Genome-wide association study of over 40,000 bipolar disorder cases provides novel biological insights

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Authors

Niamh Mullins[1,2,236,*], Andreas J. Forstner[3,4,5,236], Kevin S. O'Connell[6,7,237], Brandon Coombes[8,237], Jonathan R. I. Coleman[9,10,237], Zhen Qiao[11,237], Thomas D. Als[12,13,14], Tim B. Bigdeli[15,16], Sigrid Børte[17,18,19], Julien Bryois[20], Alexander W. Charney[2], Ole Kristian Drange[21,22], Michael J. Gandal[23], Saskia P. Hagenaars[9,10], Masashi Ikeda[24], Nolan Kamitaki[25,26], Minsoo Kim[23], Kristi Krebs[27], Georgia Panagiotaropoulou[28], Brian M. Schilder[1,29,30,31], Laura G. Sloofman[1], Stacy Steinberg[32], Vassily Trubetskoy[28], Bendik S. Winsvold[19,33], Hong-Hee Won[34], Liliya Abramova[35], Kristina Adorjan[36,37], Esben Agerbo[14,38,39], Mariam Al Eissa[40], Diego Albani[41], Ney Alliey-Rodriguez[42,43], Adebayo Anjorin[44], Verneri Antilla[45], Anastasia Antoniou[46], Swapnil Awasthi[28], Ji Hyun Baek[47], Marie Bækvad-Hansen[14,48], Nicholas Bass[40], Michael Bauer[49], Eva C. Beins[3], Sarah E. Bergen[20], Armin Birner[50], Carsten Bøcker Pedersen[14,38,39], Erlend Bøen[51], Marco P. Boks[52], Rosa Bosch[53,54,55,56], Murielle Brum[57], Ben M. Brumpton[19], Nathalie Brunkhorst-Kanaan[57], Monika Budde[36], Jonas Bybjerg-Grauholm[14,48], William Byerley[58], Murray Cairns[59], Miquel Casas[53,54,55,56], Pablo Cervantes[60], Toni-Kim Clarke[61], Cristiana Cruceanu[60,62], Alfredo Cuellar-Barboza[63,64], Julie Cunningham[65], David Curtis[66,67], Piotr M. Czerski[68], Anders M. Dale[69], Nina Dalkner[50], Friederike S. David[3], Franziska Degenhardt[3,70], Srdjan Djurovic[71,72], Amanda L. Dobbyn[1,2], Athanassios Douzenis[46], Torbjørn Elvsåshagen[18,73,74], Valentina Escott-Price[75], I. Nicol Ferrier[76], Alessia Fiorentino[40], Tatiana M. Foroud[77], Liz Forty[75], Josef Frank[78], Oleksandr Frei[6,18], Nelson B. Freimer[23,79], Louise Frisén[80], Katrin Gade[36,81], Julie Garnham[82], Joel Gelernter[83,84,85], Marianne Giørtz Pedersen[14,38,39], Ian R. Gizer[86], Scott D. Gordon[87], Katherine Gordon-Smith[88], Tiffany A. Greenwood[89], Jakob Grove[12,13,14,90], José Guzman-Parra[91], Kyooseob Ha[92], Magnus Haraldsson[93], Martin Hautzinger[94], Urs Heilbronner[36], Dennis Hellgren[20], Stefan Herms[3,95,96], Per Hoffmann[3,95,96], Peter A. Holmans[75], Laura Huckins[1,2], Stéphane Jamain[97,98], Jessica S. Johnson[1,2], Janos L. Kalman[36,37,99], Yoichiro Kamatani[100,101], James L. Kennedy[102,103,104,105], Sarah Kittel-Schneider[57,106], James A. Knowles[107,108], Manolis Kogevinas[109], Maria Koromina[110], Thorsten M. Kranz[57], Henry R. Kranzler[111,112], Michiaki Kubo[113], Ralph Kupka[114,115,116], Steven A. Kushner[117], Catharina Lavebratt[118,119], Jacob Lawrence[120], Markus Leber[121], Heon-Jeong Lee[122], Phil H. Lee[123], Shawn E. Levy[124], Catrin Lewis[75], Calwing Liao[125,126], Susanne Lucae[62], Martin Lundberg[118,119], Donald J. MacIntyre[127], Sigurdur H. 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Shilling[89], Engilbert Sigurdsson[93,146], Lea Sirignano[78], Claire Slaney[82], Olav B. Smeland[6,7], Daniel J. Smith[147], Janet L. Sobell[148], Christine Søholm Hansen[14,48], Maria Soler Artigas[53,54,56,145], Anne T. Spijker[149], Dan J. Stein[150], John S. Strauss[102], Beata Świątkowska[151], Chikashi Terao[101], Thorgeir E. Thorgeirsson[32], Claudio Toma[152,153,154], Paul Tooney[59], Evangelia-Eirini Tsermpini[110], Marquis P. Vawter[155], Helmut Vedder[156], James T. R. Walters[75], Stephanie H. Witt[78], Simon Xi[157], Wei Xu[158], Jessica Mei Kay Yang[75], Allan H. Young[159,160], Hannah Young[1], Peter P. Zandi[136], Hang Zhou[83,84], Lea Zillich[78], HUNT All-In Psychiatry[161], Rolf Adolfsson[162], Ingrid Agartz[51,130,163], Martin Alda[82,164], Lars Alfredsson[165], Gulja Babadjanova[166], Lena Backlund[118,119], Bernhard T. Baune[167,168,169], Frank Bellivier[170,171], Susanne Bengesser[50], Wade H. Berrettini[172], Douglas H. R. Blackwood[61], Michael Boehnke[173], Anders D. Børglum[14,174,175], Gerome Breen[9,10], Vaughan J. Carr[176], Stanley Catts[177], Aiden Corvin[178], Nicholas Craddock[75], Udo Dannlowski[167], Dimitris Dikeos[179], Tõnu Esko[26,27,180,181], Bruno Etain[170,171], Panagiotis Ferentinos[9,46], Mark Frye[64], Janice M. Fullerton[152,153], Micha Gawlik[106], Elliot S. Gershon[42,182], Fernando S. Goes[136], Melissa J. Green[152,176], Maria Grigoroiu-Serbanescu[183], Joanna Hauser[68], Frans Henskens[59], Jan Hillert[80], Kyung Sue Hong[47], David M. Hougaard[14,48], Christina M. Hultman[20], Kristian Hveem[19,184], Nakao Iwata[24], Assen V. Jablensky[185], Ian Jones[75], Lisa A. Jones[88], René S. Kahn[2,52], John R. Kelsoe[89], George Kirov[75], Mikael Landén[20,186], Marion Leboyer[97,98,187], Cathryn M. Lewis[9,10,188], Qingqin S. Li[189], Jolanta Lissowska[190], Christine Lochner[191], Carmel Loughland[59], Nicholas G. Martin[87,192], Carol A. Mathews[193], Fermin Mayoral[91], Susan L. McElroy[194], Andrew M. McIntosh[127,195], Francis J. McMahon[196], Ingrid Melle[6,197], Patricia Michie[59], Lili Milani[27], Philip B. Mitchell[176], Gunnar

Morken[21,198], Ole Mors[14,199], Preben Bo Mortensen[12,14,38,39], Bryan Mowry[177], Bertram Müller-Myhsok[62,200,201], Richard M. Myers[124], Benjamin M. Neale[25,45,180], Caroline M. Nievergelt[89,202], Merete Nordentoft[14,203], Markus M. Nöthen[3], Michael C. O'Donovan[75], Ketil J. Oedegaard[204,205], Tomas Olsson[206], Michael J. Owen[75], Sara A. Paciga[207], Chris Pantelis[208], Carlos Pato[108], Michele T. Pato[108], George P. Patrinos[110,209,210], Roy H. Perlis[211,212], Danielle Posthuma[213,214], Josep Antoni Ramos-Quiroga[53,54,55,56], Andreas Reif[57], Eva Z. Reininghaus[50], Marta Ribasés[53,54,56,145], Marcella Rietschel[78], Stephan Ripke[25,28,45], Guy A. Rouleau[126,215], Takeo Saito[24], Ulrich Schall[59], Martin Schalling[118,119], Peter R. Schofield[152,153], Thomas G. Schulze[36,78,81,136,216], Laura J. Scott[173], Rodney J. Scott[59], Alessandro Serretti[217], Cynthia Shannon Weickert[152,176,218], Jordan W. Smoller[25,133,219], Hreinn Stefansson[32], Kari Stefansson[32,220], Eystein Stordal[221,222], Fabian Streit[78], Patrick F. Sullivan[20,223,224], Gustavo Turecki[225], Arne E. Vaaler[226], Eduard Vieta[227], John B. Vincent[102], Irwin D. Waldman[228], Thomas W. Weickert[152,176,218], Thomas Werge[14,229,230,231], Naomi R. Wray[11,232], John-Anker Zwart[18,19,33], Joanna M. Biernacka[8,64], John I. Nurnberger[233], Sven Cichon[3,4,95,96], Howard J. Edenberg[77,234], Eli A. Stahl[1,2,180,238], Andrew McQuillin[40,238], Arianna Di Florio[75,224,238], Roel A. Ophoff[23,79,117,235,238], Ole A. Andreassen[6,7,238,*]

Abstract
Bipolar disorder (BD) is a heritable mental illness with complex etiology. We performed a genome-wide association study (GWAS) of 41,917 BD cases and 371,549 controls of European ancestry, which identified 64 associated genomic loci. BD risk alleles were enriched in genes in synaptic signaling pathways and brain-expressed genes, particularly those with high specificity of expression in neurons of the prefrontal cortex and hippocampus. Significant signal enrichment was found in genes encoding targets of antipsychotics, calcium channel blockers, antiepileptics and anesthetics. Integrating eQTL data implicated 15 genes robustly linked to BD via gene expression, including druggable genes such as *HTR6, MCHR1, DCLK3* and *FURIN*. This GWAS provides the best-powered BD polygenic scores to date, when applied in both European and diverse ancestry samples. Analyses of BD subtypes indicated high but imperfect genetic correlation between BD type I and II and identified additional associated loci. Together, these results advance our understanding of the biological etiology of BD, identify novel therapeutic leads and prioritize genes for functional follow-up studies.

Introduction
Bipolar disorder (BD) is a complex mental disorder characterized by recurrent episodes of (hypo)mania and depression. It is a common condition affecting an estimated 40 to 50 million people worldwide[1]. This, combined with the typical onset in young adulthood, an often chronic course, and increased risk of suicide[2], make BD a major public health concern and a major cause of global disability[1]. Clinically, BD is classified into two main subtypes: bipolar I disorder, in which manic episodes typically alternate with depressive episodes, and bipolar II disorder, characterized by the occurrence of at least one hypomanic and one depressive episode[3]. These subtypes have a lifetime prevalence of ~1% each in the population[4,5].

Family and molecular genetic studies provide convincing evidence that BD is a multifactorial disorder, with genetic and environmental factors contributing to its development[6]. On the basis of twin and family studies, the heritability of BD is estimated at 60-85%[7,8]. Genome-wide association studies (GWAS)[9–23] have led to valuable insights into the genetic etiology of BD. The largest such study has been conducted by the Psychiatric Genomics Consortium (PGC), in which genome-wide SNP data from 29,764 BD patients and 169,118 controls were analyzed and 30 genome-wide significant loci were identified (PGC2)[24]. SNP-based heritability (h^2_{SNP}) estimation using the same data, suggested that common genetic variants genome-wide explain ~20% of BD's phenotypic variance[24]. Polygenic risk scores generated from the results of this study explained ~4% of phenotypic variance in independent samples. Across the genome, genetic associations with BD converged on specific biological pathways including regulation of insulin secretion[25,26], retrograde endocannabinoid signaling[24], glutamate receptor signaling[27] and calcium channel activity[9].

