Genome-wide association study identifies 30 Loci Associated with Bipolar Disorder.

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Thomas G Schulze [182]; Janice M Fullerton [75]; Peter R Schofield [75]; Eystein Stordal [183]; Gunnar Morken [184]; Ulrik F Malt [185]; Ingrid Melle [186]; Sara A Paciga [187]; Nicholas G Martin [89]; Arne E Vaaler [188]; Gunnar Morken [189]; David M Hougaard [190]; Carlos Pato [100,191]; Michele T Pato [100]; Nicholas G Martin [192]; Aiden Corvin [103]; Michael Gill [103]; René S Kahn [104]; Rolf Adolfsson [105]; Josep Antoni Ramos-Quiroga [106]; Frank Bellivier [193]; Bruno Etain [193]; Marion Leboyer [107]; Thomas G Schulze [113]; Bernhard T Baune [194]; Ketil J Oedegaard [195]; Alessandro Serretti [196]; Markus M Nöthen [5,6]; Elliot S Gershon [124,197]; Thomas Werge [198]; Andrew M McIntosh [125,199]; Mikael Landén [200]; Kari Stefansson [201]; Bertram Müller-Myhsok [202]; Michael Boehnke [132]; Udo Dannlowski [203]; Janice M Fullerton [204]; Philip B Mitchell [136]; Peter R Schofield [204]; Patrick F Sullivan [205,206]; Ingrid Agartz [207]; Ingrid Melle [208]; Wade H Berrettini [209]; 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ABSTRACT:

Bipolar disorder is a highly heritable psychiatric disorder that features episodes of mania and depression. We performed the largest genome-wide association study to date, including 20,352 cases and 31,358 controls of European descent, with follow-up analysis of 881 sentinel variants at loci with $P<1x10^{-4}$ in an independent sample of 9,412 cases and 137,760 controls. In the combined analysis, 30 loci achieved genome-wide significance including 20 novel loci. These significant loci contain genes encoding ion channels and neurotransmitter transporters (*CACNA1C*, *GRIN2A*, *SCN2A, SLC4A1*), synaptic components (*RIMS1, ANK3*), immune and energy metabolism components, and multiple potential therapeutic targets for mood stabilizer drugs. Bipolar disorder type I (depressive and manic episodes; ~73% of our cases) is strongly genetically correlated with schizophrenia whereas type II (depressive and hypomanic episodes; ~17% of our cases) correlated more with major depression. Furthermore, bipolar disorder has a positive genetic correlation with educational attainment yet has no significant genetic correlation with intelligence. These findings address key clinical questions and provide potential new biological mechanisms for bipolar disorder.

INTRODUCTION

Bipolar disorder (BD) is a severe neuropsychiatric disorder characterized by recurrent episodes of mania and depression which affect thought, perception, emotion, and social behaviour. 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]. Based on twin studies, the overall heritability of BD has been estimated to be more than 70% [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. Diagnosis of BD2 is based on the lifetime occurrence of at least one depressive and one hypomanic (but no manic) episode. Although modern diagnostic systems retain the Kraepelinian dichotomy [7] between BD and schizophrenia, the distinction between the two disorders is not always clear-cut, and some patients displaying clinical features of both disorders may receive a diagnosis of schizoaffective disorder (SAB). Likewise, in genetic studies the two diagnoses 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 (GWASs) 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 BD patients and 9,250 controls and identified one

novel and three known genome-wide significant loci [9]. Three subsequent meta-analyses that included the PGC BD data [10,12,18] identified an additional 5 loci.

Estimates of the proportion of variance in liability attributable to genome-wide SNPs (SNP heritability) indicate that ~¼-⅓ of the heritability for BD is due to common genetic variants [8]. To date, only a small fraction of this heritability is explained by associated loci but results from other human complex traits suggests that many more will be identified by increasing the sample size of the GWAS [24]. Here, we report the second GWAS of the PGC Bipolar Disorder Working Group including 20,352 cases and 31,358 controls of European descent in a single, systematic analysis, with follow up of the top associations in a 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 bipolar disorder (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. This increases by 2.7-fold the number of cases in our previous GWAS [9], is the largest GWAS of BD to date, and includes 6,328 case and 7,963 control samples not previously reported. We imputed SNP dosages using the 1000 Genomes world reference panel (see Methods), retaining association results for 7,111,918 autosomal SNPs with imputation quality score $r^2 > 0.3$ and minor allele frequency ≥ 1%. We performed logistic regression of case status on imputed SNP dosage using ancestry covariates. The resulting genomic inflation factor (λ_{GC}) was 1.23 and λ_{1000} was 1.01 (**Supplementary Figure 1**). The LD-score regression intercept was not significantly different from 1, indicating that the observed genomic inflation is indicative of

polygenicity rather than stratification or cryptic population structure [25]. This was further supported by LD-score regression which yields a highly significant SNP-heritability estimate of between 0.17-0.23 (estimates adjusted to liability scale assuming population lifetime risk of between 0.5-2%). See **Supplementary Table 1A**, **Online Methods** and **Supplementary Note** for sample and method details.

