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

Eli A Stahli [1,2†&]; Andreas J Forstner [3,4,5,6†]; Andrew McQuillin [7†]; Stephan Ripke [8,9,10†]; Vassily Trubetskoy [9]; Manuel Mattheisen [11,12,13,14,15]; Weiqing Wang [2,16]; Yunpeng Wang [17,18]; Jonathan R I Coleman [19,20]; Héléna A Gaspar [19,20]; Christiaan A de Leeuw [21]; Jennifer M Whitehead Pavlides [22]; Loes M Olde Loohuis [23]; Anil P S Ori [23]; Tune H Pers [24,25]; Peter A Holmans [26]; Douglas M Ruderfer [27,27]; Phil H Lee [8,10,28]; Alexander W Charney [16,16]; Amanda L Dobbyn [2,29]; Laura Huckins [2,30]; James Boocock [31,32]; Claudia Giambartolomei [31,32]; Panos Roussos [2,16,33]; Niamh Mullins [19]; Swapnil Awasthi [9]; Esben Agerbo [34]; Thomas D Als [11,12]; Carsten Bøcker Pedersen [35]; Jakob Grove [11,12,36]; Ralph Kupka [37]; Eline J Regeer [38]; Adebayo Anjorin [39]; Miquel Casas [40]; Cristina Sánchez-Mora [40]; Pamela B Mahon [41]; Shaun M Purcell [41]; Steve McCarroll [8]; Judith Allardyce [26]; Valentina Escott-Price [26]; Liz Forty [26]; Christine Fraser [26]; Marian L Hamshere [26]; George Kirov [26]; Manolis Kogevinas [42]; Josef Frank [43]; Fabian Streit [43]; Jana Strohmaier [43]; Jens Treutlein [43]; Stephanie H Witt [43]; James L Kennedy [44,45]; John S Strauss [46]; Julie Garnham [47]; Claire O'Donovan [47]; Claire Slaney [47]; Stacy Steinberg [48]; Thorgeir E Thorgeirsson [48]; Martin Hautzinger [49]; Michael Steffens [50]; Ralph Kupka [51]; Steve McCarroll [52]; Roy H Perlis [53]; Miquel Casas [54]; Cristina Sánchez-Mora [54]; Maria Hipolito [55]; William B Lawson [55]; Evaristus A Nwulia [55]; Shawn E Levy [56]; Shaun M Purcell [16]; Tatiana M Foroud [57]; Stéphane Jamain [58]; Allan H Young [59]; James D McKay [60]; Thomas D Als [13]; Carsten Bøcker Pedersen [13]; Jakob Grove [13]; Diego Albani [61]; Peter Zandi [62]; Pamela B Mahon [63]; James B Potash [63]; Peng Zhang [64]; J Raymond DePaulo [65]; Sarah E Bergen [66]; Anders Juréus [66]; Robert Karlsson [66]; Radhika Kandaswamy [19]; Peter McGuffin [19]; Margarita Rivera [19]; Jolanta Lissowska [67]; Roy H Perlis [68]; Cristiana Cruceanu [69]; Susanne Lucae [69]; Pablo Cervantes [70]; Monika Budde [71]; Katrin Gade [71]; Urs Heilbronner [71]; Marianne Giørtz Pedersen [72]; Carsten Bøcker Pedersen [73]; Derek W Morris [74]; Cynthia Shannon Weickert [75]; Thomas W Weickert [75]; Donald J MacIntyre [76]; Jacob Lawrence [77]; Torbjørn Elvsåshagen [78,79]; Olav B Smeland [80]; Srdjan Djurovic [81]; Simon Xi [82]; Elaine K Green [83]; Piotr M Czerski [84]; Joanna Hauser [84]; Wei Xu [85]; Helmut Vedder [86]; Lilijana Oruc [87]; Anne T Spijker [88]; Scott D Gordon [89]; Sarah E Medland [90]; David Curtis [91]; Thomas W Mühleisen [92]; Judith Badner [93]; William A Scheftner [93]; Engilbert Sigurdsson [94]; Nicholas J Schork [95]; Alan F Schatzberg [96]; Marie Bækvad-Hansen [97]; Jonas Bybjerg-Grauholm [98]; Christine Søholm Hansen [97]; James A Knowles [99,100]; Helena Medeiros [100]; Szabolcs Szelinger [101]; Grant W Montgomery [102]; Derek W Morris [103]; Marco Boks [104]; Annelie Nordin Adolfsson [105]; Miquel Casas [106]; Stéphane Jamain [107]; Nicholas Bass [7]; David Curtis [108]; Per Hoffmann [109]; Michael Bauer [110]; Andrea Pfennig [110]; Markus Leber [111]; Sarah Kittel-Schneider [112]; Andreas Reif [112]; Katrin Gade [113]; Jurgen Del-Favero [114]; Sascha B Fischer [3]; Stefan Herms [3]; Per Hoffmann [3]; Thomas W Mühleisen [3]; Céline S Reinbold [3]; Srdjan Djurovic [115]; Franziska Degenhardt [5,6]; Stefan Herms [5,6]; Per Hoffmann [5,6]; Anna C Koller [5,6]; Anna Maaser [5,6]; Wolfgang Maier [116]; Nelson B Freimer [23]; Anil Ori [23]; Anders M Dale [117]; Chun Chieh Fan [118]; Tiffany A Greenwood [119]; Caroline M Nievergelt [119]; Tatyana Shehktman [120]; Paul D Shilling [119]; Olav B Smeland [121]; William Byerley [122]; William Bunney [123]; Ney Alliey-Rodriguez [124]; Douglas H R Blackwood [125]; Toni-Kim Clarke [125]; Donald J MacIntyre [126]; Margarita Rivera [127]; Chunyu Liu [128]; William Coryell [129]; Huda Akil [130]; Margit Burmeister [131]; Matthew Flickinger [132]; Jun Z Li [133]; Melvin G McInnis [134]; Fan Meng [130,134]; Robert C Thompson [134]; Stanley J Watson [134]; Sebastian Zollner [134]; Weihua Guan [135]; Melissa J Green [136]; Cynthia Shannon Weickert [136]; Thomas W Weickert [136]; Olav B Smeland [137]; David Craig [138]; Janet L Sobell [139]; Lili Milani [140]; James L Kennedy [141,142]; John S Strauss [141]; Wei Xu [143]; Katherine Gordon-Smith [144]; Sarah V Knott [144]; Amy Perry [144]; José Guzman Parra [145]; Fermin Mayoral [145]; Fabio Rivas [145]; Miquel Casas [146]; Cristina Sánchez-Mora [146]; Caroline M Nievergelt [147]; Ralph Kupka [148]; John P Rice [149]; Jack D Barchas [150]; Anders D Børglum [11,12]; Preben Bo Mortensen [151]; Ole Mors [152]; Maria Grigoroiu-Serbanescu [153]; Frank Bellivier [154]; Bruno Etain [154]; Marion Leboyer [154]; Josep Antoni Ramos-Quiroga [40]; Marta Ribasés [40]; Tõnu Esko [25]; Jordan W Smoller [8]; Nicholas Craddock [26]; Ian Jones [26]; Michael J Owen [26]; Marcella Rietschel [43]; Thomas G Schulze [43]; John Vincent [46]; Tõnu Esko [155]; Eduard Vieta [156]; Merete Nordentoft [157]; Martin Alda [47]; Hreinn Stefansson [48]; Kari Stefansson [48]; Danielle Posthuma [158,159]; Ingrid Agartz [160]; Frank Bellivier [161]; Tõnu Esko [52]; Ketil J Oedegaard [162]; Eystein Stordal [163]; Josep Antoni Ramos-Quiroga [54]; Marta Ribasés [54]; Richard M Myers [56]; René S Kahn [16]; Frank Bellivier [164]; Bruno Etain [164]; Marion Leboyer [165]; Bruno Etain [166]; Anders D Børglum [13]; Ole Mors [167]; Thomas Werge [168]; Qingqin S Li [169]; Thomas G Schulze [63]; Fernando Goes [65]; Ingrid Agartz [14]; Christina M Hultman [66]; Mikael Landén [66]; Patrick F Sullivan [66,66]; Cathryn M Lewis [19,170]; Susan L McElroy [171]; Jordan W Smoller [172,173]; Bertram Müller-Myhsok [69]; Joanna M Biernacka [174]; Mark Frye [175]; Gustavo Turecki [176]; Guy A Rouleau [177]; Thomas G Schulze [71]; Thomas Werge [178]; Guy A Rouleau [179]; Bertram Müller-Myhsok [180]; Martin Alda [181]; Francis J McMahon [182]; 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]; Vishwajit Nimgaonkar [210]; Tõnu Esko [140]; Andres Metspalu [140,211]; Lisa A Jones [144]; Josep Antoni Ramos-Quiroga [146]; Marta Ribasés [146]; John Nurnberger [212]; Naomi R Wray [22,102]; Arianna Di Florio [26,206]; Michael C O'Donovan [26]; Howard Edenberg [213]; Roel A Ophoff [104,214*]; Laura J Scott [132*]; Sven Cichon [3,5,92,109*]; Ole A Andreassen [80,137*]; Pamela Sklar [2,16,33,215*]; John Kelsoe [119*]; and Gerome Breen [19,20*&]
for the Bipolar Disorder Working Group of the Psychiatric Genomics Consortium.