Despite this considerable progress, only a fraction of the genetic etiology of BD has been identified and the specific biological mechanisms underlying the development of the disorder are still unknown. In the present study, we report the results of the third GWAS meta-analysis of the PGC Bipolar Disorder Working Group, comprising 41,917 patients with BD and 371,549 controls. These results confirm and expand on many previously reported findings, identify novel therapeutic leads and prioritize genes for functional follow-up studies[28,29]. Thus, our results further illuminate the biological etiology of BD.

Results

GWAS results

A GWAS meta-analysis was conducted of 57 BD cohorts collected in Europe, North America and Australia (Table S1), totaling 41,917 BD cases and 371,549 controls of European descent (Effective N = 101,962, see online methods). For 52 cohorts, individual-level genotype and phenotype data were shared with the PGC and cases met international consensus criteria (DSM-IV, ICD-9 or ICD-10) for lifetime BD, established using structured diagnostic interviews, clinician-administered checklists or medical record review. BD GWAS summary statistics were received for five external cohorts (iPSYCH[30], deCODE genetics[31], Estonian Biobank[32], Trøndelag Health Study (HUNT)[33] and UK Biobank[34]), in which most cases were ascertained using ICD codes. The GWAS meta-analysis identified 64 independent loci associated with BD at genome-wide significance (P < 5E-08) (Figure 1, Table 1, Table S2). Using LD Score regression (LDSC)[35] the h^2_{SNP} of BD was estimated to be 18.6% (SE=0.008, P=5.1E-132) on the liability scale, assuming a BD population prevalence of 2%, and 15.6% (SE=0.006, P=5.0E-132) assuming a population prevalence of 1% (Table S3). The genomic inflation factor (λ_{GC}) was 1.38 and the LD Score regression (LDSC) intercept was 1.04 (SE=0.01, P=2.5E-04)(Supplementary Figure 1). While the intercept has frequently been used as an indicator of confounding from population stratification, it can rise above 1 with increased sample size and heritability. The attenuation ratio - (LDSC intercept - 1)/(mean of association chi-square statistics - 1) - which is not subject to these limitations, was 0.06 (SE=0.02), indicating that the majority of inflation of the GWAS test statistics was due to polygenicity[35,36]. Of the 64 genome-wide significant loci, 33 are novel discoveries (ie. loci not overlapping with any locus previously reported as genome-wide significant for BD). Novel loci include the major histocompatibility complex (MHC) and loci previously reaching genome-wide significance for other psychiatric disorders, including 10 for schizophrenia, 4 for major depression and 3 for childhood-onset psychiatric disorders or problematic alcohol use (Table 1).

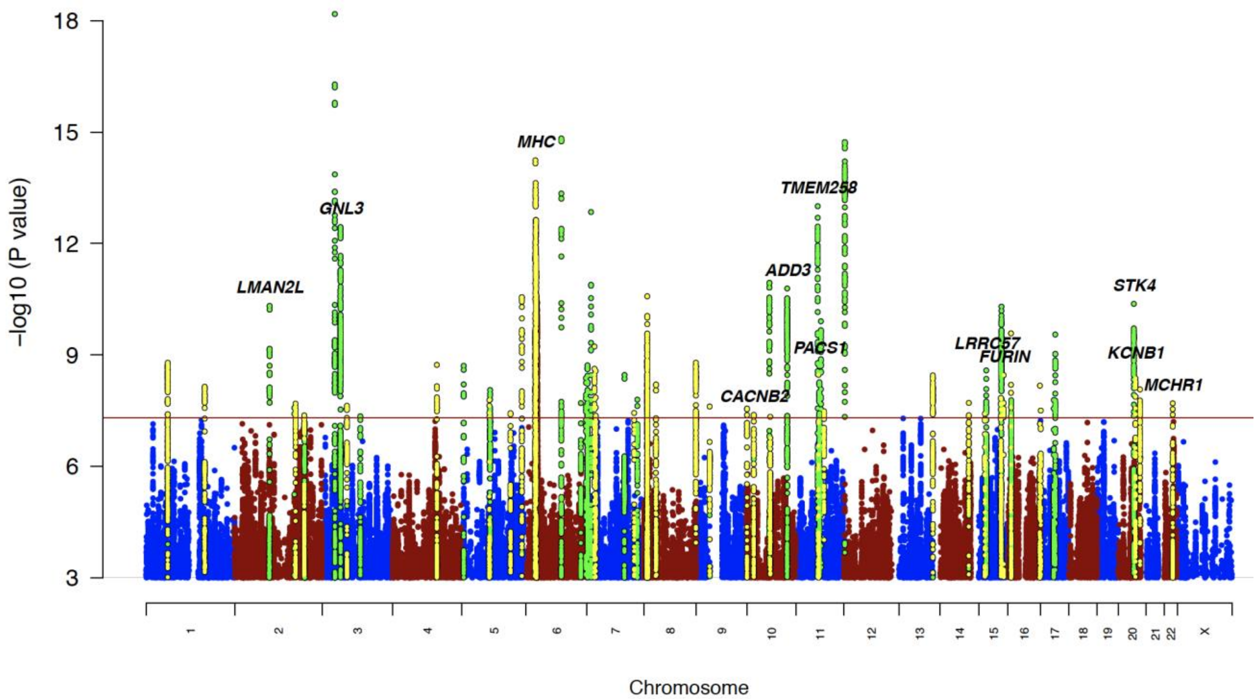

Figure 1: Manhattan plot of genome-wide association meta-analysis of 41,917 bipolar disorder cases and 371,549 controls

The *x*-axis shows genomic position (chromosomes 1-22 and X) and the *y*-axis shows statistical significance as $-\log_{10}$(P value). The red line shows the genome-wide significance threshold (P<5E-08). SNPs in genome-wide significant loci are colored green for loci previously associated with bipolar disorder and yellow for novel associations from this study. The genes labeled are those prioritized by integrative eQTL analyses or notable genes in novel loci (*MHC, CACNB2, KCNB1*).

Table 1: Genome-wide significant loci for bipolar disorder from meta-analysis of 41,917 cases and 371,549 controls

Locus	CHR	BP	SNP	P	OR	SE	A1/A2	A1 freq in controls	Previous report^ for BD (citation)	*Name for novel locus+*	Previous report^ for psychiatric disorders
1	1	61105668	rs2126180	**1.6E-09**	1.058	0.009	A/G	0.457		*LINC01748*	
2	1	163745389	rs10737496	**7.2E-09**	1.056	0.009	C/T	0.444		*NUF2*	CDG
3*	2	97416153	rs4619651	**4.8E-11**	1.068	0.010	G/A	0.670	*LMAN2L (PGC2)*		CDG
4	2	166152389	rs17183814	**2.7E-08**	1.108	0.019	G/A	0.924	*SCN2A (PGC2)*		
5	2	169481837	rs13417268	**2.1E-08**	1.064	0.011	C/G	0.758		*CERS6*	
6	2	193738336	rs2011302	**4.3E-08**	1.055	0.010	A/T	0.377		*PCGEM1*	CDG
7	2	194437889	rs2719164	**4.9E-08**	1.053	0.010	A/G	0.564	*intergenic (PGC2)*		CDG
8*	3	36856030	rs9834970	**6.6E-19**	1.087	0.009	C/T	0.481	*TRANK1 (PGC2)*		SCZ, CDG
9*	3	52626443	rs2336147	**3.6E-13**	1.070	0.009	T/C	0.498	*ITIH1 (PGC2)*		SCZ, CDG
10	3	70488788	rs115694474	**2.4E-08**	1.068	0.012	T/A	0.799		*MDFIC2*	
11	3	107757060	rs696366	**4.5E-08**	1.053	0.009	C/A	0.550	*CD47 (PGC2)*		
12*	4	123076007	rs112481526	**1.9E-09**	1.065	0.011	G/A	0.256		*KIAA1109*	MD
13*	5	7542911	rs28565152	**2.0E-09**	1.070	0.011	A/G	0.238	*ADCY2 (PGC2)*		
14*	5	78849505	rs6865469	**1.7E-08**	1.060	0.010	T/G	0.274		*HOMER1*	
15	5	80961069	rs6887473	**8.8E-09**	1.062	0.011	G/A	0.739	*SSBP2 (PGC2)*		
16*	5	137712121	rs10043984	**3.7E-08**	1.062	0.011	T/C	0.236		*KDM3B*	CDG
17	5	169289206	rs10866641	**2.8E-11**	1.065	0.009	T/C	0.575		*DOCK2*	
18*	6	26463575	rs13195402	**5.8E-15**	1.146	0.018	G/T	0.919		*MHC*	MD, SCZ, CDG, MOOD
19*	6	98565211	rs1487445	**1.5E-15**	1.078	0.009	T/C	0.487	*POU3F2 (PGC2)*		CDG
20	6	152793572	rs4331993	**2.0E-08**	1.056	0.010	A/T	0.382	*SYNE1 (Green, 2013)*		
21*	6	166995260	rs10455979	**4.2E-09**	1.057	0.010	G/C	0.500	*RPS6KA2 (PGC2)*		
22*	7	2020995	rs12668848	**1.9E-09**	1.059	0.010	G/A	0.575	*MAD1L1 (Hou, 2016, Ikeda, 2017)*		MD, SCZ, CDG
23*	7	11871787	rs113779084	**1.4E-13**	1.079	0.010	A/G	0.299	*THSD7A (PGC2)*		
24*	7	21492589	rs6954854	**5.9E-10**	1.060	0.009	G/A	0.425		*SP4*	
25	7	24647222	rs12672003	**2.7E-09**	1.096	0.016	G/A	0.113		*MPP6*	SCZ, CDG, MOOD
26	7	105043229	rs11764361	**3.5E-09**	1.063	0.010	A/G	0.668	*SRPK2 (PGC2)*		SCZ, ASD, CDG
27	7	131870597	rs6946056	**3.7E-08**	1.055	0.010	C/A	0.623		*PLXNA4*	
28	7	140676153	rs10255167	**1.6E-08**	1.068	0.012	A/G	0.778	*MRPS33 (PGC2)*		CDG
29*	8	9763581	rs62489493	**2.6E-11**	1.094	0.014	G/C	0.128		*miR124-1*	SCZ,ALC, ASD
30*	8	10226355	rs3088186	**2.1E-08**	1.058	0.010	T/C	0.287		*MSRA*	SCZ,ALC, ASD
31	8	34152492	rs2953928	**6.3E-09**	1.124	0.020	A/G	0.067		*RP1-84O15.2 (lincRNA)*	SCZ, ADHD, CDG
32*	8	144993377	rs6992333	**1.6E-09**	1.062	0.010	G/A	0.410		*PLEC*	
33	9	37090538	rs10973201	**2.5E-08**	1.101	0.017	C/T	0.110		*ZCCHC7*	MD, CDG, MOOD
34*	9	141066490	rs62581014	**2.8E-08**	1.067	0.012	T/C	0.366		*TUBBP5*	
35*	10	18751103	rs1998820	**4.1E-08**	1.087	0.015	T/A	0.886		*CACNB2*	SCZ, CDG
36*	10	62322034	rs10994415	**1.1E-11**	1.125	0.017	C/T	0.082	*ANK3 (PGC2)*		
37	10	64525135	rs10761661	**4.7E-08**	1.053	0.009	T/C	0.472		*ADO*	
38*	10	111648659	rs2273738	**1.6E-11**	1.096	0.014	T/C	0.135	*ADD3 (Charney,2017, PGC2)*		
39*	11	61618608	rs174592	**9.9E-14**	1.074	0.010	G/A	0.395	*FADS2 (PGC2)*		MD, CDG, MOOD
40	11	64009879	rs4672	**3.4E-09**	1.107	0.017	A/G	0.083		*FKBP2*	
41*	11	65848738	rs475805	**2.0E-09**	1.070	0.011	A/G	0.767	*PACS1 (PGC2)*		
42*	11	66324583	rs678397	**5.5E-09**	1.056	0.009	T/C	0.457	*PC (PGC1, PGC2)*		
43*	11	70517927	rs12575685	**1.2E-10**	1.067	0.010	A/G	0.327	*SHANK2 (PGC2)*		MD
44	11	79092527	rs12289486	**3.3E-08**	1.086	0.015	T/C	0.115	*ODZ4 (PGC1)*		
45*	12	2348844	rs11062170	**1.9E-15**	1.081	0.010	C/G	0.333	*CACNA1C (PGC2)*		SCZ, CDG, MOOD
46	13	113869045	rs35306827	**3.6E-09**	1.068	0.011	G/A	0.775		*CUL4A*	
47	14	99719219	rs2693698	**2.0E-08**	1.055	0.009	G/A	0.551		*BCL11B*	SCZ, CDG
48*	15	38973793	rs35958438	**3.8E-08**	1.066	0.012	G/A	0.772		*C15orf53*	CDG
49*	15	42904904	rs4447398	**2.6E-09**	1.086	0.014	A/C	0.131	*STARD9 (PGC2)*		
50	15	83531774	rs62011709	**1.4E-08**	1.064	0.011	T/A	0.747		*HOMER2*	SCZ
51*	15	85149575	rs748455	**5.0E-11**	1.070	0.010	T/C	0.719	*ZNF592 (PGC2)*		SCZ, CDG
52	15	91426560	rs4702	**3.5E-09**	1.059	0.010	G/A	0.446		*FURIN*	SCZ, CDG
53	16	9230816	rs28455634	**2.6E-10**	1.065	0.010	G/A	0.620		*C16orf72*	
54	16	9926348	rs7199910	**1.7E-08**	1.057	0.010	G/T	0.312	*GRIN2A (PGC2)*		SCZ, CDG
55	16	89632725	rs12932628	**6.7E-09**	1.058	0.010	T/G	0.487		*RPL13*	
56	17	1835482	rs4790841	**3.1E-08**	1.075	0.013	T/C	0.151		*RTN4RL1*	
57	17	38129841	rs11870683	**2.8E-08**	1.059	0.010	T/A	0.650	*ERBB2 (Hou, 2016)*		
58	17	38220432	rs61554907	**1.6E-08**	1.091	0.015	T/G	0.124	*ERBB2 (Hou, 2016)*		
59*	17	42191893	rs228768	**2.8E-10**	1.067	0.010	G/T	0.294	*HDAC5 (PGC2)*		
60*	20	43682551	rs67712855	**4.2E-11**	1.070	0.010	T/G	0.687	*STK4 (PGC2)*		
61*	20	43944323	rs6032110	**1.0E-09**	1.059	0.009	A/G	0.512	*WFDC12 (PGC2)*		
62*	20	48033127	rs237460	**4.3E-09**	1.057	0.009	T/C	0.412		*KCNB1*	CDG
63	20	60865815	rs13044225	**8.5E-09**	1.056	0.010	G/A	0.440		*OSBPL2*	
64	22	41153879	rs5758064	**2.0E-08**	1.054	0.009	T/C	0.523		*SLC25A17*	MD, SCZ, CDG, MOOD

