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**Genome-wide association study identifies 30 loci associated with bipolar disorder**

eQTLGen Consortium; BIOS Consortium; the Bipolar Disorder Working Group of the Psychiatric Genomics Consortium

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# Genome-wide association study identifies 30 loci associated with bipolar disorder

**Bipolar disorder is a highly heritable psychiatric disorder. We performed a genome-wide association study (GWAS) including 20,352 cases and 31,358 controls of European descent, with follow-up analysis of 822 variants with $P < 1 \times 10^{-4}$ in an additional 9,412 cases and 137,760 controls. Eight of the 19 variants that were genome-wide significant ($P < 5 \times 10^{-8}$) in the discovery GWAS were not genome-wide significant in the combined analysis, consistent with small effect sizes and limited power but also with genetic heterogeneity. In the combined analysis, 30 loci were genome-wide significant, including 20 newly identified loci. The significant loci contain genes encoding ion channels, neurotransmitter transporters and synaptic components. Pathway analysis revealed nine significantly enriched gene sets, including regulation of insulin secretion and endocannabinoid signaling. Bipolar I disorder is strongly genetically correlated with schizophrenia, driven by psychosis, whereas bipolar II disorder is more strongly correlated with major depressive disorder. These findings address key clinical questions and provide potential biological mechanisms for bipolar disorder.**

Bipolar disorder (BD) is a severe neuropsychiatric disorder characterized by recurrent episodes of mania and depression that affect thought, perception, emotion and social behavior. A lifetime prevalence of 1−2%, elevated morbidity and mortality, onset in young adulthood and a frequently chronic course make BD a major public health problem and a leading cause of the global burden of disease[1]. Clinical, twin and molecular genetic data all strongly suggest that BD is a multifactorial disorder[2]. On the basis of twin studies, the overall heritability of BD has been estimated to be more than 70% (refs. [3,4]), suggesting a substantial involvement of genetic factors in the development of the disorder, although non-genetic factors also influence risk.

BD can be divided into two main clinical subtypes[5,6]: bipolar I disorder (BD1) and bipolar II disorder (BD2). In BD1, manic episodes typically alternate with depressive episodes during the course of illness. BD2 diagnosis is based on the lifetime occurrence of at least one depressive and one hypomanic (but not manic) episode. Although modern diagnostic systems retain the Kraepelinian dichotomy[7] between BD and schizophrenia (SCZ), the distinction between the two disorders is not always clear-cut and patients who display clinical features of both disorders may receive a diagnosis of schizoaffective disorder–bipolar type (SAB). Likewise, in genetic studies, BD and SCZ are usually treated separately, although recent epidemiological and molecular genetic studies provide strong evidence for some overlap between the genetic contributions to their etiology[2,8].

Recent genome-wide association studies in BD have identified a number of significant associations between disease status and common genetic variants[9–23]. The first large collaborative BD GWAS by the multinational Psychiatric Genomics Consortium (PGC) Bipolar Disorder Working Group comprised 7,481 patients with BD and 9,250 controls and identified four genome-wide-significant loci[9]. Three subsequent meta-analyses that included the PGC BD data[10,12,18] identified an additional four loci.

Estimates of the proportion of variance in liability attributable to common variants genome wide (SNP heritability) indicate that ~30% of the heritability for BD is due to common genetic variants[8]. So far, only a small fraction of this heritability is explained by associated loci, but results from other human complex traits suggest that many more will be identified by increasing the sample size of GWAS[24]. Here, we report the second GWAS of the PGC Bipolar Disorder Working Group, comprising 20,352 cases and 31,358 controls of European descent in a single, systematic analysis, with follow-up of top findings in an independent sample of 9,412 cases and 137,760 controls. Some of our findings reinforce specific hypotheses regarding BD neurobiology; however, the majority of the findings suggest new biological insights.

## Results

**GWAS of BD.** We performed a GWAS meta-analysis of 32 cohorts from 14 countries in Europe, North America and Australia (Supplementary Table 1a), totaling 20,352 cases and 31,358 controls of European descent (effective sample size 46,582). This is a large GWAS of BD, a 2.7-fold increase in the number of cases compared with our previous GWAS[9] and includes 6,328 case and 7,963 control samples not previously reported. We imputed variant dosages using the 1000 Genomes reference panel, retaining association results for 9,372,253 autosomal variants with imputation quality score INFO > 0.3 and minor allele frequency (MAF) ≥1% in both cases and controls. We performed logistic regression of case status on imputed variant dosage using genetic ancestry covariates. The resulting genomic inflation factor ($\lambda_{GC}$) was 1.23, 1.01 when scaled to 1,000 cases and 1,000 controls ($\lambda_{1,000}$) (Supplementary Fig. 1). The linkage disequilibrium (LD) score regression intercept was 1.021 (s.e.m. = 0.010), and the attenuation ratio of 0.053 (s.e.m. = 0.027) was non-significant, indicating that the observed genomic inflation is indicative of polygenicity rather than stratification or cryptic population structure[25]. The LD score regression SNP heritability estimates for BD were 0.17–0.23 on the liability scale assuming population prevalence of 0.5–2% (see Supplementary Table 1a, Methods and Supplementary Note for sample and method details).

We found a marked increase in phenotypic variance explained by genome-wide polygenic risk scores (PRS) compared with previous publications (sample size weighted-mean-observed Nagelkerke's $R^2 = 0.08$ across datasets, liability scale $R^2 = 0.04$, for $P$ threshold of 0.01; Supplementary Fig. 2 and Supplementary Table 2). Among the different datasets, we observed no association between the PRS $R^2$

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and: (1) the sex distribution of the BD cases ($P=0.51$); (2) the proportion of cases with psychosis ($P=0.61$); (3) the proportion with a family history of BD ($P=0.82$); or (4) the median age of onset for BD ($P=0.64$). In our primary genome-wide analysis, we identified 19 loci exceeding genome-wide significance ($P<5\times10^{-8}$; Table 1).

