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

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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 822 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 reached genome-wide significant evidence for association, of which 20 were novel. These significant loci contain genes encoding ion channels and neurotransmitter transporters (*CACNA1C*, *GRIN2A*, *SCN2A, SLC4A1*), synaptic components (*RIMS1, ANK3*), immune and energy metabolism components. Bipolar disorder type I (depressive and manic episodes; ~73% of our cases) is strongly genetically correlated with schizophrenia whereas bipolar disorder type II (depressive and hypomanic episodes; ~17% of our cases) is more strongly correlated with major depressive disorder. 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 patients who display 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 (GWAS) 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 four 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 common variants genome-wide (SNP-heritability) indicate that ~30% 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 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 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 (effective sample size 46,582). This is the largest GWAS of BD to date and includes 6,328 case and 7,963 control samples not previously reported, a 2.7-fold increase in the number of cases compared to our previous GWAS [9]. We imputed variant dosages using the 1,000 Genomes reference panel (see Methods), retaining association results for 9,372,253 autosomal variants with imputation quality score INFO > 0.3 and minor allele frequency ≥ 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 (λ_{GC}) was 1.23 and scaled to 1,000 cases and 1,000 controls (λ_{1000}) was 1.01 (**Supplementary Figure 1**). The LD-score regression intercept did not significantly differ from one, 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 lifetime risk of 0.5-2%). See **Supplementary Table 1A**, **Online Methods** and **Supplementary Note** for sample and method details.

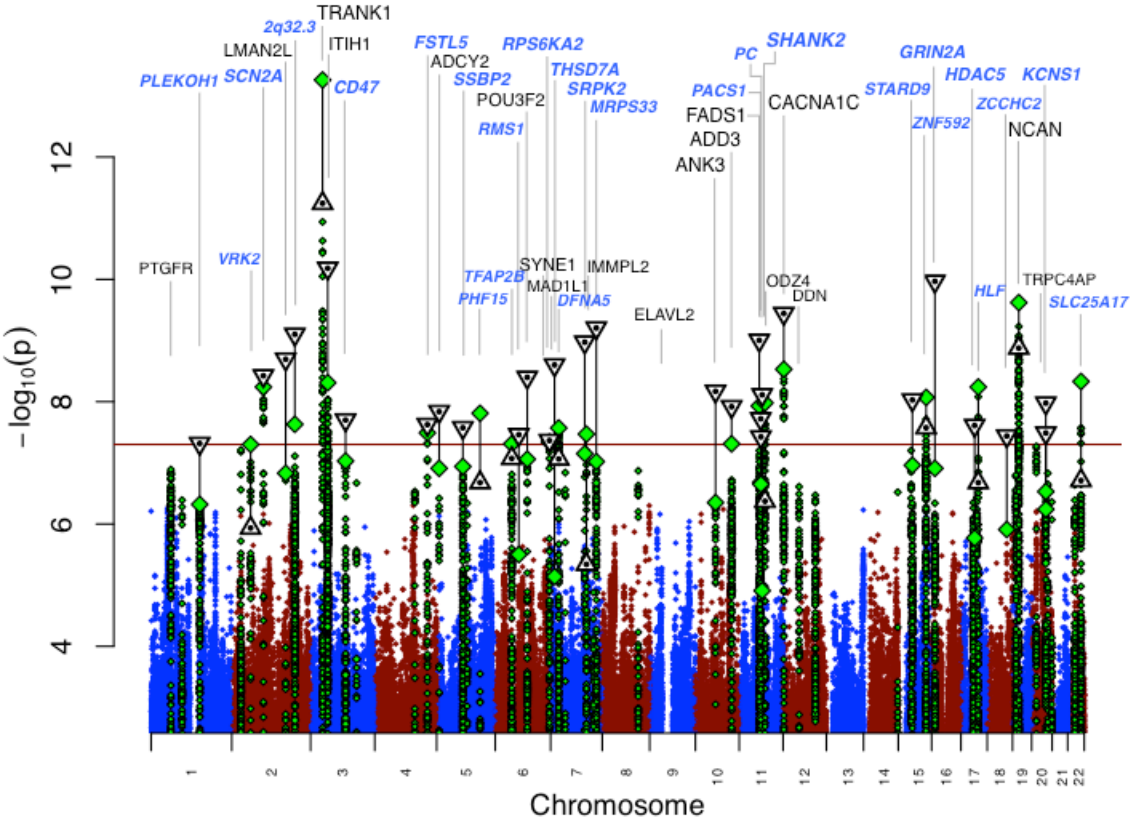
We find a marked increase in phenotypic variance explained by genomewide polygenic risk scores (PRS) compared to previous publications (sample size weighted mean observed Nagelkerke's R^2 = 0.08 across datasets, liability scale R^2=0.04, for P-threshold ≤ 0.01; **Supplementary Figure 2** and **Supplementary Table 2**). Among the different datasets, we observed no association between the PRS and: (i) the gender distribution of the BD cases (p=0.51); (ii) the proportion of cases with psychosis (p=0.61); (iii) the proportion with a family history of BD (p=0.82); or (iv) the median age of onset for BD (p=0.64). In our primary genome-wide analysis, we identified 19 loci exceeding genome-wide significance ($P< 5x10^{-8}$).