† Equal contribution * Co-last authors
& Correspondence to: gerome.breen@kcl.ac.uk or eli.stahl@mssm.edu

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 18 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 $\geq 1\%$. We performed logistic regression of case status

115 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
120 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
125 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
130 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
135 (**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.

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
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)

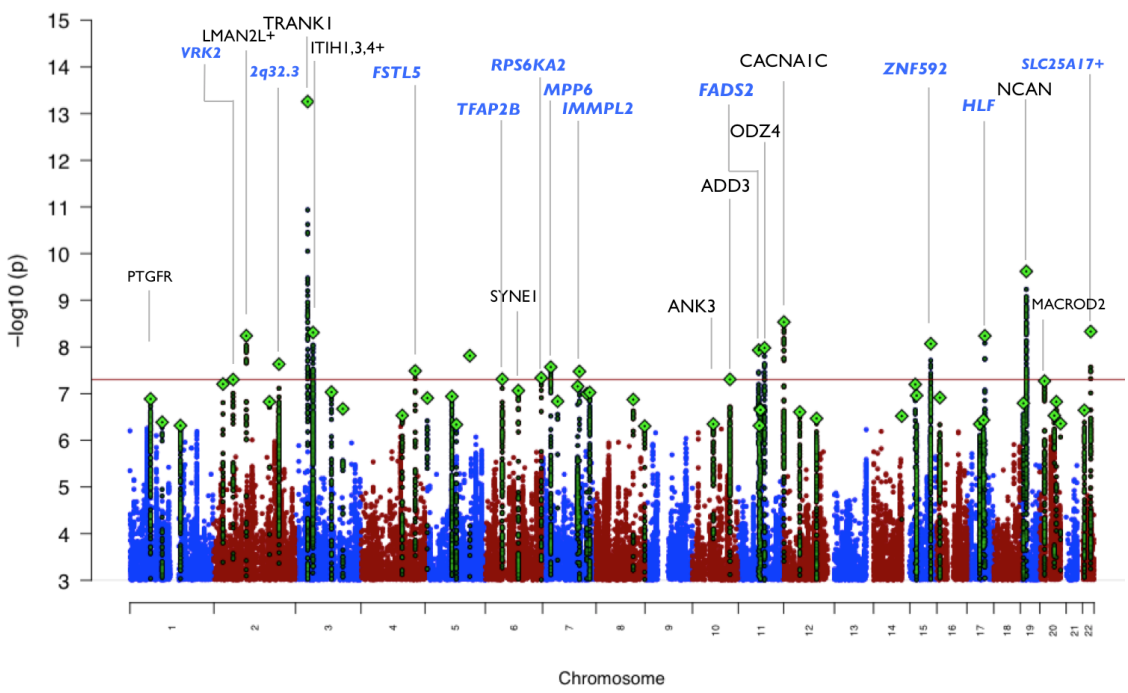

Figure 1. Manhattan plot for our primary genomewide association analysis of 20,352 cases and 31,358 controls. -log10P-values are plotted for all SNPs across chromosomes 1-22 (green if P<10-6). Labels correspond to gene symbols previously reported for known loci (black) and the nearest genes for novel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

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.