**Follow-up of suggestive loci in additional samples.** We tested lead variants that were significant at $P<1\times10^{-4}$ in our discovery GWAS meta-analysis, comprising a total of 794 autosomal and 28 X-chromosome variants, for association in follow-up samples totaling 9,412 cases and 137,760 controls of European ancestry (effective sample size 23,005; Supplementary Note and Supplementary Table 1b). We first compared discovery and follow-up sample summary statistics using LD score regression, and estimated their genetic correlation to be 0.98 (s.e.m. = 0.07), consistent with homogeneous genetic effects between the two samples. Discovery and follow-up samples also show similar patterns of significant genetic correlations with a range of other human diseases and traits in the LD Hub database[26] (Supplementary Table 3; correlation of 0.93, $P=8.3\times10^{-14}$, Supplementary Fig. 3).

Thirty autosomal loci achieved genome-wide significance ($P<5\times10^{-8}$) in fixed-effect meta-analysis of our GWAS and follow-up samples (Fig. 1, Table 1a, Supplementary Data 1–3 and Supplementary Table 4). In Supplementary Table 5, we present detailed descriptions of the associated loci and genes, with bioinformatic and literature evidence for their potential roles in BD. Of the 30 genome-wide-significant loci from our combined analysis, 20 are novel BD risk loci. These include 19 loci that were significant only in the combined analysis, of which 3 were reported to have genome-wide-significant SNPs in previous studies (*ADCY2* (ref. [18]), *POU3F2* (ref. [18]), *ANK3* (refs. [12,18])), and 11 that were significant in our primary GWAS. We refer to loci by the gene name attributed in previous BD GWAS publications, or by the name of the closest gene for newly identified loci, without implication that the named gene is causal. Results for all variants tested in the follow-up study are presented in Supplementary Table 4.

Of the 19 variants that were genome-wide significant in the discovery GWAS, 8 were not genome-wide significant in the combined analysis (Table 1b), and 11 were non-significant in one-tailed association tests in the follow-up samples ($P>0.05$ in Table 1). Still, the follow-up results for these 19 variants are clearly non-null in aggregate: all 19 had consistent directions of effect between discovery GWAS and follow-up (9.5 expected by chance, binomial test $P=4\times10^{-6}$), and 8 of the 19 had follow-up one-tailed $P<0.05$ (1 expected by chance, sign test $P=2\times10^{-6}$). Using effect sizes corrected for winner's curse[27,28] for each of the 19 variants that were genome-wide significant in the GWAS, we calculated power to achieve significant results (one-tailed $P<0.05$) in the follow-up samples or genome-wide significance in combined analysis (Supplementary Note, Supplementary Table 6 and Supplementary Fig. 4). We found that the number of variants significant in follow-up was close to expectation (8 observed with follow-up $P<0.05$, 8.26 expected, Poisson binomial $P=0.57$), and that 11 variants achieving genome-wide significance in the combined analysis were also within the expected range ($P=0.29$). As an alternative to winner's curse correction, we conducted a polygenic inference analysis using a mixture of Gaussian effect size distributions to model BD genetic architecture and estimate the variants' true effect sizes[29] (Supplementary Note and Supplementary Fig. 5). Under this model, we found that only two variants were nominally significantly weaker in follow-up than expected by chance (*TRANK1*, rs9834970 $P=0.012$, and rs13821 $P=0.026$; Supplementary Table 7), and none were Bonferroni significant ($P>0.05/19=0.0026$). Thus, the overall replication rate is within the expected range given the polygenic architecture of BD.

We next asked if the variants tested in the follow-up samples were, in aggregate, consistent with the presence of additional sub genome-wide-significant BD association signals. After excluding 47 variants that were genome-wide significant in our GWAS, our combined analysis or previous BD GWAS, 775 variants remained in our follow-up experiment. Of these, 551 variants had the same direction of effect in the discovery GWAS and follow-up (71%, compared to a null expectation of 50%, sign test $P=1.3\times10^{-32}$), and 110 variants had the same direction of effect and were nominally significant ($P<0.05$) in the follow-up (14%, compared to an expected value of 5%, binomial test $P=2.1\times10^{-22}$). This consistency between our GWAS and follow-up results suggests that many more true BD associations exist among these variants.

To identify additional independent signals, we conducted conditional analyses across each of the 30 significant BD loci (Supplementary Table 8). We used the effective number of independent variants on the basis of LD structure within loci[30] to calculate a multiple test-corrected significance threshold ($P=1.01\times10^{-5}$, see Supplementary Note). Only one locus showed evidence for an independent association signal (rs114534140 in locus no. 8, *FSTL5*; $P_{\text{conditional}}=2\times10^{-6}$). At another locus (no. 30, *STK4* on chromosome 20), we found two SNPs with genome-wide significance in low LD ($r^2<0.1$); however, conditional analysis showed that their associations were not independent.

**Shared loci and genetic correlations with other traits.** We next examined the genetic relationships of BD to other psychiatric disorders and traits. Of the 30 genome-wide-significant BD loci, 8 also harbor schizophrenia (SCZ) associations[31,32]. On the basis of conditional analyses, the BD and SCZ associations appear to be independent at three of the eight shared loci (*NCAN*, *TRANK1* and chr7q22.3:105 megabases (Mb)) (Supplementary Table 9). No genome-wide-significant BD locus overlapped with those identified for depression (DEPR), including 44 risk loci identified in the most recent PGC GWAS of major depression[33] and those reported in a large study of depressive symptoms or subjective well-being[34]. As previously reported[35], we found substantial and highly significant genetic correlations between BD and SCZ[31] (LD score regression estimated genetic correlation $r_g=0.70$, s.e.m. = 0.020) and between BD and DEPR[33] ($r_g=0.35$, s.e.m. = 0.026). The BD and DEPR genetic correlation was similar to that observed for SCZ and DEPR ($r_g=0.34$, s.e.m. = 0.025) (Supplementary Table 10a).

