietschel, G.A.R., T.S., M.S., P.R.S., T.G.S., C.S.W., J.W.S., G.T., J.B.V., T.W.W., T.W., J.M.B., J.I.N., H.J.E., R.A.O., O.A.A. Statistical analysis: N.M., K.S.O'C., B.C., J.R.I.C., Z.Q., T.D.A., T.B.B., S. Børte, J.B., A.W.C., O.K.D., M. J. Gandal, S.P.H., N.K., M. Kim, K.K., G.P., B.M.S., L.G.S., S. Steinberg, V.T., B.S.W., H.-H.W., V.A., S.A., S.E.B., B.M.B., A.M.D., A.L.D., V.E.-P., T.M.F., O.F., S.D.G., T.A.G., J. Grove, P.A.H., L.H., J.S.J., Y.K., M. Kubo, C. Lavebratt, M. Leber, P.H.L., S.H.M., A. Maihofer, M.M., S.A.M., S.E.M., L.M.O.L., A.F.P., T.R., P.R., D.M.R., O.B.S., C. Terao, T.E.T., J.T.R.W., W.X., J.M.K.Y., H.Y., P.P.Z., H.Z., A.D.B., G. Breen, E.S.G., F.S.G., Q.S.L., B.M.-M., C.M.N., D.P., S.R., H.S., P.F.S., T.W., N.R.W., J.M.B., E.A.S. K.S.O'C., B.C., J.R.I.C. and Z.Q. contributed equally to this work and should be regarded as joint second authors.

Competing interests

T.E.T., S. Steinberg, H.S. and K.S. are employed by deCODE Genetics/Amgen. Multiple additional authors work for pharmaceutical or biotechnology companies in a manner directly analogous to academic coauthors and collaborators. A.H.Y. has given paid lectures and served on advisory boards relating to drugs used in affective and related disorders for several companies (AstraZeneca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allergan, Bionomics and Sumitomo Dainippon Pharma), was Lead Investigator for Embolden Study (AstraZeneca), BCI Neuroplasticity study and Aripiprazole Mania Study, and is an investigator for Janssen, Lundbeck, Livanova and Compass. J.I.N. is an investigator for Janssen. P.F.S. reports the following potentially competing financial interests: Lundbeck (advisory committee), Pfizer (Scientific Advisory Board member) and Roche (grant recipient, speaker reimbursement). G. Breen reports consultancy and speaker fees from Eli Lilly and Illumina and grant funding from Eli Lilly. M. Landén has received speaker fees from Lundbeck. O.A.A. has received speaker fees from Lundbeck and Sunovion, and is a consultant to HealthLytix. J.A.R.-Q. was on the speakers bureau and/or acted as consultant for Eli Lilly, Janssen-Cilag, Novartis, Shire, Lundbeck, Almirall, Braingaze, Sincrolab and Rubió in the last 5 years. He also received travel awards (air tickets and hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire and Eli Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli Lilly, Lundbeck, Janssen-Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious and Rubió. E.V. has received grants and served as a consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Bristol Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Catalan Government (AGAUR and PERIS), the Spanish Ministry of Science, Innovation, and Universities (AES and CIBERSAM), the Seventh European Framework Programme and Horizon 2020 and the Stanley Medical Research Institute. T. Elvsåshagen has received speaker fees from Lundbeck. S.K.-S. received author's and consultant honoraria from Medice Arzneimittel Pütter GmbH and Shire/Takeda. A.S. is or has been a consultant/speaker for: Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boheringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, Servier. J.R.D. has served as an unpaid consultant to Myriad – Neuroscience (formerly Assurex Health) in 2017 and 2019 and owns stock in CVS Health. H.R.K. serves as an advisory board member for Dicerna Pharmaceuticals, and is a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was sponsored in the past 3 years by AbbVie, Alkermes, Amygdala Neurosciences, Arbor Pharmaceuticals, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka and Pfizer. H.R.K. is named as an inventor on PCT patent application no. 15/878,640 entitled: Genotype-guided dosing of opioid agonists, filed January 24, 2018. B.M.N. is a member of the scientific advisory board at Deep Genomics and consultant for Camp4 Therapeutics, Takeda Pharmaceutical and Biogen. All other authors declare no financial interests or potential conflicts of interest.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41588-021-00857-4.