CHR, chromosome; BP, GRCh37 basepair position; SNP, single nucleotide polymorphism; OR, odds ratio; SE, standard error, A1, tested allele; A2, other allele; freq, frequency; BD, bipolar disorder; CDG, Cross-disorder GWAS of the Psychiatric Genomics Consortium; MD, major depression; SCZ, schizophrenia; MOOD, mood disorders; ASD, Autism Spectrum Disorder; ALC, Alcohol use disorder or problematic alcohol use; ADHD, attention deficit/hyperactivity disorder. *Locus overlaps with genome-wide significant locus for bipolar I disorder. ^Previous report refers to previous association of a SNP in the locus with the psychiatric disorder at genome-wide significance. PGC1 = PMID 21926972, PGC2 = PMID 31043756, Hou, 2016 = PMID 27329760, Ikeda, 2017 = PMID:28115744, Green, 2013 = PMID 22565781. Charney,2017 = PMID 28072414. +Novel loci are named using the nearest gene to the index SNP.

Enrichment analyses

Genome-wide analyses using MAGMA[37] indicated significant enrichment of BD associations in 161 genes (Table S4) and 4 gene sets, related to synaptic signaling (Table S5). The BD association signal was enriched amongst genes expressed in different brain tissues (Table S6), especially genes with high specificity of gene expression in neurons (both excitatory and inhibitory) versus other cell types, within cortical and subcortical brain regions in mice (Supplementary Figure 2)[38]. In human brain samples, signal enrichment was also observed in hippocampal pyramidal neurons and interneurons of the prefrontal cortex and hippocampus, compared with other cell types (Supplementary Figure 2).

In a gene-set analysis of the targets of individual drugs (from the Drug-Gene Interaction Database DGIdb v.2[39] and the Psychoactive Drug Screening Database Ki DB[40]), the targets of the calcium channel blockers mibefradil and nisoldipine were significantly enriched (Table S7). Grouping drugs according to their Anatomical Therapeutic Chemical (ATC) classes[41], there was significant enrichment in the targets of four broad drug classes (Table S8): psycholeptics (drugs with a calming effect on behavior) (especially hypnotics and sedatives, antipsychotics and anxiolytics), calcium channel blockers, antiepileptics and (general) anesthetics. (Table S8).

eQTL integrative analyses

A transcriptome-wide association study (TWAS) was conducted using FUSION[42] and eQTL data from the PsychENCODE Consortium (1,321 brain samples)[43]. BD-associated alleles significantly influenced expression of 77 genes in the brain (Table S9, Supplementary Figure 3). These genes encompassed 40 distinct regions. TWAS fine-mapping was performed using FOCUS[44] to model the correlation among the TWAS signals and prioritize the most likely causal gene(s) in each region. Within the 90%-credible set, FOCUS prioritised 22 genes with a posterior inclusion probability (PIP) > 0.9 (encompassing 20 distinct regions) and 32 genes with a PIP > 0.7 (29 distinct regions) (Table S10).

Summary data-based Mendelian randomization (SMR)[45,46] was used to identify putative causal relationships between SNPs and BD via gene expression by integrating the BD GWAS results with brain eQTL summary statistics from the PsychENCODE[43] Consortium and blood eQTL summary statistics from the eQTLGen Consortium (31,684 whole blood samples)[47]. The eQTLGen results represent the largest existing eQTL study and provide independent eQTL data. Of the 32 genes fine-mapped with PIP > 0.7, 15 were significantly associated with BD in the SMR analyses and passed the HEIDI (heterogeneity in dependent instruments) test[45,46], suggesting that their effect on BD is mediated via gene expression in the brain and/or blood (Table S11). The genes located in genome-wide significant loci are labeled in Figure 1. Other significant genes included *HTR6, DCLK3*, *HAPLN4* and *PACSIN2*.

MHC locus

Variants within and distal to the major histocompatibility complex (MHC) locus were associated with BD at genome-wide significance. The most highly associated SNP was rs13195402, 3.2 megabases distal to any *HLA* gene or the complement component 4 (*C4*) genes (Supplementary Figure 4). Imputation of *C4* alleles using SNP data uncovered no association between the five most common structural forms of the *C4A/C4B* locus (BS, AL, AL-BS, AL-BL, and AL-AL) and BD, either before or after conditioning on rs13195402 (Supplementary Figure 5). While genetically predicted *C4A* expression initially showed a weak association with BD, this association was non-significant after controlling for rs13195402 (Supplementary Figure 6).

Polygenic risk scoring

The performance of polygenic risk scores (PRS) based on these GWAS results was assessed by excluding cohorts in turn from the meta-analysis to create independent test samples. PRS explained ~4.57% of phenotypic variance in BD on the liability scale (at GWAS P value threshold (p_T) < 0.1, BD population prevalence 2%), based on the weighted mean R^2 across cohorts (Figure 2, Table S12). This corresponds to a weighted mean area under the curve (AUC) of 65%. Results per cohort and per wave of recruitment to the PGC are in Tables S12-S13 and Supplementary Figure 7. At $p_T < 0.1$, individuals in the top 10% of BD PRS had an odds ratio of 3.5 (95% CI 1.7-7.3) of being affected with the disorder compared with individuals in the middle decile (based on the weighted mean OR across PGC cohorts), and an odds ratio of 9.3 (95% CI 1.7-49.3) compared with individuals in the lowest decile. The generalizability of PRS from this meta-analysis was examined in several non-European cohorts. PRS explained up to 2.3% and 1.9% of variance in BD in two East Asian samples, and 1.2% and 0.4% in two admixed African American samples (Figure 2, Table S14). The variance explained by the PRS increased in every cohort with increasing sample size of the PGC BD European discovery sample (Supplementary Figure 8, Table S14).

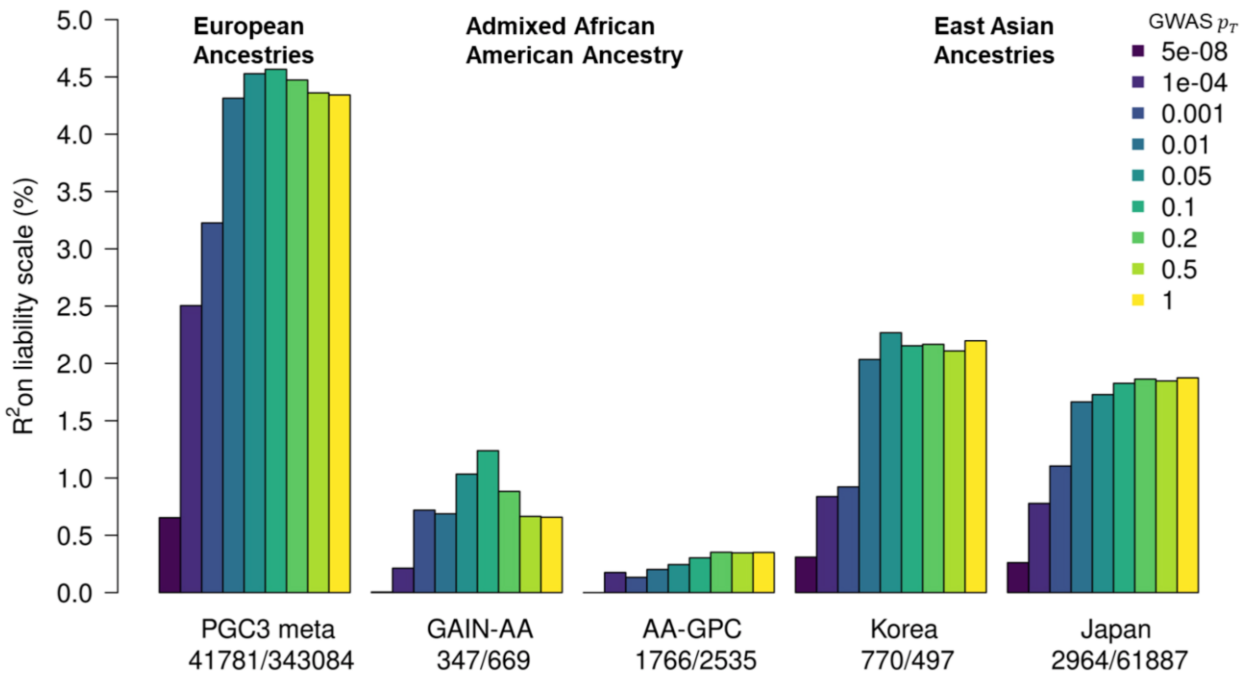

Figure 2: Phenotypic variance in bipolar disorder explained by polygenic risk scores
Variance explained is presented on the liability scale, assuming a BD population prevalence of 2%. For European ancestry, the results shown are the weighted mean R^2 values across all cohorts analyzed, calculated weighted by the effective N per cohort. The numbers of cases and controls are shown under the barplot for each study. GWAS p_T - the color of the bars represents the P value threshold used to select SNPs from the discovery GWAS. GAIN-AA - Genetic Association Information Network African American cohort, AA-GPC - African American Genomic Psychiatry Cohort.