We found significant genetic correlations between BD and other psychiatric-relevant traits (Supplementary Table 10b), including autism spectrum disorder[8] ($r_g=0.18$, $P=2\times10^{-4}$), anorexia nervosa[36] ($r_g=0.23$, $P=9\times10^{-8}$) and subjective well-being[34] ($r_g=-0.22$, $P=4\times10^{-7}$). There was suggestive positive overlap with anxiety disorders ($r_g=0.21$, $P=0.04$)[37] and neuroticism ($r_g=0.12$, $P=0.002$)[38]. Significant $r_g$ values were seen with measures of education: college attendance[39] ($r_g=0.21$, $P=1=\times10^{-7}$) and education years[40] ($r_g=0.20$, $P=6\times10^{-14}$), but not with childhood IQ[41] ($r_g=0.05$, $P=0.5$) or intelligence[42] ($r_g=-0.05$, $P=0.08$). Among a large number of variants in BD risk loci that were associated with additional traits in the GWAS catalog[43], we found a handful of loci with non-independent associations (in one overlapping locus with each of educational attainment, biliary atresia, bone mineral density and lipid-related biomarkers) (Supplementary Table 9). Biliary atresia and lipid-related biomarkers, however, did not show significant genetic correlation with BD (Supplementary Table 10b).

**BD subtypes.** We performed a secondary GWAS focusing on three clinically recognized subtypes of bipolar disorder: BD1 ($n=14,879$ cases), BD2 ($n=3,421$ cases) and SAB ($n=977$ cases) (Supplementary Note, Supplementary Tables 1a and 11 and Supplementary Fig. 6). We observed variants in 14 loci with genome-wide significance

