

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

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^ deceased. This paper is dedicated to the memory of Psychiatric Genomics Consortium founding member and Bipolar disorder working group co-chair Pamela Sklar

1

2 **ABSTRACT:**

3 Bipolar disorder is a highly heritable psychiatric disorder that features episodes of mania and  
4 depression. We performed the largest genome-wide association study to date, including 20,352  
5 cases and 31,358 controls of European descent, with follow-up analysis of 822 sentinel variants  
6 at loci with  $P < 1 \times 10^{-4}$  in an independent sample of 9,412 cases and 137,760 controls. In the  
7 combined analysis, 30 loci reached genome-wide significant evidence for association, of which  
8 20 were novel. These significant loci contain genes encoding ion channels and neurotransmitter  
9 transporters (*CACNA1C*, *GRIN2A*, *SCN2A*, *SLC4A1*), synaptic components (*RIMS1*, *ANK3*), immune  
10 and energy metabolism components. Bipolar disorder type I (depressive and manic episodes;  
11 ~73% of our cases) is strongly genetically correlated with schizophrenia whereas bipolar  
12 disorder type II (depressive and hypomanic episodes; ~17% of our cases) is more strongly  
13 correlated with major depressive disorder. These findings address key clinical questions and  
14 provide potential new biological mechanisms for bipolar disorder.

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## 1 INTRODUCTION

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

10 BD can be divided into two main clinical subtypes <sup>5,6</sup>: bipolar I disorder (BD1) and bipolar  
11 II disorder (BD2). In BD1, manic episodes typically alternate with depressive episodes during the  
12 course of illness. Diagnosis of BD2 is based on the lifetime occurrence of at least one depressive  
13 and one hypomanic (but no manic) episode. Although modern diagnostic systems retain the  
14 Kraepelinian dichotomy <sup>7</sup> between BD and schizophrenia, the distinction between the two  
15 disorders is not always clear-cut, and patients who display clinical features of both disorders  
16 may receive a diagnosis of schizoaffective disorder (SAB). Likewise, in genetic studies the two  
17 diagnoses are usually treated separately, although recent epidemiological and molecular genetic  
18 studies provide strong evidence for some overlap between the genetic contributions to their  
19 etiology <sup>2,8</sup>.

20 Recent genome-wide association studies (GWAS) in BD have identified a number of  
21 significant associations between disease status and common genetic variants <sup>9-23</sup>. The first large  
22 collaborative BD GWAS by the multinational Psychiatric Genomics Consortium (PGC) Bipolar  
23 Disorder Working Group comprised 7,481 BD patients and 9,250 controls and identified four  
24 genome-wide significant loci <sup>9</sup>. Three subsequent meta-analyses that included the PGC BD data

1 <sup>10,12,18</sup> identified an additional 5 loci.

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

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## 12 **RESULTS**

### 13 **GWAS of bipolar disorder (BD)**

14 We performed a GWAS meta-analysis of 32 cohorts from 14 countries in Europe, North America  
15 and Australia (**Supplementary Table 1A**), totaling 20,352 cases and 31,358 controls of European  
16 descent (effective sample size 46,582). This is the largest GWAS of BD to date and includes 6,328  
17 case and 7,963 control samples not previously reported, a 2.7-fold increase in the number of  
18 cases compared to our previous GWAS <sup>9</sup>. We imputed variant dosages using the 1,000 Genomes  
19 reference panel (see Methods), retaining association results for 9,372,253 autosomal variants  
20 with imputation quality score INFO > 0.3 and minor allele frequency ≥ 1% in both cases and  
21 controls. We performed logistic regression of case status on imputed variant dosage using  
22 genetic ancestry covariates. The resulting genomic inflation factor ( $\lambda_{GC}$ ) was 1.23 and scaled to  
23 1,000 cases and 1,000 controls ( $\lambda_{1000}$ ) was 1.01 (**Supplementary Figure 1**). The LD-score  
24 regression intercept did not significantly differ from one, indicating that the observed genomic

1 inflation is indicative of polygenicity rather than stratification or cryptic population structure <sup>25</sup>.  
2 The LD-score regression SNP-heritability estimates for BD were 0.17-0.23 (on the liability scale,  
3 assuming population lifetime risk of 0.5-2%). See **Supplementary Table 1A, Online Methods**  
4 and **Supplementary Note** for sample and method details.

5 We find a marked increase in phenotypic variance explained by genomewide polygenic  
6 risk scores (PRS) compared to previous publications (sample size weighted mean observed  
7 Nagelkerke's  $R^2 = 0.08$  across datasets, liability scale  $R^2=0.04$ , for P-threshold  $\geq 0.01$ ;  
8 **Supplementary Figure 2** and **Supplementary Table 2**). Among the different datasets, we  
9 observed no association between the PRS and: (i) the gender distribution of the BD cases  
10 ( $p=0.51$ ); (ii) the proportion of cases with psychosis ( $p=0.61$ ); (iii) the proportion with a family  
11 history of BD ( $p=0.82$ ); or (iv) the median age of onset for BD ( $p=0.64$ ). In our primary genome-  
12 wide analysis, we identified 19 loci exceeding genome-wide significance ( $P < 5 \times 10^{-8}$ ).