Genetic architecture of BD and other traits
The genome-wide genetic correlation (r_g) of BD with a range of diseases and traits was assessed on LD Hub[48]. After correction for multiple testing, BD showed significant r_g with 16 traits among 255 tested from published GWAS (Table S15). Genetic correlation was positive with all psychiatric disorders assessed,

particularly schizophrenia (r_g = 0.68) and major depression (r_g=0.44), and to a lesser degree anorexia, attention deficit/hyperactivity disorder and autism spectrum disorder ($r_g \approx 0.2$). We found evidence of positive r_g between BD and smoking initiation, cigarettes per day, problematic alcohol use and drinks per week (Figure 3). BD was also positively genetically correlated with measures of sleep quality (daytime sleepiness, insomnia, sleep duration) (Figure 3). Among 514 traits measured in the general population of the UK Biobank, there was significant r_g between BD and many psychiatric-relevant traits or symptoms, dissatisfaction with interpersonal relationships, poorer overall health rating and feelings of loneliness or isolation (Table S16).

Bivariate gaussian mixture models were applied to the GWAS summary statistics for BD and other complex traits using the MiXeR tool[49,50] to estimate the number of variants influencing each trait that explain 90% of h^2_{SNP} and their overlap between traits. MiXeR estimated that approximately 8.6 k (SE=0.2 k) variants influence BD, which is similar to the estimate for schizophrenia (9.7 k, SE=0.2 k) and somewhat lower than that for major depression (12.3 k, SE=0.6 k) (Table S17, Supplementary Figure 9). When considering the number of shared loci as a proportion of the total polygenicity of each trait, the vast majority of loci influencing BD were also estimated to influence major depression (97%) and schizophrenia (96%) (Table S17, Supplementary Figure 9). Interestingly, within these shared components, the variants that influenced both BD and schizophrenia had high concordance in direction of effect (80%, SE=2%), while the portion of concordant variants between BD and MDD was only 69% (SE=1%) (Table S17).

Genetic and causal relationships between BD and modifiable risk factors
Ten traits associated with BD from clinical and epidemiological studies were investigated in detail for genetic and potentially causal relationships with BD via LDSC[35], generalized summary statistics-based Mendelian randomization (GSMR)[51] and bivariate gaussian mixture modeling[49]. BD has been strongly linked with sleep disturbances[52], alcohol use[53] and smoking[54], higher educational attainment[55,56] and mood instability[57]. Most of these traits had modest but significant genetic correlations with BD (r_g -0.05-0.35) (Figure 3). Examining the effects of these traits on BD via GSMR, smoking initiation was associated with BD, corresponding to an OR of 1.49 (95% CI 1.38-1.61) for developing the disorder (P=1.74E-22) (Figure 3). Testing the effect of BD on the traits, BD was significantly associated with reduced likelihood of being a morning person and increased number of drinks per week (P<1.47E-03) (Figure 3). Positive bi-directional relationships were identified between BD and longer sleep duration, problematic alcohol use, educational attainment (EA) and mood instability (Figure 3). Notably, the instrumental variables for mood instability were selected from a GWAS conducted in the general population, excluding individuals with psychiatric disorders[58]. For all of the aforementioned BD-trait relationships, the effect size estimates from GSMR were consistent with those calculated using the inverse variance weighted regression method, and there was no evidence of bias from horizontal pleiotropy. Full MR results are in Tables S18-19. Bivariate gaussian mixture modeling using MiXeR, indicated large proportions of variants influencing both BD and all other traits tested, particularly educational attainment, where approximately 98% of variants influencing BD were estimated to also influence EA. While cigarettes per day was a trait of interest, MiXeR could not model these data due to low polygenicity and heritability, and the effect of cigarettes per day on BD was inconsistent between MR methods, suggesting a violation of MR assumptions (Tables S18-20).

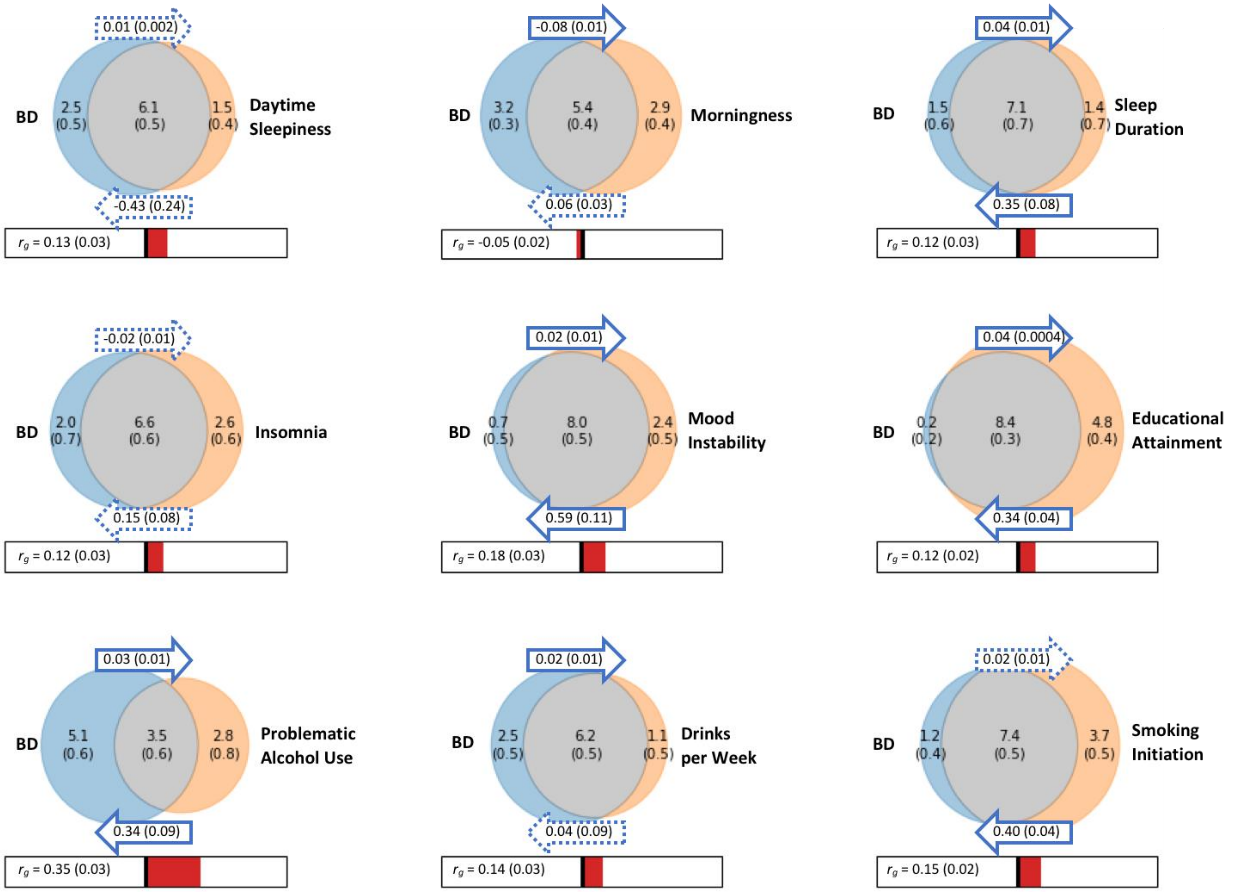

Figure 3: Relationships between bipolar disorder and modifiable risk factors based on genetic correlations, generalized summary statistics-based Mendelian randomization and bivariate gaussian mixture modeling

Venn diagrams depict MiXeR results of the estimated number of influencing variants shared between BD and each trait of interest (grey), unique to BD (blue) and unique to the trait of interest (orange). The number of influencing variants and standard error are shown in thousands. The size of the circles reflects the polygenicity of each trait, with larger circles corresponding to greater polygenicity. The estimated genetic correlation (r_g) between BD and each trait of interest and standard error from LD Score regression is shown below the corresponding Venn diagram, with an accompanying scale (-1 to +1). The arrows above and below the Venn diagrams indicate the results of generalized summary statistics-based Mendelian randomization (GSMR) of BD on the trait of interest, and the trait of interest on BD, respectively. The GSMR effect size and standard error is shown inside the corresponding arrow. Solid arrows indicate a significant relationship between the exposure and the outcome, after correction for multiple comparisons (P<1.47E-03) and dashed arrows indicate a non-significant relationship.

BD subtypes

We conducted GWAS meta-analyses of bipolar I disorder (BD I) (25,060 cases, 449,978 controls) and bipolar II disorder (BD II) (6,781 cases, 364,075 controls). The BD I analysis identified 44 genome-wide significant loci, 31 of which overlapped with genome-wide significant loci from the main BD GWAS (Table 1, Table S21). The remaining 13 genome-wide significant loci for BD I all had P < 4.0E-05 in the main BD GWAS. One genome-wide significant locus was identified in the GWAS meta-analysis of BD II and had a P < 1.1E-04 in the main GWAS of BD (Table S21). The h^2_{SNP} estimates on the liability scale for BD I and BD II were 20.9% (SE=0.009, P=1.0E-111) and 11.6% (SE=0.01, P = 3.9E-15), respectively, assuming a 1%

population prevalence of each subtype. These heritability values are significantly different from each other (P=2.4E-25, block jackknife). The genetic correlation between BD I and BD II was 0.85 (SE=0.05, P = 2.88E-54), which is significantly different from 1 (P=1.6E-03). The genetic correlation of BD I with schizophrenia (r_g=0.66, SE=0.02) was higher than that of BD II (r_g=0.54 SE=0.05), whereas major depression was more strongly genetically correlated with BD II (r_g=0.66, SE=0.05) than with BD I (r_g=0.34, SE=0.03) (Table S22).

Discussion

In a GWAS of 41,917 BD cases, we identify 64 associated genomic loci, 33 of which are novel discoveries. With a 1.5-fold increase in effective sample size compared with the PGC2 BD GWAS, this study more than doubled the number of associated loci, representing an inflection point in the rate of risk variant discovery. We observed consistent replication of known BD loci, including 28/30 loci from the PGC2 GWAS[24] and several implicated by other BD GWAS[15,16,17], including a study of East Asian cases[59].

The 33 novel loci discovered here encompass genes of expected biological relevance to BD, such as the ion channels *CACNB2* and *KCNB1.* Amongst the 64 BD loci, 17 have previously been implicated in GWAS of schizophrenia[60], and seven in GWAS of major depression[61], representing the first overlap of genome-wide significant loci between the mood disorders. For the BD loci shared across disorders, 17/17 and 5/7 of the BD index SNPs had the same direction of effect on schizophrenia and major depression respectively (Table S23). More generally, 50/64 and 62/64 BD loci had a shared direction of effect on major depression and schizophrenia respectively, considerably greater than chance (P<1E-05, binomial test). Bivariate gaussian mixture modeling estimated that across the entire genome, almost all variants influencing BD also influence schizophrenia and major depression, albeit with variable effects[62]. SNPs in and around the MHC locus reached genome-wide significance for BD for the first time. However, unlike in schizophrenia, we found no influence of *C4* structural alleles or gene expression[63]. Rather the association was driven by variation outside the classical MHC locus, with the index SNP (rs13195402) being a missense variant in *BTN2A1*, a brain-expressed gene[64] encoding a plasma membrane protein.