We find a marked increase in polygenic risk score (PRS) variance explained compared to previous studies (weighted mean observed Nagelkerke's R^2 = 0.08 (liability scale R^2=0.04) across datasets for P-threshold ≤ 0.01; **Supplemental Figure 2**). Between the different sample sites, we observed no correlation between the PRS and: the gender distribution of the bipolar disorder subjects; the proportion of subjects with psychosis; the proportion with a family history of bipolar disorder; or by the median age of onset for bipolar disorder (p=0.17-0.82); see **Supplementary Note**). Overall, in our GWAS analysis, we identified 19 loci exceeding genome-wide significance ($P< 5x10^{-8}$) and then followed up these loci along with other loci reaching suggestive significance ($p<1x10^{-4}$) in additional samples (see below).

Follow-up of suggestive loci in additional samples

We meta-analysed all lead SNPs within LD clumps (a total of 881 SNPs) which were significant at $P<1x10^{-4}$ with additional samples totaling 9,412 cases and 137,760 controls (**Supplementary Note** and **Supplementary Table 1B**). Thirty-one SNPs in 30 loci achieved genome-wide significance ($P< 5x10^{-8}$) (**Figure 1**, **Table 1**, **Supplementary Figure 3**, **Supplementary Table 2**), including 12 of the 19 loci from our GWAS analysis and three other loci previously reported to be genome-wide significant. Of the 30 significant loci from this combined analysis, 20 are novel. Excluding these 30 loci, association results in the remaining 850 SNPs genotyped in the follow-up sample still contain an excess of nominally significant and directionally consistent results. 12% or

104 SNPs had $P_{Rep,1t} < 0.05$ (binomial test $P = 7x10^{-10}$) and 69% or 585 SNPs had the same direction of effect (sign test $P < 2x10^{-16}$), indicating that within this set additional associations remain to be discovered in future GWAS.

Lead SNPs for loci achieving genome-wide significance are tabulated in **Table 1**, and additional SNP associations ($P<1x10^{-4}$) from the BD GWAS that we tested further in the follow-up samples are presented in **Supplementary Table 2**. In **Supplementary Table 3**, we present detailed descriptions of the associated loci and genes, with bioinformatic and literature evidence for their role in BD.