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#### 14 **Follow-up of suggestive loci in additional samples**

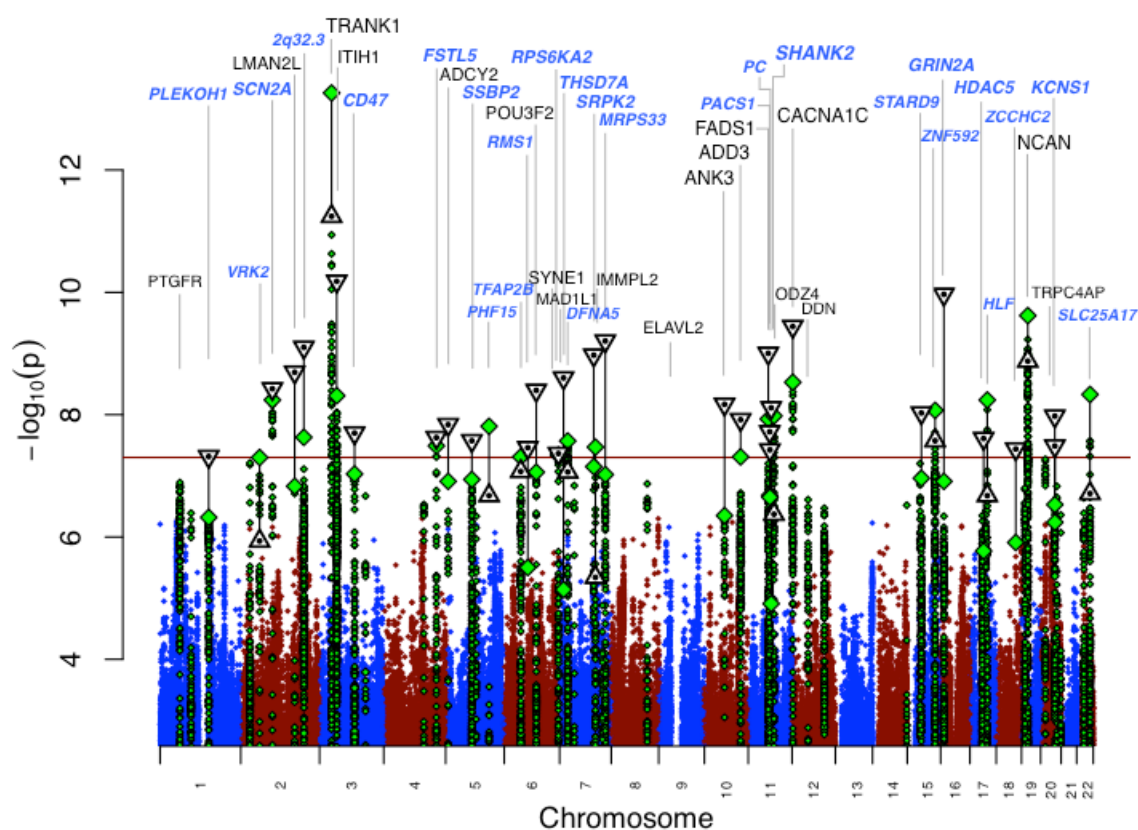
15 We meta-analyzed lead variants that were significant at  $P < 1 \times 10^{-4}$  in our discovery meta-analysis,  
16 (a total of 794 autosomal and 28 X chromosome variants) with follow-up samples totaling 9,412  
17 cases and 137,760 controls of European ancestry (**Supplementary Note** and **Supplementary**  
18 **Table 1B**). Thirty autosomal loci achieved combined sample genome-wide significance ( $P < 5 \times 10^{-8}$ )  
19 <sup>8</sup>) (**Figure 1, Table 1, Supplementary Figure 3, Supplementary Table 3**). These include 19 loci  
20 that were significant only in the combined analysis, of which three were reported to have  
21 genome-wide significant SNPs in previous studies (*ADCY2* <sup>18</sup>, *POU3F2* <sup>18</sup>, *ANK3* <sup>12,18</sup>), and 11 that  
22 were significant in our GWAS. Eight variants were genome-wide significant in the GWAS but not  
23 in the combined analysis. Using effect sizes corrected for winner's curse <sup>26,27</sup> for each of the 19  
24 variants with GWAS  $P < 5 \times 10^{-8}$ , we found that 11 variants achieving genome-wide significance in

1 our combined analysis is within the expected range (Poisson binomial test  $P = 0.29$ ,

2 **Supplementary Note** and **Supplementary Figure 4**).

3       Lead variants for the 30 loci achieving genome-wide significance in the combined  
4 analysis are shown in **Table 1A**. We show results in **Table 1B** for 8 additional loci with  $P < 5 \times 10^{-8}$   
5 in our discovery GWAS but not in the combined analysis. Results for all variants tested in the  
6 follow-up study are presented in **Supplementary Table 3**. We refer to loci by the gene name  
7 attributed in previous BD GWAS publications, or by the name of the closest gene for novel loci,  
8 without implication that the named gene is causal. Of the 30 genome-wide significant loci from  
9 our combined analysis, 20 are novel BD risk loci. In **Supplementary Table 4**, we present detailed  
10 descriptions of the associated loci and genes, with bioinformatic and literature evidence for  
11 their potential roles in BD.