Follow-up of suggestive loci in additional samples

We meta-analyzed lead variants that were significant at $P<1x10^{-4}$ in our discovery meta-analysis, (a total of 794 autosomal and 28 X chromosome variants) with follow-up samples totaling 9,412 cases and 137,760 controls of European ancestry (**Supplementary Note** and **Supplementary Table 1B**). Thirty autosomal loci achieved combined sample genome-wide significance ($P< 5x10^{-8}$) (**Figure 1**, **Table 1**, **Supplementary Figure 3**, **Supplementary Table 3**). These include 19 loci that were significant only in the combined analysis, of which three were reported to have genome-wide significant SNPs in previous studies (*ADCY2* [18], *POU3F2* [18], *ANK3* [12,18]), and 11 that were significant in our GWAS. Eight variants were genome-wide significant in the GWAS but not in the combined analysis. Using effect sizes corrected for winner's curse [26,27] for each of the 19 variants with GWAS $P<5x10^{-8}$, we found that 11 variants achieving genome-wide significance in

our combined analysis is within the expected range (Poisson binomial test P = 0.29, **Supplementary Note** and **Supplementary Figure 4**).

Lead variants for the 30 loci achieving genome-wide significance in the combined analysis are shown in **Table 1A**. We show results in **Table 1B** for 8 additional loci with $P < 5x10^{-8}$ in our discovery GWAS but not in the combined analysis. Results for all variants tested in the follow-up study are presented in **Supplementary Table 3**. We refer to loci by the gene name attributed in previous BD GWAS publications, or by the name of the closest gene for novel loci, without implication that the named gene is causal. Of the 30 genome-wide significant loci from our combined analysis, 20 are novel BD risk loci. In **Supplementary Table 4**, we present detailed descriptions of the associated loci and genes, with bioinformatic and literature evidence for their potential roles in BD.



1

2

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 > 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 < 5×10^{-8}.

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Table 1. Genome-wide significant bipolar disorder risk loci

					GWAS Meta-analysis			Follow-up samples		Combined	
Locus Name*	Lead SNP	CHR	BP	A1/A2	Freq. A1	OR	P-value	OR	P-value	OR	P-value
A. Thirty loci with lead SNP P < 5x10-8 in combined GWAS+followup analysis											
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,FSTL5	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**	rs111444407	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. Additional loci with lead SNP P < 5x10-8 in GWAS analysis											
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.

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 $P < 2.2x10^{-16}$), 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 $P < 2.2x10^{-16}$). 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

independent variants based on LD structure within loci [28] to calculate a multiple test-corrected significance threshold ($P=1.01x10^{-5}$, see **Supplementary Note**). One locus showed evidence for an independent association signal (rs114534140 in locus #8, *FSTL5*; $P_{conditional} = 2x10^{-6}$). At one locus (#30, STK4 on chr 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. Thus only the *FSTL5* locus demonstrated clear evidence of more than one independent association.