The genetic correlation of BD with other psychiatric disorders was consistent with previous reports[65,66]. Our results also corroborate previous genetic and clinical evidence of associations between BD and sleep disturbances[67], problematic alcohol use[68] and smoking[69]. While the genome-wide genetic correlations with these traits were modest (r_g -0.05-0.35), MiXeR estimated that for all traits, more than 55% of trait-influencing variants also influence BD (Figure 3). Taken together, these results point to shared biology as one possible explanation for the high prevalence of substance use in BD. However, excluding genetic variants associated with both traits, MR analyses suggested that smoking is also a putatively “causal” risk factor for BD, while BD has no effect on smoking, consistent with a previous report[70]. [We use the word “causal” with caution here as we consider MR an exploratory analysis to identify potentially modifiable risk factors which warrant more detailed investigations to understand their complex relationship with BD.] In contrast, MR indicated that BD had bi-directional “causal” relationships with problematic alcohol use, longer sleep duration and mood instability. Insights into the relationship of such behavioral correlates with BD may have future impact on clinical decision making in the prophylaxis or management of the disorder. Higher educational attainment has previously been associated with BD in epidemiological studies[55,56], while lower educational attainment has been associated with schizophrenia and major depression[71,72]. Here, educational attainment had a significant positive effect on risk of BD and vice versa. Interestingly, MiXeR estimated that almost all variants that influence BD also influence educational attainment. The substantial genetic overlap observed between BD and the other phenotypes suggests that many variants likely influence multiple phenotypes which may be differentiated by phenotype-specific effect size distributions among the shared influencing variants.

The integration of eQTL data with our GWAS results yielded 15 high-confidence genes for which there was converging evidence that their association with BD is mediated via gene expression. Amongst these were *HTR6*, encoding a serotonin receptor targeted by antipsychotics and antidepressants[73] and *MCHR1* (melanin-concentrating hormone receptor 1), a target of the antipsychotic haloperidol[73]. We note that for both of these genes, their top eQTLs have opposite directions of effect on gene expression in the brain and blood, possibly playing a role in the tissue-specific gene regulation influencing BD[74]. BD was associated with decreased expression of *FURIN,* a gene with a neurodevelopmental function which has already been the subject of functional genomics experiments in neuronal cells, following its association with schizophrenia in GWAS[75]. The top association in our GWAS was in the *TRANK1* locus on chromosome 3, which has previously been implicated in BD[12,18,59]. Although BD-associated SNPs in this locus are known to regulate *TRANK1* expression[76], our eQTL analyses support a stronger but correlated regulation of *DCLK3*, located 87 kb upstream of *TRANK1*[43,77]. Both *FURIN* and *DCLK3* also encode druggable proteins (although they are not targets for any current psychiatric medications)[73,78]. These eQTL results provide promising BD candidate genes for functional follow-up experiments[29]. While several of these are in genome-wide significant loci, many are not the closest gene to the index SNP, highlighting the value of probing underlying molecular mechanisms to prioritize the most likely causal genes in the loci.

GWAS signals were enriched in the gene targets of existing BD pharmacological agents, such as antipsychotics, mood stabilizers, and antiepileptics. However, enrichment was also found in the targets of calcium channel blockers used to treat hypertension and GABA-receptor targeting anesthetics (Table S8). Calcium channel antagonists have long been investigated for the treatment of BD, without becoming an established therapeutic approach, and there is evidence that some antiepileptics have calcium channel-inhibiting effects[79,80]. These results underscore the opportunity for repurposing some classes of drugs, particularly calcium channel antagonists, as potential BD treatments[81].

BD associations were enriched in gene sets involving neuronal parts and synaptic signaling. Neuronal and synaptic pathways have been described in cross-disorder GWAS of multiple psychiatric disorders including BD[82–84]. Dysregulation of such pathways has also been suggested by previous functional and animal studies[85]. Analysis of single-cell gene expression data revealed enrichment in genes with high specificity of gene expression in neurons (both excitatory and inhibitory), of many brain regions, in particular the cortex and hippocampus. These findings are similar to those reported in GWAS data of schizophrenia[86] and major depressive disorder[38].

PRS for BD explained on average 4.57% of phenotypic variance (liability scale) across European cohorts, although this varied in different waves of the BD GWAS, ranging from 6.6% in the PGC1 cohorts to 2.9% in the External biobank studies (Supplementary Figure 7, Table S12). These results are in line with the h^2_{SNP} of BD per wave, which ranged from 24.6% (SE=0.01) in PGC1 to 11.9% (SE=0.01) in External studies (Table S3). Some variability in h^2_{SNP} estimates may arise from the inclusion of cases from population biobanks, who may have more heterogeneous clinical presentations or less severe illness than BD patients ascertained via inpatient or outpatient psychiatric clinics. Across the waves of clinically ascertained samples within the PGC, h^2_{SNP} and the R^2 of PRS also varied, likely reflecting clinical and genetic heterogeneity in the type of BD cases ascertained; the PGC1 cohorts consisted mostly of BD I cases[9], known to be the most heritable of the BD subtypes[11,24], while later waves included more individuals with BD II[24]. Overall, the h^2_{SNP} of BD calculated from the meta-analysis summary statistics was 18% on the liability scale, a decrease of ~2% compared with the PGC2 GWAS[24], which may be due to the addition of cohorts with lower h^2_{SNP} estimates and heterogeneity between cohorts (Table S3). However, despite differences in h^2_{SNP} and R^2 of PRS per wave, the genetic correlation of BD between all waves was high (weighted mean r_g=0.94, SE=0.03), supporting our rationale for combining cases with different BD subtypes or ascertainment to increase power for discovery of risk variants. In Europeans, individuals in the top 10% of PRS had an OR of 3.5 for BD, compared with individuals with average PRS (middle decile), which translates into a modest absolute lifetime risk of the disorder (7% based on PRS alone). While PRS are invaluable tools in research settings, the current BD PRS lack sufficient power to separate individuals into clinically meaningful risk categories, and therefore have no clinical utility at present[87,88]. PRS from this European BD meta-analysis yield higher R^2 values in diverse ancestry samples than PRS based on any currently available BD GWAS within the same ancestry[59]. However, performance still greatly lags behind that in Europeans, with ~2% variance explained in East Asian samples and substantially less in admixed African American samples, likely due to differences in allele frequencies and LD structures, consistent with previous studies[89,90]. There is a pressing need for more and larger studies in other ancestry groups to ensure that any future clinical utility is broadly applicable. Exploiting the differences in LD structure between diverse ancestry samples will also assist in the fine-mapping of risk loci for BD.

Our analyses confirmed that BD is a highly polygenic disorder, with an estimated 8.6 k variants explaining 90% of its h^2_{SNP}. Hence, many more SNPs than those identified here are expected to account for the common variant architecture underlying BD. This GWAS marks an inflection point in risk variant discovery and we expect that from this point forward, the addition of more samples will lead to a dramatic increase in genetic findings. Nevertheless, fewer genome-wide significant loci have been identified in BD than in a schizophrenia GWAS of comparable sample size[60]. This may be due to the clinical and genetic heterogeneity that exists in BD.

Our GWAS of subtypes BD I and BD II identified additional associated loci. Consistent with previous findings[24], our analysis showed that the two subtypes were highly but imperfectly genetically correlated (r_g=0.85), and that BD I is more genetically correlated with schizophrenia, while BD II has stronger genetic correlation with major depression. The subtypes are sufficiently similar to justify joint analysis as BD, but are not identical in their genetic composition, and as such contribute to the genetic heterogeneity of BD[91]. We identified thirteen loci passing genome-wide significance for BD I, and one for BD II, which did not reach significance in the main BD GWAS, further illustrating the partially differing genetic composition of the two subtypes. Understanding the shared and distinct genetic components of BD subtypes and symptoms requires detailed phenotyping efforts in large cohorts and is an important area for future psychiatric genetics research.

In summary, these new data advance our understanding of the biological etiology of BD and prioritize a set of candidate genes for functional follow-up experiments. Several lines of evidence converge on the involvement of calcium channel signaling, providing a promising avenue for future therapeutic development.

Methods

Sample description

The meta-analysis sample comprises 57 cohorts collected in Europe, North America and Australia, totaling 41,917 BD cases and 371,549 controls of European descent (Table S1). The total effective N, equivalent to an equal number of cases and controls in each cohort (4*Ncases*Ncontrols/(Ncases+Ncontrols)), is 101,962. For 52 cohorts, individual-level genotype and phenotype data were shared with the PGC. Cohorts have been added to the PGC in five waves (PGC1[9], PGC2[24], PGC PsychChip, PGC3 and External Studies); all cohorts from previous PGC BD GWAS were included. The source and inclusion/exclusion criteria for cases and controls for each cohort, are described in the Supplementary Note. 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. For five cohorts (iPSYCH[30], deCODE genetics[31], Estonian Biobank[32], Trøndelag Health Study (HUNT)[33] and UK Biobank[34]), GWAS summary statistics for BD were shared with the PGC. In these cohorts, BD cases were ascertained using ICD codes or self-report during a nurse interview, and the majority of controls were screened for the absence of psychiatric disorders via ICD codes. Follow-up analyses included four non-European BD case-control cohorts, two from East Asia (Japan[59] and Korea[92]), and two admixed African American cohorts[22,93], providing a total of 5,847 cases and 65,588 controls. These BD cases were ascertained using international consensus criteria (DSM-IV)[22,93] through psychiatric interviews (Supplementary Note).

Genotyping, quality control and imputation

PGC cohorts were genotyped following local protocols, after which standardized quality control, imputation and statistical analyses were performed centrally using RICOPILI (Rapid Imputation for COnsortias PIpeLIne)[94], separately for each cohort. Briefly, the quality control parameters for retaining SNPs and subjects were: SNP missingness < 0.05 (before sample removal), subject missingness < 0.02, autosomal heterozygosity deviation ($F_{het} < 0.2$), SNP missingness < 0.02 (after sample removal), difference in SNP missingness between cases and controls < 0.02, SNP Hardy-Weinberg equilibrium (P > 10E-10 in psychiatric cases and P > 10E-06 in controls). Relatedness was calculated across cohorts using identity by descent and one of each pair of related individuals (pi_hat > 0.2) was excluded. Genotype imputation was performed using the pre-phasing/ imputation stepwise approach implemented in Eagle v2.3.5[95] and Minimac3[96] to the Haplotype Reference Consortium (HRC) reference panel v1.0[97]. The five external cohorts were processed by the collaborating research teams using comparable procedures and imputed to the HRC or a custom reference panel as appropriate. Full details of the genotyping, quality control and imputation for each cohort are available in the Supplementary Note. Identical individuals between PGC cohorts and the Estonian Biobank and UK Biobank cohorts were detected using genotype-based checksums (https://personal.broadinstitute.org/sripke/share_links/zpXkV8INxUg9bayDpLToG4g58TMtjN_PGC_SCZ_w3.0718d.76) and removed from PGC cohorts.

Genome-wide association study

For PGC cohorts, GWAS were conducted within each cohort using an additive logistic regression model in PLINK v1.90[98]. Ancestry informant principal components (PCs) were calculated within each cohort and included as covariates, as required. Association analyses of the X chromosome were conducted in males and females separately using the same procedures, with males coded as 0 or 2 for 0 or 1 copies of the reference allele. Results from males and females were then meta-analyzed within each cohort. For external cohorts, GWAS were conducted by the collaborating research teams using comparable procedures (Supplementary Note). To control test statistic inflation at SNPs with low minor allele frequency (MAF) in small cohorts, SNPs were retained only if cohort MAF was > 1% and minor allele count was > 10 in either cases or controls (whichever had smaller N). There was no evidence of stratification artifacts or uncontrolled inflation of test statistics in the results from any cohort (λ_{GC} 0.97-1.05)(Table S1). Meta-analysis of GWAS summary statistics was conducted using an inverse variance-weighted fixed effects model in METAL[99]. A genome-wide significant locus was defined as the region around a SNP with P<5E-08, with linkage disequilibrium (LD) $r^2 > 0.1$, within a 3000 kilobase (kb) window.