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Figure 1. Manhattan plot for our primary genomewide 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+followup  $-\log_{10}P$ -values for lead SNPs reaching genome-wide significance in either GWAS or combined analysis (triangles, inverted if GWAS+followup  $-\log_{10}P > \text{GWAS } -\log_{10}P$ ). Labels correspond to gene symbols previously reported for published loci (black) and the nearest genes for novel loci (blue), at top if GWAS+followup  $P < 5 \times 10^{-8}$ .

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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
<b>A. Thirty loci with lead SNP P &lt; 5x10-8 in combined GWAS+followup analysis</b>											
1,PLEKHO1	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,SCN2A	rs17183814	2	166,152,389	A/G	0.075	0.87	1.5E-07	0.89	0.0033	0.88	2.0E-09
4,[Intergenic]***	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**	rs2302417	3	52,814,256	A/T	0.49	0.92	4.9E-09	0.94	0.0024	0.93	6.6E-11
7,CD47	rs3804640	3	107,793,709	A/G	0.53	1.075	9.3E-08	1.044	0.032	1.065	2.0E-08
8,FTSL5	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,SSBP2	rs10035291	5	80,796,368	T/C	0.68	1.081	1.1E-07	1.047	0.036	1.070	2.7E-08
11,RIMS1	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,RPS6KA2	rs10455979	6	166,995,260	C/G	0.53	0.93	4.6E-08	0.97	0.092	0.94	4.3E-08
14,THSD7A	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,SRPK2	rs73188321	7	105,048,158	T/C	0.33	0.92	7.0E-08	0.94	0.0030	0.92	1.1E-09
16,MRPS33	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,PACS1	rs10896090	11	65,945,186	A/G	0.81	1.094	2.1E-07	1.062	0.018	1.084	1.9E-08
21,PC	rs7122539	11	66,662,731	A/G	0.35	0.93	2.2E-07	0.96	0.030	0.94	3.8E-08
22,SHANK2	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,STARD9	rs4447398	15	42,904,904	A/C	0.12	1.112	1.1E-07	1.072	0.016	1.099	9.4E-09
25,ALPK3	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
26GRIN2A	rs11647445	16	9,926,966	T/G	0.65	0.93	1.2E-07	0.93	1.96E-04	0.93	1.1E-10
27,HDAC5	rs112114764	17	42,201,041	T/G	0.69	0.93	1.7E-06	0.94	0.0042	0.93	2.5E-08
28,ZCCHC2	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**	rs11444407	19	19,358,207	T/C	0.15	1.124	2.4E-10	1.040	0.15	1.097	1.3E-09
30,STK4	chr20_43682549_I	20	43,682,549	I/D	0.28	0.923	3.0E-07	0.942	0.009	0.929	1.1E-08
<b>B. Additional loci with lead SNP P &lt; 5x10-8 in GWAS analysis</b>											
TFAP2B	rs55648125	6	50816718	A/G	0.90	0.89	4.9E-08	0.95	0.14	0.91	8.5E-08
DFNA5	rs17150022	7	24771777	T/C	0.88	0.89	2.7E-08	0.96	0.17	0.91	8.6E-08
SLC25A17	rs138321	22	41209304	A/G	0.50	1.083	4.7E-09	1.012	0.55	1.060	1.9E-07
HLF	rs884301	17	53367464	T/C	0.37	1.084	5.8E-09	1.013	0.52	1.061	2.1E-07
PHF15	rs329319	5	133906609	A/G	0.43	1.082	1.5E-08	1.019	0.36	1.061	2.1E-07
ODZ4**	rs73496688	11	79156748	A/T	0.14	1.11	1.0E-08	1.016	0.58	1.083	4.2E-07
[Intergenic]***	rs57681866	2	57975714	A/G	0.06	0.85	5.0E-08	0.97	0.45	0.89	1.2E-06
[Intergenic]***	rs13231398	7	110197412	C/G	0.11	0.89	3.4E-08	0.998	0.95	0.92	4.6E-06

\* Loci are numbered 1 to 30, ordered by genomic position, with previously reported gene name for published loci

\*\* Previously published and named loci. (Locus 12 would be named as Intergenic, nearest gene is POU3F2 691Kb.)

\*\*\* Intergenic loci nearest genes: Locus 4 PCGEM1 824kb, Table 1B chr2 locus VRK2 298Kb, Table 1B chr7 IMMP2L 106Kb.

