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Citation for final published version:

Mullins, Niamh, Forstner, Andreas J., O'Connell, Kevin S., Coombes, Brandon, Coleman, Jonathan R. I., Qiao, Zhen, Als, Thomas D., Bigdeli, Tim B., Børte, Sigrid, Bryois, Julien, Charney, Alexander W., Drange, Ole Kristian, Gandal, Michael J., Hagenaars, Saskia P., Ikeda, Masashi, Kamitaki, Nolan, Kim, Minsoo, Krebs, Kristi, Panagiotaropoulou, Georgia, Schilder, Brian M., Sloofman, Laura G., Steinberg, Stacy, Trubetskoy, Vassily, Winsvold, Bendik S., Won, Hong-Hee, Abramova, Liliya, Adorjan, Kristina, Agerbo, Esben, Al Eissa, Mariam, Albani, Diego, Alliey-Rodriguez, Ney, Anjorin, Adebayo, Antilla, Verner, Antoniou, Anastasia, Awasthi, Swapnil, Baek, Ji Hyun, Bækvad-Hansen, Marie, Bass, Nicholas, Bauer, Michael, Beins, Eva C., Bergen, Sarah E., Birner, Armin, Bøcker Pedersen, Carsten, Bøen, Erlend, Boks, Marco P., Bosch, Rosa, Brum, Murielle, Brumpton, Ben M., Brunkhorst-Kanaan, Nathalie, Budde, Monika, Bybjerg-Grauholm, Jonas, Byerley, William, Cairns, Murray, Casas, Miquel, Cervantes, Pablo, Clarke, Toni-Kim, Cruceanu, Cristiana, Cuellar-Barboza, Alfredo, Cunningham, Julie, Curtis, David, Czerski, Piotr M., Dale, Anders M., Dalkner, Nina, David, Friederike S., Degenhardt, Franziska, Djurovic, Srdjan, Dobbyn, Amanda L., Douzenis, Athanassios, Elvsåshagen, Torbjørn, Escott-Price, Valentina, Ferrier, I. Nicol, Fiorentino, Alessia, Foroud, Tatiana M., Forty, Liz, Frank, Josef, Frei, Oleksandr, Freimer, Nelson B., Frisén, Louise, Gade, Katrin, Garnham, Julie, Gelernter, Joel, Giørtz Pedersen, Marianne, Gizer, Ian R., Gordon, Scott D., Gordon-Smith, Katherine, Greenwood, Tiffany A., Grove, Jakob, Guzman-Parra, José, Ha, Kyooseob, Haraldsson, Magnus, Hautzinger, Martin, Heilbronner, Urs, Hellgren, Dennis, Herms, Stefan, Hoffmann, Per, Holmans, Peter A., Huckins, Laura, Jamain, Stéphane, Johnson, Jessica S., Kalman, Janos L., Kamatani, Yoichiro, Kennedy, James L., Kittel-Schneider, Sarah, Knowles, James A., Kogevinas, Manolis, Koromina, Maria, Kranz, Thorsten M., Kranzler, Henry R., Kubo, Michiaki, Kupka, Ralph, Kushner, Steven A., Lavebratt, Catharina, Lawrence, Jacob, Leber, Markus, Lee, Heon-Jeong, Lee, Phil H., Levy, Shawn E., Lewis, Catrin, Liao, Calwing, Lucae, Susanne, Lundberg, Martin, MacIntyre, Donald J., Magnusson, Sigurdur H., Maier, Wolfgang, Maihofer, Adam, Malaspina, Dolores, Maratou, Eirini, Martinsson, Lina, Mattheisen, Manuel, McCarroll, Steven A., McGregor, Nathaniel W., McGuffin, Peter, McKay, James D., Medeiros, Helena, Medland, Sarah E., Millischer, Vincent, Montgomery, Grant W., Moran, Jennifer L., Morris, Derek W., Mühleisen, Thomas W., O'Brien, Niamh, O'Donovan, Claire, Olde Loohuis, Loes M., Oruc, Lilijana, Papiol, Sergi, Pardini, Antonio F., Perry, Amy, Pfennig, Andrea, Porichi, Evgenia, Potash, James B., Quedstedt, Digby, Raj, Towfique, Rapaport, Mark H., DePaulo, J. Raymond, Regeer, Eline J., Rice, John P., Rivas, Fabio, Rivera, Margarita, Roth, Julian, Roussos, Panos, Rudolf, Douglas M., Sánchez-Mora, Cristina, Schulte, Eva C., Senner, Fanny, Sharp, David, Shilling, Paul D., Sigurdsson, Engilbert, Sirignano, Lea, Slaney, Claire, Smeeth, David B., Smith, Daniel J., Sobell, Janet L., Sørholm Hansen, Christine, Soler Artigas, Maria, Spijker, Anne T., Stein, Dan J., Strauss, John S., Świątkowska, Beata,

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10.1038/s41588-021-00857-4

Publishers page: <http://dx.doi.org/10.1038/s41588-021-00857-4>

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Title: Genome-wide association study of over 40,000 bipolar disorder cases provides new insights into the underlying biology

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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, encoding druggable targets such as HTR6, MCHR1, DCLK3 and FURIN. 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 worldwide¹. This, combined with the typical onset in young adulthood, an often chronic course, and increased risk of suicide², make BD a major public health concern and a major cause of global disability¹. 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 episode³. 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 development⁶. 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_{SNP}^2) estimation using the same data, suggested that common genetic variants genome-wide explain ~20% of BD's phenotypic variance²⁴. 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 signaling²⁴, glutamate receptor signaling²⁷ and calcium channel activity⁹.

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 (iPSYCH³⁰, deCODE genetics³¹, Estonian Biobank³², Trøndelag Health Study (HUNT)³³ and UK Biobank³⁴), 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_{SNP}^2 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).

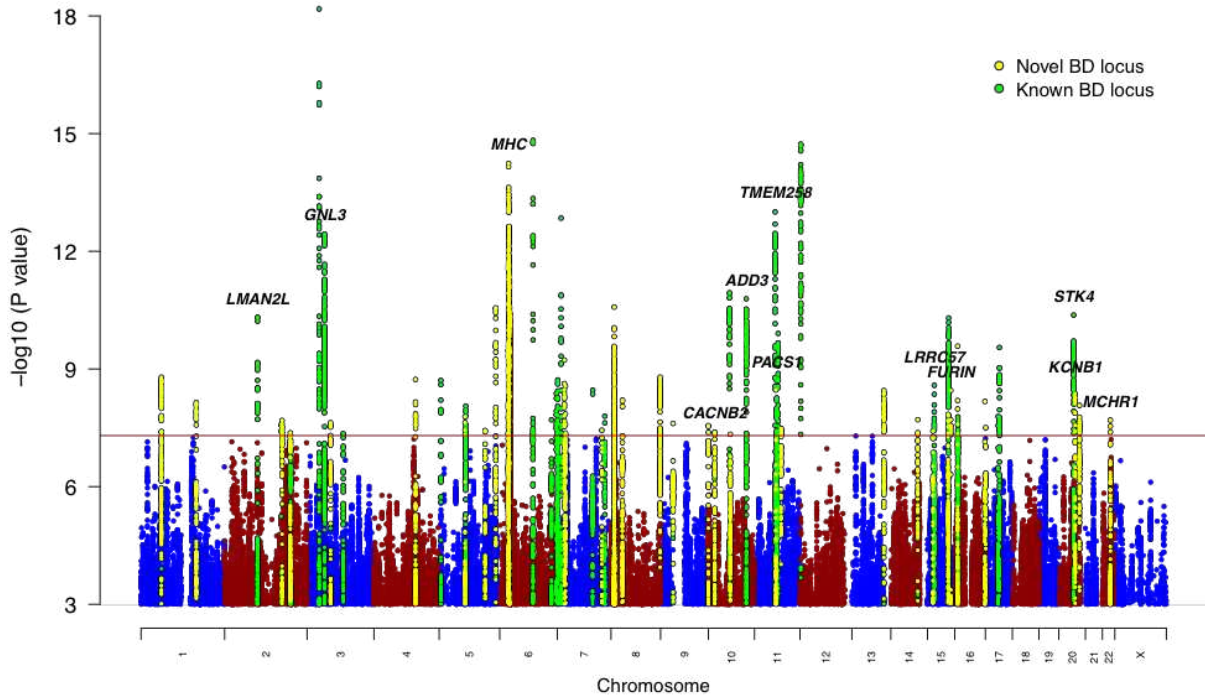


Figure 1: Manhattan plot of genome-wide association meta-analysis of 41,917 bipolar disorder cases and 371,549 controls

The x-axis shows genomic position (chromosomes 1-22 and X) and the y-axis shows statistical significance as $-\log_{10}(P \text{ value})$. P values are two-sided and based on an inverse variance weighted fixed effects meta-analysis. 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 (BD) 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*).