Table 1. Genome-wide significant bipolar disorder risk loci

Locus Name	Lead SNP	CHR	BP	A1/A2	GWAS Meta-analysis			Follow-up samples		Combined	
					Freq. A1	OR	P-value	OR	P-value	OR	P-value
1	rs7544145	1	150,138,699	T/C	0.81	1.095	4.8E-07	1.064	0.021	1.085	**4.8E-08**
2,LMAN2L	chr2_97376407_I	2	97,376,407	I/D	0.34	0.92	**5.8E-09**	0.96	0.059	0.93	**3.8E-09**
3	rs17183814	2	166,152,389	A/G	0.075	0.87	1.5E-07	0.89	0.0033	0.88	**2.0E-09**
4	chr2_194465711_D	2	194,465,711	I/D	0.41	0.93	**2.3E-08**	0.95	0.0063	0.93	**7.9E-10**
5,TRANK1	rs9834970	3	36,856,030	T/C	0.51	0.90	**5.5E-14**	0.98	0.30	0.93	**5.7E-12**
6,ITIH1,3	rs2302417	3	52,814,256	A/T	0.49	0.92	**4.9E-09**	0.94	0.0024	0.93	**6.6E-11**
7	rs3804640	3	107,793,709	A/G	0.53	1.075	9.3E-08	1.044	0.032	1.065	**2.0E-08**
8	rs11724116	4	162,294,038	T/C	0.16	0.90	**3.3E-08**	0.95	0.061	0.92	**2.4E-08**
9,ADCY2	chr5_7587236_D	5	7,587,236	I/D	0.82	0.91	1.2E-07	0.94	0.023	0.92	**1.5E-08**
10	rs10035291	5	80,796,368	T/C	0.68	1.081	1.1E-07	1.047	0.036	1.070	**2.7E-08**
11	chr6_72519394_D	6	72,519,394	D/I	0.44	1.066	3.1E-06	1.062	0.0033	1.064	**3.5E-08**
12,POU3F2	rs2388334	6	98,591,622	A/G	0.52	0.93	8.6E-08	0.95	0.010	0.94	**4.0E-09**
13	rs10455979	6	166,995,260	C/G	0.53	0.93	**4.6E-08**	0.97	0.092	0.94	**4.3E-08**
14	rs113779084	7	11,871,787	A/G	0.30	1.068	7.3E-06	1.095	5.7E-05	1.076	**2.5E-09**
15	rs73188321	7	105,048,158	T/C	0.33	0.92	7.0E-08	0.94	0.0030	0.92	**1.1E-09**
16	chr7_140700006_I	7	140,700,006	D/I	0.25	0.92	9.4E-08	0.93	0.0015	0.92	**6.2E-10**
17,ANK3	rs10994318	10	62,125,856	C/G	0.057	1.151	4.5E-07	1.130	0.0041	1.145	**6.8E-09**
18,ADD3	chr10_111745562_I	10	111,745,562	I/D	0.16	1.105	**5.0E-08**	1.059	0.034	1.090	**1.2E-08**
19,FADS2	rs12226877	11	61,591,907	A/G	0.29	1.095	**1.2E-08**	1.062	0.015	1.085	**9.9E-10**
20	rs10896090	11	65,945,186	A/G	0.81	1.094	2.1E-07	1.062	0.018	1.084	**1.9E-08**
21	rs7122539	11	66,662,731	A/G	0.35	0.93	2.2E-07	0.96	0.030	0.94	**3.8E-08**
22	rs12575685	11	70,517,927	A/G	0.31	1.066	1.2E-05	1.088	1.1E-04	1.073	**7.7E-09**
23,CACNA1C	rs10744560	12	2,387,099	T/C	0.34	1.087	**2.9E-09**	1.052	0.017	1.076	**3.6E-10**
24	rs4447398	15	42,904,904	A/C	0.12	1.112	1.1E-07	1.072	0.016	1.099	**9.4E-09**
25	chr15_85357857_I	15	85,357,857	I/D	0.28	0.92	**8.5E-09**	0.97	0.16	0.93	**2.7E-08**
26	rs11647445	16	9,926,966	T/G	0.65	0.93	1.2E-07	0.93	2.00E-04	0.93	**1.1E-10**
27	rs112114764	17	42,201,041	T/G	0.69	0.93	1.7E-06	0.94	0.0042	0.93	**2.5E-08**
28	rs11557713	18	60,243,876	A/G	0.29	1.074	1.2E-06	1.059	0.0077	1.069	**3.6E-08**
29,NCAN	rs111444407	19	19,358,207	T/C	0.15	1.124	**2.4E-10**	1.040	0.15	1.097	**1.3E-09**
30	chr20_43682549_I	20	43,682,549	I/D	0.28	0.92	3.0E-07	0.94	0.0086	0.93	**1.1E-08**
30*	rs6130764	20	43,750,410	T/C	0.57	1.070	5.8E-07	1.051	0.014	1.064	**3.2E-08**

* Locus 30 contained two lead SNPs in low linkage disequilibrium (r2<0.1)