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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. 551 variants had the same direction of effect in the discovery GWAS and follow-up samples (71% compared to a null expectation of 50%, sign test  $P < 2.2 \times 10^{-16}$ ), and 110 variants had the same direction of effect and were nominally significant ( $p < 0.05$ ) in the follow-up samples (14% compared to an expected value of 2.5%, binomial test  $P < 2.2 \times 10^{-16}$ ). This consistency between our GWAS and follow-up samples suggests that many 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 5**). We used the effective number of



1 independent variants based on LD structure within loci<sup>28</sup> to calculate a multiple test-corrected  
2 significance threshold ( $P=1.01 \times 10^{-5}$ , see **Supplementary Note**). One locus showed evidence for  
3 an independent association signal (rs114534140 in locus #8, *FSTL5*;  $P_{\text{conditional}} = 2 \times 10^{-6}$ ). At one  
4 locus (#30, *STK4* on chr 20), we found two SNPs with genome-wide significance in low LD ( $r^2 <$   
5  $0.1$ ); however, conditional analysis showed that their associations were not independent. Thus  
6 only the *FSTL5* locus demonstrated clear evidence of more than one independent association.

7

### 8 **Shared loci and genetic correlations with schizophrenia, depression and other GWAS traits**

9 We next examined the genetic relationships of BD to other psychiatric disorders and traits. Of  
10 the 30 genome-wide significant BD loci, 8 also harbor schizophrenia (SCZ) associations<sup>29–31</sup>.  
11 Based on conditional analyses the BD and SCZ associations appear to be independent at 3 of the  
12 8 shared loci (*NCAN*, *TRANK1* and chr7q22.3:105Mb loci) (**Supplementary Table 6**). No genome-  
13 wide significant BD locus overlapped with those identified for major depression (DEPR),  
14 including 44 risk loci identified in the most recent PGC study based on 130,664 depression cases  
15 and 330,470 controls<sup>32</sup>, and those reported in a large study of depressive symptoms or  
16 subjective well-being<sup>33</sup>. As previously reported<sup>34</sup>, we found substantial and highly significant  
17 genetic correlations between BD and SCZ (LD-score regression estimated genetic correlation  $r_g =$   
18  $0.70$ ,  $se = 0.020$ ) and between BD and DEPR ( $r_g = 0.35$ ,  $se = 0.026$ ) The BD and DEPR genetic  
19 correlation was similar to that observed for SCZ and DEPR ( $r_g = 0.34$ ,  $se = 0.025$ ) (**Supplementary**  
20 **Table 7A**).

21 We found significant genetic correlations between BD and other psychiatric-relevant  
22 traits (**Supplementary Table 7B**), including with autism spectrum disorder<sup>8</sup> ( $r_g = 0.18$ ,  $P=2 \times 10^{-4}$ ),  
23 anorexia nervosa<sup>35</sup> ( $r_g = 0.23$ ,  $P=9 \times 10^{-8}$ ), and subjective well-being<sup>33</sup> ( $r_g = -0.22$ ,  $P=4 \times 10^{-7}$ ). There  
24 was suggestive positive overlap with anxiety disorders ( $r_g=0.21$ ,  $P=0.04$ )<sup>36</sup> and neuroticism

1 ( $r_g=0.12$ ,  $P=0.002$ )<sup>37</sup>. Significant  $r_g$ s were seen with measures of education: college attendance  
2 <sup>38</sup> ( $r_g = 0.21$ ,  $P=1 \times 10^{-7}$ ) and education years <sup>39</sup> ( $r_g=0.20$ ,  $P=6 \times 10^{-14}$ ), but not with childhood IQ <sup>40</sup>  
3 ( $r_g=0.05$ ,  $P=0.5$ ) or intelligence <sup>41</sup> ( $r_g=-0.05$ ,  $P=0.08$ ). Among a large number of BD risk locus SNPs  
4 associated with additional traits from GWAS catalog, we found a handful of loci with non-  
5 independent associations (in one overlapping locus each with educational attainment, biliary  
6 atresia, bone mineral density, lipid-related biomarkers) (**Supplementary Table 6**). Biliary atresia  
7 and lipid- related biomarkers, however, did not show significant genetic correlation with BD  
8 (**Supplementary Table 7B**).