Enrichment analyses

Genome-wide analyses using MAGMA³⁷ 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 DGldb v.2³⁹ and the Psychoactive Drug Screening Database Ki DB⁴⁰), the targets of the calcium channel blockers mibefradil and nisoldipine were significantly enriched (Table S7). Grouping drugs according to their Anatomical Therapeutic Chemical (ATC) classes⁴¹, 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 FUSION⁴² 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 FOCUS⁴⁴ 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 PsychENCODE⁴³ 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 *PACSN2*.

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).

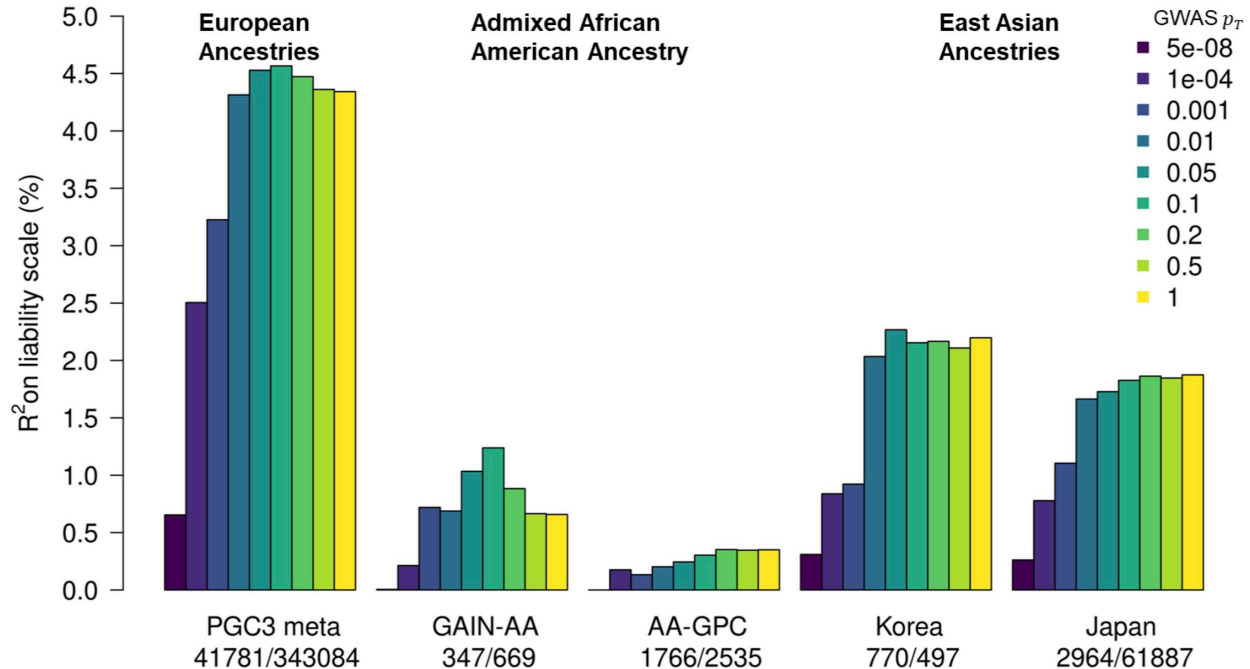


Figure 2: Phenotypic variance in bipolar disorder explained by polygenic risk scores

Variance explained is presented on the liability scale, assuming a 2% population prevalence of bipolar disorder. For European ancestries, the results shown are the weighted mean R^2 values across all 57 cohorts in the PGC3 meta-analysis, weighted by the effective N per cohort. The numbers of cases and controls are shown from left to right 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 Hub⁴⁸. 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_{SNP}^2 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 LDSC³⁵, generalized summary statistics-based Mendelian randomization (GSMR)⁵¹ and bivariate gaussian mixture modeling⁴⁹. BD has been strongly linked with sleep disturbances⁵², alcohol use⁵³ and smoking⁵⁴, higher educational attainment^{55,56} and mood instability⁵⁷. 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 bidirectional 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 disorders⁵⁸. 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).

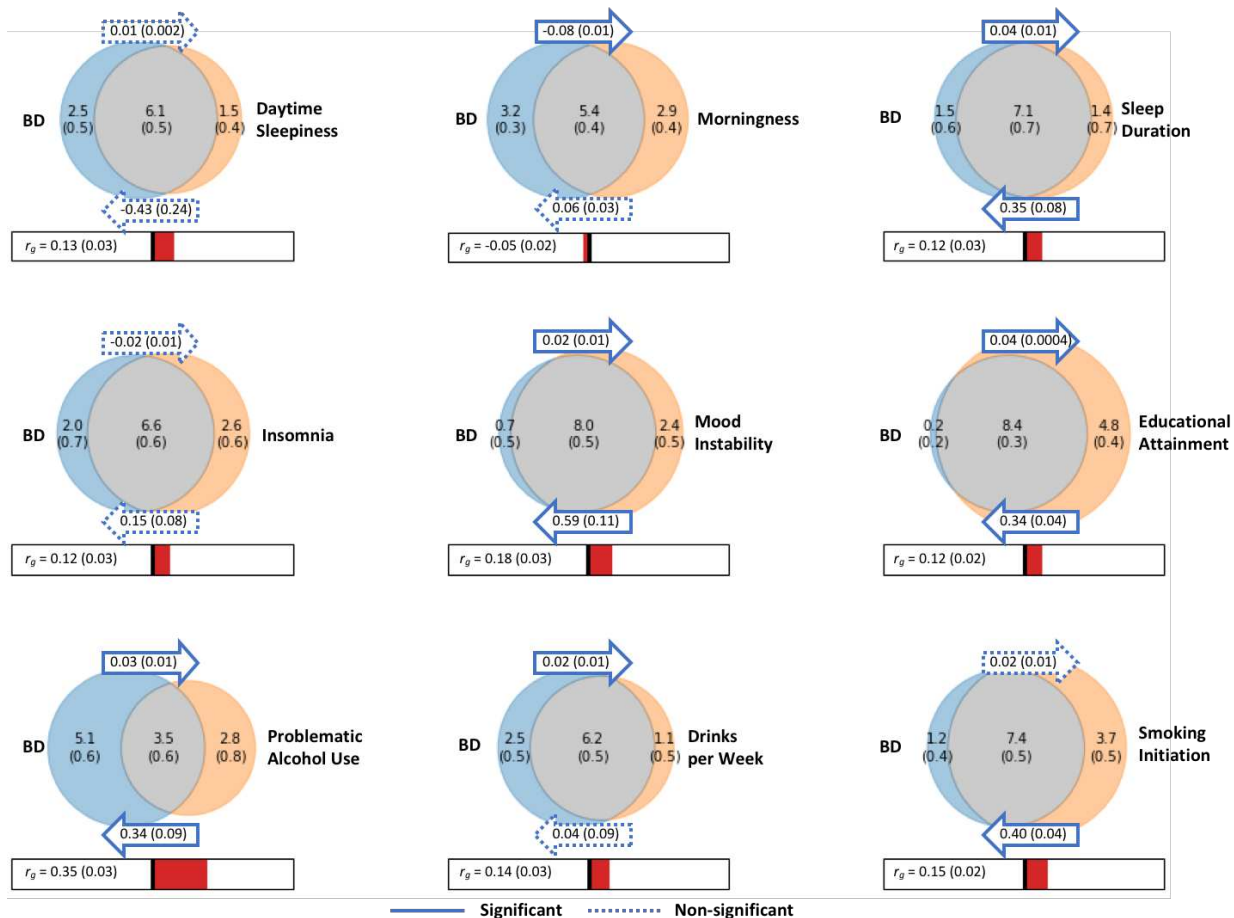


Figure 3: Relationships between bipolar disorder and modifiable risk factors based on genetic correlations, generalized summary statistics-based Mendelian randomization and bivariate gaussian mixture modeling

Venn diagrams depict MiXeR results of the estimated number of influencing variants shared between bipolar disorder (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_{SNP}^2 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 GWAS²⁴ and several implicated by other BD GWAS^{15,16,17}, including a study of East Asian cases⁵⁹.