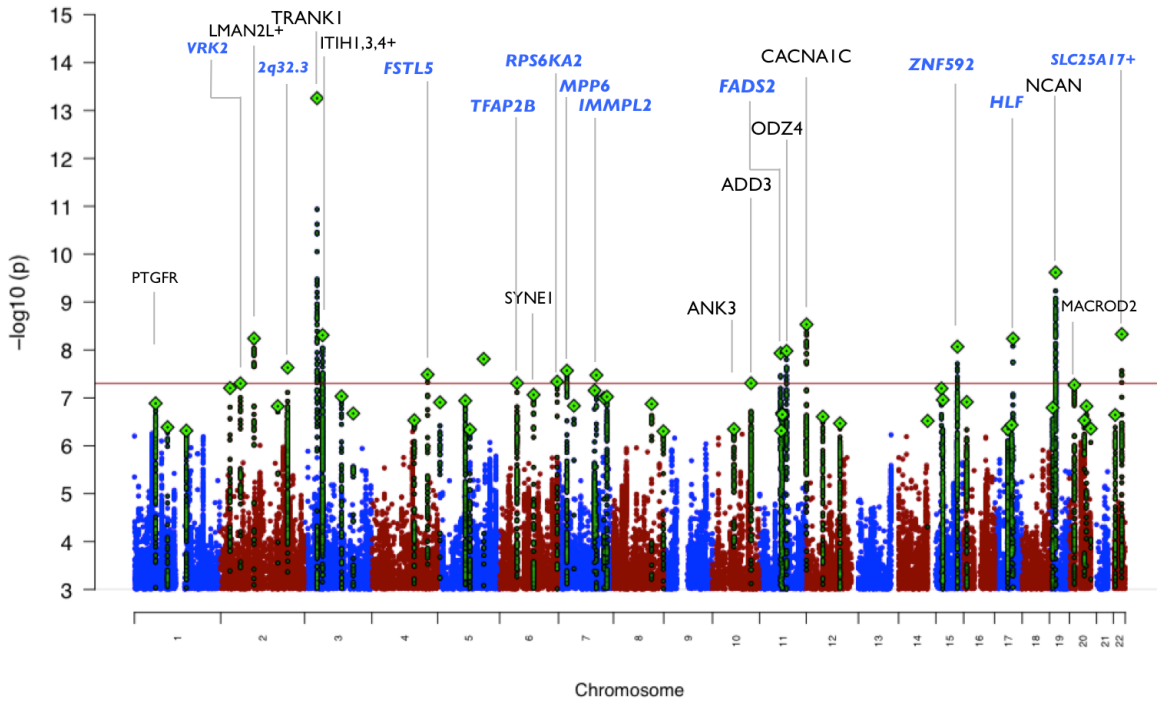

Figure 1. Manhattan plot for our primary genomewide association analysis of 20,352 cases and 31,358 controls. -log10P-values are plotted for all SNPs across chromosomes 1-22 (green if P<10-6). Labels correspond to gene symbols previously reported for known loci (black) and the nearest genes for novel bipolar risk loci (blue).

We conducted conditional analyses across each of the 30 genome-wide significant loci found in the GWAS sample (**Supplementary Table 4**). Using the LD structure within loci to compute a multiple-test-corrected conditional significance threshold [26] of $P=1.01\times10^{-5}$, one locus showed evidence for an independent association signal (rs114534140 near *FSTL5* with $P_{conditional} = 2\times10^{-6}$; all other loci had minimum $P_{conditional} > 0.0002$). Conditional analyses including the lead SNPs in the present GWAS for lead SNPs reported in previous bipolar disorder GWAS studies were consistent with the same association signal at all loci ($P_{conditional} > 0.01$), despite low LD between published and current lead SNPs in some cases (see **Supplementary Note**). Thus only the *FSTL5* locus demonstrated clear evidence of two causal variants, and all other loci were consistent with a single causal variant.

BD subtype GWAS

We performed secondary GWAS focusing on three clinically recognised subtypes: BD1 (n=14,879 cases), BD2 (n=3,421 cases), and SAB (n= 977 cases; **Supplementary Tables 1A** and **5, Supplementary Note**; **Supplementary Figure 4**). A few suggestive subtype-specific associations are noted, although the smaller BD2- and SAB-specific GWAS did not identify significant associations. BD1, BD2 and SAB all have significant common variant heritabilities (h^2_{snp} BD1 = 0.25, se = 0.01; BD2: 0.13, se = 0.028; SAB: 0.26, se = 0.10), and genetic correlations among BD subtypes show that these represent closely related, yet partially distinct, phenotypes (see below).

Shared loci and genetic correlations with SCZ, Depression and other GWAS traits

In a series of conditional analyses within bipolar risk loci and genome-wide genetic correlation analyses, we examined the relationships of BD to other psychiatric disorders and other traits for which GWAS have been conducted. Looking at individual loci, 8 of the 30 genome-wide significant BD loci also harbor SCZ associations [27–29]. Conditional analyses suggest that the BD and SCZ associations are not independent at 5 of the 8 shared loci (**Supplementary Table 6**), the exceptions being the *NCAN*, *TRANK1* and chr7q22.3 (105Mb) loci. We did not find any BD loci (at $p<5x10^{-8}$) that overlap with those identified for major depression, including 44 risk loci identified in the most recent PGC study based on 130,664 major depression cases and 330,470 controls[30], or those reported in a large study of depressive symptoms or subjective well-being [31]. As reported in smaller studies of BD, we found substantial genome-wide correlation between BD and SCZ (LD-score regression estimated genetic correlation $r_g = 0.70$ (se = 0.02)). The SCZ-depression ($r_g = 0.34$, se = 0.025) and BD-depression genetic correlations ($r_g = 0.35$, se = 0.026), although significant, are much smaller than seen for BD-SCZ (**Supplementary Table 7A**).