**Table 1 | Genome-wide-significant bipolar disorder risk loci**

| Locus name[a] | Lead SNP | Chr | Base pairs | A1/A2 | GWAS meta-analysis | | | Follow-up samples | | Combined | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Freq. A1 | OR | P value[b] | OR | P value[c] | OR | P value[b] |
| **(a) 30 loci with lead SNP $P < 5 \times 10^{-8}$ in combined GWAS + follow-up analysis** | | | | | | | | | | | |
| 1, PLEKHO1 | rs7544145 | 1 | 150,138,699 | T/C | 0.81 | 1.095 | $4.8 \times 10^{-7}$ | 1.064 | **0.010** | 1.085 | **$4.8 \times 10^{-8}$** |
| 2, LMAN2L[d] | rs57195239 | 2 | 97,376,407 | I/D | 0.34 | 0.92 | **$5.8 \times 10^{-9}$** | 0.96 | **0.030** | 0.93 | **$3.8 \times 10^{-9}$** |
| 3, SCN2A | rs17183814 | 2 | 166,152,389 | A/G | 0.075 | 0.87 | $1.5 \times 10^{-7}$ | 0.89 | **0.0017** | 0.88 | **$2.0 \times 10^{-9}$** |
| 4, [Intergenic][e] | rs61332983 | 2 | 194,465,711 | I/D | 0.41 | 0.93 | **$2.3 \times 10^{-8}$** | 0.95 | **0.0031** | 0.93 | **$7.9 \times 10^{-10}$** |
| 5, TRANK1[d] | rs9834970 | 3 | 36,856,030 | T/C | 0.51 | 0.90 | **$5.5 \times 10^{-14}$** | 0.98 | 0.15 | 0.93 | **$5.7 \times 10^{-12}$** |
| 6, ITIH1[d] | rs2302417 | 3 | 52,814,256 | A/T | 0.49 | 0.92 | **$4.9 \times 10^{-9}$** | 0.94 | **0.0012** | 0.93 | **$6.6 \times 10^{-11}$** |
| 7, CD47 | rs3804640 | 3 | 107,793,709 | A/G | 0.53 | 1.075 | $9.3 \times 10^{-8}$ | 1.044 | **0.016** | 1.065 | **$2.0 \times 10^{-8}$** |
| 8, FSTL5 | rs11724116 | 4 | 162,294,038 | T/C | 0.16 | 0.90 | **$3.3 \times 10^{-8}$** | 0.95 | **0.031** | 0.92 | **$2.4 \times 10^{-8}$** |
| 9, ADCY2[d] | rs200550695 | 5 | 7,587,236 | I/D | 0.82 | 0.91 | $1.2 \times 10^{-7}$ | 0.94 | **0.011** | 0.92 | **$1.5 \times 10^{-8}$** |
| 10, SSBP2 | rs10035291 | 5 | 80,796,368 | T/C | 0.68 | 1.081 | $1.1 \times 10^{-7}$ | 1.047 | **0.018** | 1.070 | **$2.7 \times 10^{-8}$** |
| 11, RIMS1 | rs57970360 | 6 | 72,519,394 | D/I | 0.44 | 1.066 | $3.1 \times 10^{-6}$ | 1.062 | **0.0016** | 1.064 | **$3.5 \times 10^{-8}$** |
| 12, POU3F2[e] | rs2388334 | 6 | 98,591,622 | A/G | 0.52 | 0.93 | $8.6 \times 10^{-8}$ | 0.95 | **0.0051** | 0.94 | **$4.0 \times 10^{-9}$** |
| 13, RPS6KA2 | rs10455979 | 6 | 166,995,260 | C/G | 0.53 | 0.93 | $4.6 \times 10^{-8}$ | 0.97 | **0.046** | 0.94 | **$4.3 \times 10^{-8}$** |
| 14, THSD7A | rs113779084 | 7 | 11,871,787 | A/G | 0.30 | 1.068 | $7.3 \times 10^{-6}$ | 1.095 | **$2.9 \times 10^{-5}$** | 1.076 | **$2.5 \times 10^{-9}$** |
| 15, SRPK2 | rs73188321 | 7 | 105,048,158 | T/C | 0.33 | 0.92 | $7.0 \times 10^{-8}$ | 0.94 | <u>**0.0015**</u> | 0.92 | **$1.1 \times 10^{-9}$** |
| 16, MRPS33 | rs201231874 | 7 | 140,700,006 | D/I | 0.25 | 0.92 | $9.4 \times 10^{-8}$ | 0.93 | **0.0008** | 0.92 | **$6.2 \times 10^{-10}$** |
| 17, ANK3[d] | rs10994318 | 10 | 62,125,856 | C/G | 0.057 | 1.151 | $4.5 \times 10^{-7}$ | 1.130 | **0.0021** | 1.145 | **$6.8 \times 10^{-9}$** |
| 18, ADD3[d] | rs59134449 | 10 | 111,745,562 | I/D | 0.16 | 1.105 | $5.0 \times 10^{-8}$ | 1.059 | **0.017** | 1.090 | **$1.2 \times 10^{-8}$** |
| 19, FADS2[d] | rs12226877 | 11 | 61,591,907 | A/G | 0.29 | 1.095 | **$1.2 \times 10^{-8}$** | 1.062 | **0.0073** | 1.085 | **$9.9 \times 10^{-10}$** |
| 20, PACS1 | rs10896090 | 11 | 65,945,186 | A/G | 0.81 | 1.094 | $2.1 \times 10^{-7}$ | 1.062 | **0.0089** | 1.084 | **$1.9 \times 10^{-8}$** |
| 21, PC | rs7122539 | 11 | 66,662,731 | A/G | 0.35 | 0.93 | $2.2 \times 10^{-7}$ | 0.96 | **0.015** | 0.94 | **$3.8 \times 10^{-8}$** |
| 22, SHANK2 | rs12575685 | 11 | 70,517,927 | A/G | 0.31 | 1.066 | $1.2 \times 10^{-5}$ | 1.088 | **$5.7 \times 10^{-5}$** | 1.073 | **$7.7 \times 10^{-9}$** |
| 23, CACNA1C[d] | rs10744560 | 12 | 2,387,099 | T/C | 0.34 | 1.087 | **$2.9 \times 10^{-9}$** | 1.052 | **0.0086** | 1.076 | **$3.6 \times 10^{-10}$** |
| 24, STARD9 | rs4447398 | 15 | 42,904,904 | A/C | 0.12 | 1.112 | $1.1 \times 10^{-7}$ | 1.072 | **0.0079** | 1.099 | **$9.4 \times 10^{-9}$** |
| 25, ZNF592 | rs139221256 | 15 | 85,357,857 | I/D | 0.28 | 0.92 | **$8.5 \times 10^{-9}$** | 0.97 | 0.082 | 0.93 | **$2.7 \times 10^{-8}$** |
| 26, GRIN2A | rs11647445 | 16 | 9,926,966 | T/G | 0.65 | 0.93 | $1.2 \times 10^{-7}$ | 0.93 | **$9.8 \times 10^{-5}$** | 0.93 | **$1.1 \times 10^{-10}$** |
| 27, HDAC5 | rs112114764 | 17 | 42,201,041 | T/G | 0.69 | 0.93 | $1.7 \times 10^{-6}$ | 0.94 | **0.0021** | 0.93 | **$2.5 \times 10^{-8}$** |
| 28, ZCCHC2 | rs11557713 | 18 | 60,243,876 | A/G | 0.29 | 1.074 | $1.2 \times 10^{-6}$ | 1.059 | **0.0038** | 1.069 | **$3.6 \times 10^{-8}$** |
| 29, NCAN[d] | rs111444407 | 19 | 19,358,207 | T/C | 0.15 | 1.124 | **$2.4 \times 10^{-10}$** | 1.040 | 0.075 | 1.097 | **$1.3 \times 10^{-9}$** |
| 30, STK4 | rs202012857 | 20 | 43,682,549 | I/D | 0.28 | 0.923 | $3.0 \times 10^{-7}$ | 0.942 | **0.0043** | 0.929 | **$1.1 \times 10^{-8}$** |
| **(b) Additional loci with lead SNP $P < 5 \times 10^{-8}$ in GWAS analysis** | | | | | | | | | | | |
| TFAP2B | rs55648125 | 6 | 50,816,718 | A/G | 0.90 | 0.89 | **$4.9 \times 10^{-8}$** | 0.95 | 0.068 | 0.91 | $8.5 \times 10^{-8}$ |
| DFNA5 | rs17150022 | 7 | 24,771,777 | T/C | 0.88 | 0.89 | **$2.7 \times 10^{-8}$** | 0.96 | 0.087 | 0.91 | $8.6 \times 10^{-8}$ |
| SLC25A17 | rs138321 | 22 | 41,209,304 | A/G | 0.50 | 1.083 | **$4.7 \times 10^{-9}$** | 1.012 | 0.28 | 1.060 | $1.9 \times 10^{-7}$ |
| HLF | rs884301 | 17 | 53,367,464 | T/C | 0.37 | 1.084 | **$5.8 \times 10^{-9}$** | 1.013 | 0.26 | 1.061 | $2.1 \times 10^{-7}$ |
| PHF15 | rs329319 | 5 | 133,906,609 | A/G | 0.43 | 1.082 | **$1.5 \times 10^{-8}$** | 1.019 | 0.18 | 1.061 | $2.1 \times 10^{-7}$ |
| ODZ4[d] | rs73496688 | 11 | 79,156,748 | A/T | 0.14 | 1.11 | **$1.0 \times 10^{-8}$** | 1.016 | 0.29 | 1.083 | $4.2 \times 10^{-7}$ |
| [Intergenic][e] | rs57681866 | 2 | 57,975,714 | A/G | 0.06 | 0.85 | **$5.0 \times 10^{-8}$** | 0.97 | 0.23 | 0.89 | $1.2 \times 10^{-6}$ |
| [Intergenic][e] | rs13231398 | 7 | 110,197,412 | C/G | 0.11 | 0.89 | **$3.4 \times 10^{-8}$** | 0.998 | 0.47 | 0.92 | $4.6 \times 10^{-6}$ |