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 schizophrenia⁶⁰, and seven in GWAS of major depression⁶¹, representing the first overlap of genome-wide significant loci between the mood disorders. For these genome-wide significant 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 consistent 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 effects⁶². 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 expression⁶³. 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 gene⁶⁴ 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 disturbances⁶⁷, problematic alcohol use⁶⁸ and smoking⁶⁹. 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 report⁷⁰. [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 antidepressants⁷³ and *MCHR1* (melanin-concentrating hormone receptor 1), encoding a target of the antipsychotic haloperidol⁷³. 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 BD⁷⁴. BD was associated with decreased expression of *FURIN*, a gene with a neurodevelopmental role which has already been the subject of functional genomics experiments in neuronal cells, following its association with schizophrenia in GWAS⁷⁵. 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* expression⁷⁶, 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 experiments²⁹. 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 treatments⁸¹.

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 BD⁸²⁻⁸⁴. Dysregulation of such pathways has also been suggested by previous functional and animal studies⁸⁵. 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 schizophrenia⁸⁶ and major depressive disorder³⁸.

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_{SNP}^2 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_{SNP}^2 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_{SNP}^2 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 cases⁹, known to be the most heritable of the BD subtypes^{11,24}, while later waves included more individuals with

BD II²⁴. Overall, the h_{SNP}^2 of BD calculated from the meta-analysis summary statistics was 18% on the liability scale, a decrease of ~2% compared with the PGC2 GWAS²⁴, which may be due to the addition of cohorts with lower h_{SNP}^2 estimates and heterogeneity between cohorts (Table S3). However, despite differences in h_{SNP}^2 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 ancestry⁵⁹. 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_{SNP}^2 . 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 size⁶⁰. 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 findings²⁴, 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 BD⁹¹. 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.

Acknowledgements

We thank the participants who donated their time, life experiences and DNA to this research and the clinical and scientific teams that worked with them. We are deeply indebted to the investigators who comprise the PGC. 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 and the

Mount Sinai high performance computing cluster (<http://hpc.mssm.edu>), which is supported by the Office of Research Infrastructure of the National Institutes of Health under award numbers S10OD018522 and S10OD026880. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Full acknowledgements are included in the Supplementary Note.

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Obtained funding for BD samples:

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Competing interests

T.E. Thorgeirsson, S.H. Magnusson, 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.

References (for main text *only*)

Figure Legends

Tables

Locus	CHR	BP	SNP	P	OR	SE	A1/A2	A1 freq in controls	Previous report ^A for BD (citation)	Name for novel locus ⁺	Previous report ^A 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		<i>CERS6</i>	
6	2	193738336	rs2011302	4.3E-08	1.055	0.010	A/T	0.377		<i>PCGEM1</i>	CDG
7	2	194437889	rs2719164	4.9E-08	1.053	0.010	A/G	0.564	<i>intergenic (PGC2)</i>		CDG
8*	3	36856030	rs9834970	6.6E-19	1.087	0.009	C/T	0.481	<i>TRANK1 (PGC2)</i>		SCZ, CDG
9*	3	52626443	rs2336147	3.6E-13	1.070	0.009	T/C	0.498	<i>ITIH1 (PGC2)</i>		SCZ, CDG
10	3	70488788	rs115694474	2.4E-08	1.068	0.012	T/A	0.799		<i>MDFIC2</i>	
11	3	107757060	rs696366	4.5E-08	1.053	0.009	C/A	0.550	<i>CD47 (PGC2)</i>		
12*	4	123076007	rs112481526	1.9E-09	1.065	0.011	G/A	0.256		<i>KIAA1109</i>	MD
13*	5	7542911	rs28565152	2.0E-09	1.070	0.011	A/G	0.238	<i>ADCY2 (PGC2)</i>		
14*	5	78849505	rs6865469	1.7E-08	1.060	0.010	T/G	0.274		<i>HOMER1</i>	
15	5	80961069	rs6887473	8.8E-09	1.062	0.011	G/A	0.739	<i>SSBP2 (PGC2)</i>		
16*	5	137712121	rs10043984	3.7E-08	1.062	0.011	T/C	0.236		<i>KDM3B</i>	CDG
17	5	169289206	rs10866641	2.8E-11	1.065	0.009	T/C	0.575		<i>DOCK2</i>	
18*	6	26463575	rs13195402	5.8E-15	1.146	0.018	G/T	0.919		<i>MHC</i>	MD, SCZ, CDG, MOOD
19*	6	98565211	rs1487445	1.5E-15	1.078	0.009	T/C	0.487	<i>POU3F2 (PGC2)</i>		CDG
20	6	152793572	rs4331993	2.0E-08	1.056	0.010	A/T	0.382	<i>SYNE1 (Green, 2013)</i>		
21*	6	166995260	rs10455979	4.2E-09	1.057	0.010	G/C	0.500	<i>RPS6KA2 (PGC2)</i>		

22*	7	2020995	rs12668848	1.9E-09	1.059	0.010	G/A	0.575	<i>MAD1L1</i> (Hou, 2016, Ikeda, 2017)		MD, SCZ, CDG
23*	7	11871787	rs113779084	1.4E-13	1.079	0.010	A/G	0.299	<i>THSD7A</i> (PGC2)		
24*	7	21492589	rs6954854	5.9E-10	1.060	0.009	G/A	0.425		<i>SP4</i>	
25	7	24647222	rs12672003	2.7E-09	1.096	0.016	G/A	0.113		<i>MPP6</i>	SCZ, CDG, MOOD
26	7	105043229	rs11764361	3.5E-09	1.063	0.010	A/G	0.668	<i>SRPK2</i> (PGC2)		SCZ, ASD, CDG
27	7	131870597	rs6946056	3.7E-08	1.055	0.010	C/A	0.623		<i>PLXNA4</i>	
28	7	140676153	rs10255167	1.6E-08	1.068	0.012	A/G	0.778	<i>MRPS33</i> (PGC2)		CDG
29*	8	9763581	rs62489493	2.6E-11	1.094	0.014	G/C	0.128		<i>miR124-1</i>	SCZ, ALC, ASD
30*	8	10226355	rs3088186	2.1E-08	1.058	0.010	T/C	0.287		<i>MSRA</i>	SCZ, ALC, ASD
31	8	34152492	rs2953928	6.3E-09	1.124	0.020	A/G	0.067		<i>RP1-84O15.2</i> (lincRNA)	SCZ, ADHD, CDG
32*	8	144993377	rs6992333	1.6E-09	1.062	0.010	G/A	0.410		<i>PLEC</i>	
33	9	37090538	rs10973201	2.5E-08	1.101	0.017	C/T	0.110		<i>ZCCHC7</i>	MD, CDG, MOOD
34*	9	141066490	rs62581014	2.8E-08	1.067	0.012	T/C	0.366		<i>TUBBP5</i>	
35*	10	18751103	rs1998820	4.1E-08	1.087	0.015	T/A	0.886		<i>CACNB2</i>	SCZ, CDG
36*	10	62322034	rs10994415	1.1E-11	1.125	0.017	C/T	0.082	<i>ANK3</i> (PGC2)		
37	10	64525135	rs10761661	4.7E-08	1.053	0.009	T/C	0.472		<i>ADO</i>	
38*	10	111648659	rs2273738	1.6E-11	1.096	0.014	T/C	0.135	<i>ADD3</i> (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		<i>RTN4RL1</i>	
57	17	38129841	rs11870683	2.8E-08	1.059	0.010	T/A	0.650	<i>ERBB2 (Hou, 2016)</i>		
58	17	38220432	rs61554907	1.6E-08	1.091	0.015	T/G	0.124	<i>ERBB2 (Hou, 2016)</i>		
59*	17	42191893	rs228768	2.8E-10	1.067	0.010	G/T	0.294	<i>HDAC5 (PGC2)</i>		
60*	20	43682551	rs67712855	4.2E-11	1.070	0.010	T/G	0.687	<i>STK4 (PGC2)</i>		
61*	20	43944323	rs6032110	1.0E-09	1.059	0.009	A/G	0.512	<i>WFDC12 (PGC2)</i>		
62*	20	48033127	rs237460	4.3E-09	1.057	0.009	T/C	0.412		<i>KCNB1</i>	CDG
63	20	60865815	rs13044225	8.5E-09	1.056	0.010	G/A	0.440		<i>OSBPL2</i>	
64	22	41153879	rs5758064	2.0E-08	1.054	0.009	T/C	0.523		<i>SLC25A17</i>	MD, SCZ, CDG, MOOD

CHR, chromosome; BP, GRCh37 base pair 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. P values are two-sided and based on an inverse variance weighted fixed effects meta-analysis.