9

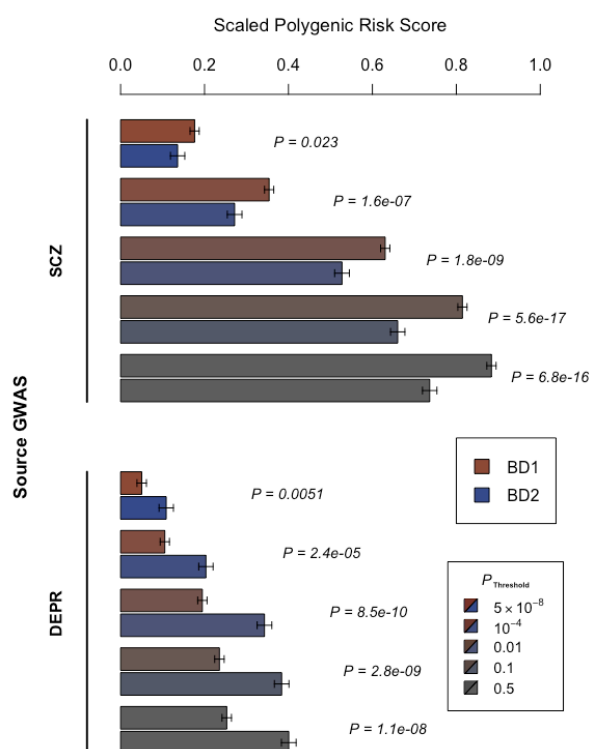
## 10 **BD subtype GWAS**

11 We performed secondary GWAS focusing on three clinically recognized subtypes of bipolar  
12 disorder: BD1 (n=14,879 cases), BD2 (n=3,421 cases), and SAB (n=977 cases) (**Supplementary**  
13 **Note, Supplementary Tables 1A & 8, Supplementary Figure 5**). We observed variants in 14 loci  
14 with genome-wide significance for BD1, 10 of which were in genome-wide significant loci in the  
15 combined BD GWAS analysis. Not surprisingly given the sample overlap, 3 of the 4 remaining loci  
16 genome-wide significant for BD1 have  $P < 10^{-6}$  in either our GWAS or combined analysis. The  
17 remaining locus (MAD1L1, chr7:1.9Mb, GWAS  $P = 2.4 \times 10^{-6}$ ) was recently published in two BD  
18 GWAS that included Asian samples<sup>42,43</sup>. We did not observe genome-wide significant results for  
19 the smaller BD2 and SAB analyses. BD1, BD2 and SAB all have significant common variant  
20 heritabilities (BD1  $h^2_{\text{snp}} = 0.25$ ,  $se = 0.014$ ,  $P = 3.2 \times 10^{-77}$ ; BD2  $h^2_{\text{snp}} = 0.11$ ,  $se = 0.028$ ,  $P = 5.8 \times 10^{-5}$ ;  
21 SAB  $h^2_{\text{snp}} = 0.25$ ,  $se = 0.10$ ,  $P = 0.0071$ ). Genetic correlations among BD subtypes show that these  
22 represent closely related, yet partially distinct, phenotypes (**Supplementary Table 9**).

23 Polygenic risk scores and genetic correlations provide support for a continuum of SCZ-  
24 BD1-BD2-DEPR genetic effects, with significantly greater genetic SCZ polygenic risk scores (PRS)

1 in BD1 cases than in BD2 cases (min  $P=5.6 \times 10^{-17}$ ,  $P$  threshold = 0.1), and greater DEPR PRS in BD2  
2 cases than in BD1 cases (min  $P=8.5 \times 10^{-10}$ ,  $P$  threshold = 0.01) (**Figure 2, Supplementary Table**  
3 **10**). Genetic correlations from LD-score regression support these results; genetic correlations  
4 were greater for SCZ with BD1 ( $r_g = 0.71$ ,  $se = 0.025$ ) than with BD2 ( $r_g = 0.51$ ,  $se = 0.072$ ), with  
5  $P_{diff} = 0.0056$ , and were greater for DEPR with BD2 ( $r_g = 0.69$ ,  $se = 0.093$ ) than with BD1 ( $r_g =$   
6  $0.30$ ,  $se = 0.028$ ), with  $P_{diff} = 2.9 \times 10^{-5}$  (**Supplementary Table 9**).

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**Figure 2. Association of BD1 and BD2 subtypes with schizophrenia (SCZ) and major depression (DEPR) polygenic risk scores (PRS). Shown are mean PRS values (1 s.e. error bars), adjusted for study and ancestry covariates and scaled to the PRS mean and sd in control subjects, in BD1 (red) and BD2 (blue) cases, for increasing source GWAS P-value thresholds (increasing grey) as indicated. P-values (italics) test BD1 vs BD2 mean PRS, in logistic regression of case subtype on PRS with covariates. Results are detailed in Supplementary Table 10.**

9

10

## 1 **Systems biology and *in silico* functional analyses of BD GWAS results**

2 To identify genes with functional variation in gene expression that might explain the  
3 associations, we used summary Mendelian randomization (SMR)<sup>44</sup> to integrate our BD discovery  
4 GWAS with eQTL data from brain dorsolateral prefrontal cortex<sup>45</sup> as well as a large-sample  
5 whole blood eQTL dataset<sup>46</sup> (**Supplemental Table 11**). SMR identified six transcriptome-wide  
6 significant genes without signs of heterogeneity between GWAS and eQTL association signals.  
7 Among these, four genes were present in four different loci from our combined BD GWAS and  
8 follow-up sample meta-analysis: *LMAN2L* (blood), *FADS1* (brain), *NMB* (blood) and *C17ORF65*  
9 (blood).

10 We tested for functional genomic enrichment in our BD GWAS using partitioned LD-  
11 score regression<sup>47</sup> (**Supplementary Note, Supplementary Table 12**). Annotations tested  
12 included open chromatin DHS peaks in a range of tissues<sup>48</sup>, genic annotations, conservation,  
13 and a number of functional genomic annotations across tissues. SNP-based BD heritability was  
14 most substantially enriched in open chromatin annotations in central nervous system  
15 (proportion SNPs = 0.14, proportion  $h^2_{\text{snp}} = 0.60$ , enrichment = 3.8,  $P = 4.2 \times 10^{-17}$ ). We also used  
16 DEPICT<sup>49</sup> to test for expression of BD associated genes across tissues, and found significant  
17 enrichment of central nervous system ( $P \leq 1.3 \times 10^{-3}$ , FDR < 0.01) and neurosecretory system ( $P$   
18  $\leq 2.0 \times 10^{-6}$ , FDR < 0.01) genes (**Supplementary Table 13**).