[a] Loci are numbered 1 to 30, ordered by genomic position, with previously reported gene name for published loci. [b] P values for GWAS and combined analyses are two-tailed and bold if $P < 5 \times 10^{-8}$. [c] P values for follow-up are one-tailed on the basis of the direction of effect in the discovery GWAS and bold if $P < 0.05$. [d] Previously published and named loci. (Locus 12 would be named as Intergenic; nearest gene is POU3F2 691 kb.) [e] Intergenic loci nearest genes: locus 4 PCGEM1 824 kb, (**b**) chr2 locus VRK2 298 kb, (**b**) chr7 IMMP2L 106 kb.

for BD1, 10 of which were in genome-wide-significant loci in the combined BD GWAS analysis. Not surprisingly, given the sample overlap, three of the four remaining loci genome-wide significant for BD1 have $P < 10^{-6}$ in either our discovery GWAS or combined analysis. The remaining locus (MAD1L1, chr7:1.9 Mb, discovery GWAS $P = 2.4 \times 10^{-6}$) was recently published in two BD GWAS that included Asian-ancestry samples[17,44]. We did not observe

genome-wide-significant results for the smaller BD2 and SAB analyses. BD1, BD2 and SAB all have significant common variant heritabilities (BD1 $h^2_{snp} = 0.25$, s.e.m. $= 0.014$, $P = 3.2 \times 10^{-77}$; BD2 $h^2_{snp} = 0.11$, s.e.m. $= 0.028$, $P = 5.8 \times 10^{-5}$; SAB $h^2_{snp} = 0.25$, s.e.m. $= 0.10$, $P = 0.0071$). Genetic correlations among BD subtypes show that these represent closely related, yet partially distinct, phenotypes (Supplementary Table 12).
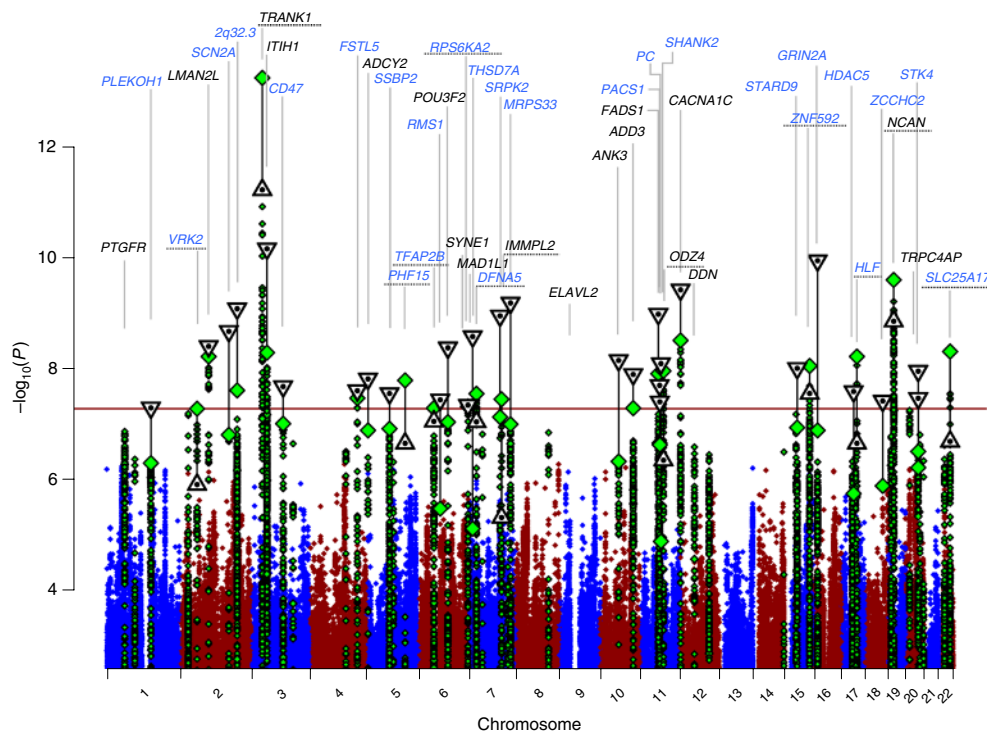
**Fig. 1 | Manhattan plot for our primary genome-wide association analysis of 20,352 cases and 31,358 controls.** GWAS $-\log_{10}P$ values are plotted for all SNPs across chromosomes 1–22 (diamonds, green for loci with lead SNP GWAS $P < 10^{-6}$). Combined GWAS + follow-up $-\log_{10}P$ for lead SNPs reaching genome-wide significance in either GWAS or combined analysis (triangles, inverted if GWAS + follow-up $-\log_{10}P >$ GWAS $-\log_{10}P$). Labels correspond to gene symbols previously reported for published loci (black) and the nearest genes for newly identified loci (blue), at top if GWAS + follow-up $P < 5 \times 10^{-8}$. Loci with one-tailed follow-up $P > 0.05$ (Table 1) have dotted underlined locus names.

We conducted PRS analyses to explore the relationship between genetic risk of SCZ and DEPR, and BD subtypes and psychosis (Fig. 2 and Supplementary Table 13). PRS calculated from SCZ[31] were significantly higher in BD1 cases than in BD2 cases ($P = 5.6 \times 10^{-17}$, $P$ threshold = 0.1) and in cases with psychosis compared to those without psychosis ($P = 2.12 \times 10^{-6}$, $P$ threshold = 0.1). Conversely, PRS calculated from DEPR[33] were significantly higher in BD2 cases than in BD1 cases ($P = 8.5 \times 10^{-10}$, $P$ threshold = 0.01), independent of psychosis. Genetic correlations from LD score regression support these results; genetic correlations were greater for SCZ with BD1 ($r_g = 0.71$, s.e.m. = 0.025) than with BD2 ($r_g = 0.51$, s.e.m. = 0.072), and were greater for DEPR with BD2 ($r_g = 0.69$, s.e.m. = 0.093) than with BD1 ($r_g = 0.30$, s.e.m. = 0.028) (Supplementary Table 12).