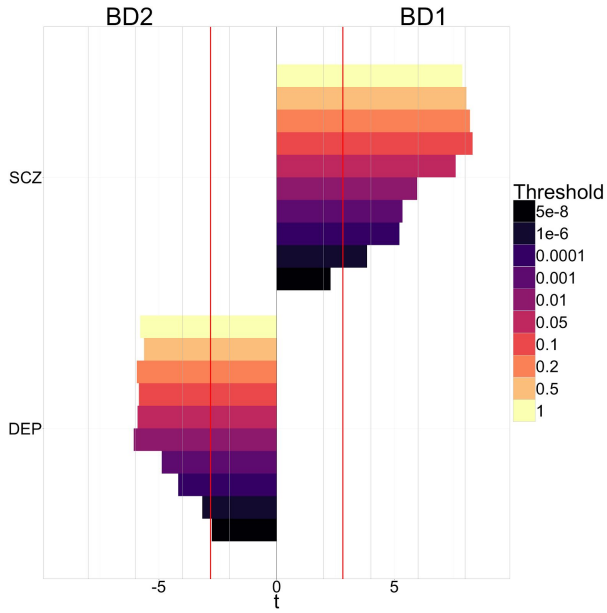

Figure 2. Association of BD subtypes with polygenic risk scores (PRS) derived from PGC2 studies of SCZ and major depression. X-axis = t-statistic from regression of PRS on BD subtypes. Red line = Bonferroni threshold for 10 thresholds tested. Results are detailed in Supplementary Table 8.

Polygenic risk scores and genetic correlations (**Figure 2**, **Supplementary Tables 7A** and **8**) provide support for a continuum of SCZ-BD1-BD2-Depression genetic effects, with significantly greater genetic SCZ polygenic risk scores (PRS) in BD1 cases than in BD2 cases (min $P=1.00\times10^{-18}$, P threshold = 0.1), and greater Depression PRS in BD2 cases than in BD1 cases (min $P=3.03\times10^{-9}$, P threshold = 0.2). LD-score regression derived genetic correlations support these results, showing greater genetic correlations for SCZ with BD1 (r_g = 0.71, se = 0.025) than with BD2 (r_g = 0.51, se = 0.072), P_{diff} = 0.0056, and for depression with BD2 (r_g = 0.69, se = 0.093) than with BD1 (r_g = 0.30, se = 0.028), $P_{diff} = 2.9\times10^{-5}$.

We found significant genetic correlations between BD and other psychiatric-relevant traits (**Supplementary Table 7B**). These include significant genetic overlaps with autism (r_g =

0.18, P=2x10^{-4}) [8], anorexia nervosa (r_g = 0.23, P=9x10^{-8}) [32], and subjective well-being (r_g = -0.22, P=4x10^{-7}) [31]. There was suggestive overlap with anxiety disorders (r_g=0.21, P=0.04) [33] and neuroticism (r_g=0.12, P=0.002) [34]. Significant r_gs are seen with measures of education: college attendance (r_g = 0.21, P=1=x10^{-7}) [35], education years (r_g=0.20, P=6x10^{-14}) [36], but not with childhood IQ (r_g=0.05, P=0.5) [37] or intelligence (r_g=-0.05, P=0.08) [38]. Among a large number of bipolar risk locus SNPs associated with additional traits from GWAS catalog, we found a handful of non-independent associations (with educational attainment, biliary atresia, lipid-related biomarkers) (**Supplementary Table 6**). However, among these, only educational attainment showed significant genomewide genetic correlations with bipolar disorder (**Supplementary Table 7B**).