19 Finally, we used MAGMA<sup>50</sup> to conduct a gene-wise BD GWAS and to test for enrichment  
20 of pathways curated from multiple sources (see **Supplementary Note**). We note that  
21 significance levels were assigned to genes by physical proximity of SNPs, and do not imply that  
22 significant genes are causal for BD. Genic association results included 154 Bonferroni significant  
23 genes (MAGMA  $P_{\text{JOINT}} < 2.8 \times 10^{-6}$ ), including 82 genes in 20 genome-wide significant loci, and  
24 73 genes in 27 additional loci that did not reach genome-wide significance in either our GWAS or

1 combined analysis (**Supplementary Table 14**). Nine related pathways were significantly enriched  
2 for genes with stronger BD associations ( $P < 7.0 \times 10^{-5}$ ,  $FDR < 0.05$ ), including abnormal motor  
3 coordination/balance pathways (from mice), regulation of insulin secretion and  
4 endocannabinoid signaling pathways (**Supplementary Table 15, Supplementary Figure 6**).

## 5 **DISCUSSION**

6 We carried out the largest bipolar disorder (BD) GWAS to date and identified 30  
7 genome-wide significant loci, including 20 novel BD risk loci. Previous BD GWAS have reported a  
8 total of 20 loci significantly associated with BD<sup>9-23</sup>; twelve of these previously reported loci were  
9 not genome-wide significant in our GWAS meta analysis but had  $P_{\text{GWAS}} \leq 1.3 \times 10^{-5}$ . Of the 19 loci  
10 identified in our discovery GWAS, only 11 were genome-wide significant in meta-analysis of our  
11 GWAS and follow-up samples. Although these results are not unexpected given small effect sizes  
12 and the winner's curse<sup>27,51</sup> (**Supplementary Note and Supplementary Figure 4**), genetic  
13 heterogeneity has been shown between BD GWAS cohorts<sup>8</sup>. We observed variable polygenic  
14 effects between BD subtypes and between cohorts in our study (**Figure 2, Supplementary Figure**  
15 **2, Supplementary Tables 2 & 10**) and acknowledge a diversity of clinical case phenotypic criteria  
16 among cohorts in our study (**Supplementary Note**). Remarkably, our strongest association  
17 signal, observed at the *TRANK1* locus (rs9834970;  $P_{\text{combined}} = 5.7 \text{E-}12$ , OR = 0.93), exhibited  
18 significant heterogeneity among discovery GWAS cohorts (Cochran's Q  $P = 1.9 \times 10^{-4}$ , and did not  
19 replicate in the follow-up sample (1-tailed  $P_{\text{followup}} = 0.3$ ) (**Supplementary Figure 3B & 3C**, fifth  
20 and first plots respectively). This locus has been observed in recent<sup>11,12,17,18</sup> but not earlier BD  
21 GWAS<sup>9,13,20</sup>, surprisingly given its relatively large apparent effect size. Thus, complex polygenic  
22 architecture as well as phenotypic heterogeneity among BD GWAS cohorts may contribute to  
23 the inconsistency of genome-wide significant findings within and across BD GWAS studies. The

1 observed heterogeneity is a major challenge for GWAS of psychiatric disorders and calls for  
2 careful and systematic clinical assessment of cases and controls in addition to continued efforts  
3 to collect larger sample sizes.

4 Of the 30 BD associated loci, 8 also harbor associations<sup>29–31</sup> with schizophrenia (SCZ);  
5 however, conditional analyses suggest that the BD and SCZ associations at 3 of the 8 shared loci  
6 (in the *NCAN*, *TRANK1* and chr7q22.3 [105Mb] loci) may be independent (**Supplementary Table**  
7 **6**). Differential BD and SCZ associations may represent opportunities to understand the genetic  
8 distinctions between these closely related and sometimes clinically difficult to distinguish  
9 disorders. We did not find BD loci that overlap with those associated with major depression<sup>32</sup>.

10 The confirmed association within loci containing *CACNA1C* and other voltage-gated  
11 calcium channels supports the rekindled interest in calcium channel antagonists as potential  
12 treatments for BD with similar examination ongoing for other genes implicated by current  
13 GWAS<sup>52</sup>. These processes are important in neuronal hyperexcitability<sup>53</sup>, an excess of which has  
14 been reported in iPSC derived neurons from BD patients, and which has been shown to be  
15 affected by the classic mood stabilizing drug lithium<sup>54</sup>. Other genes within novel associated loci  
16 include those coding for neurotransmitter channels (*GRIN2A*), ion channels and transporters  
17 (*SCN2A*, *SLC4A1*) and synaptic components (*RIMS1*, *ANK3*). Further study will confirm whether  
18 or not these are the causal genes in these loci.