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 $P=1.01x10^{-5}$, one locus showed evidence for an independent association signal (rs114534140 near *FSTL5* with $P_{conditional} = 2x10^{-6}$;

155 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
160 a single causal variant.

BD subtype GWAS

We performed secondary analyses of the GWAS dataset, 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
165 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).

170 **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
175 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**).

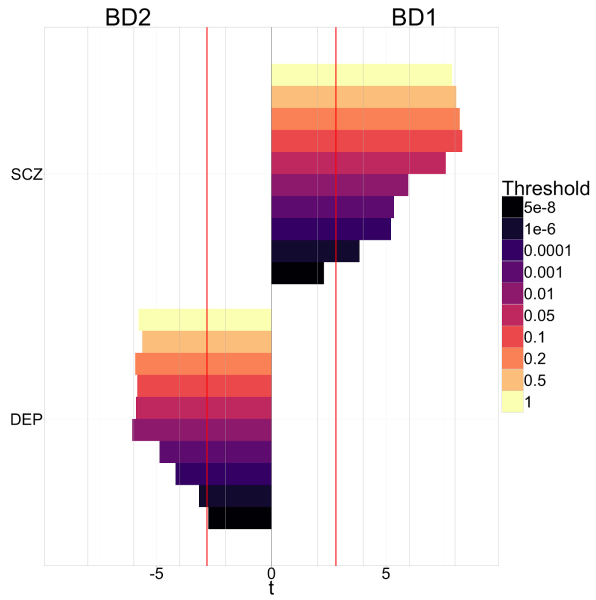

Figure 2. Association of BD subtypes with polygenic risk scores (PRS) derived from PGC2 studies of SCZ and major depression. X-axis = t-statistic from regression of PRS on BD subtypes. Red line = Bonferroni threshold for 10 thresholds tested. Results are detailed in Supplementary Table 8.

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

$P=1.00x10^{-18}$, P threshold = 0.1), and greater Depression PRS in BD2 cases than in BD1 cases (min $P=3.03x10^{-9}$, 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), $P_{diff} = 2.9x10^{-5}$.

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.

220 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
225 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
230 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 ($r_g = 0.70$, $P = 2.5\times10^{-287}$). Our findings address key clinical questions and suggest potential new biological mechanisms for bipolar disorder.

Online Methods

Methods.

GWAS cohorts. We performed 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. 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)**.**

Follow-up cohorts. We meta-analysed the 881 variants that had a $p<10^{-4}$ in the BD GWAS data with data from European-ancestry cohorts (totaling 9,412 cases and 137,760 controls). **Supplementary Table 1** summarizes the source and inclusion/exclusion criteria for cases and controls for each cohort. Genotyping and quality control. Genotyping procedures can be found in the GWAS reports or reference publications for each cohort (**Supplementary Table 1** and **Supplementary Note**). Individual genotype data for all GWAS cohorts and the iPSYCH cohort were processed using the PGC "ricopili" pipeline (URLs) for standardized quality control, imputation, and analysis [52]. The follow-up cohorts from were processed by the collaborating research teams using comparable procedures. Quality control filters applied to each cohort included imputation marker INFO score $\geq$ 0.6 and allele frequencies $\geq$0.01 and $\leq$0.99.

Quality control and imputation on the GWAS cohorts was performed according to standards from the PGC. SNPs and insertion-deletion polymorphisms were imputed using the 1000 Genomes Project multi-ancestry reference panel (URLs)[53] . Principal components based on ld independent SNPs were calculated to be used as covariates in final association analysis. Further details of SNP and individual level QC can be found in the Supplementary Note.

Statistical analysis. In each cohort, logistic regression association tests were conducted for imputed marker dosages with principal components covariates to control for population stratification. Ancestry was evaluated using principal components analysis applied to directly genotyped SNPs [54]. We tested 20 principal components for association with BD and included 6 principal components covariates for the GWAS cohorts; all other cohorts adopted similar strategies. The results were combined across samples using an inverse-weighted fixed effects model [52]. For all GWAS cohorts, X-chromosome association results were conducted separately by sex, and then meta-analysed across sexes. X chromosome genotype data was not available for the follow-up cohorts.

Defining loci. GWA findings implicate genomic regions containing multiple significant SNPs ("loci"). These are not independent associations but result from LD between SNPs. We collapsed the significant SNPs to 30 loci via steps described in the Supplementary Note.

Polygenic risk score (PRS) analyses. To demonstrate the validity of our GWAS results, we conducted a series of PRS prediction analyses. Detailed results for all *P*-value thresholds are reported for the anchor cohorts in **Supplementary Table 14**. We next examined whether the PRSs for major depression and for SCZ differ between BD type I and type II cases using the entire GWAS cohort as the target sample. We tested the standardized PRS between BD I cases (N=8044) and BD II cases (N=3365) by regressing the scores on the two subtypes while adjusting for ancestry principal components and a batch (in this case, cohort) indicator (**Supplementary**

Table 8) using logistic regression [55].