Shared loci and genetic correlations with schizophrenia, depression and other GWAS 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 [29–31]. Based on conditional analyses the BD and SCZ associations appear to be independent at 3 of the 8 shared loci (*NCAN*, *TRANK1* and chr7q22.3:105Mb loci) (**Supplementary Table 6**). No genome-wide significant BD locus overlapped with those identified for major depression (DEPR), including 44 risk loci identified in the most recent PGC study based on 130,664 depression cases and 330,470 controls[32], and those reported in a large study of depressive symptoms or subjective well-being [33]. As previously reported [34], we found substantial and highly significant genetic correlations between BD and SCZ (LD-score regression estimated genetic correlation r_g = 0.70, se = 0.020) and between BD and DEPR (r_g = 0.35, se = 0.026) The BD and DEPR genetic correlation was similar to that observed for SCZ and DEPR (r_g = 0.34, se = 0.025) (**Supplementary Table 7A**).

We found significant genetic correlations between BD and other psychiatric-relevant traits (**Supplementary Table 7B**), including with autism spectrum disorder [8] (r_g = 0.18, $P=2x10^{-4}$), anorexia nervosa [35] (r_g = 0.23, $P=9x10^{-8}$), and subjective well-being [33] (r_g = -0.22, $P=4x10^{-7}$). There was suggestive positive overlap with anxiety disorders (r_g=0.21, P=0.04) [36] and neuroticism

(r_g=0.12, P=0.002) [37]. Significant r_gs were seen with measures of education: college attendance [38] (r_g = 0.21, P=1=x10^{-7}) and education years [39] (r_g=0.20, P=6x10^{-14}), but not with childhood IQ [40] (r_g=0.05, P=0.5) or intelligence [41] (r_g=-0.05, P=0.08). Among a large number of BD risk locus SNPs associated with additional traits from GWAS catalog, we found a handful of loci with non-independent associations (in one overlapping locus each with educational attainment, biliary atresia, bone mineral density, lipid-related biomarkers) (**Supplementary Table 6**). Biliary atresia and lipid- related biomarkers, however, did not show significant genetic correlation with BD (**Supplementary Table 7B**).

BD subtype GWAS

We performed 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** & **8, Supplementary Figure 5**). We observed variants in 14 loci with genome-wide significance for BD1, 10 of which were in genome-wide significant loci in the combined BD GWAS analysis. Not surprisingly given the sample overlap, 3 of the 4 remaining loci genome-wide significant for BD1 have P < 10^{-6} in either our GWAS or combined analysis. The remaining locus (MAD1L1, chr7:1.9Mb, GWAS P = 2.4x10^{-6}) was recently published in two BD GWAS that included Asian samples [42,43]. 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, se = 0.014, P = 3.2x10^{-77}; BD2 h^2_{snp} = 0.11, se = 0.028, P = 5.8x10^{-5}; SAB h^2_{snp} = 0.25, se = 0.10, P = 0.0071). Genetic correlations among BD subtypes show that these represent closely related, yet partially distinct, phenotypes (**Supplementary Table 9)**.

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

in BD1 cases than in BD2 cases (min P=5.6x10^{-17}, P threshold = 0.1), and greater DEPR PRS in BD2 cases than in BD1 cases (min P=8.5x10^{-10}, P threshold = 0.01) (**Figure 2**, **Supplementary Table 10**). Genetic correlations from LD-score regression support these results; genetic correlations were greater for SCZ with BD1 (r_g = 0.71, se = 0.025) than with BD2 (r_g = 0.51, se = 0.072), with P_{diff} = 0.0056, and were greater for DEPR with BD2 (r_g = 0.69, se = 0.093) than with BD1 (r_g = 0.30, se = 0.028), with P_{diff} = 2.9x10^{-5} (**Supplementary Table 9**).