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 ($4 * N_{cases} * N_{controls} / (N_{cases} + N_{controls})$), 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 (PGC1⁹, PGC2²⁴, 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 (iPSYCH³⁰, deCODE genetics³¹, Estonian Biobank³², Trøndelag Health Study (HUNT)³³ and UK Biobank³⁴), 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 (Japan⁵⁹ and Korea⁹²), 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

For 52 cohorts internal to the PGC, genotyping was performed following local protocols and genotypes were called using standard genotype calling softwares from commercial sources (Affymetrix and Illumina). Subsequently, standardized quality control, imputation and statistical analyses were performed centrally using RICOPIILI (Rapid Imputation for COnsortias PIpeLIine) (version 2018_Nov_23.001)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. Principal components (PCs) were generated using genotyped SNPs in each cohort separately using EIGENSTRAT v6.1.4⁹⁵. Based on visual inspection of plots of PCs for each dataset (which were all of European descent according to self-report/clinical data), we excluded samples to obtain more clearly homogeneous datasets. Genotype imputation was performed using the pre-phasing/ imputation stepwise approach implemented in Eagle v2.3.5⁹⁶ and Minimac3⁹⁷ to the Haplotype Reference Consortium (HRC) reference panel v1.0⁹⁸. Data on the X chromosome were available for 50 cohorts internal to the PGC and one external cohort (HUNT), and the X chromosome was imputed to the HRC reference panel in males and females separately within each cohort. 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 of these cohorts 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 v1.90⁹⁹, covarying for PCs 1-5 and any others 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 (version 2011-03-25)¹⁰⁰ across 57 cohorts for the autosomes (41,917 BD cases and 371,549 controls) and 51 cohorts for the X chromosome (35,691 BD cases and 96,731 controls). 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. Regional association plots and forest plots of the index SNP for all genome-wide significant loci are presented in Supplementary Data 1 and 2 respectively.

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 depression⁶¹, schizophrenia⁶⁰, attention deficit/hyperactivity disorder¹⁰¹, post-traumatic stress disorder¹⁰², lifetime anxiety disorder¹⁰³, Tourette's Syndrome¹⁰⁴, anorexia nervosa¹⁰⁵, alcohol use disorder or problematic alcohol use⁶⁸, autism spectrum disorder¹⁰⁶, mood disorders⁹¹ and the cross-disorder GWAS of the Psychiatric Genomics Consortium⁶⁶. The boundaries of the genome-wide significant loci were calculated in the original publications. Overlap of loci was calculated using bedtools v2.29.2¹⁰⁷.

Enrichment analyses

P values quantifying the degree of association of genes and gene sets with BD were calculated using MAGMA v1.08³⁷, implemented in FUMA v1.3.6a^{64,108}. 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)^{64,108}.

For single-cell enrichment analyses, publicly available single-cell RNA-seq data were compiled from five studies of the adult human and mouse brain^{86,109–112}. The mean expression for each gene in each cell type was computed from the single-cell expression data (if not provided). For the Zeisel dataset¹⁰⁹, we used the mean expression at level 4 (39 cell types from 19 regions for the mouse nervous system). For the Saunders dataset¹¹⁰, we computed the mean expression of the different classes in each of the 9 different brain regions sampled (88 cell types in total). We filtered out any genes with non-unique names, genes not expressed in any cell types, non-protein coding genes, and, for mouse datasets, genes that had no expert curated 1:1 orthologs between mouse and human (Mouse Genome Informatics, The Jackson laboratory, version 11/22/2016, <http://www.informatics.jax.org/downloads/reports/index.html#homology>), resulting in 16,472 genes. Gene expression was then scaled to a total of 1 million UMIs (unique molecular identifiers) (or transcript per million (TPM)) for each cell type/tissue. Using a previously described method³⁸, 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). We then selected the top 10% most specific genes for each cell type/tissue for enrichment analysis. MAGMA v1.08³⁷ was used to test gene-set enrichment using GWAS summary statistics, covarying for gene size, gene density, mean sample size for tested SNPs per gene, the inverse of the minor allele counts per gene and the log of these metrics. We excluded any SNPs with INFO score < 0.6, with MAF < 1% or with estimated odds ratio > 25 or smaller than 1/25, as well as SNPs located in the MHC region (chr6:25-34 Mb). We set a window of 35 kb upstream to 10 kb downstream of the gene coordinates to compute gene-level association statistics and used the European reference panel from the phase 3 of the 1000 genomes project as the reference population¹¹³. We then used MAGMA to test whether the 10% most specific genes (with an expression of at least 1 TPM or 1 UMI per million) for each cell type/tissue were associated with BD. The *P* value threshold for significance was *P* < 9.1E-03, representing a 5% false discovery rate (FDR) across datasets.

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 previously⁴¹. Gene-level

and gene-set analyses were performed in MAGMA v1.08³⁷. Gene boundaries were defined using build 37 reference data from the NCBI, available on the MAGMA website (<https://ctg.cncr.nl/software/magma>), extended 35kb upstream and 10kb downstream to include regulatory regions outside of the transcribed region. Gene-level association statistics were defined as the aggregate of the mean and the lowest variant-level P value within the gene boundary, converted to a Z-value. Gene sets were defined comprising the targets of each drug in the Drug-Gene Interaction database DGIdb v.2³⁹ and in the Psychoactive Drug Screening Database Ki DB⁴⁰, both downloaded in June 2016⁴¹. Analyses were performed using competitive gene-set analyses in MAGMA. Results from the drug-set analysis were then grouped according to the Anatomical Therapeutic Chemical class of the drug⁴¹. Only drug classes with at least 10 valid drug gene sets within them were analyzed. Drug-class analysis was performed using enrichment curves. All drug gene sets were ranked by their association in the drug set analysis, and then for a given drug class an enrichment curve was drawn scoring a "hit" if the drug gene set was within the class, or a "miss" if it was outside of the class. The area under the curve was calculated, and a p-value for this calculated as the Wilcoxon Mann-Whitney test comparing drug gene sets within the class to drug gene sets outside of the class⁴¹. Multiple testing was controlled using a Bonferroni-corrected significance threshold of $P < 5.60E-05$ for drug-set analysis and $P < 7.93E-04$ 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 software⁴². For genes with significant *cis*-SNP heritability (13,435 genes), FUSION software (vOct 1, 2019) 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, v0.6.10)⁴⁴. Regions were defined using the correlation matrix of predicted effects on gene expression around TWAS significant genes⁴⁴. A posterior inclusion probability (PIP) was assigned to each gene for being causal for the observed TWAS association signal. Based on the PIP of each gene and a null model, whereby no gene in the region is causal for the TWAS signal, the 90%-credible gene set for each region was computed⁴⁴.

Summary data-based Mendelian randomization (SMR) (v1.03)^{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 PsychENCODE⁴³ 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 $P_{\text{HEIDI}} \geq 0.01$ 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 cohort¹¹⁴. Briefly, imputation of *C4* as a multi-allelic variant was performed using Beagle v4.1^{115,116}, using SNPs from the MHC region that were also in the haplotype reference panel. Within the Beagle pipeline, the reference

panel was first converted to bref format. We used the conform-gt tool to perform strand-flipping and filtering of specific SNPs for which strand remained ambiguous. Beagle was run using default parameters with two key exceptions: we used the GRCh37 PLINK recombination map, and we set the output to include genotype probability (i.e., GP field in VCF) for correct downstream probabilistic estimation of *C4A* and *C4B* joint dosages. The output consisted of dosage estimates for each of the common *C4* structural haplotypes 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 $0.70 < r^2 < 1.00$). 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 described⁶³. 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.

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 v1.90⁹⁹ (r^2 0.1 within a 500 kb window) based on the LD structure of the HRC reference panel⁹⁸. 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 RICOPII^{94,99}. 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%¹¹⁷. 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 sample⁵⁹, a Korean sample⁹² 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_{SNP}^2 of BD from GWAS summary statistics. h_{SNP}^2 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 Hub⁴⁸. 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 causal mixture models^{49,118} to the GWAS summary statistics, using MiXeR v1.3. 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. For each SNP, i , univariate MiXeR models its additive genetic effect of allele substitution, β_i , as a point-normal mixture, $\beta_i = (1 - \pi_1)N(0,0) + \pi_1N(0, \sigma_\beta^2)$,

where π_1 represents the proportion of non-null SNPs ('polygenicity') and σ_β^2 represents variance of effect sizes of non-null SNPs ('discoverability'). Then, for each SNP, j , MiXeR incorporates LD information and allele frequencies for $M=9,997,231$ SNPs extracted from 1000 Genomes Phase3 data to estimate the expected probability distribution of the signed test statistic, $z_j = \delta_j + \epsilon_j = \sqrt{N}\Sigma_i \sqrt{H_i}r_{ij}\beta_i + \epsilon_j$, where N is sample size, H_i indicates heterozygosity of i -th SNP, r_{ij} indicates allelic correlation between i -th and j -th SNPs, and $\epsilon_j \sim N(0, \sigma_0^2)$ is the residual variance. Further, the three parameters, $\pi_1, \sigma_\beta^2, \sigma_0^2$, are fitted by direct maximization of the likelihood function. The optimization is based on a set of approximately 600,000 SNPs, obtained by selecting a random set of 2,000,000 SNPs with minor allele frequency of 5% or higher, followed by LD pruning procedure at LD $r^2=0.8$ threshold. The random SNP selection and full optimization procedure are repeated 20 times to obtain mean and standard errors of model parameters. The log-likelihood figures show individual curves for each of the 20 runs, each shifted vertically so that best log-likelihood point is shown at zero ordinate.