Correspondence and requests for materials should be addressed to N.M. or O.A.A.

Peer review information *Nature Genetics* thanks Na Cai, Qiang Wang and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

Reprints and permissions information is available at www.nature.com/reprints.

nature research

Corresponding author(s): Niamh Mullins, Ole A Andreassen

Last updated by author(s): Mar 24, 2021

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Ascertainment of all cohorts is described in the Supplementary Note. Data were generated at many sites using standard genotyping pipelines and calling softwares from commercial sources (Affymetrix and Illumina).
Data analysis	Analyses were performed using the publicly available RICOPILI software suite (version 2018_Nov_23.001) which provides wrappers for standard genetic analysis software including PLINK v1.09, Minimac3, Eagle v2.3.5, EIGENSTRAT v6.1.4 and METAL (version 2011-03-25). Post-GWAS analyses were conducted using FUMA v1.3.6a, MAGMA v1.08, FUSION (vOct 1, 2019), FOCUS 0.6.10, SMR v1.03, LDSC v1.0.0, MiXeR v1.3, GSMR implemented in GCTA software v1.93.1f beta, bedtools v2.29.2, TwoSampleMR v0.5.4 and MR-PRESSO v1.0 R packages. All software is publicly available. Any additional analysis code is detailed in Methods and the Supplementary Note.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

GWAS summary statistics are publicly available on the PGC website (https://www.med.unc.edu/pgc/results-and-downloads). Individual-level data are accessible through collaborative analysis proposals to the Bipolar Disorder Working Group of the PGC (https://www.med.unc.edu/pgc/shared-methods/how-to/). This study included some publicly available datasets accessed through dbGaP (PGC bundle phs001254.v1.p1) and the Haplotype Reference Consortium reference panel v1.0

(http://www.haplotype-reference-consortium.org/home). Databases used: Drug-Gene Interaction Database DGIdb v.2 https://www.dgidb.org Psychoactive Drug Screening Database Ki DB https://pdsp.unc.edu/databases/kidb.php DrugBank 5.0 www.drugbank.ca LDHub http://ldsc.broadinstitute.org FUMA https://fuma.ctglab.nl

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size was not predetermined but all available cohorts of bipolar disorder cases and controls were included to maximize sample size. This study provides a 1.5-fold increase in effective sample size compared with previous GWAS of bipolar disorder, increasing statistical power to detect novel genetic associations.
Data exclusions	Predetermined phenotypic data exclusions, for both cases and controls, are detailed in the Supplementary Note. Genotype data exclusions were also predetermined and were performed for quality control; these included high missing call rate, high or low heterozygosity, inconsistent genotype versus clinical data sex, and ancestry outlier status based on visual inspection of genotype principal component analysis results. Phenotypic and genotypic exclusions were applied to the GWAS and all post-GWAS analyses.
Replication	All available cohorts of bipolar disorder cases and controls were included in the primary analysis and therefore we do not perform replication of genetic associations in independent cohorts here. Post-GWAS analyses were replicated using different statistical genetics methods or by integrating different publicly available biological datasets where possible.
Randomization	Samples/participants were allocated into experimental groups by clinical cohort (which included country of origin) and genotype data collection batches. Association analyses were performed in each dataset and meta-analyzed across datasets. Ancestry covariates derived from genotype principal components analysis were included in association tests, which were logistic regression.
Blinding	Case and control groups were assigned by trained researchers or interviewers during cohort ascertainment, or using predefined International Classification of Diseases codes applied to biobanks. Therefore case/ control status was fixed at ascertainment. Experimenters were not blind to case/ control status while performing statistical analyses of the genetic data as this was not practical.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	This is fully described in the Online Methods and associated Supplementary Note and Tables.
Recruitment	This is fully described in the Online Methods and associated Supplementary Note and Tables.
Ethics oversight	All local IRBs approved of this study. This is fully described in the Online Methods and associated Supplementary Note and Tables.

Note that full information on the approval of the study protocol must also be provided in the manuscript.