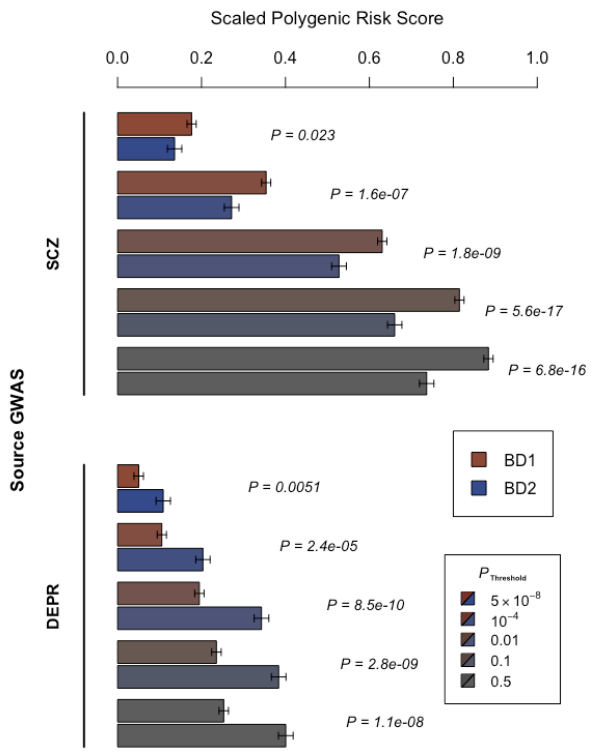

Figure 2. Association of BD1 and BD2 subtypes with schizophrenia (SCZ) and major depression (DEPR) polygenic risk scores (PRS). Shown are mean PRS values (1 s.e. error bars), adjusted for study and ancestry covariates and scaled to the PRS mean and sd in control subjects, in BD1 (red) and BD2 (blue) 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.

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

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

We tested for functional genomic enrichment in our BD GWAS using partitioned LD-score regression [47] (**Supplementary Note**, **Supplementary Table 12**). Annotations tested included open chromatin DHS peaks in a range of tissues [48], genic annotations, conservation, and a number of functional genomic annotations across tissues. SNP-based BD heritability was most substantially enriched in open chromatin annotations in central nervous system (proportion SNPs = 0.14, proportion h^2_{snp} = 0.60, enrichment =3.8, P = 4.2 x 10^{-17}) . We also used DEPICT [49] to test for expression of BD associated genes across tissues, and found significant enrichment of central nervous system (P <= 1.3x10^{-3}, FDR < 0.01) and neurosecretory system (P <= 2.0x10^{-6}, FDR < 0.01) genes (**Supplementary Table 13**).

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 < 2.8x10^{-6}), including 82 genes in 20 genome-wide significant loci, and 73 genes in 27 additional loci that did not reach genome-wide significance in either our GWAS or

combined analysis (**Supplementary Table 14**). Nine related pathways were significantly enriched for genes with stronger BD associations ($P < 7.0x10^{-5}$, FDR < 0.05), including abnormal motor coordination/balance pathways (from mice), regulation of insulin secretion and endocannabinoid signaling pathways (**Supplementary Table 15, Supplementary Figure 6**).

DISCUSSION

We carried out the largest bipolar disorder (BD) GWAS to date and identified 30 genome-wide significant loci, including 20 novel BD risk loci. 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 meta analysis but had $P_{GWAS} \leq 1.3x10^{-5}$. 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. Although these results are not unexpected given small effect sizes and the winner's curse [27,51] (**Supplementary Note** and **Supplementary Figure 4**), genetic heterogeneity has been shown between BD GWAS cohorts[8]. We observed variable polygenic effects between BD subtypes and between cohorts in our study (**Figure 2**, **Supplementary Figure 2**, **Supplementary Tables 2** & **10**) and acknowledge a diversity of clinical case phenotypic criteria among cohorts in our study (**Supplementary Note**). Remarkably, our strongest association signal, observed at the *TRANK1* locus (rs9834970; $P_{combined}$ = 5.7E-12, OR = 0.93), exhibited significant heterogeneity among discovery GWAS cohorts (Cochran's Q $P = 1.9x10^{-4}$, and did not replicate in the follow-up sample (1-tailed $P_{followup}$ = 0.3) (**Supplementary Figure 3B & 3C**, fifth and first plots respectively). This locus has been observed in recent [11,12,17,18] but not earlier BD GWAS [9,13,20], surprisingly given its relatively large apparent effect size. Thus, complex polygenic architecture as well as phenotypic heterogeneity among BD GWAS cohorts 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 addition to continued efforts to collect larger sample sizes.

Of the 30 BD associated loci, 8 also harbor associations [29–31] with schizophrenia (SCZ); however, conditional analyses suggest that the BD and SCZ associations at 3 of the 8 shared loci (in the *NCAN*, *TRANK1* and chr7q22.3 [105Mb] loci) may be independent (**Supplementary Table 6**). 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[32].