Overlap of loci with other psychiatric disorders

Genome-wide significant loci for BD were assessed for overlap with genome-wide significant loci for other psychiatric disorders, using the largest available GWAS results for major depression[61], schizophrenia[60], attention deficit/hyperactivity disorder[100], post-traumatic stress disorder[101], lifetime anxiety disorder[102], Tourette's Syndrome[103], anorexia nervosa[104], alcohol use disorder or problematic alcohol use[68], autism spectrum disorder[105], mood disorders[91] and the cross-disorder GWAS of the Psychiatric Genomics Consortium[66]. The boundaries of the genome-wide significant loci were calculated in the original publications. Overlap of loci was calculated using bedtools[106].

Enrichment analyses

P values quantifying the degree of association of genes and gene sets with BD were calculated using MAGMA v1.08[37], implemented in FUMA v1.3.6a[64,107]. Gene-based tests were performed for 19,576 genes (Bonferroni-corrected *P* value threshold = 2.55E-06). A total of 11,858 curated gene sets including at least 10 genes from MSigDB V7.0 were tested for association with BD (Bonferroni-corrected P value threshold = 4.22E-06). Competitive gene-set tests were conducted correcting for gene size, variant density and LD within and between genes. Tissue-set enrichment analyses were also performed using MAGMA implemented in FUMA, to test for enrichment of association signal in genes expressed in 54 tissue types from GTEx V8 (Bonferroni-corrected P value threshold = 9.26E-04)[64,107].

For single-cell enrichment analyses, publicly available single-cell RNA-seq data were compiled from five studies of the adult human and mouse brain[86,108–111]. Using a previously described method[38], a metric of gene expression specificity was calculated by dividing the expression of each gene in each cell type by the total expression of that gene in all cell types, leading to values ranging from 0 to 1 for each gene (0 meaning that the gene is not expressed in that cell type and 1 meaning that all of the expression of the gene is in that cell type). MAGMAv1.08[37] was used to test whether the 10% most specific genes for each cell type were associated with BD, including relevant covariates. The P value threshold for significance was P < 9.1E-03, representing a 5% false discovery rate (FDR) across datasets. Full details are in the Supplementary Note.

Further gene-set analyses were performed restricted to genes targeted by drugs, assessing individual drugs and grouping drugs with similar actions. This approach has been described previously[41]. Two groups of gene sets were defined. The first group comprised the targets of each drug in the Drug-Gene Interaction Database DGIdb v.2[39] and in the Psychoactive Drug Screening Database Ki DB[40], both downloaded in June 2016[41]. The second set were drug sets grouped according to Anatomical Therapeutic Chemical (ATC) classes[41]. All analyses were performed using competitive gene-set analyses in MAGMA v1.08[37]. Multiple testing was controlled using a Bonferroni-corrected significance threshold of P < 5.60E-05 for drug-set analysis and P < 7.93E-03 for drug-class analysis, accounting for 893 drug-sets and 63 drug classes tested.

eQTL integrative analysis

A transcriptome-wide association study (TWAS) was conducted using the precomputed gene expression weights from PsychENCODE data (1,321 brain samples)[43], available online with the FUSION software[42]. For genes with significant *cis*-SNP heritability (13,435 genes), FUSION software was used to test whether SNPs influencing gene expression are also associated with BD (Bonferroni-corrected P value threshold < 3.72E-06). For regions including a TWAS significant gene, TWAS fine-mapping of the region was conducted using FOCUS (fine-mapping of causal gene sets)[44]. A posterior inclusion probability (PIP) was assigned to each gene for being causal for the observed TWAS association signal and used to generate the 90%-credible gene set for each region[44].

Summary data-based Mendelian randomization (SMR)[45,46] was applied to further investigate putative causal relationships between SNPs and BD via gene expression. SMR was performed using eQTL summary statistics from the eQTLGen (31,684 blood samples)[47] and PsychENCODE[43] consortia. SMR analysis is limited to transcripts with at least one significant *cis*-eQTL ($P < 5E-08$) in each dataset (15,610 in eQTLGen; 10,871 in PsychENCODE). The Bonferroni-corrected significance threshold was $P < 3.20E-06$ and $P < 4.60E-06$ for eQTLGen and PsychENCODE respectively. The significance threshold for the HEIDI test (heterogeneity in dependent instruments) was $P_{HEIDI} \geq 0.01$[46]. While the results of TWAS and SMR indicate an association between BD and gene expression, a non-significant HEIDI test additionally indicates either a direct causal role or a pleiotropic effect of the BD-associated SNPs on gene expression.

Complement component 4 (C4) imputation

To investigate the major histocompatibility complex (MHC; chr6:24-34 Mb on hg19), the alleles of complement component 4 genes (*C4A* and *C4B*) were imputed in 47 PGC cohorts for which individual-level genotype data were accessible, totaling 32,749 BD cases and 53,370 controls. The imputation reference panel comprised 2,530 reference haplotypes of MHC SNPs and *C4* alleles, generated using a sample of 1,265 individuals with whole-genome sequence data, from the Genomic Psychiatry cohort[112]. Briefly, imputation of *C4* as a multi-allelic variant was performed using Beagle v4.1[113,114], using SNPs from the MHC region that were also in the haplotype reference panel. The output consisted of dosage estimates for each of the common *C4* structural haplotypes (e.g., AL-BS, AL-AL, etc.) for each individual. The five most common structural forms of the *C4A/C4B* locus (BS, AL, AL-BS, AL-BL, and AL-AL) could be inferred with reasonably high accuracy (generally $0.70 < r2 < 1.00$). The imputed *C4* alleles were tested for association with BD in a joint logistic regression that included (i) terms for dosages of the five most common *C4* structural haplotypes (AL-BS, AL-BL, AL-AL, BS, and AL), (ii) rs13195402 genotype (top lead SNP in the MHC) and (iii) PCs as per the GWAS. The genetically regulated expression of *C4A* was predicted from the imputed *C4* alleles using a model previously described[63]. Predicted *C4A* expression was tested for association with BD in a joint logistic regression that included (i) predicted *C4A* expression, (ii) rs13195402 genotype (top lead SNP in the MHC) and (iii) PCs as per the GWAS. Full details are in the Supplementary Note.

Polygenic risk scoring

PRS from our GWAS meta-analysis were tested for association with BD in individual cohorts, using a discovery GWAS where the target cohort was left out of the meta-analysis. Briefly, the GWAS results from each discovery GWAS were pruned for LD using the P value informed clumping method in PLINK v1.90[98] (r^2 0.1 within a 500 kb window) based on the LD structure of the HRC reference panel[97]. Subsets of SNPs were selected from the results below nine increasingly liberal P value thresholds (p_T) (5E-08, 1E-04, 1E-03, 0.01, 0.05, 0.1, 0.2, 0.5, 1). Sets of alleles, weighted by their log odds ratios from the discovery GWAS, were summed into PRS for each individual in the target datasets, using PLINK v1.90 implemented via RICOPILI[94,98]. PRS were tested for association with BD in the target dataset using logistic regression, covarying for PCs as per the GWAS in each cohort. PRS were tested in the external cohorts by the collaborating research teams using comparable procedures. The variance explained by the PRS (R^2) was converted to the liability scale to account for the proportion of cases in each target dataset, using a BD population prevalence of 2% and 1%[115]. The weighted average R^2 values were calculated using the effective N for each cohort. The odds ratios for BD for individuals in the top decile of PRS compared with those in the lowest decile and middle decile were calculated in the 52 datasets internal to the PGC. To assess cross-ancestry performance, PRS generated from the meta-analysis results were tested for association with BD using similar methods in a Japanese sample[59], a Korean sample[92] and two admixed

African American samples. Full details of the QC, imputation and analysis of these samples are in the Supplementary Note.

LD score regression

LD Score regression (LDSC)[35] was used to estimate the h^2_{SNP} of BD from GWAS summary statistics. h^2_{SNP} was converted to the liability scale, using a lifetime BD prevalence of 2% and 1%. LDSC bivariate genetic correlations attributable to genome-wide SNPs (r_g) were estimated with 255 human diseases and traits from published GWAS and 514 GWAS of phenotypes in the UK Biobank from LD Hub (http://ldsc.broadinstitute.org)[48]. Adjusting for the number of traits tested, the Bonferroni-corrected P value thresholds were P < 1.96E-04 and P < 9.73E-05 respectively.

MiXeR

We applied bivariate gaussian mixture models to the GWAS summary statistics for BD and other complex traits, using MiXeR v1.3[49,50]. MiXeR provides univariate estimates of the proportion of non-null SNPs ("polygenicity") and the variance of effect sizes of non-null SNPs ("discoverability") in each phenotype. In the cross-trait analysis, MiXeR models additive genetic effects as a mixture of four components, representing SNPs not influencing either trait, SNPs influencing only one of the two traits, and SNPs influencing both traits. These components are then plotted in Venn diagrams. After fitting parameters of the model, the dice coefficient, which represents the proportion of overlapping variants, is calculated. Further details are provided in the Supplementary Note.

Mendelian randomization

Seventeen traits associated with BD in clinical or epidemiological studies were selected for Mendelian randomization (MR) to dissect their relationship with BD (Supplementary Note). Bi-directional generalized summary statistics-based MR (GSMR)[51] analyses were performed between BD and the traits of interest using GWAS summary statistics. The instrumental variables (IVs) were selected by a clumping procedure internal to the GSMR software with parameters: *--gwas-thresh 5e-8 --clump-r2 0.01*. Traits with less than 10 IVs available were excluded from the GSMR analyses to avoid conducting underpowered tests[51], resulting in 10 traits tested (Bonferroni-corrected P value threshold < 2.5E-03). The HEIDI-outlier test (heterogeneity in dependent instruments) was applied to test for horizontal pleiotropy ($P_{\text{HEIDI}} < 0.01$)[51]. For comparison, the MR analyses were also performed using the inverse variance weighted regression method, implemented via the TwoSampleMR R package, using the IVs selected by GSMR[116,117]. To further investigate horizontal pleiotropy, the MR Egger intercept test was conducted using the TwoSampleMR package[116,117] and MR-PRESSO software was used to perform the Global Test and Distortion Test[118].

BD subtypes

GWAS meta-analyses were conducted for BD I (25,060 cases, 449,978 controls from 55 cohorts, effective N = 64,802) and BD II (6,781 cases, 364,075 controls from 31 cohorts, effective N = 22,560) using the same procedures described for the main GWAS. BD subtypes were defined based on international consensus criteria (DSM-IV, ICD-9 or ICD-10), established using structured diagnostic instruments from assessments by trained interviewers, clinician-administered checklists or medical record review. In the external biobank cohorts, BD subtypes were defined using ICD codes (Supplementary Note). LDSC[35] was used to estimate the h^2_{SNP} of each subtype, and the genetic correlation between the subtypes. The difference between the LDSC h^2_{SNP}estimates for BD I and BD II was tested for deviation from 0 using the block jackknife[119]. The LDSC genetic correlation (r_g) was tested for difference from 1 by calculating a chi-square statistic corresponding to the estimated r_g as $[(r_g - 1)/ \text{se}]^2$.