The total number of trait influencing variants is estimated as $M\pi_1$, where $M=9,997,231$ gives the number of SNPs in the reference panel. MiXeR Venn diagrams report the effective number of influencing variants, $\eta M\pi_1$, where η is a fixed number, $\eta=0.319$, which gives the fraction of influencing variants contributing to 90% of trait's heritability (with rationale for this adjustment being that the remaining 68.1% of influencing variants are small and cumulatively explain only 10% of trait's heritability). Phenotypic variance explained on average by an influencing genetic variant is calculated as $\underline{H}\sigma_\beta^2$, where $\underline{H} = \frac{1}{M}\sum_i H_i = 0.2075$ is the average heterozygosity across SNPs in the reference panel. Under the assumptions of the MiXeR model, SNP-heritability is then calculated as $h_{SNP}^2 = M\pi_1 \times \underline{H}\sigma_\beta^2$.

In the cross-trait analysis, MiXeR models additive genetic effects as a mixture of four components, representing null SNPs in both traits (π_0); SNPs with a specific effect on the first and on the second trait (π_1 and π_2 , respectively); and SNPs with non-zero effect on both traits (π_{12}). In the last component, MiXeR models variance-covariance matrix as $\Sigma_{12} = \begin{bmatrix} \sigma_1^2 & \rho_{12}\sigma_1\sigma_2 \\ \rho_{12}\sigma_1\sigma_2 & \sigma_2^2 \end{bmatrix}$ where ρ_{12} indicates correlation of effect sizes within the shared component, and σ_1^2 and σ_2^2 correspond to the discoverability parameter estimated in the univariate analysis of the two traits. These components are then plotted in Venn diagrams. After fitting parameters of the model, the Dice coefficient of polygenic overlap is then calculated as $\frac{2\pi_{12}}{\pi_1+2\pi_{12}+\pi_2}$, and genetic correlation is calculated as $r_g = \frac{\rho_{12}\pi_{12}}{\sqrt{(\pi_1+\pi_{12})(\pi_2+\pi_{12})}}$. Fraction of influencing variants with concordant effect direction is calculated as twice the multivariate normal CDF at point (0, 0) for the bivariate normal distribution with zero mean and variance-covariance matrix Σ_{12} . All code is available online (<https://github.com/precimed/mixer>).

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, implemented in GCTA software (v1.93.1f beta). 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 tests⁵¹, 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 ($P_{HEIDI} < 0.01$)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^{119,120}. To further investigate horizontal pleiotropy, the MR Egger intercept test was conducted using the TwoSampleMR package^{119,120} and MR-PRESSO software was used to perform the Global Test and Distortion Test¹²¹.

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) (Table S1) 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). LDSC³⁵ was used to estimate the h_{SNP}^2 of each subtype, and the genetic correlation between the subtypes. The difference between the LDSC h_{SNP}^2 estimates for BD I and BD II was tested for deviation from 0 using the block jackknife¹²². 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 $[(r_g - 1)/se]^2$.

Data availability

GWAS summary statistics are publicly available on the PGC website (<https://www.med.unc.edu/pgc/results-and-downloads>). Individual-level data are accessible through collaborative analysis proposals to 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) and the Haplotype Reference Consortium reference panel v1.0 (<http://www.haplotype-reference-consortium.org/home>). Databases used: Drug-Gene Interaction Database DGIdb v.2 <https://www.dgidb.org> Psychoactive Drug Screening Database Ki DB <https://pdsp.unc.edu/databases/kidb.php> DrugBank 5.0 www.drugbank.ca LDHub <http://ldsc.broadinstitute.org> FUMA <https://fuma.ctglab.nl>

Code availability

All software used is publicly available at the URLs or references cited.

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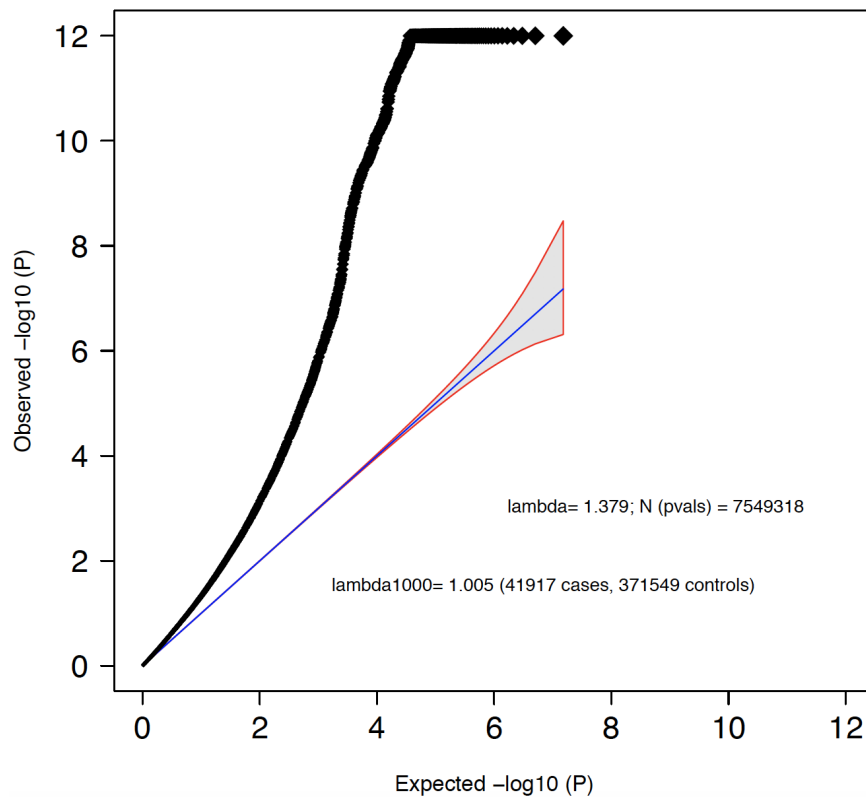
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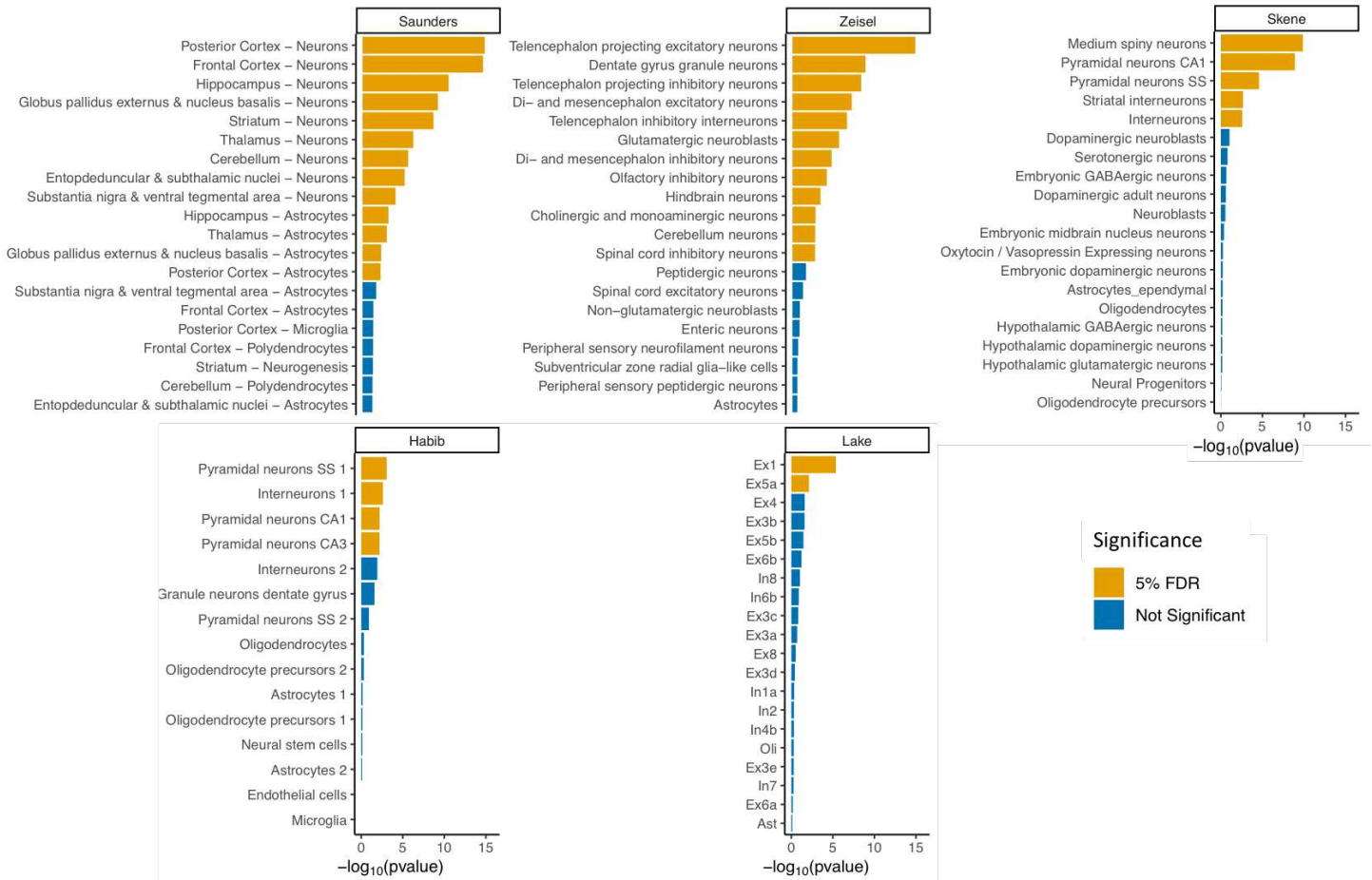
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Supplementary Figures: Genome-wide association study of over 40,000 bipolar disorder cases provides novel biological insights