**Systems biology and in silico functional analyses.** We tested for functional genomic enrichment in our BD GWAS using partitioned LD score regression and a range of functional annotations across tissues[45] (Supplementary Note and Supplementary Table 14). SNP-based BD heritability was most enriched in open chromatin annotations in the central nervous system (proportion SNPs = 0.14, proportion $h^2_{snp} = 0.60$, enrichment = 3.8, $P = 3 \times 10^{-14}$). We also used DEPICT[46] to test for expression of BD-associated genes across tissues, and found significant enrichment of central nervous system ($P < 1.4 \times 10^{-3}$, false discovery rate (FDR) < 0.01) and neurosecretory system ($P = 2.0 \times 10^{-6}$, FDR < 0.01) genes (Supplementary Table 15).

To prioritize genes that may play a functional role in BD, we integrated BD GWAS association statistics with eQTL (SNP–gene expression association) and mQTL (SNP–DNA methylation association) data using summary Mendelian randomization (SMR)[47–49] (Supplementary Table 16 and Supplementary Note). SMR identified 21 genes using eQTL data that were significant after multiple testing

correction, without evidence of heterogeneity between GWAS and eQTL association signals. Association with *GNL3* was observed in both brain and blood, highlighting the utility of using blood eQTL data as proxy for brain eQTLs[49]. Methylation profiles at six CpGs in the brain and ten CpGs in the blood were associated with BD, four of which overlapped between brain and blood mQTL: *MUSTN1*, *GLT8D1*, *HAPLN4* and *FADS2*.

Finally, we used MAGMA[50] to conduct a gene-wise BD GWAS and to test for enrichment of pathways curated from multiple sources (see Supplementary Note). We note that significance levels were assigned to genes by physical proximity of SNPs, and do not imply that significant genes are causal for BD. Genic association results included 154 Bonferroni significant genes (MAGMA $P_{JOINT} < 2.8 \times 10^{-6}$), including 82 genes in 20 genome-wide-significant loci, and 73 genes in 27 additional loci that did not reach genome-wide significance (Supplementary Table 17). Nine related pathways were significantly enriched for genes with BD associations ($P < 7.0 \times 10^{-5}$, FDR < 0.05), including abnormal motor coordination/balance pathways (from mice), regulation of insulin secretion and endocannabinoid signaling (Supplementary Table 18 and Supplementary Fig. 7).

## Discussion

We carried out a large bipolar disorder GWAS and identified 30 genome-wide-significant loci, including 20 that were newly identified. Previous BD GWAS have reported a total of 20 loci significantly associated with BD[9–23]; 12 of these previously reported loci were not genome-wide significant in our GWAS meta-analysis, but all had $P_{GWAS} \leq 1.3 \times 10^{-5}$ (Supplementary Table 4c). Our recent GWAS of BD and SCZ[51], which included our discovery GWAS data jointly analyzed with published SCZ data[31] (without overlapping control subjects), highlighted similarities and differences in BD
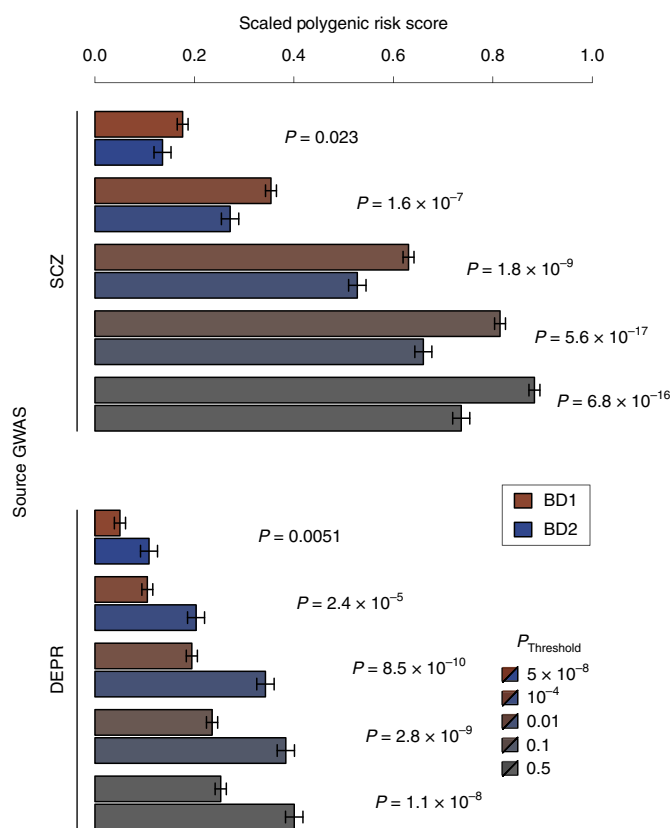
**Fig. 2 | Association of BD1 and BD2 subtypes with SCZ and DEPR PRS.** The mean PRS values (1 s.e.m. error bars) are shown, adjusted for study and ancestry covariates and scaled to the PRS mean and s.d. in control subjects, in BD1 (red) and BD2 (blue) cases, for increasing source GWAS P value thresholds (increasing gray) as indicated. P values (italics) test BD1 versus BD2 mean PRS, in logistic regression of case subtype on PRS with covariates. Results are detailed in Supplementary Table 13.

and SCZ in terms of known associated SNPs and PRS–subphenotype associations; here, we maximized power to identify BD associations. The phenotypic variance explained by PRS on the basis of our BD GWAS data is ~8% (observed scale; 4% on the liability scale[52]), an increase from 2.8% (1.2% on the liability scale) in our previous study[9]. The results of our BD subtype PRS analyses support the nosological distinction between BD1 and BD2, but also highlight the importance of psychosis beyond DSM subtypes, corroborating and expanding evidence from previous clinical[53] and genetic studies[51,54,55]. The DEPR versus BD PRS analyses provide further support for the distinction between BD1 and BD2, independent of the presence of psychosis.