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

The estimated variance explained by polygenic risk scores (PRS) based on our BD GWAS data is ~8% (observed scale; 4% on the liability scale [55]), an increase from 2.8% from our previous study [9]. Using PRS, we found that BD1 cases have significantly greater schizophrenia genetic risk than BD2 cases, while BD2 cases have significantly greater major depression genetic risk than BD1 cases, consistent with a spectrum of related psychiatric diagnoses[7,56]. 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 increased educational attainment may be independent of general intelligence. This result is inconsistent with suggestions from epidemiological studies [57], but in agreement with a recent clinical study [58].

In summary, findings from the largest 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 METHODS

Methods

GWAS and follow-up cohorts. Our discovery GWAS sample was comprised 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. A selected set of variants (see below) were tested in 7 follow-up cohorts of European descent (**Supplementary Table 1B**), totalling 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, ICD-9, or ICD-10) for a lifetime diagnosis of BD established using structured diagnostic instruments from assessments by trained interviewers, clinician-administered checklists, or medical record review. In most cohorts, controls were screened for the absence of lifetime psychiatric disorders and randomly selected from the population.

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 (PCs 1-6, 19). In each cohort, we performed logistic regression association tests for BD with imputed marker dosages including 7 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 35 subtype cases and filtering SNPs for MAF > 0.02**.** Results were combined across cohorts using an inverse variance-weighted fixed effects meta-analysis [59]. We used Plink 'clumping' [60,61] to identify an LD-pruned set of discovery GWAS meta-analysis BD-associated variants ($P < 0.0001$, and distance >500kb 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 QC 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.

Polygenic risk score (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 [62]. In pairwise case subtype analyses (**Figure 2**, **Supplementary Table 10**), we regressed subtype case status (BD1 n=8044, BD2 n=3,365, SAB n=977) 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 (**Figure 2**).

Linkage disequilibrium (LD) score regression. LD score regression [25,63] 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 with LD-Hub [63]. We also used LD score regression to partition heritability by genomic features [47].

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. [64] We used summary-data-based Mendelian randomization (SMR) [44] 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).

Gene-wise and pathway analysis. Guided by rigorous method comparisons conducted by PGC members [50,65], p-values quantifying the degree of association of genes and gene sets with BD were generated using MAGMA (v1.06) [50]. We used ENSEMBL gene coordinates for 18,172 genes giving a Bonferroni corrected *P*-value threshold of 2.8×10^{-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 1,000 Genomes Project (Phase 3 v5a, MAF ≥ 0.01, European-ancestry subjects) [66]. 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 Figure 6**) was constructed using the kernel generative topographic mapping algorithm (k-GTM) as described by [67]. 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 through the PGC (URLs).

URLs

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

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

1000 Genomes Project multi-ancestry imputation panel,

https://mathgen.stats.ox.ac.uk/impute/data_download_1000G_phase1_integrated.html

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

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

CommonMind Consortium, http://commonmind.org

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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, Lundbeck, Sunovion, Servier, Livanova. A.H. Young is Lead Investigator for Embolden Study (Astrazenaca), BCI Neuroplasticity study and Aripiprazole Mania Study, which are investigator-initiated studies from Astrazenaca, Eli Lilly, Lundbeck, and Wyeth. J. Nurnberger is an investigator for Janssen. P.F. Sullivan reports the following potentially competing financial interests: Lundbeck (advisory committee), Pfizer (Scientific Advisory Board member), and Roche (grant recipient, speaker reimbursement). G. Breen reports consultancy and speaker fees from Eli Lilly and Illumina and grant funding from Eli Lilly. O.A. Andreassen has received speaker fees from Lundbeck. All other authors declare no financial interests or potential conflicts of interest.

DISPLAY ITEMS (inline above in this manuscript version):

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 $-\log_{10}P >$ 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 $P < 5x10^{-8}$.

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

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.

References:

1. Ferrari, A. J. *et al.* The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. *Bipolar Disord.* **18,** 440–450 (2016).
2. Lichtenstein, P. *et al.* Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* **373,** 234–239 (2009).
3. Edvardsen, J. *et al.* Heritability of bipolar spectrum disorders. Unity or heterogeneity? *J. Affect. Disord.* **106,** 229–240 (2008).
4. McGuffin, P. *et al.* The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch. Gen. Psychiatry* **60,** 497–502 (2003).
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. (American Psychiatric Pub, 2013).
6. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. (World Health Organization, 1992).
7. Craddock, N. & Owen, M. J. The Kraepelinian dichotomy - going, going... but still not gone. *Br. J. Psychiatry* **196,** 92–95 (2010).
8. Lee, S. H. *et al.* Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* **45,** 984–994 (2013).
9. Sklar, P. *et al.* Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat. Genet.* **43,** 977–U162 (2011).
10. Baum, A. E. *et al.* A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Mol. Psychiatry* **13,** 197–207 (2008).
11. Charney, A. W. *et al.* Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder. *Transl. Psychiatry* **7,** e993 (2017).