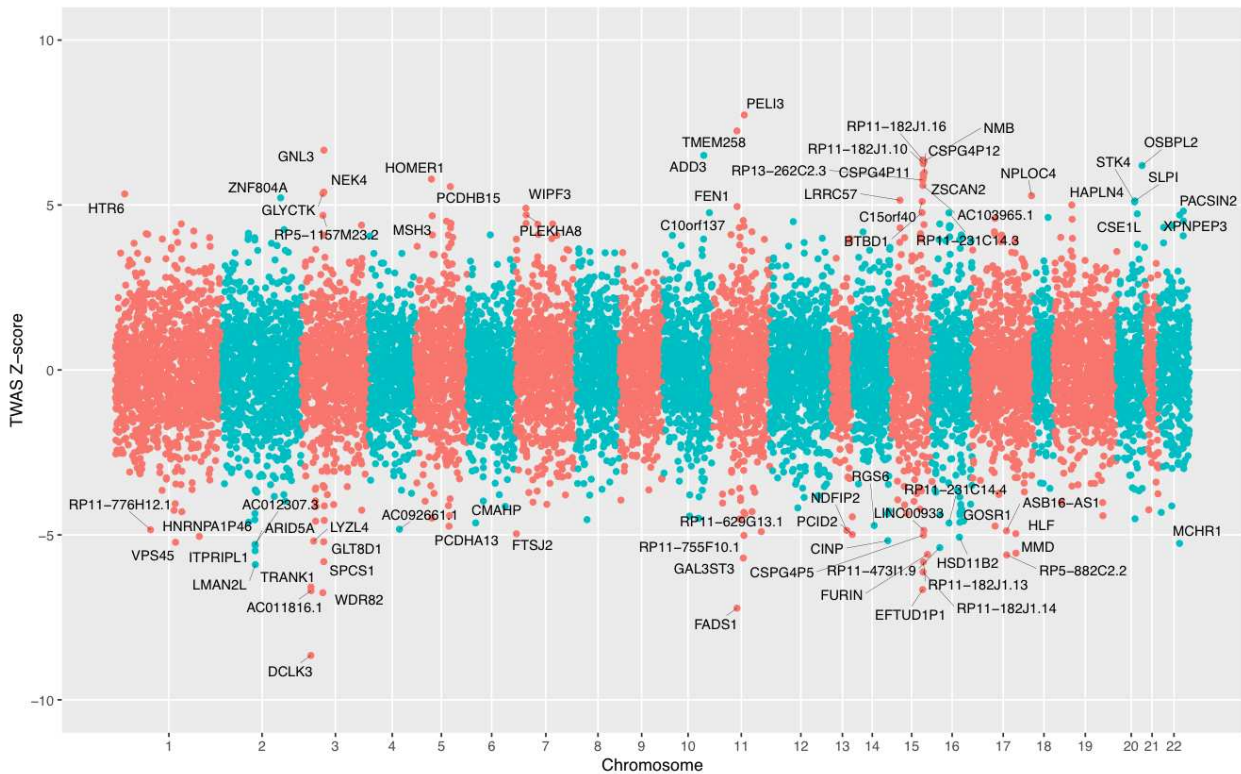
Supplementary Figure 1: Quantile-quantile plot of association test results from genome-wide association meta-analysis of bipolar disorder

The y axis is truncated at $P=1E-12$. SNPs plotted have a minor allele frequency $\geq 1\%$ and an imputation INFO score ≥ 0.6 . Observed results are based on an inverse variance weighted fixed effects meta-analysis of 41,917 bipolar disorder cases and 371,549 controls. P values are uncorrected and two-sided.



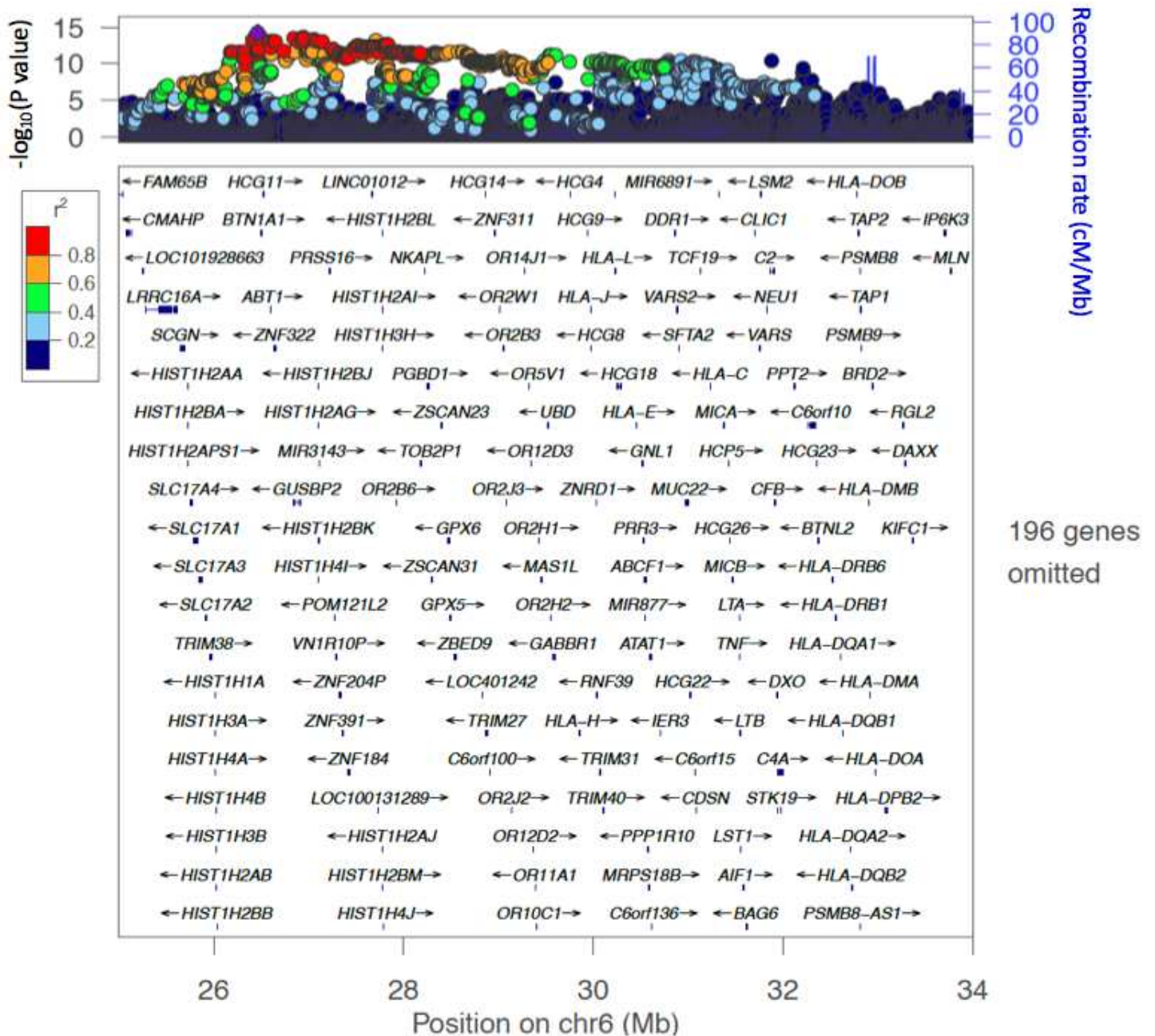
Supplementary Figure 2: Top brain cell types enriched for bipolar disorder association signal