Of the 19 loci identified in our discovery GWAS, only 11 were genome-wide significant in meta-analysis of our GWAS and follow-up samples. These results are not unexpected given the small effect sizes and the winner's curse[28,56] (Supplementary Note and Supplementary Fig. 4); SNPs can teeter-totter around the genome-wide-significance threshold even as sample sizes increase. Genetic heterogeneity observed among BD GWAS cohorts[8] could also contribute to inconsistent replication results; we observed variable polygenic effects between BD subtypes (Fig. 2 and Supplementary Table 13) as well as between cohorts in our study (Supplementary Fig. 2 and Supplementary Table 4) which used a diversity of criteria to define cases (Supplementary Note). Remarkably, the strongest association signal from the discovery GWAS, at the *TRANK1* locus (rs9834970; $P_{combined} = 5.7 \times 10^{-12}$, odds ratio, OR = 0.93), exhibited significant heterogeneity among discovery GWAS cohorts

(Cochran's $Q\ P = 1.9 \times 10^{-4}$), and did not replicate in the follow-up sample (one-tailed $P_{follow-up} = 0.15$) (Supplementary Data 2 and 3). This locus has been significant in recent[11,12,17,18] but not earlier BD GWAS[9,13,20]. Thus, complex genetic architecture as well as phenotypic heterogeneity may contribute to the inconsistency of genome-wide-significant findings within and across BD GWAS studies. The observed heterogeneity is a major challenge for GWAS of psychiatric disorders and calls for careful and systematic clinical assessment of cases and controls in parallel with continued efforts to collect larger sample sizes.

Of the 30 BD-associated loci, 8 also harbor associations[31,32,57] with schizophrenia (SCZ); however, conditional analyses suggest that the BD and SCZ associations at three of the eight shared loci (in the *NCAN*, *TRANK1* and chr7q22.3:105 Mb loci) may be independent (Supplementary Table 9). Differential BD and SCZ associations may represent opportunities to understand the genetic distinctions between these closely related and sometimes clinically difficult to distinguish disorders. We did not find BD loci that overlap with those associated with major depression[33].

The confirmed association within loci containing *CACNA1C* and other voltage-gated calcium channel genes supports the rekindled interest in calcium channel antagonists as potential treatments for BD, with similar examination ongoing for other genes implicated in SCZ GWAS[58]. Other genes within novel BD-associated loci include those coding for other ion channels and transporters (*SCN2A*, *SLC4A1*), neurotransmitter receptors (*GRIN2A*) and synaptic components (*RIMS1*, *ANK3*). Further study will confirm whether or not these are the causal genes in the loci. These processes are important in neuronal hyperexcitability[59], an excess of which has been reported in induced pluripotent-stem-cell-derived neurons from patients with BD, and which has been shown to be affected by the classic mood-stabilizing drug lithium[60]. In addition, SMR eQTL and mQTL analyses implicate *GLT8D1*, which is involved in proliferation and differentiation of neural stem cells[61]. Pathway analyses reveal genetic evidence for insulin secretion and endocannabinoid signaling in BD. There is evidence of insulin action in the brain[62] and in BD[63]. The endocannabinoid system has possible roles in schizophrenia[64,65] and depression[66]. Top genes appearing in these pathways include calcium and potassium channel subunits, MAP kinase and GABA-A receptor subunit genes (Supplementary Table 18).

We observe significant positive genetic correlations with educational attainment, but not with either adult or childhood IQ, suggesting that the role of BD genetics in educational attainment may be independent of general intelligence. This result is inconsistent with suggestions from epidemiological studies[67], but in agreement with results from a recent clinical study[68].

In summary, findings from the genome-wide analysis of BD reveal an extensive polygenic genetic architecture of the disease, implicate brain calcium channels and neurotransmitter function in BD etiology, and confirm that BD is part of a spectrum of highly correlated psychiatric and mood disorders.

## Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of code and data availability and associated accession codes are available at https://doi.org/10.1038/s41588-019-0397-8.

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## Competing interests

## Additional information

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## Methods

**GWAS and follow-up cohorts.** Our discovery GWAS sample comprises 32 cohorts from 14 countries in Europe, North America and Australia (Supplementary Table 1a), totaling 20,352 cases and 31,358 controls of European descent. A selected set of variants (see 'Follow-up cohort analysis') were tested in seven follow-up cohorts of European descent (Supplementary Table 1b), totaling 9,025 cases and 142,824 controls ($N_{eff} = 23,991$). The Supplementary Note summarizes the source and inclusion/exclusion criteria for cases and controls for each cohort. All cohorts in the initial PGC BD paper were included[9]. Cases were required to meet international consensus criteria (DSM-IV 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.

**GWAS cohort analysis.** We tested 20 principal components for association with BD using logistic regression; seven were significantly associated with phenotype and used in GWAS association analysis (principal components 1–6, 19). In each cohort, we performed logistic regression association tests for BD with imputed marker dosages including seven principal components to control for population stratification. For all GWAS cohorts, X-chromosome association analyses were conducted separately by sex and then meta-analyzed across sexes. We also conducted BD1, BD2, and SAB GWAS, retaining only cohorts with at least 30 subtype cases and filtering SNPs for MAF > 0.02. Results were combined across cohorts using an inverse variance-weighted fixed-effects meta-analysis[69]. We used Plink 'clumping'[70,71] to identify an LD-pruned set of discovery GWAS meta-analysis BD-associated variants ($P < 0.0001$, and distance > 500 kilobases (kb) or LD $r^2 < 0.1$, $n$ variants = 822) for analysis in the follow-up cohorts. Conditional analyses were conducted within each GWAS cohort and meta-analyzed as above.

**Follow-up cohort analysis.** In each follow-up cohort we performed BD association analysis of the 822 selected GWAS variants (when available), including genetic ancestry covariates, following quality control and analysis methods of the individual study contributors. We performed inverse variance-weighted fixed-effects meta-analyses of the association results from the follow-up cohorts, and of the discovery GWAS and follow-up analyses.