Systems biology and functional analyses of GWAS results

In order to try to identify genes with functional variation that might explain the associations, we used Mendelian randomisation (SMR) [39] to integrate our bipolar disorder GWAS with eQTL data from dorsolateral prefrontal cortex [40] as well as a large-sample whole blood eQTL dataset [41]. This identified six transcriptome-wide significant genes without signs of heterogeneity between GWAS and eQTL signals (**Supplementary Table 9**). Among these, expression of *LMAN2L* is indicated as putatively causal for bipolar disorder risk within the chr2q11.2 (97.4Mb) locus. In addition, *FADS1*, *NMB* and *C17ORF65* are highlighted as novel candidates within genome-wide significant loci, although other genes in these loci show suggestive evidence of expression mediating disease risk.

We tested for functional genomic enrichment in our bipolar disorder GWAS using partitioned LD-score regression [42] (**Supplementary Note**, **Supplementary Table 10** and **Supplemental Figure 7**). Annotations tested included tracks representing open chromatin DHS

peaks in a range of tissues [43], as well as genic annotations, conservation, a number of functional genomic annotations across tissues that comprise the baseline model for partitioned LD-score regression. BD associations were significantly enriched in open chromatin annotations in brain compared with those in other tissues. (**Supplementary Table 11**).

Finally, we used MAGMA [44] to calculate gene-wide association p-values, and to use these to test curated pathways from multiple sources (see Supplementary Note) for enrichment in BD associations. Genic association results (**Supplementary Table 12**) identify 154 Bonferroni significant genes in total, including 82 genes in 20 genome-wide significant loci (range 1-15 genes per locus) and 73 genes in 27 novel loci. Seven related pathways were enriched (FDR < 0.05) for association including neuron number, endocannabinoid signaling, and several ion channel transport pathways. (**Supplementary Table 13, Supplementary Figure 5**).

DISCUSSION

We carried out the largest BD GWAS to date, aiming to identify genetic variants associated with BD, examine the genetic relationships among BD, BP1, BP2, SAB and SCZ, and identify biological pathways related to BD through systems genomics. Our GWAS analysis identified 19 genome-wide significant loci, including 12 loci not previously associated with BD. Previous BD GWAS have reported a total of 20 loci significantly associated with BD [9–23]; twelve of these previously reported loci were not genome-wide significant in our GWAS analysis but had $P_{GWAS} \leq 1.3x10^{-5}$. Given the small effect sizes of BD associated SNPs, these results are not unexpected, reflecting the effects of Winner's curse, amongst other issues [45]. When we performed a combined meta analysis of the top 881 SNPs (with $p<1x10^{-4}$), 31 SNPs in 30 loci achieved genome-wide significance ($P_{combined} < 5x10^{-8}$), including 19 SNPs in 18 loci that were not previously genome-wide significant in our main analysis. Our combined analysis identified 10

previously known loci as genome-wide significant, and a total of twenty novel bipolar disorder risk loci.

Of these 30 overall loci, 8 also harbor SCZ associations [27–29]. Conditional analyses suggest that the BD and SCZ associations are not independent at 5 of the 8 shared loci (**Supplementary Table 6**), the exceptions being the *NCAN*, *TRANK1* and chr7q22.3 (105Mb) loci. *TRANK1* is our strongest associated locus; differential BD and SCZ associations there and our other loci may represent opportunities to understand the genetic distinctions between these closely related disorders. We did not find BD loci that overlap with those associated with major depression [30]. The lack of overlapping loci with major depression may be due to the variants underlying the genetic correlation seen between major depression and BD having individual lower effect sizes than our BD GWAS loci.

The confirmed association with *CACNA1C* and other voltage-gated calcium channels supports the rekindled interest in calcium channel antagonists as potential treatments for BD with similar examination ongoing of other genes implicated by current GWASs [46]. Other biological pathways implicated by loci associated with BD include energy metabolism and calcium channel processes. These process are both important in neuronal hyperexcitability [47], an excess of which has been reported in iPSC derived neurons from BD patients, where lithium, a classic mood stabilizing drug, differentially affects neuronal excitability [48]. Other genes mapping to associated loci include those coding for neurotransmitter channels (*GRIN2A*), ion channels and transporters (*SCN2A, SLC4A1*) and synaptic components (*RIMS1, ANK3*).