The significance level ($-\log_{10}(\text{p value})$) of MAGMA is shown for the top 20 most associated cell types in diverse datasets. The genes tested for each cell type are the top 10% of genes most specifically expressed in that cell type compared with all other cell types in the dataset. The color indicates whether the cell type is enriched for BD association signal at a 5% false discovery rate (FDR) across datasets. P values are based on a linear regression and are uncorrected and one-sided. The Zeisel, Saunders and Skene datasets are derived from mouse samples, while the Habib and Lake datasets are derived from human samples. SS - somato-sensory cortex, Ex - excitatory, In - inhibitory, Oli - oligodendrocyte. The numbers after the cell types refer to the cluster of cells with a similar gene expression profile, defined using clustering algorithms in the original publications.



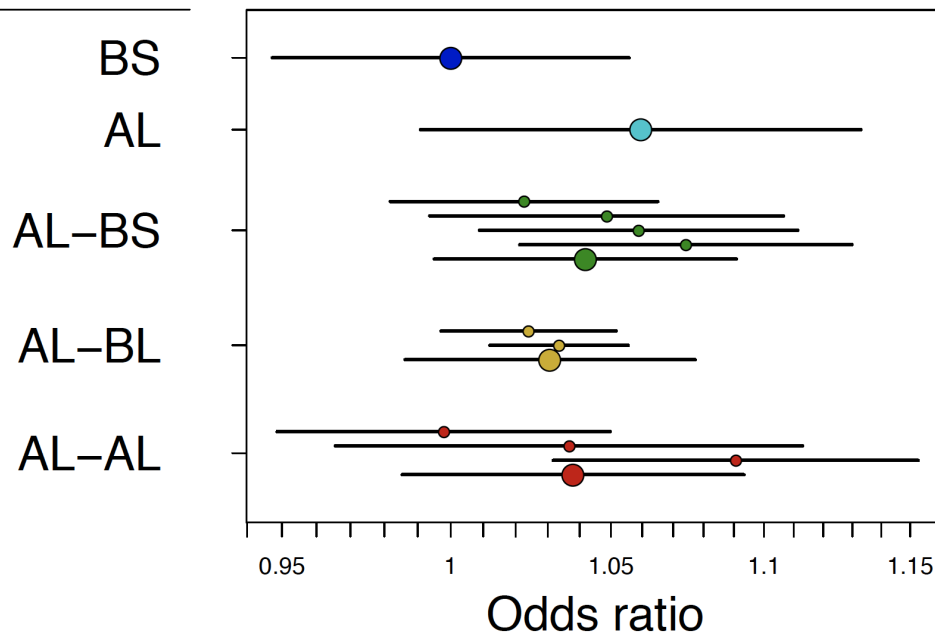
Supplementary Figure 3: Results of transcriptome-wide association study of bipolar disorder performed using FUSION and eQTL data from the PsychENCODE Consortium

Genes which are labeled passed the Bonferroni corrected significance threshold of $P < 3.72 \times 10^{-6}$, adjusting for 13,435 genes tested. Association results are based on two-sided tests conducted using least absolute shrinkage and selection operator (lasso), bayesian sparse linear mixed model (bslmm), elastic net or best linear unbiased prediction (blup) models. TWAS Z-score - direction of effect of bipolar disorder risk alleles on predicted gene expression level.



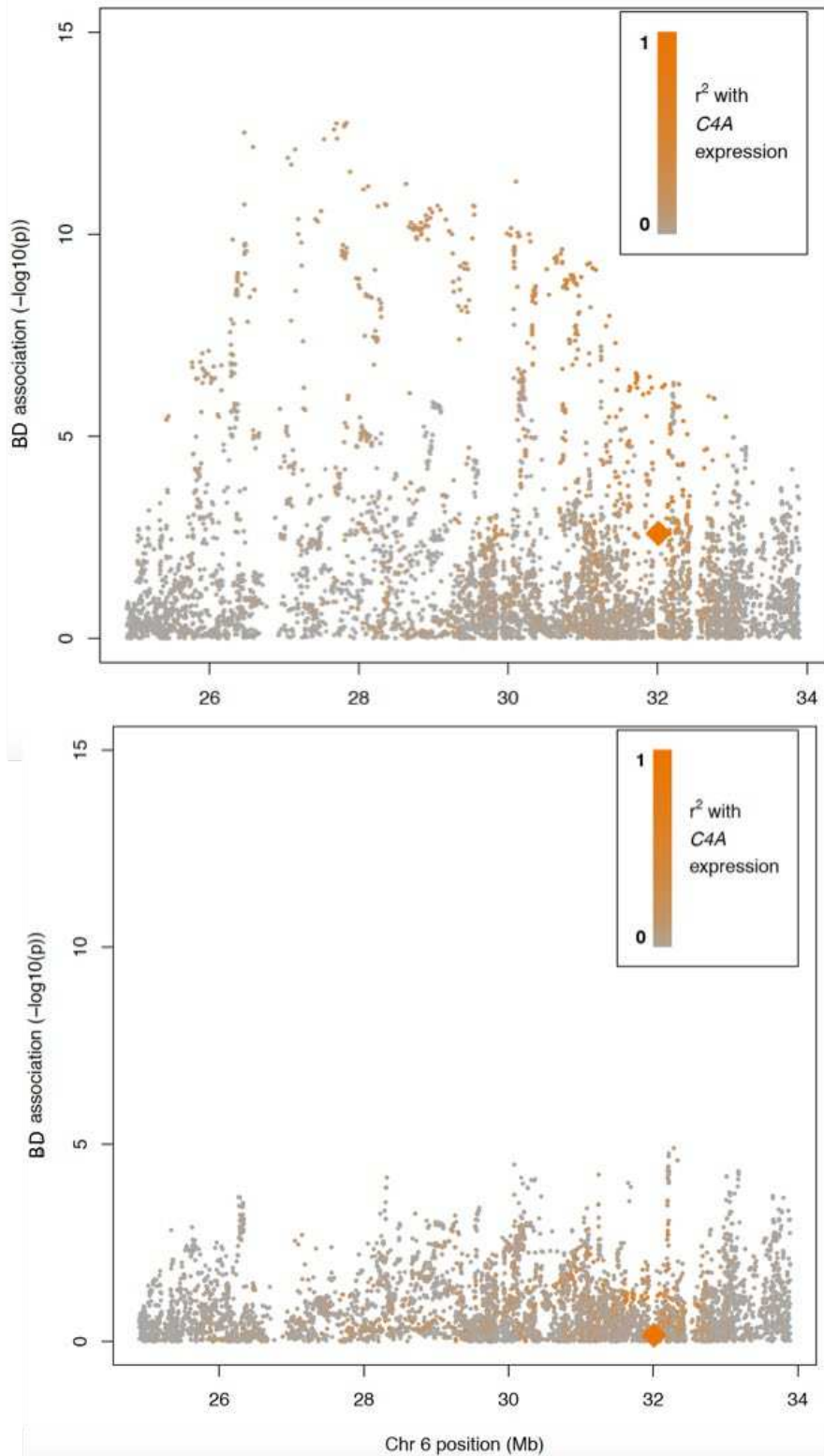
Supplementary Figure 4: Regional plot of bipolar disorder association statistics in the extended major histocompatibility complex (MHC)

The x axis shows genomic position and the y axis shows statistical significance as $-\log_{10}(P \text{ value})$. P values are based on an inverse variance weighted fixed effects meta-analysis of 41,917 bipolar disorder cases and 371,549 controls. P values are uncorrected and two-sided. SNPs are colored by linkage disequilibrium (r^2) to the top lead SNP rs13195402, which is shown as a purple diamond.