12. Chen, D. T. *et al.* Genome-wide association study meta-analysis of European and Asian-ancestry samples identifies three novel loci associated with bipolar disorder. *Mol. Psychiatry* **18,** 195–205 (2013).
13. Cichon, S. *et al.* Genome-wide association study identifies genetic variation in neurocan as a susceptibility factor for bipolar disorder. *Am. J. Hum. Genet.* **88,** 372–381 (2011).
14. Ferreira, M. A. R. *et al.* Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat. Genet.* **40,** 1056–1058 (2008).
15. Green, E. K. *et al.* Association at SYNE1 in both bipolar disorder and recurrent major depression. *Mol. Psychiatry* **18,** 614–617 (2013).
16. Green, E. K. *et al.* Replication of bipolar disorder susceptibility alleles and identification of two novel genome-wide significant associations in a new bipolar disorder case-control sample. *Mol. Psychiatry* **18,** 1302–1307 (2013).
17. Hou, L. *et al.* Genome-wide association study of 40,000 individuals identifies two novel loci associated with bipolar disorder. *Hum. Mol. Genet.* **25,** 3383–3394 (2016).
18. Mühleisen, T. W. *et al.* Genome-wide association study reveals two new risk loci for bipolar disorder. *Nat. Commun.* **5,** 3339 (2014).
19. Schulze, T. G. *et al.* Two variants in Ankyrin 3 (ANK3) are independent genetic risk factors for bipolar disorder. *Mol. Psychiatry* **14,** 487–491 (2009).
20. Scott, L. J. *et al.* Genome-wide association and meta-analysis of bipolar disorder in individuals of European ancestry. *Proc. Natl. Acad. Sci. U. S. A.* **106,** 7501–7506 (2009).
21. Sklar, P. *et al.* Whole-genome association study of bipolar disorder. *Mol. Psychiatry* **13,** 558–569 (2008).
22. Smith, E. N. *et al.* Genome-wide association study of bipolar disorder in European American and African American individuals. *Mol. Psychiatry* **14,** 755–763 (2009).

23. Burton, P. R. *et al.* Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447,** 661–678 (2007).

24. Gratten, J., Wray, N. R., Keller, M. C. & Visscher, P. M. Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nat. Neurosci.* **17,** 782–790 (2014).

25. Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47,** 291–295 (2015).

26. Palmer, C. & Pe'er, I. Statistical correction of the Winner's Curse explains replication variability in quantitative trait genome-wide association studies. *PLoS Genet.* **13,** e1006916 (2017).

27. Zhong, H. & Prentice, R. L. Bias-reduced estimators and confidence intervals for odds ratios in genome-wide association studies. *Biostatistics* **9,** 621–634 (2008).

28. Gao, X., Starmer, J. & Martin, E. R. A multiple testing correction method for genetic association studies using correlated single nucleotide polymorphisms. *Genet. Epidemiol.* **32,** 361–369 (2008).

29. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511,** 421–427 (2014).

30. Goes, F. S. *et al.* Genome-wide association study of schizophrenia in Ashkenazi Jews. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **168,** 649–659 (2015).

31. Ripke, S. *et al.* Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat. Genet.* **45,** 1150–1159 (2013).

32. Wray, N. R. & Sullivan, P. F. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *bioRxiv* (2017).

33. Okbay, A. *et al.* Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nat. Genet.* (2016).

doi:10.1038/ng.3552

34. Cross-Disorder Group of the Psychiatric Genomics Consortium *et al.* Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* **45,** 984–994 (2013).

35. Duncan, L. *et al.* Significant Locus and Metabolic Genetic Correlations Revealed in Genome-Wide Association Study of Anorexia Nervosa. *Am. J. Psychiatry* appiajp201716121402 (2017).

36. Otowa, T. *et al.* Meta-analysis of genome-wide association studies of anxiety disorders. *Mol. Psychiatry* **21,** 1391–1399 (2016).