Data availability

The PGC's policy is to make genome-wide summary results public. Summary statistics will be made available through the PGC website upon publication (https://www.med.unc.edu/pgc/results-and-downloads). Data are accessible with collaborative analysis proposals through the Bipolar Disorder Working Group of the PGC (https://www.med.unc.edu/pgc/shared-methods/how-to/). This study included some publicly available datasets accessed through dbGaP - PGC bundle phs001254.v1.p1**.**

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Author contribution statement

Writing group:

N.M., A.J.F., K.S.O'C., B.C., J.R.I.C., J.M.B., J.I.N., S.Cichon, H.J.E., E.A.S., A.McQuillin, A.D.F., R.A.O., O.A.A.

PGC BD PI group:

A.J.F., M.I., H-H.W., D.C., R.A., I.A., M.A., L.Alfredsson, G.Babadjanova, L.B., B.T.B., F.B., S.Bengesser, W.H.B., D.H.R.B., M.Boehnke, A.D.B., G.Breen, V.J.C., S.Catts, A.C., N.C., U.D., D.D., T.Esko, B.E., P.F., M.F., J.M.F., M.G., E.S.G., F.S.G., M.J.Green, M.G-S., J.Hauser, F.H., J.Hillert, K.S.H., D.M.H., C.M.H., K.Hveem, N.I., A.V.J., I.J., L.A.J., R.S.K., J.R.K., G.K., M.Landén, M.Leboyer, C.M.L., Q.S.L., J.Lissowska, C.Lochner, C.Loughland, N.G.M., C.A.M., F.M., S.L.M., A.M.M., F.J.M., I.M., P.Michie, L.Milani, P.B.Mitchell, G.M., O.M., P.B.Mortensen, B.M., B.M-M., R.M.M., B.M.N., C.M.N., M.N., M.M.N., M.C.O'D., K.J.O., T.O., M.J.O., S.A.P., C.Pantelis, C.Pato, M.T.P., G.P.P., R.H.P., D.P., J.A.R-Q., A.R., E.Z.R., M.Ribasés, M.Rietschel, S.R., G.A.R., T.S., U.S., M.S., P.R.S., T.G.S., L.J.S., R.J.S., A.S., C.S.W., J.W.S., H.S., K.S., E.Stordal, F.Streit, P.F.S., G.T., A.E.V., E.V., J.B.V., I.D.W., T.W.W., T.W., N.R.W., J-A.Z., J.M.B., J.I.N., S.Cichon, H.J.E., E.A.S., A.McQuillin, A.D.F., R.A.O., O.A.A.

Bioinformatics:

N.M., A.J.F., J.R.I.C., S.Børte, M.J.Gandal, M.Kim, B.M.S., L.G.S., B.S.W., H-H.W., N.A-R., S.E.B., B.M.B., V.E-P., S.H., P.A.H., Y.K., M.Koromina, M.Kubo, M.Leber, P.H.L., C.Liao, L.M.O.L., T.R., P.R., P.D.S., M.S.A., C.Terao, T.E.T., S.X., H.Y., P.P.Z., S.Bengesser, G.Breen, P.F., E.S.G., Q.S.L., G.A.R., H.S., T.W., E.A.S.

Clinical:

O.K.D., M.I., L.Abramova, K.A., E.A., N.A-R., A.Anjorin, A.Antoniou, J.H.B., N.B., M.Bauer, A.B., C.B.P., E.B., M.P.B., R.B., M.Brum, N.B-K., M.Budde, W.B., M.Cairns, M.Casas, P.C., A.C-B., D.C., P.M.C., N.D., A.D., T.Elvsåshagen, L.Forty, L.Frisén, K.G., J.Garnham, M.G.P., I.R.G., K.G-S., J.Grove, J.G-P., K.Ha, M.Haraldsson, M.Hautzinger, U.H., D.H., J.L.Kalman, J.L.Kennedy, S.K-S., M.Kogevinas, T.M.K., R.K., S.A.K., J.L., H-J.L., C.Lewis, S.L., M.Lundberg, D.J.M., W.M., D.M., L.Martinsson, M.M., P.McGuffin, H.M., V.M., C.O'D., L.O., S.P., A.Perry, A.Pfennig, E.P., J.B.P., D.Q., M.H.R., J.R.D., E.J.R., J.P.R., F.R., J.R., E.C.S., F.Senner, E.Sigurdsson, L.S., C.S., O.B.S., D.J.Smith, J.L.S., A.T.S., J.S.S., B.S., P.T., M.P.V., H.V., A.H.Y., L.Z., HUNT All-In Psychiatry, R.A., I.A., M.A., G.Babadjanova, L.B., B.T.B., F.B., S.Bengesser, D.H.R.B., A.D.B., A.C., N.C., U.D., D.D., B.E., P.F., M.F., M.G., E.S.G., F.S.G., M.J.Green, M.G-S., J.Hauser, K.S.H., N.I., I.J., L.A.J., R.S.K., G.K., M.Landén, C.M.L., J.Lissowska, N.G.M., C.A.M., F.M., S.L.M., A.M.M., I.M., P.B.Mitchell, G.M., O.M., P.B.Mortensen, M.C.O'D., K.J.O., M.J.O., C.Pato, M.T.P., R.H.P., J.A.R-Q., A.R., E.Z.R., M.Rietschel, T.S., T.G.S., A.S., C.S.W., J.W.S., E.Stordal, F.Streit, A.E.V., E.V., J.B.V., I.D.W., T.W.W., T.W., J.I.N., A.McQuillin, A.D.F.

Genomic assays/data generation:

A.J.F., M.I., E.A., M.A.E., D.A., M.B-H., E.C.B., C.B.P., J.B-G., M.Cairns, T-K.C., C.C., J.C., F.S.D., F.D., S.D., A.F., J.F., N.B.F., J.Gelernter, M.G.P., P.H., S.J., Y.K., H.R.K., M.Kubo, S.E.L., C.Liao, E.M., N.W.M., J.D.M., G.W.M., J.L.M., D.W.M., T.W.M., N.O'B., M.Rivera, C.S-M., S.Sharp, C.S.H., C.Terao, C.Toma, E-E.T., S.H.W., HUNT All-In Psychiatry, G.Breen, A.C., T.Esko, J.M.F., E.S.G., D.M.H., N.I., F.J.M., L.Milani, R.M.M., M.M.N., M.Ribasés, G.A.R., T.S., G.T., S.Cichon

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M.I., M.Cairns, I.N.F., L.Frisén, S.J., Y.K., J.A.K., M.Kubo, C.Lavebratt, S.L., D.M., P.McGuffin, G.W.M., J.B.P., M.H.R., J.R.D., D.J.Stein, J.S.S., C.Terao, A.H.Y., P.P.Z., M.A., L.Alfredsson, L.B., B.T.B., F.B., W.H.B., M.Boehnke, A.D.B., G.Breen, A.C., N.C., B.E., M.F., J.M.F., E.S.G., M.J.Green, M.G-S., K.S.H., K.Hveem, N.I., I.J., L.A.J., M.Landén, M.Leboyer, N.G.M., F.J.M., P.B.Mitchell, O.M., P.B.Mortensen, B.M.N., M.N., M.M.N., M.C.O'D., T.O., M.J.O., C.Pato, M.T.P., G.P.P., M.Rietschel, G.A.R., T.S., M.S., P.R.S., T.G.S., C.S.W., J.W.S., G.T., J.B.V., T.W.W., T.W., J.M.B., J.I.N., H.J.E., R.A.O.

Statistical analysis:

N.M., K.S.O'C., B.C., J.R.I.C., Z.Q., T.D.A., T.B.B., S.Børte, J.B., A.W.C., O.K.D., M.J.Gandal, S.P.H., N.K., M.Kim, K.K., G.P., B.M.S., L.G.S., S.Steinberg, V.T., B.S.W., H-H.W., V.A., S.A., S.E.B., B.M.B., A.M.D., A.L.D., V.E-P., T.M.F., O.F., S.D.G., T.A.G., J.Grove, P.A.H., L.H., J.S.J., Y.K., M.Kubo, C.Lavebratt, M.Leber, P.H.L., S.H.M., A.Maihofer, M.M., S.E.M., L.M.O.L., A.F.P., T.R., P.R., D.M.R., O.B.S., C.Terao, T.E.T., J.T.R.W., W.X., J.M.K.Y., H.Y., P.P.Z., H.Z., A.D.B., G.Breen, E.S.G., F.S.G., Q.S.L., B.M-M., C.M.N., D.P., S.R., H.S., P.F.S., T.W., N.R.W., J.M.B., E.A.S.

Competing interests

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. Full details of competing interests for all co-authors are included in the Supplementary Note.

Affiliations

[1]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [2]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [3]Institute of Human Genetics, University of Bonn, School of Medicine and University Hospital Bonn, Bonn, Germany. [4]Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany. [5]Centre for Human Genetics, University of Marburg, Marburg, Germany. [6]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. [7]NORMENT, University of Oslo, Oslo, Norway. [8]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA. [9]Social, Genetic and Developmental Psychiatry Centre, King's College London, London, UK. [10]NIHR Maudsley BRC, King's College London, London, UK. [11]Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia. [12]iSEQ, Center for Integrative Sequencing, Aarhus University, Aarhus, Denmark. [13]Department of Biomedicine - Human Genetics, Aarhus University, Aarhus, Denmark. [14]iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark. [15]Department of Psychiatry and Behavioral Sciences, SUNY Downstate Health Sciences University, Brooklyn, NY, USA. [16]VA NY Harbor Healthcare

System, Brooklyn, NY, USA. [17]Research and Communication Unit for Musculoskeletal Health, Division of Clinical Neuroscience, Oslo University Hospital, Ullevål, Oslo, Norway. [18]Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [19]K. G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. [20]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [21]Department of Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. [22]Department of Østmarka, Division of Mental Health Care, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. [23]Department of Psychiatry and Biobehavioral Science, Semel Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA. [24]Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Japan. [25]Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, USA. [26]Department of Genetics, Harvard Medical School, Boston, MA, USA. [27]Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia. [28]Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, Germany. [29]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [30]Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [31]Estelle and Daniel Maggin Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [32]deCODE Genetics / Amgen, Reykjavik, Iceland. [33]Department of Research, Innovation and Education, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway. [34]Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Samsung Medical Center, Seoul, South Korea. [35]Russian Academy of Medical Sciences, Mental Health Research Center, Moscow, Russian Federation. [36]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany. [37]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany. [38]National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark. [39]Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark. [40]Division of Psychiatry, University College London, London, UK. [41]Department of Neuroscience, Istituto Di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy. [42]Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA. [43]Northwestern University, Chicago, IL, USA. [44]Psychiatry, Berkshire Healthcare NHS Foundation Trust, Bracknell, UK. [45]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. [46]National and Kapodistrian University of Athens, 2nd Department of Psychiatry, Attikon General Hospital, Athens, Greece. [47]Department of Psychiatry, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea. [48]Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark. [49]Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. [50]Medical University of Graz, Department of Psychiatry and Psychotherapeutic Medicine, Graz, Austria. [51]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway. [52]Psychiatry, Brain Center UMC Utrecht, Utrecht, The Netherlands. [53]Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health (CIBERSAM), Madrid, Spain. [54]Department of Psychiatry, Hospital Universitari Vall d´Hebron, Barcelona, Spain. [55]Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain. [56]Psychiatric Genetics Unit, Group of Psychiatry Mental Health and Addictions, Vall d´Hebron Research Institut (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain. [57]Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany. [58]Psychiatry, University of California San Francisco, San Francisco, CA, USA. [59]University of Newcastle, Newcastle, NSW, Australia. [60]Department of Psychiatry, Mood Disorders Program, McGill University Health Center, Montreal, QC, Canada. [61]Division of Psychiatry, University of Edinburgh, Edinburgh, UK. [62]Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany. [63]Department of Psychiatry, Universidad Autonoma de Nuevo Leon, Monterrey, Mexico. [64]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA. [65]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. [66]Centre for Psychiatry, Queen Mary University of London, London, UK. [67]UCL Genetics Institute, University College London, London, UK. [68]Department of Psychiatry, Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland. [69]Center for Multimodal Imaging and Genetics, Departments of Neurosciences, Radiology, and Psychiatry, University of California, San Diego, CA, USA. [70]Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Essen, University of Duisburg-Essen, Duisburg, Germany. [71]Department of Medical Genetics, Oslo University Hospital Ullevål, Oslo, Norway. [72]NORMENT, Department of Clinical Science, University of Bergen, Bergen, Norway. [73]Department of Neurology, Oslo University