The estimated variance explained by polygenic risk scores (PRS) based on our BD GWAS data is ~8% (observed scale; 4% on the liability scale [49]), an increase from 2.8% from our previous study [9]. Using PRS for other psychiatric phenotypes, we identified differential sharing of risk alleles between common subtypes of BD (BD1 and BD2) with schizophrenia and major

depression, effects that are mirrored by the patterns of LD score genetic correlations between the traits (Figure 2). In particular we were able to show that BD1 is genetically more closely related to schizophrenia while BD2 is more closely related to major depression. This finding may make a useful contribution to a topic which has been much debated [3] although further studies are needed to examine the genetic relationship between severe recurrent depression, for which we did not have GWAS data, and BD2 [50]. Likewise, while we see significant genetic correlations of BD with educational attainment, we do not see significant r_gs of BD with either adult or childhood IQ, suggesting the role of BD genetics in increased educational attainment, as suggested by epidemiological studies [51], may be independent of general intelligence, despite its significant r_g with educational attainment (r_g = 0.70, P = 2.5×10^{-287}). Our findings address key clinical questions and suggest potential new biological mechanisms for bipolar disorder.

ONLINE METHODS

Methods

GWAS and follow-up cohorts. We included 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. Top SNPs were tested in 7 additional cohorts of European descent (**Supplementary Table 1B**), totalling 9,025 cases and 142,824 controls (Neff = 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, 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 (see **Supplementary**

Note). Controls in most cohorts were screened for the absence of lifetime psychiatric disorders and randomly selected from the population. We also conducted BD subtype GWAS (see **Supplementary Note** for details)**.**

GWA cohort analysis We tested 20 principal components for association with BD using logistic regression; seven were significantly associated and used in GWAS association analysis. In each cohort, we performed logistic regression association tests for bipolar disorder with imputed marker dosages including 7 principal components to control for population stratification. The results were combined across cohorts using an inverse-weighted fixed effects meta-analysis [52]. For all GWAS cohorts, X-chromosome association results were conducted separately by sex, and then meta-analysed across sexes. We selected an LD-pruned set of discovery GWAS meta-analysis BD-associated SNPs ($P < 0.0001$ and $r^2 < 0.1$, n variants =881) for follow-up cohort and combined analyses.

Follow-up cohort analysis and defining significant loci. In each follow-up cohort we performed BD association analysis of the 881 selected GWAS variants (when available) as described above, including study specific covariates. We performed fixed-effects meta-analyses of the association results from the follow-up cohorts and the GWAS discovery cohorts. We clumped the genome-wide significant SNPs to 30 loci, one of which had 2 independent SNPS, via steps described in the **Supplementary Note**.

Polygenic risk score (PRS) analyses. To assess the validity of the results from each GWAS cohort, 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. Leave-one-out PRS results for all *P*-value thresholds are reported for the discovery GWAS cohorts in **Supplementary Table 14**. To test genetic overlaps with other psychiatric diseases, we examined whether the PRS for DEP and for SCZ differ between BD1 and BD2 cases in the GWAS cohorts. We regressed BD1 (N=8044) versus

BD2 (N=3365) case status on the PRS adjusting for ancestry principal components and a cohort indicator (**Supplementary Table 8**) using logistic regression [55].

Linkage disequilibrium (LD) score regression. LD score regression [25,56] was used to conduct SNP-heritability analyses from GWA summary statistics. LD score regression bivariate genetic correlations attributable to genome-wide SNPs were estimated between the full BD GWAS, BD subtype GWASs, and other traits and disorders, using the internal PGC GWA library and with LD-Hub [56]. We also used LD score regression to partition heritability by genomic features [42].

Relation of BD GWA findings to tissue and cellular gene expression. We used partitioned LD score regression to evaluate which somatic tissues and brain tissues were enriched for BD heritability. [57] We used summary-data-based Mendelian randomization (SMR) [39] to identify loci with strong evidence of causality via gene expression (**Supplementary Table 9**). Since the aim of SMR is to prioritize variants and genes for subsequent studies, a test for heterogeneity excludes regions that may harbor multiple causal loci (pHET < 0.05).

DNA looping using Hi-C. To examine the 31 significant loci we conducted analysis of DNA looping between top SNPs and nearby genes. This did not yield any significant results; full methods can be found in the **Supplementary Note**.

Gene-wise and pathway analysis. Our approach was guided by rigorous method comparisons conducted by PGC members [44,58]. *P*-values quantifying the degree of association of genes and gene sets with BD were generated using MAGMA (v1.06) [44]. We used ENSEMBL gene co-ordinates for 19,079 genes giving a Bonferroni corrected *P*-value threshold of 2.6×10^{-6}. These aggregate gene-wide p-values are then used to perform rests of association enrichment in gene sets using a competitive analysis that tests whether genes in a gene set are more strongly associated with the phenotype than other gene sets, correcting for gene size, SNP density, and LD within and between genes. We used European-ancestry subjects from 1,000 Genomes

Project (Phase 3 v5a, MAF ≥ 0.01) [53] for the LD reference. The gene window used was 35 kb upstream and 10 kb downstream to include regulatory elements.