Linkage disequilibrium (LD) score regression [25,56] was used to estimate heritability and bivariate genetic correlations from GWA summary statistics. LD score regression bivariate genetic correlations attributable to genome-wide SNPs were estimated across BD cohorts and between the full BD cohort and other traits and disorders. Additional QC steps were carried out dependant on the properties of each set of summary statistics (see **Supplementary Note).**

LD score regression was also used to partition by genomic features [42]. We also used LD score regression to estimate genetic correlation between BD and a range of other disorders, diseases, and human traits [56]. These calculations were done using the internal PGC GWA library and with LD-Hub [56].

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]. MAGMA was used to calculate gene-wide association by using Brown's method to combine SNP p-values, accounting for the LD structure present in the gene. The resulting p-values are then combined into aggregate p-values

(using Brown's method to correct for correlation between them), thereby increasing power across a range of genetic architectures. 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 $\geq$ 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

375 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

380 PGC “ricopili” GWA pipeline, https://github.com/Nealelab/ricopili

Affiliations:

1. Medical and Population Genetics, Broad Institute, Cambridge, MA, USA
2. Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA
3. Department of Biomedicine, University of Basel, Basel, CH
4. Department of Psychiatry (UPK), University of Basel, Basel, CH
5. Institute of Human Genetics, University of Bonn, Bonn, DE
6. Life&Brain Center, Department of Genomics, University of Bonn, Bonn, DE
7. Division of Psychiatry, University College London, London, GB
8. Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, USA
9. Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, DE
10. Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA
11. Department of Biomedicine, Aarhus University, Aarhus, DK
12. iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK
13. iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, DK
14. Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, SE
15. Stockholm Health Care Services, Stockholm County Council, Stockholm, SE
16. Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
17. Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Copenhagen, DK
18. Institute of Clinical Medicine, University of Oslo, Oslo, NO
19. MRC Social, Genetic and Developmental Psychiatry Centre, King's College London, London, GB
20. National Institute of Health Research Maudsley Biomedical Research Centre, King's College London, London, GB
21. Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, NL
22. Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU
23. Center for Neurobehavioral Genetics, University of California Los Angeles, Los Angeles, CA, USA
24. Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, MA, USA
25. Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA
26. Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, GB
27. Medicine, Psychiatry, Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA
28. Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, USA
29. Division of Psychiatric Genomics, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, Icahn School of Medicine at Mount Sinai, New York, NY, USA
30. Psychiatric Genomics, Icahn School of Medicine at Mount Sinai, New York, NY, USA
31. Human Genetics, University of California Los Angeles, New York, NY, USA
32. Human Genetics, University of California Los Angeles, Los Angeles, CA, USA
33. Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA
34. BSS, NCRR, CIRRAU, Aarhus University, Aarhus, DK
35. Centre for Integrated Register-based Research, CIRRAU, Aarhus University, Aarhus, DK
36. Bioinformatics Research Centre (BiRC), Aarhus University, Aarhus, DK
37. Psychiatry, Altrecht, Utrecht, NL
38. Outpatient Clinic for Bipolar Disorder, Altrecht, Utrecht, NL
39. Psychiatry, Berkshire Healthcare NHS Foundation Trust, Bracknell, GB
40. Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health (CIBERSAM), Madrid, ES
41. Psychiatry, Brigham and Women's Hospital, Boston, MA, USA
42. Center for Research in Environmental Epidemiology (CREAL), Barcelona, ES
43. Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty

Mannheim, Heidelberg University, Mannheim, DE
44. Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, CA
45. Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, ON, CA
46. Centre for Addiction and Mental Health, Toronto, ON, CA
47. Department of Psychiatry, Dalhousie University, Halifax, NS, CA
48. deCODE Genetics / Amgen, Reykjavik, IS
49. Department of Psychology, Eberhard Karls Universität Tübingen, Tubingen, DE
50. Research Division, Federal Institute for Drugs and Medical Devices (BfArM), Bonn, DE
51. Psychiatry, GGZ inGeest, Amsterdam, NL
52. Department of Genetics, Harvard Medical School, Boston, MA, USA
53. Psychiatry, Harvard Medical School, Boston, MA, USA
54. Department of Psychiatry, Hospital Universitari Vall d´Hebron, Barcelona, Spain, Barcelona, ES
55. Department of Psychiatry and Behavioral Sciences, Howard University Hospital, Washington, DC, USA
56. HudsonAlpha Institute for Biotechnology, Huntsville, AL, USA
57. Department of Medical & Molecular Genetics, Indiana University, Indianapolis, IN, USA
58. Psychiatrie Translationnelle, Inserm U955. Créteil, FR
59. Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, GB
60. Genetic Cancer Susceptibility Group, International Agency for Research on Cancer, Lyon, FR
61. NEUROSCIENCE, Istituto Di Ricerche Farmacologiche Mario Negri, Milano, IT
62. Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA
63. Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
64. Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
65. Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
66. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE
67. Cancer Epidemiology and Prevention, M. Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, PL
68. Division of Clinical Research, Massachusetts General Hospital, Boston, MA, USA
69. Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE
70. Department of Psychiatry, Mood Disorders Program, McGill University Health Center, Montreal, QC, CA
71. Institute of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich, Munich, DE
72. Department of Economics and Business Economics, National Centre for Register-based Research, Aarhus University, Aarhus, DK
73. National Centre for Register-Based Research, Aarhus University, Business and Social Sciences, Aarhus, DK
74. Discipline of Biochemistry, Neuroimaging and Cognitive Genomics (NICOG) Centre, University College Galway, Galway, IE
75. Neuroscience Research Australia, Sydney, NSW, AU
76. Mental Health, NHS 24. Glasgow, GB
77. Psychiatry, North East London NHS Foundation Trust, Ilford, GB
78. Department of Neurology, Oslo University Hospital, Oslo, NO
79. NORMENT, KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, NO
80. Div Mental Health and Addiction, Oslo University Hospital, Oslo, NO
81. Department of Medical Genetics, Oslo University Hospital Ullevål, Oslo, NO
82. Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, USA
83. School of Biomedical and Healthcare Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, GB