19 The estimated variance explained by polygenic risk scores (PRS) based on our BD GWAS  
20 data is ~8% (observed scale; 4% on the liability scale<sup>55</sup>), an increase from 2.8% from our  
21 previous study<sup>9</sup>. Using PRS, we found that BD1 cases have significantly greater schizophrenia  
22 genetic risk than BD2 cases, while BD2 cases have significantly greater major depression genetic  
23 risk than BD1 cases, consistent with a spectrum of related psychiatric diagnoses<sup>7,56</sup>. We observe  
24 significant positive genetic correlations with educational attainment, but not with either adult or

1 childhood IQ, suggesting that the role of BD genetics in increased educational attainment may  
2 be independent of general intelligence. This result is inconsistent with suggestions from  
3 epidemiological studies<sup>57</sup>, but in agreement with a recent clinical study<sup>58</sup>.

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

8

## 9 **ONLINE METHODS**

### 10 **Methods**

11 GWAS and follow-up cohorts. Our discovery GWAS sample was comprised of 32 cohorts from  
12 14 countries in Europe, North America and Australia (**Supplementary Table 1A**), totaling 20,352  
13 cases and 31,358 controls of European descent. A selected set of variants (see below) were  
14 tested in 7 follow-up cohorts of European descent (**Supplementary Table 1B**), totalling 9,025  
15 cases and 142,824 controls ( $N_{\text{eff}} = 23,991$ ). The **Supplementary Note** summarizes the source and  
16 inclusion/exclusion criteria for cases and controls for each cohort. All cohorts in the initial PGC  
17 BD paper were included<sup>9</sup>. Cases were required to meet international consensus criteria (DSM-  
18 IV, ICD-9, or ICD-10) for a lifetime diagnosis of BD established using structured diagnostic  
19 instruments from assessments by trained interviewers, clinician-administered checklists, or  
20 medical record review. In most cohorts, controls were screened for the absence of lifetime  
21 psychiatric disorders and randomly selected from the population.

22 GWAS cohort analysis We tested 20 principal components for association with BD using logistic  
23 regression; seven were significantly associated with phenotype and used in GWAS association

1 analysis (PCs 1-6, 19). In each cohort, we performed logistic regression association tests for BD  
2 with imputed marker dosages including 7 principal components to control for population  
3 stratification. For all GWAS cohorts, X-chromosome association analyses were conducted  
4 separately by sex, and then meta-analyzed across sexes. We also conducted BD1, BD2, and SAB  
5 GWAS, retaining only cohorts with at least 35 subtype cases and filtering SNPs for MAF > 0.02.  
6 Results were combined across cohorts using an inverse variance-weighted fixed effects meta-  
7 analysis<sup>59</sup>. We used Plink 'clumping'<sup>60,61</sup> to identify an LD-pruned set of discovery GWAS meta-  
8 analysis BD-associated variants ( $P < 0.0001$ , and distance >500kb or LD  $r^2 < 0.1$ , n variants =822)  
9 for analysis in the follow-up cohorts. Conditional analyses were conducted within each GWAS  
10 cohort and meta-analyzed as above.

11 Follow-up cohort analysis. In each follow-up cohort we performed BD association analysis of the  
12 822 selected GWAS variants (when available) including genetic ancestry covariates, following QC  
13 and analysis methods of the individual study contributors. We performed inverse variance-  
14 weighted fixed-effects meta-analyses of the association results from the follow-up cohorts, and  
15 of the discovery GWAS and follow-up analyses.

16 Polygenic risk score (PRS) analyses. We tested PRS for our primary GWAS on each GWAS cohort  
17 as a target set, using a GWAS where the target cohort was left out of the meta-analysis

18 **(Supplementary Table 2).** To test genetic overlaps with other psychiatric diseases, we calculated  
19 PRS for DEPR and SCZ in our GWAS cohort BD cases<sup>62</sup>. In pairwise case subtype analyses **(Figure**  
20 **2, Supplementary Table 10)**, we regressed subtype case status (BD1 n=8044, BD2 n=3,365, SAB  
21 n=977) on the PRS adjusting for ancestry principal components and a cohort indicator using  
22 logistic regression, and visualized covariate-adjusted PRS in BD1 and BD2 subtypes **(Figure 2).**

23 Linkage disequilibrium (LD) score regression. LD score regression<sup>25,63</sup> was used to conduct SNP-  
24 heritability analyses from GWAS summary statistics. LD score regression bivariate genetic



1 correlations attributable to genome-wide common variants were estimated between the full BD  
2 GWAS, BD subtype GWASs, and other traits and disorders with LD-Hub<sup>63</sup>. We also used LD score  
3 regression to partition heritability by genomic features<sup>47</sup>.

4 Relation of BD GWA findings to tissue and cellular gene expression. We used partitioned LD  
5 score regression to evaluate which somatic tissues and brain tissues were enriched for BD  
6 heritability.<sup>64</sup> We used summary-data-based Mendelian randomization (SMR)<sup>44</sup> to identify loci  
7 with strong evidence of causality via gene expression (**Supplementary Table 9**). Since the aim of  
8 SMR is to prioritize variants and genes for subsequent studies, a test for heterogeneity excludes  
9 regions that may harbor multiple causal loci (pHET < 0.05).