37. Gale, C. R. *et al.* Pleiotropy between neuroticism and physical and mental health: findings from 108 038 men and women in UK Biobank. *Transl. Psychiatry* **6,** e791 (2016).

38. Rietveld, C. A. *et al.* GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *Science* **340,** 1467–1471 (2013).

39. Okbay, A. *et al.* Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* **533,** 539–542 (2016).

40. Benyamin, B. *et al.* Childhood intelligence is heritable, highly polygenic and associated with FNBP1L. *Mol. Psychiatry* **19,** 253–258 (2014).

41. Sniekers, S. *et al.* Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. *Nat. Genet.* **49,** 1107–1112 (2017).

42. Hou, L. *et al.* Genome-wide association study of 40,000 individuals identifies two novel loci associated with bipolar disorder. *Hum. Mol. Genet.* **25,** 3383–3394 (2016).

43. Ikeda, M. *et al.* A genome-wide association study identifies two novel susceptibility loci and trans population polygenicity associated with bipolar disorder. *Mol. Psychiatry* (2017). doi:10.1038/mp.2016.259

44. Zhu, Z. *et al.* Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48,** 481–487 (2016).

45. Fromer, M. *et al.* Gene expression elucidates functional impact of polygenic risk for schizophrenia. *Nat. Neurosci.* **19,** 1442–1453 (2016).

46. Westra, H. J. *et al.* Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nat. Genet.* **45,** 1238–1243 (2013).

47. Finucane, H. K. *et al.* Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* **47,** 1228–1235 (2015).

48. Roadmap Epigenomics Consortium *et al.* Integrative analysis of 111 reference human epigenomes. *Nature* **518,** 317–330 (2015).

49. Pers, T. H. *et al.* Biological interpretation of genome-wide association studies using predicted gene functions. *Nat. Commun.* **6,** 5890 (2015).

50. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11,** e1004219 (2015).

51. Palmer, C. & Pe'er, I. Statistical Correction of the Winner9s Curse Explains Replication Variability in Quantitative Trait Genome-Wide Association Studies. *bioRxiv* 104786 (2017).

52. Gaspar, H. A. & Breen, G. Pathways analyses of schizophrenia GWAS focusing on known and novel drug targets. *Biorxiv* (2017). doi:10.1101/091264

53. Camandola, S. & Mattson, M. P. Aberrant subcellular neuronal calcium regulation in aging and Alzheimer's disease. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* **1813,** 965–973 (2011).

54. Mertens, J. *et al.* Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. *Nature* **527,** 95–99 (2015).

55. Lee, S. H., Goddard, M. E., Wray, N. R. & Visscher, P. M. A better coefficient of

determination for genetic profile analysis. *Genet. Epidemiol.* **36,** 214–224 (2012).

56. Nolen, W. A. The continuum of unipolar depression - bipolar II depression - bipolar I depression: different treatments indicated? *World Psychiatry* **10,** 196–197 (2011).

57. MacCabe, J. H. *et al.* Excellent school performance at age 16 and risk of adult bipolar disorder: national cohort study. *Br. J. Psychiatry* **196,** 109–115 (2010).

58. Vreeker, A. *et al.* High educational performance is a distinctive feature of bipolar disorder: a study on cognition in bipolar disorder, schizophrenia patients, relatives and controls. *Psychol. Med.* **46,** 807–818 (2016).

59. Ripke, S. Ricopili: a tool for visualizing regions of interest in select GWAS data sets. (2014).

60. Purcell, S. *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81,** 559–575 (2007).

61. Chang, C. C. *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4,** 7 (2015).

62. Euesden, J., Lewis, C. M. & O'Reilly, P. F. PRSice: Polygenic Risk Score software. *Bioinformatics* **31,** 1466–1468 (2015).

63. Zheng, J. *et al.* LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics* **33,** 272–279 (2017).

64. Finucane, H. *et al.* Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. doi:10.1101/103069

65. O'Dushlaine, C. *et al.* Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat. Neurosci.* **18,** 199–209 (2015).

66. 1000 Genomes Project Consortium *et al.* A global reference for human genetic variation. *Nature* **526,** 68–74 (2015).

67. Olier, I., Vellido, A. & Giraldo, J. Kernel generative topographic mapping. in *ESANN* **2010,** 481–486 (2010).