84. Department of Psychiatry, Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, PL
85. Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, CA
86. Psychiatry, Psychiatrisches Zentrum Nordbaden, Wiesloch, DE
87. Department of Clinical Psychiatry, Psychiatry Clinic, Clinical Center University of Sarajevo, Sarajevo, BA
88. Mood Disorders, PsyQ, Rotterdam, NL
89. Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, AU
90. Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Herston, QLD, AU
91. Centre for Psychiatry, Queen Mary University of London, London, GB
92. Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, DE
93. Psychiatry, Rush University Medical Center, Chicago, IL, USA
94. Faculty of Medicine, Department of Psychiatry, School of Health Sciences, University of Iceland, Reykjavik, IS
95. Scripps Translational Science Institute, La Jolla, CA, USA
96. Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA
97. Statens Serum Institut, Copenhagen, DK
98. Neonatal Genetik, Statens Serum Institut, Copenhagen, DK
99. Cell Biology, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA
100. Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA
101. Neurogenomics, TGen, Los Angeles, AZ, USA
102. Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU
103. Neuropsychiatric Genetics Research Group, Dept of Psychiatry and Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, IE
104. Psychiatry, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, NL
105. Department of Clinical Sciences, Psychiatry, Umeå University Medical Faculty, Umeå, SE
106. Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, ES
107. Faculté de Médecine, Université Paris Est, Créteil, FR
108. UCL Genetics Institute, University College London, London, GB
109. Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, CH
110. Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, DE
111. Clinic for Psychiatry and Psychotherapy, University Hospital Cologne, Cologne, DE
112. Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, DE
113. Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, DE
114. Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium
115. NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, Bergen, NO
116. Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, DE
117. Neurosciences, Radiology, Psychiatry, Cognitive Science, University of California San Diego, La Jolla, CA, USA
118. Cognitive Science, University of California San Diego, La Jolla, CA, USA
119. Department of Psychiatry, University of California San Diego, La Jolla, CA, USA
120. Institute of Genomic Medicine, University of California San Diego, 0.
121. Department of Neurosciences, University of California San Diego, La Jolla, CA, USA
122. Psychiatry, University of California San Francisco, San Francisco, CA, USA
123. Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, USA
124. Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA
125. Division of Psychiatry, University of Edinburgh, Edinburgh, GB
126. Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, GB
127. Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, ES

128. Psychiatry, University of Illinois at Chicago College of Medicine, Chicago, IL, USA
129. University of Iowa Hospitals and Clinics, Iowa City, IA, USA
130. Molecular & Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI, USA
131. Molecular & Behavioral Neuroscience Institute and Department of Computational Medicine & Bioinformatics, University of Michigan, Ann Arbor, MI, USA
132. Center for Statistical Genetics and Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA
133. Department of Human Genetics, University of Michigan, Ann Arbor, MI, USA
134. Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA
135. Biostatistics, University of Minnesota System, Minneapolis, MN, USA
136. School of Psychiatry, University of New South Wales, Sydney, NSW, AU
137. NORMENT, University of Oslo, Oslo, NO
138. Translational Genomics, University of Southern California, Los Angeles, CA, USA
139. Psychiatry and the Behavioral Sciences, University of Southern California, Los Angeles, CA, USA
140. Estonian Genome Center, University of Tartu, Tartu, EE
141. Department of Psychiatry, University of Toronto, Toronto, ON, CA
142. Institute of Medical Sciences, University of Toronto, Toronto, ON, CA
143. Dalla Lana School of Public Health, University of Toronto, Toronto, ON, CA
144. Department of Psychological Medicine, University of Worcester, Worcester, GB
145. Mental Health Department, University Regional Hospital. Biomedicine Institute (IBIMA), Málaga, ES
146. Psychiatric Genetics Unit, Group of Psychiatry Mental Health and Addictions, Vall d´Hebron Research Institut (VHIR), Universitat Autònoma de Barcelona, Barcelona, ES
147. Research/Psychiatry, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA
148. Psychiatry, VU medisch centrum, Amsterdam, NL
149. Department of Psychiatry, Washington University in Saint Louis, Saint Louis, MO, USA
150. Department of Psychiatry, Weill Cornell Medical College, NY, NY, USA
151. National Centre for Register-based Research, Aarhus University, Aarhus, DK
152. Psychosis Research Unit, Aarhus University Hospital, Risskov, Aarhus, DK
153. Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, RO
154. Department of Psychiatry and Addiction Medicine, Assistance Publique - Hôpitaux de Paris, Paris, FR
155. Division of Endocrinology, Children's Hospital Boston, Boston, MA, USA
156. Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, SP
157. Mental Health Centre Copenhagen, Copenhagen University Hospital, Copenhagen, DK
158. Department of Clinical Genetics, Amsterdam Neuroscience, Vrije Universiteit Medical Center, Amsterdam, NL
159. Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, NL
160. Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, NO
161. Paris Bipolar and TRD Expert Centres, FondaMental Foundation, Paris, FR
162. Division of Psychiatry, Haukeland Universitetssjukehus, Bergen, NO
163. Department of Psychiatry, Hospital Namsos, Namsos, NO
164. UMR-S1144 Team 1 : Biomarkers of relapse and therapeutic response in addiction and mood disorders, INSERM, Paris, FR
165. INSERM, Paris, FR
166. Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, London, GB
167. Aarhus University Department of Clinical Medicine, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, DK
168. iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Copenhagen, DK
169. Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, USA
170. Department of Medical & Molecular Genetics, King's College London, London, GB
171. Research Institute, Lindner Center of HOPE, Mason, OH, USA
172. Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

173. Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, USA
174. Health Sciences Research, Mayo Clinic, Rochester, MN, USA
175. Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, USA
176. Department of Psychiatry, McGill University, Montreal, QC, CA
177. Department of Neurology and Neurosurgery, McGill University, Faculty of Medicine, Montreal, QC, CA
178. Institute of Biological Psychiatry, Mental Health Center Sct. Hans, Mental Health Services Capital Region of Denmark, Copenhagen, DK
179. Montreal Neurological Institute and Hospital, Montreal, QC, CA
180. Munich Cluster for Systems Neurology (SyNergy), Munich, DE
181. National Institute of Mental Health, Klecany, CZ
182. Human Genetics Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA
183. Department of Neuroscience, Norges Teknisk Naturvitenskapelige Universitet Fakultet for naturvitenskap og teknologi, Trondheim, NO
184. Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology - NTNU, Trondheim, NO
185. Research and Education, Division of Clinical Neuroscience, Oslo Universitetssykehus, Oslo, NO
186. Division of Mental Health and Addiction, Oslo University Hospital, Oslo, NO
187. Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, USA
188. Dept of Psychiatry, Sankt Olavs Hospital Universitetssykehuset i Trondheim, Trondheim, NO
189. Psychiatry, St Olavs University Hospital, Trondheim, NO
190. Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK
191. Dean, College of Medicine Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA
192. School of Psychology, The University of Queensland, Brisbane, QLD, AU
193. Psychiatry, Université Paris Diderot, Paris, FR
194. Discipline of Psychiatry, University of Adelaide, Adelaide, SA, AU
195. Faculty of Medicine and Dentistry, University of Bergen, Bergen, NO
196. Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, IT
197. Department of Human Genetics, University of Chicago, Chicago, IL, USA
198. Institute of Clinical Medicine, University of Copenhagen, Copenhagen, DK
199. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB
200. Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, SE
201. Faculty of Medicine, University of Iceland, Reykjavik, IS
202. University of Liverpool, Liverpool, GB
203. Department of Psychiatry, University of Münster, Münster, DE
204. School of Medical Sciences, University of New South Wales, Sydney, NSW, AU
205. Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
206. Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
207. NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Institute of Clinical Medicine and Diakonhjemmet Hospital, University of Oslo, Oslo, NO
208. Division of Mental Health and Addiction, University of Oslo, Institute of Clinical Medicine, Oslo, NO
209. Psychiatry, University of Pennsylvania, Philadelphia, PA, USA
210. Psychiatry and Human Genetics, University of Pittsburgh, Pittsburgh, PA, USA
211. Institute of Molecular and Cell Biology, University of Tartu, Tartu, EE
212. Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA
213. Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, USA
214. Jane and Terry Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA, USA
215. Departments of Genetics and Genomic Sciences, Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Funding:

Study	Lead investigator	Country, Funder, Award number
PGC	P Sullivan	USA, NIMH MH109528
PGC	D Posthuma	Netherlands, Scientific Organization Netherlands, 480-05-003
PGC	D Posthuma	Dutch Brain Foundation and the VU University Amsterdam Netherlands
Analysis, UK - BDRN (Cardiff)	PA Holmans	Medical Research Council (MRC) Centre (G0801418) and Program Grants (G0800509)
Analysis	NR Wray	NHMRC 1078901,108788
BACCS	G Breen	GB, JRIC, HG, CL were supported in part by the NIHR Maudsley Biomedical Research Centre ('BRC') hosted at King's College London and South London and Maudsley NHS Foundation Trust, and funded by the National Institute for Health Research under its Biomedical Research Centres funding initiative.
BD_TRS	U Dannlowski	Germany, DFG, Grant FOR2107 DA1151/5-1; Grant SFB-TRR58, Project C09
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
BiGS, University of Pittsburgh	V Nimgaonkar	US, NIMH MH63480
BOMA-Australia	JM Fullerton	Australia, National Health and Medical Research Council, grant numbers: 1037196; 1066177; 1063960
BOMA-Australia	SE Medland	Australia, National Health and Medical Research Council, grant numbers: 1103623
BOMA-Australia	PB Mitchell	Australia, National Health and Medical Research Council, grant numbers: 1037196
BOMA-Australia	GW Montgomery	Australia, National Health and Medical Research Council, grant numbers: 1078399
BOMA-Australia	PR Schofield	Australia, National Health and Medical Research Council, grant numbers: 1037196
BOMA-Romania	M Grigoroiu-Serbanescu	Romania, UEFISCDI, Grant no. 89/2012
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
BOMA-Germany I, II, III, PsyCourse, BiGS	TG Schulze	Germany, Dr. Lisa-Oehler Foundation (Kassel, Germany)
Fran	M Leboyer	France, Inserm, ANR
Halifax	M Alda	CIHR grant #64410
iPSYCH BP group	AD Børglum	Denmark, Lundbeck Foundation, R102-A9118 and R155-2014-1724 (iPSYCH)
iPSYCH BP group	AD Børglum	Denmark, Aarhus University, iSEQ and CIRRAU
iPSYCH BP group	AD Børglum	USA, Stanley Medical Research Institute
iPSYCH BP group	AD Børglum	EU, European Research Council, 294838
Michigan	M Boehnke	US, NIMH, R01 MH09414501A1; US, NIMH, MH105653
Mount Sinai	EA Stahl	NARSAD Young Investigator Award