Hospital, Oslo, Norway. [74]NORMENT, KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, Norway. [75]Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK. [76]Academic Psychiatry, Newcastle University, Newcastle upon Tyne, UK. [77]Department of Medical and Molecular Genetics, Indiana University, Indianapolis, IN, USA. [78]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany. [79]Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA, USA. [80]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. [81]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany. [82]Department of Psychiatry, Dalhousie University, Halifax, NS, Canada. [83]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA. [84]Veterans Affairs Connecticut Healthcare System, West Haven, CT, USA. [85]Departments of Genetics and Neuroscience, Yale University School of Medicine, New Haven, CT, USA. [86]Department of Psychological Sciences, University of Missouri, Columbia, MO, USA. [87]Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia. [88]Psychological Medicine, University of Worcester, Worcester, UK. [89]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA. [90]Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark. [91]Mental Health Department, University Regional Hospital, Biomedicine Institute (IBIMA), Málaga, Spain. [92]Department of Psychiatry, Seoul National University College of Medicine, Seoul, South Korea. [93]Landspitali University Hospital, Reykjavik, Iceland. [94]Department of Psychology, Eberhard Karls Universität Tübingen, Tubingen, Germany. [95]Department of Biomedicine, University of Basel, Basel, Switzerland. [96]Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland. [97]Neuropsychiatrie Translationnelle, Inserm U955, Créteil, France. [98]Faculté de Santé, Université Paris Est, Créteil, France. [99]International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany. [100]Laboratory of Complex Trait Genomics, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan. [101]Laboratory for Statistical and Translational Genetics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. [102]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada. [103]Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, ON, Canada. [104]Department of Psychiatry, University of Toronto, Toronto, ON, Canada. [105]Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada. [106]Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg, Würzburg, Germany. [107]Cell Biology, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA. [108]Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA. [109]ISGlobal, Barcelona, Spain. [110]University of Patras, School of Health Sciences, Department of Pharmacy, Laboratory of Pharmacogenomics and Individualized Therapy, Patras, Greece. [111]Mental Illness Research, Education and Clinical Center, Crescenz VAMC, Philadelphia, PA, USA. [112]Center for Studies of Addiction, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. [113]RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. [114]Psychiatry, Altrecht, Utrecht, The Netherlands. [115]Psychiatry, GGZ inGeest, Amsterdam, The Netherlands. [116]Psychiatry, VU medisch centrum, Amsterdam, The Netherlands. [117]Department of Psychiatry, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. [118]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden. [119]Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden. [120]Psychiatry, North East London NHS Foundation Trust, Ilford, UK. [121]Clinic for Psychiatry and Psychotherapy, University Hospital Cologne, Cologne, Germany. [122]Department of Psychiatry, Korea University College of Medicine, Seoul, South Korea. [123]Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. [124]HudsonAlpha Institute for Biotechnology, Huntsville, AL, USA. [125]Department of Human Genetics, McGill University, Montréal, QC, Canada. [126]Montreal Neurological Institute and Hospital, McGill University, Montréal, QC, Canada. [127]Division of Psychiatry, Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, UK. [128]Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany. [129]National and Kapodistrian University of Athens, Medical School, Clinical Biochemistry Laboratory, Attikon General Hospital, Athens, Greece. [130]Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden. [131]Systems Genetics Working Group, Department of Genetics, Stellenbosch University, Stellenbosch, South Africa. [132]Genetic Cancer Susceptibility Group, International Agency for Research on Cancer, Lyon, France. [133]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA. [134]Centre for Neuroimaging and Cognitive Genomics (NICOG), National University of Ireland Galway, Galway, Ireland. [135]Medical faculty, University Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina. [136]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [137]Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK. [138]Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK. [139]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA. [140]Outpatient Clinic for Bipolar Disorder, Altrecht, Utrecht, The Netherlands. [141]Department of Psychiatry, Washington University in Saint Louis, Saint Louis, MO, USA. [142]Department of Biochemistry and Molecular Biology II, Faculty of Pharmacy, University of Granada, Spain. [143]Institute of Neurosciences, Biomedical Research Center (CIBM), University of Granada, Spain. [144]Medicine, Psychiatry, Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA. [145]Department of Genetics, Microbiology and Statistics, Faculty of Biology, Universitat de Barcelona, Barcelona, Catalonia, Spain. [146]Faculty of Medicine, Department of Psychiatry, School of Health Sciences, University of Iceland, Reykjavik, Iceland. [147]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK. [148]Psychiatry and the Behavioral Sciences, University of Southern California, Los Angeles, CA, USA. [149]Mood Disorders, PsyQ, Rotterdam, The Netherlands. [150]SAMRC Unit on Risk and Resilience in Mental Disorders, Dept of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa. [151]Department of Environmental Epidemiology, Nofer Institute of Occupational Medicine, Lodz, Poland. [152]Neuroscience Research Australia, Sydney, NSW, Australia. [153]School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia. [154]Centro de Biología Molecular Severo Ochoa, Universidad Autónoma de Madrid and CSIC, Madrid, Spain. [155]Department of Psychiatry and Human Behavior, School of Medicine, University of California, Irvine, CA, USA. [156]Psychiatry, Psychiatrisches Zentrum Nordbaden, Wiesloch, Germany. [157]Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, USA. [158]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada. [159]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [160]South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Monks Orchard Road, Beckenham, Kent, UK. [161]A list of members and affiliations appears in the Supplementary Note. [162]Department of Clinical Sciences, Psychiatry, Umeå University Medical Faculty, Umeå, Sweden. [163]NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Institute of Clinical Medicine and Diakonhjemmet Hospital, University of Oslo, Oslo, Norway. [164]National Institute of Mental Health, Klecany, Czech Republic. [165]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. [166]Institute of Pulmonology, Russian State Medical University, Moscow, Russian Federation. [167]Department of Psychiatry, University of Münster, Münster, Germany. [168]Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, VIC, Australia. [169]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia. [170]Université de Paris, INSERM, Optimisation Thérapeutique en Neuropsychopharmacologie, UMRS-1144, Paris, France. [171]APHP Nord, DMU Neurosciences, GHU Saint Louis-Lariboisière-Fernand Widal, Département de Psychiatrie et de Médecine Addictologique, Paris, France. [172]Psychiatry, University of Pennsylvania, Philadelphia, PA, USA. [173]Center for Statistical Genetics and Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA. [174]Department of Biomedicine and the iSEQ Center, Aarhus University, Aarhus, Denmark. [175]Center for Genomics and Personalized Medicine, CGPM, Aarhus, Denmark. [176]School of Psychiatry, University of New South Wales, Sydney, NSW, Australia. [177]University of Queensland, Brisbane, QLD, Australia. [178]Neuropsychiatric Genetics Research Group, Dept of Psychiatry and Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland. [179]National and Kapodistrian University of Athens, 1st Department of Psychiatry, Eginition Hospital, Athens, Greece. [180]Medical and Population Genetics, Broad Institute, Cambridge, MA, USA. [181]Division of Endocrinology, Children's Hospital Boston, Boston, MA, USA. [182]Department of Human Genetics, University of Chicago, Chicago, IL, USA. [183]Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania. [184]HUNT Research Center, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. [185]University of Western Australia, Nedlands, WA, Australia. [186]Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden. [187]Department of Psychiatry and Addiction Medicine, Assistance Publique - Hôpitaux de Paris, Paris, France. [188]Department of Medical and Molecular Genetics, King's College London, London, UK. [189]Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, USA. [190]Cancer Epidemiology and Prevention, M. Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland. [191]SA MRC Unit on Risk and Resilience in Mental Disorders, Dept of Psychiatry, Stellenbosch University, Stellenbosch, South Africa. [192]School of Psychology, The University of Queensland, Brisbane, QLD, Australia. [193]Department of Psychiatry and Genetics Institute, University of Florida, Gainesville, FL, USA. [194]Research Institute,

Lindner Center of HOPE, Mason, OH, USA. [195]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK. [196]Human Genetics Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA. [197]Division of Mental Health and Addiction, University of Oslo, Institute of Clinical Medicine, Oslo, Norway. [198]Psychiatry, St Olavs University Hospital, Trondheim, Norway. [199]Psychosis Research Unit, Aarhus University Hospital - Psychiatry, Risskov, Denmark. [200]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. [201]University of Liverpool, Liverpool, UK. [202]Research/Psychiatry, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA. [203]Mental Health Services in the Capital Region of Denmark, Mental Health Center Copenhagen, University of Copenhagen, Copenhagen, Denmark. [204]Division of Psychiatry, Haukeland Universitetssjukehus, Bergen, Norway. [205]Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway. [206]Department of Clinical Neuroscience and Center for Molecular Medicine, Karolinska Institutet at Karolinska University Hospital, Solna, Sweden. [207]Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, USA. [208]University of Melbourne, VIC, Australia. [209]United Arab Emirates University, College of Medicine and Health Sciences, Department of Pathology, Al-Ain, United Arab Emirates. [210]United Arab Emirates University, Zayed Center of Health Sciences, Al-Ain, United Arab Emirates. [211]Psychiatry, Harvard Medical School, Boston, MA, USA. [212]Division of Clinical Research, Massachusetts General Hospital, Boston, MA, USA. [213]Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. [214]Department of Clinical Genetics, Amsterdam Neuroscience, Vrije Universiteit Medical Center, Amsterdam, The Netherlands. [215]Department of Neurology and Neurosurgery, McGill University, Faculty of Medicine, Montreal, QC, Canada. [216]Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA. [217]Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy. [218]Department of Neuroscience, SUNY Upstate Medical University, Syracuse, NY, USA. [219]Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, USA. [220]Faculty of Medicine, University of Iceland, Reykjavik, Iceland. [221]Department of Psychiatry, Hospital Namsos, Namsos, Norway. [222]Department of Neuroscience, Norges Teknisk Naturvitenskapelige Universitet Fakultet for naturvitenskap og teknologi, Trondheim, Norway. [223]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [224]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [225]Department of Psychiatry, McGill University, Montreal, QC, Canada. [226]Dept of Psychiatry, Sankt Olavs Hospital Universitetssykehuset i Trondheim, Trondheim, Norway. [227]Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain. [228]Department of Psychology, Emory University, Atlanta, GA, USA. [229]Institute of Biological Psychiatry, Mental Health Services, Copenhagen University Hospital, Copenhagen, Denmark. [230]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. [231]Center for GeoGenetics, GLOBE Institute, University of Copenhagen, Copenhagen, Denmark. [232]Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia. [233]Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA. [234]Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, USA. [235]Department of Human Genetics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA. [236]These authors contributed equally as first authors: Niamh Mullins, Andreas J. Forstner. [237]These authors contributed equally as second authors: Kevin S. O'Connell, Brandon Coombes, Jonathan R. I. Coleman, Zhen Qiao. [238]These authors jointly supervised this work: Eli A. Stahl, Andrew McQuillin, Arianna Di Florio, Roel A. Ophoff, Ole A. Andreassen.
[*]Corresponding authors: Niamh Mullins, niamh.mullins@mssm.edu; Ole A. Andreassen, ole.andreassen@medisin.uio.no

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