**PRS analyses.** We tested PRS for our primary GWAS on each GWAS cohort as a target set, using a GWAS where the target cohort was left out of the meta-analysis (Supplementary Table 2). To test genetic overlaps with other psychiatric diseases, we calculated PRS for DEPR and SCZ in our GWAS cohort BD cases[72]. In pairwise case subtype or psychosis analyses (Fig. 2 and Supplementary Table 13), we regressed outcome on the PRS adjusting for ancestry principal components and a cohort indicator using logistic regression, and visualized covariate-adjusted PRS in BD1 and BD2 subtypes (Fig. 2). Outcome sample sizes were BD1 $n = 8,044$, BD2 $n = 3,365$, SAB $n = 977$; BD1 cases with and without psychosis $n = 2,175$ and $n = 798$, respectively, BD2 cases with and without psychosis $n = 146$ and $n = 660$, respectively.

**LD score regression.** LD score regression[25,26] was used to conduct SNP heritability analyses from GWAS summary statistics. LD score regression bivariate genetic correlations attributable to genome-wide common variants were estimated between the full BD GWAS, BD subtype GWASs and other traits and disorders in LD Hub[26]. We also used LD score regression to partition heritability by genomic features[45].

**Relation of BD GWAS findings to tissue and cellular gene expression.** We used partitioned LD score[46,73] and DEPICT[46] regression to evaluate which somatic tissues and brain tissues were enriched in the BD GWAS. We used SMR[47,49] to identify SNPs with strong evidence of causality of brain or blood gene expression or methylation in BD risk (Supplementary Table 16), with a test for heterogeneity to exclude regions with LD between distinct causal SNPs ($P_{HET} < 0.01$).

**Gene-wise and pathway analysis.** Guided by rigorous method comparisons conducted by PGC members[50,74], $P$ values quantifying the degree of association of genes and gene sets with BD were generated using MAGMA (v.1.06)[50]. We used ENSEMBL gene coordinates for 18,172 genes giving a Bonferroni-corrected $P$ value threshold of $2.8 \times 10^{-6}$. Joint multi-SNP LD-adjusted gene-level $P$ values were calculated using SNPs 35 kb upstream to 10 kb downstream, adjusting for LD using 1000 Genomes Project (Phase 3 v5a, MAF ≥ 0.01, European ancestry subjects)[75]. Gene sets were compiled from multiple sources. Competitive gene-set tests were conducted correcting for gene size, variant density and LD within and between genes. The pathway map (Supplementary Fig. 5) was constructed using the kernel generative topographic mapping algorithm (k-GTM) as described in ref. [76].

**Genome build.** All genomic coordinates are given in NCBI Build 37/UCSC hg19 (http://genome.ucsc.edu/cgi-bin/hgGateway?db=hg19).

**Accession codes.** Accessioned data were part of the following datasets analyzed in this study. Fat2: phs000167.v1.p1 or PGC bundle phs001254.v1.p1 (MGS nonGAIN controls). Gain: dbGAP phs000017.v3.p1 (GAIN Bip cases/controls), phs000021.v3.p2 (GAIN scz controls); also part of the PGC dbGAP bundle phs001254.v1.p1. Jjst: phs000092.v1.p1 or PGC bundle phs001254.v1.p1 (SAGE controls). St2c, NIMH RGR Bipolar Study 19 (STEP-BD; https://www.nimhgenetics.org/download-tool/BP), dbGAP phs000294.v1.p1 (MIGEN controls). Mich: NIMH RGR Bipolar Study 2 (Pritzker). Wtcc: EGAD00000000002.

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

## Data availability

The PGC's policy is to make genome-wide summary results public. Summary statistics for our meta-analysis are available through the PGC (https://www.med.unc.edu/pgc/results-and-downloads). Data are accessible with collaborative analysis proposals through the Bipolar Disorder Working Group of the PGC (https://med.unc.edu/pgc).

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# nature research

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|---|---|---|
| ☐ | ☒ | The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement |
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| ☐ | ☒ | 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 |
| ☐ | ☒ | Clearly defined error bars<br>*State explicitly what error bars represent (e.g. SD, SE, CI)* |

*Our web collection on statistics for biologists may be useful.*

## Software and code

Policy information about availability of computer code

| Data collection | Data were generated at many sites using standard genotype calling softwares from commercial sources (Affymetrix and Illumina). |
|---|---|
| Data analysis | Analyses were performed using the Ricopili software suite, which provides wrappers for standard genetic analysis software including plink v1.09, shapeit and impute2. All of these are 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/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

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- 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

Full summary statistics for the GWAS will be made available through the Psychiatric Genomics Consortium (PGC), at https://www.med.unc.edu/pgc/results-and-

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# 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 was maximized by the inclusion of datasets in this study. Sample sizes in this study are larger than previous analyses, which revealed some significant findings and showed that additional true positives remained to be discovered. |
| 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. |
| Replication | Follow-up samples were tested for SNPs identified as significant with $P<1e-4$ in our primary GWAS. Significance was defined as $P<5e-8$ in the combined GWAS+follow-up samples analysis. Consistency of association signal across datasets and rates of combined analysis significance were assessed as detailed in the Supplementary Note. |
| 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 | Standard quality control and analysis pipelines were run such that blinding is not relevant to this study. |

# Materials & experimental systems

Policy information about availability of materials

| n/a | Involved in the study |
|---|---|
| ☒ | Unique materials |
| ☒ | Antibodies |
| ☒ | Eukaryotic cell lines |
| ☒ | Research animals |
| ☐ | ☒ Human research participants |

## Human research participants

Policy information about studies involving human research participants

| | |
|---|---|
| Population characteristics | Human subjects were used in the datasets that were analyzed as part of this study, as described in Methods and the Supplementary Note. Phenotypes used and covariates assessed and used in analyses are also described. All local IRBs approved of this study. |

# Method-specific reporting

| n/a | Involved in the study |
|---|---|
| ☒ | ChIP-seq |
| ☒ | Flow cytometry |
| ☒ | Magnetic resonance imaging |