Mount Sinai, STEP-BD, FAST	P Sklar	US NIH R01MH106531, R01MH109536
NeuRA-CASSI-Australia	C Shannon Weickert	Australia, National Health and Medical Research Council, grant number: 568807
NeuRA-CASSI-Australia	TW Weickert	Australia, National Health and Medical Research Council, grant number: 568807
NeuRA-IGP-Australia	MJ Green	Australia, National Health and Medical Research Council, grant numbers: 630471, 1081603
Norway	I Agartz	Sweden, Swedish Research Council
Norway	OA Andreassen	Norway, Research Council of Norway (#217776, #223273, #248778, #249711), KG Jebsen Stiftelsen, The South-East Norway Regional Health Authority (#2012-132, #2012-131, #2017-004)
Norway	T Elvsåshagen	Norway, The South-East Norway Regional Health Authority (#2015-078) and a research grant from Mrs. Throne-Holst.
Norway	I Melle	Norway, Research Council of Norway (#421716,#223273), KG Jebsen Stiftelsen, The South-East Norway Regional Health Authority (#2011085, #2013088, #2014102)
Norway	KJ Oedegaard	Norway, the Western Norway Regional Health Authority
Norway	OB Smeland	Norway, The South-East Norway Regional Health Authority (#2016-064, #2017-004)
Span2	M Ribasés	Spain, Instituto de Salud Carlos III, Ministerio de Economía, Industria y Competitividad, CP09/00119 and CPII15/00023
Span2	C Sánchez-Mora	Spain, Instituto de Salud Carlos III, Ministerio de Economía, Industria y Competitividad, CD15/00199 and MV16/00039
State University of New York, Downstate Medical Center (SUNY DMC)	JA Knowles	US, National Institutes of Health, R01MH085542
State University of New York, Downstate Medical Center (SUNY DMC)	H Medeiros	US, National Institutes of Health, R01MH085542
State University of New York, Downstate Medical Center (SUNY DMC)	C Pato	US, National Institutes of Health, R01MH085542
State University of New York, Downstate Medical Center (SUNY	MT Pato	US, National Institutes of Health, R01MH085542

DMC)		
SWEBIC	M Landén	The Stanley Center for Psychiatric Research, Broad Institute from a grant from Stanley Medical Research Institute; NIMH MH077139 (PFS)
SWEBIC	M Landén	The Swedish Research Council (K2014-62X-14647-12-51 and K2010-61P-21568-01-4), and the Swedish foundation for Strategic Research (KF10-0039)
UCL	A McQuillin	Medical Research Council (MRC) - G1000708
UCLA-Utrecht (Los Angeles)	NB Freimer	US, National Institutes of Health, R01MH090553, U01MH105578
UCLA-Utrecht (Los Angeles)	LM Olde Loohuis	US, National Institutes of Health, R01MH090553, U01MH105578
UCLA-Utrecht (Los Angeles)	RA Ophoff	US, National Institutes of Health, R01MH090553, U01MH105578
UCLA-Utrecht (Los Angeles)	APS Ori	US, National Institutes of Health, R01MH090553, U01MH105578
UK - BDRN (Cardiff)	G Kirov	Medical Research Council (MRC) Centre (G0801418) and Program Grants (G0800509)
UK - BDRN (Cardiff)	MC O'Donovan	Medical Research Council (MRC) Centre (G0801418) and Program Grants (G0800509)
UK - BDRN (Cardiff)	MJ Owen	Medical Research Council (MRC) Centre (G0801418) and Program Grants (G0800509)
UK - BDRN (Worcester)	LA Jones	UK, Wellcome Trust, 078901; USA, Stanley Medical Research Institute, 5710002223-01
UNIBO / University of Barcelona, Hospital Clinic, IDIBAPS, CIBERSAM	E Vieta	Grants PI15/00283 (Spain) and 2014 SGR 398 (Catalonia)
USC	JL Sobell	USA, National Institutes of Health, R01MH085542
WTCCC	AH Young	NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK); Janssen (UK)

Acknowledgments:

PGC: We are deeply indebted to the investigators who comprise the PGC, and to the subjects who have shared their life experiences with PGC investigators. The PGC has received major funding from the US National Institute of Mental Health (PGC3: U01 MH109528, PGC2: U01 MH094421, PGC1: U01 MH085520). Statistical analyses were carried out on the NL Genetic Cluster Computer (http://www.geneticcluster.org) hosted by SURFsara.

BACCS: This work was supported in part by the NIHR Maudsley Biomedical Research Centre ('BRC') hosted at King's College London and South London and Maudsley NHS Foundation Trust, and funded by the National Institute for Health Research under its Biomedical Research Centres funding initiative. The views expressed are those of the authors and not necessarily those of the BRC, the NHS, the NIHR or the Department of Health or King's College London. We gratefully acknowledge capital equipment funding from the Maudsley Charity (Grant Reference 980) and Guy's and St Thomas's Charity (Grant Reference STR130505).

BD_TRS: This work was funded by the German Research Foundation (DFG, grant FOR2107 DA1151/5-1 to UD; SFB-TRR58, Project C09 to UD) and the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/012/17 to UD).

BiGS, GAIN: FJM was supported by the NIMH Intramural Research Program, NIH, DHHS.

BOMA-Australia: JMF would like to thank Janette M O'Neil and Betty C Lynch for their support.

BOMA-Germany I, BOMA-Germany II, BOMA-Germany III, PsyCourse: This work was supported by the German Ministry for Education and Research (BMBF) through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under the auspices of the e:Med program (grant 01ZX1314A/01ZX1614A to MMN and SC, grant 01ZX1314G/01ZX1614G to MR, grant 01ZX1314K to TGS). This work was supported by the German Ministry for Education and Research (BMBF) grants NGFNplus MooDS (Systematic

Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia; grant 01GS08144 to MMN and SC, grant 01GS08147 to MR). This work was also supported by the Deutsche Forschungsgemeinschaft (DFG), grant NO246/10-1 to MMN (FOR 2107), grant RI 908/11-1 to MR (FOR 2107), grant WI 3429/3-1 to SHW, grants SCHU 1603/4-1, SCHU 1603/5-1 (KFO 241) and SCHU 1603/7-1 (PsyCourse) to TGS. This work was supported by the Swiss National Science Foundation (SNSF, grant 156791 to SC). MMN is supported through the Excellence Cluster ImmunoSensation. TGS is supported by an unrestricted grant from the Dr. Lisa-Oehler Foundation. MH was supported by the Deutsche Forschungsgemeinschaft.

Edinburgh: DJM is supported by an NRS Clinical Fellowship funded by the CSO.