Gene sets were compiled from multiple sources. The pathway map (**Supplementary Figure 5**) was constructed using the kernel generative topographic mapping algorithm (k-GTM) as described by [59]. See **Supplementary Note** for further details.

Genome build. All genomic coordinates are given in NCBI Build 37/UCSC hg19.

Availability of results. The PGC's policy is to make genome-wide summary results public. Summary statistics for our meta-analysis of the GWAS cohort samples are available on the PGC web site (URLs). Availability of genotype data for the anchor cohorts can be applied for via http://www.med.unc.edu/pgc/shared-methods. For the expanded cohorts, interested users should contact the lead PIs of these cohorts (which are separate from the PGC).

URLs

1000 Genomes Project multi-ancestry imputation panel, https://mathgen.stats.ox.ac.uk/impute/data_download_1000G_phase1_integrated.html

Bedtools, https://bedtools.readthedocs.io

Genotype-based checksums for relatedness determination, http://www.broadinstitute.org/~sripke/share_links/checksums_download

GTEx, http://www.gtexportal.org/home/datasets

GTMapTool, http://infochim.u-strasbg.fr/mobyle-cgi/portal.py#forms::gtmaptool

LD-Hub, http://ldsc.broadinstitute.org

MDD summary results are available on the PGC website, https://pgc.unc.edu

NIH NeuroBiobank, https://neurobiobank.nih.gov

PGC "ricopili" GWA pipeline, https://github.com/Nealelab/ricopili

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Analysis	NR Wray	NHMRC 1078901,108788
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BiGS, Uchicago	ES Gershon	R01 MH103368
BiGS, GAIN	FJ McMahon	US, NIMH, R01 MH061613, ZIA MH002843
BiGS, UCSD	J Kelsoe	US, NIMH, MH078151, MH081804, MH59567
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BOMA-Germany I, II, III	S Cichon	Germany, BMBF Integrament, 01ZX1314A/01ZX1614A

BOMA-Germany I, II, III	S Cichon	Germany, BMBF NGFNplus MooDS, 01GS08144
BOMA-Germany I, II, III	S Cichon	Switzerland, SNSF, 156791
BOMA-Germany I, II, III	MM Nöthen	Germany, BMBF Integrament, 01ZX1314A/01ZX1614A
BOMA-Germany I, II, III	MM Nöthen	Germany, BMBF NGFNplus MooDS, 01GS08144
BOMA-Germany I, II, III	MM Nöthen	Germany, Deutsche Forschungsgemeinschaft, Excellence Cluster ImmunoSensation
BOMA-Germany I, II, III	MM Nöthen	Germany, Deutsche Forschungsgemeinschaft, NO246/10-1
BOMA-Germany I, II, III	SH Witt	Germany, Deutsche Forschungsgemeinschaft, WI 3429/3-1
BOMA-Germany I, II, III, BOMA-Spain	M Rietschel	Germany, BMBF Integrament, 01ZX1314G/01ZX1614G
BOMA-Germany I, II, III, BOMA-Spain	M Rietschel	Germany, BMBF NGFNplus MooDS, 01GS08147
BOMA-Germany I, II, III, BOMA-Spain	M Rietschel	Germany, Deutsche Forschungsgemeinschaft, RI 908/11-1
BOMA-Germany I, II, III, PsyCourse, BiGS	TG Schulze	Germany, BMBF Integrament, 01ZX1314K
BOMA-Germany I, II, III, PsyCourse, BiGS	TG Schulze	Germany, DFG, SCHU 1603/4-1, SCHU 1603/5-1, SCHU 1603/7-1
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Conflicts of Interest:

T.E. Thorgeirsson, S. Steinberg, H. Stefansson and K. Stefansson are employed by deCODE Genetics/Amgen. Multiple additional authors work for pharmaceutical or biotechnology companies in a manner directly analogous to academic co-authors and collaborators. A.H. Young has given paid lectures and is on advisory boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Eli Lilly, Janssen, Lundeck, Sunovion, Servier, Livanova. A.H. Young is Lead Investigator for Embolden Study (Astrazenaca), BCI Neuroplasticity

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DISPLAY ITEMS

Figure 1.

Table 1.

Figure 2.

Figure 3.

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