10 Gene-wise and pathway analysis. Guided by rigorous method comparisons conducted by PGC  
11 members<sup>50,65</sup>, p-values quantifying the degree of association of genes and gene sets with BD  
12 were generated using MAGMA (v1.06)<sup>50</sup>. We used ENSEMBL gene coordinates for 18,172 genes  
13 giving a Bonferroni corrected *P*-value threshold of  $2.8 \times 10^{-6}$ . Joint multi-SNP LD-adjusted gene-  
14 level p-values were calculated using SNPs 35 kb upstream to 10 kb downstream, adjusting for LD  
15 using 1,000 Genomes Project (Phase 3 v5a, MAF  $\geq 0.01$ , European-ancestry subjects)<sup>66</sup>. Gene  
16 sets were compiled from multiple sources. Competitive gene set tests were conducted  
17 correcting for gene size, variant density, and LD within and between genes. The pathway map  
18 (**Supplementary Figure 6**) was constructed using the kernel generative topographic mapping  
19 algorithm (k-GTM) as described by<sup>67</sup>. See **Supplementary Note** for further details.

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

21 Availability of results. The PGC's policy is to make genome-wide summary results public.  
22 Summary statistics for our meta-analysis of the GWAS cohort samples are available through the  
23 PGC (URLs).

1 **URLs**

2 Psychiatric Genomics Consortium, PGC, <https://med.unc.edu/pgc>

3 PGC “ricopili” GWA pipeline, <https://github.com/Nealelab/ricopili>

4 1000 Genomes Project multi-ancestry imputation panel,

5 [https://mathgen.stats.ox.ac.uk/impute/data\\_download\\_1000G\\_phase1\\_integrated.html](https://mathgen.stats.ox.ac.uk/impute/data_download_1000G_phase1_integrated.html)

6 LD-Hub, <http://ldsc.broadinstitute.org>

7 GTEx, <http://www.gtexportal.org/home/datasets>

8 CommonMind Consortium, <http://commonmind.org>

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3

4 **Conflicts of Interest:**

5 T.E. Thorgeirsson, S. Steinberg, H. Stefansson and K. Stefansson are employed by deCODE  
6 Genetics/Amgen. Multiple additional authors work for pharmaceutical or biotechnology  
7 companies in a manner directly analogous to academic co-authors and collaborators. A.H. Young  
8 has given paid lectures and is on advisory boards for the following companies with drugs used in  
9 affective and related disorders: Astrazenaca, Eli Lilly, Janssen, Lundbeck, Sunovion, Servier,  
10 Livanova. A.H. Young is Lead Investigator for Embolden Study (Astrazenaca), BCI Neuroplasticity  
11 study and Aripiprazole Mania Study, which are investigator-initiated studies from Astrazenaca,  
12 Eli Lilly, Lundbeck, and Wyeth. J. Nurnberger is an investigator for Janssen. P.F. Sullivan reports  
13 the following potentially competing financial interests: Lundbeck (advisory committee), Pfizer  
14 (Scientific Advisory Board member), and Roche (grant recipient, speaker reimbursement). G.  
15 Breen reports consultancy and speaker fees from Eli Lilly and Illumina and grant funding from Eli  
16 Lilly. O.A. Andreassen has received speaker fees from Lundbeck. All other authors declare no  
17 financial interests or potential conflicts of interest.

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1 **DISPLAY ITEMS (inline above in this manuscript version):**

2 Figure 1. Manhattan plot for our primary genomewide association analysis of 20,352 cases and  
3 31,358 controls. GWAS  $-\log_{10}P$ -values are plotted for all SNPs across chromosomes 1-22  
4 (diamonds, green for loci with lead SNP GWAS  $P < 10^{-6}$ ). Combined GWAS+followup  $-\log_{10}P$ -  
5 values for lead SNPs reaching genome-wide significance in either GWAS or combined analysis  
6 (triangles, inverted if GWAS+followup  $-\log_{10}P > \text{GWAS } -\log_{10}P$ ). Labels correspond to gene  
7 symbols previously reported for published loci (black) and the nearest genes for novel loci  
8 (blue), at top if GWAS+followup  $P < 5 \times 10^{-8}$ .

9 Table 1. Genome-wide significant bipolar disorder risk loci.

10 Figure 2. Association of BD1 and BD2 subtypes with schizophrenia (SCZ) and major depression  
11 (DEPR) polygenic risk scores (PRS). Shown are mean PRS values (1 s.e. error bars), adjusted for  
12 study and ancestry covariates and scaled to the PRS mean and sd in control subjects, in BD1  
13 (red) and BD2 (blue) cases, for increasing source GWAS P-value thresholds (increasing grey) as  
14 indicated. P-values (*italics*) test BD1 vs BD2 mean PRS, in logistic regression of case subtype on  
15 PRS with covariates. Results are detailed in Supplementary Table 10.

16

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