Fran: This research was supported by Foundation FondaMental, Créteil, France and by the Investissements d'Avenir Programs managed by the ANR under references ANR-11-IDEX-0004-02 and ANR-10-COHO-10-01.

Halifax: Halifax data were obtained with support from the Canadian Institutes of Health Research.

iPSYCH BP group: ADB and the iPSYCH team acknowledges funding from The Lundbeck Foundation (grant no R102-A9118 and R155-2014-1724), the Stanley Medical Research Institute, an Advanced Grant from the European Research Council (project no: 294838), and grants from Aarhus University to the iSEQ and CIRRAU centers.

Michigan (NIMH/Pritzker Neuropsychiatric Disorders Research Consortium): We thank the participants who donated their time and DNA to make this study possible. We thank members of the NIMH Human Genetics Initiative and the University of Michigan Prechter Bipolar DNA Repository for generously providing phenotype data and DNA samples. Many of the authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property

agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, HudsonAlpha Institute of Biotechnology, the Universities of California at Davis, and at Irvine, to encourage the development of appropriate findings for research and clinical applications.

Mount Sinai: This work was funded in part by a NARSAD Young Investigator award to EAS.

NeuRA-CASSI-Australia: This work was funded by the NSW Ministry of Health, Office of Health and Medical Research. CSW was a recipient of National Health and Medical Research Council (Australia) Fellowships (#1117079, #1021970).

NeuRA-IGP-Australia: MJG was supported by a NHMRC Career Development Fellowship (1061875).

Norway: TE was funded by The South-East Norway Regional Health Authority (#2015-078) and a research grant from Mrs. Throne-Holst.

Span2: CSM is a recipient of a Sara Borrell contract (CD15/00199) and a mobility grant (MV16/00039) from the Instituto de Salud Carlos III, Ministerio de Economía, Industria y Competitividad, Spain. MR is a recipient of a Miguel de Servet contract (CP09/00119 and CPII15/00023) from the Instituto de Salud Carlos III, Ministerio de Economía, Industria y Competitividad, Spain. This investigation was supported by Instituto de Salud Carlos III (PI12/01139, PI14/01700, PI15/01789, PI16/01505), and cofinanced by the European Regional Development Fund (ERDF), Agència de Gestió d'Ajuts Universitaris i de Recerca-AGAUR, Generalitat de Catalunya (2014SGR1357), Departament de Salut, Generalitat de Catalunya, Spain, and a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation. This project has also received funding from the European Union's Horizon 2020 Research and Innovation Programme under the grant agreements No 667302 and 643051.

SWEBIC: We are deeply grateful for the participation of all subjects contributing to this research,

and to the collection team that worked to recruit them. We also wish to thank the Swedish National Quality Register for Bipolar Disorders: BipoläR. Funding support was provided by the Stanley Center for Psychiatric Research, Broad Institute from a grant from Stanley Medical Research Institute, the Swedish Research Council, and the NIMH.

UK - BDRN: BDRN would like to acknowledge funding from the Wellcome Trust and Stanley Medical Research Institute, and especially the research participants who continue to give their time to participate in our research.

UNIBO / University of Barcelona, Hospital Clinic, IDIBAPS, CIBERSAM: EV thanks the support of the Spanish Ministry of Economy and Competitiveness (PI15/00283) integrated into the Plan Nacional de I+D+I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (2014 SGR 398).

WTCCC: AHY is funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

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

study and Aripiprazole Mania Study, which are investigator-initiated studies from Astrazenaca, Eli Lilly, Lundbeck, and Wyeth. J. Nurnberger is an investigator for Janssen. PF 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. All other authors declare no financial interests or potential conflicts of interest.

DISPLAY ITEMS

Figure 1.

Table 1.

Figure 2.

Figure 3.

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. 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).

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

28. 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).

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

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

31. 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

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

33. Otowa, T. *et al.* Meta-analysis of genome-wide association studies of anxiety disorders.

1125 *Mol. Psychiatry* **21,** 1391–1399 (2016).

34. 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).
35. Rietveld, C. A. *et al.* GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *Science* **340,** 1467–1471 (2013).
36. Okbay, A. *et al.* Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* **533,** 539–542 (2016).
37. Benyamin, B. *et al.* Childhood intelligence is heritable, highly polygenic and associated with FNBP1L. *Mol. Psychiatry* **19,** 253–258 (2014).
38. 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).
39. Zhu, Z. *et al.* Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48,** 481–487 (2016).
40. Fromer, M. *et al.* Gene expression elucidates functional impact of polygenic risk for schizophrenia. *Nat. Neurosci.* **19,** 1442–1453 (2016).
41. Westra, H. J. *et al.* Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nat. Genet.* **45,** 1238–1243 (2013).
42. Finucane, H. K. *et al.* Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* **47,** 1228–1235 (2015).
43. Roadmap Epigenomics Consortium *et al.* Integrative analysis of 111 reference human epigenomes. *Nature* **518,** 317–330 (2015).
44. 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).
45. Palmer, C. & Pe'er, I. Statistical Correction of the Winner9s Curse Explains Replication

Variability in Quantitative Trait Genome-Wide Association Studies. *bioRxiv* 104786 (2017).

46. Gaspar, H. A. & Breen, G. Pathways analyses of schizophrenia GWAS focusing on known and novel drug targets. doi:10.1101/091264

47. 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).

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

49. 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).

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

51. 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).

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

53. 1000 Genomes Project Consortium *et al.* A global reference for human genetic variation. *Nature* **526,** 68–74 (2015).

54. Price, A. L. *et al.* Principal components analysis corrects for stratification in genome-wide association studies. *Nat. Genet.* **38,** 904–909 (2006).

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

56. 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).

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

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

1175 59. Olier, I., Vellido, A. & Giraldo, J. Kernel generative topographic mapping. in *ESANN* **2010,** 481–486 (2010).