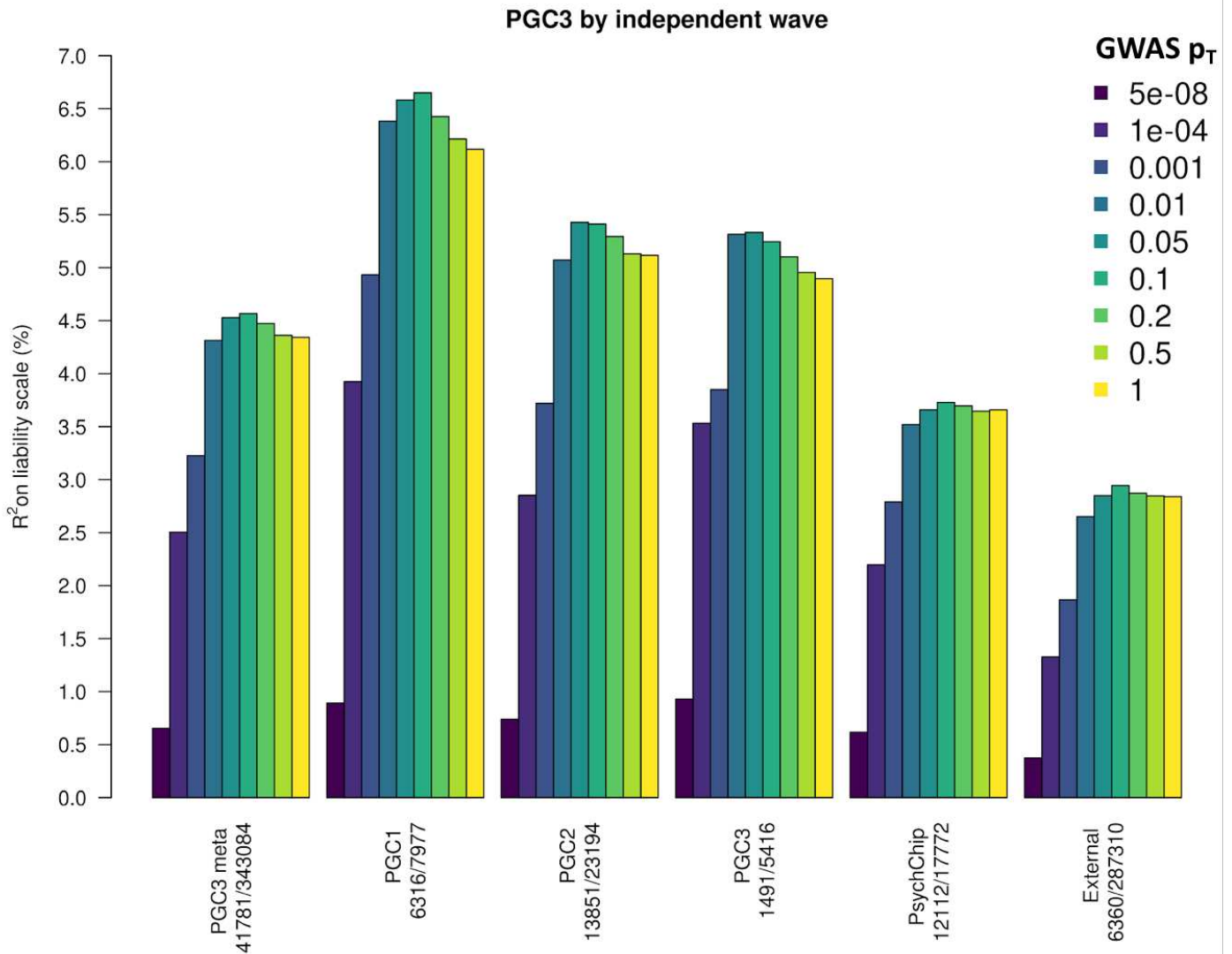
Supplementary Figure 5: Odds ratio for bipolar disorder for the five most common *C4* locus structures, in a joint analysis that includes lead SNP rs13195402

C4 alleles were imputed for 32,749 bipolar disorder cases and 53,370 controls. Odds ratios are calculated relative to the BS haplotype. Error bars represent the 95% confidence interval around the effect size estimate for each allele. Because many *C4* alleles have arisen on multiple SNP haplotype backgrounds, results are shown for each specific haplogroup (small circles) as well as their combined association (large circles). There is no clear difference in bipolar disorder risk levels across these *C4* haplotypes.



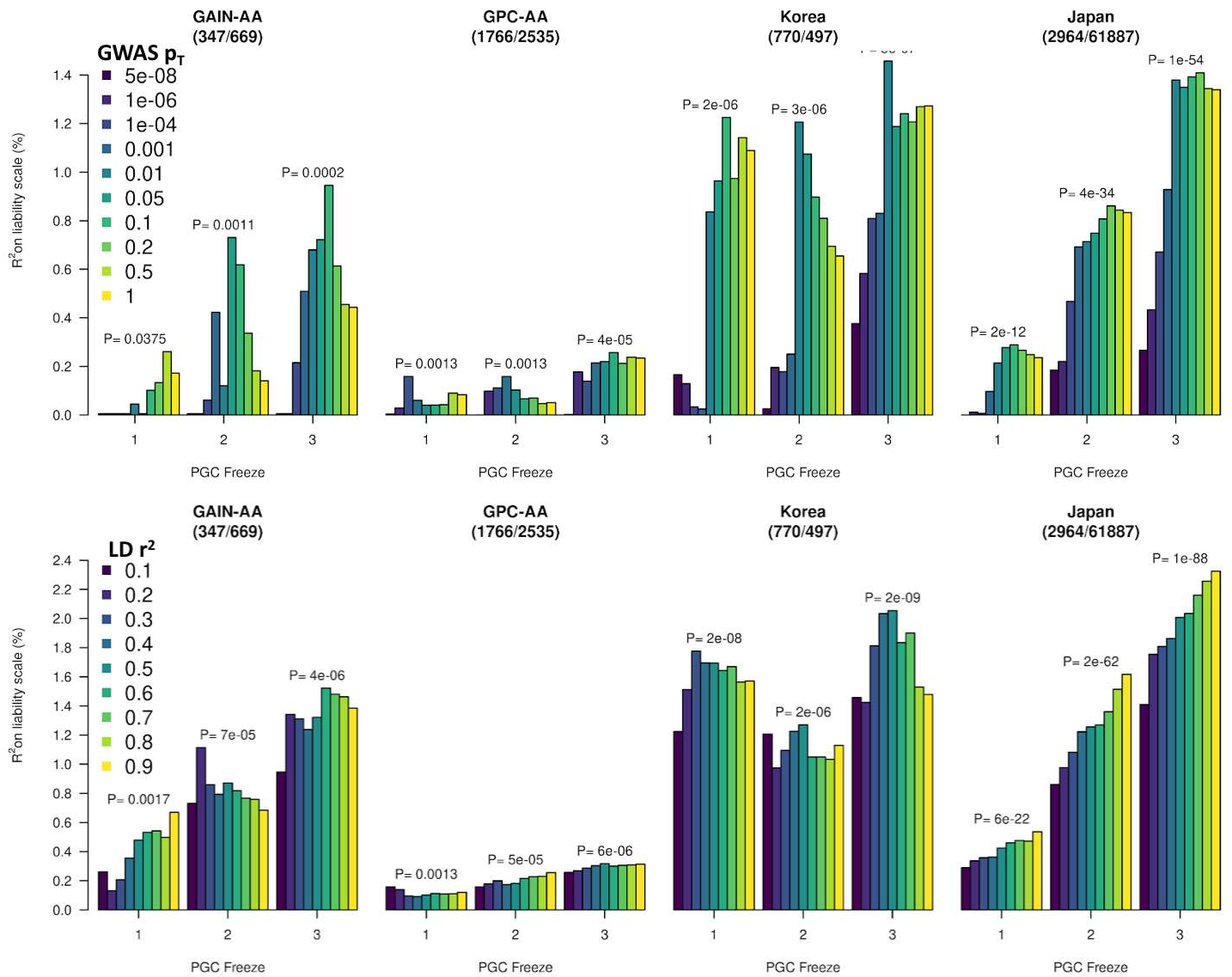
Supplementary Figure 6: Association of bipolar disorder to chromosome 6 variation around and within the MHC locus, including genetically predicted expression of *C4A*

The height of each point represents the statistical strength ($-\log_{10}(P \text{ value})$) of association with bipolar disorder (BD). Genetically predicted *C4A* expression is represented by the orange diamond. SNPs are colored by their level of correlation to genetically predicted *C4A* expression level. Above: unconditioned analysis. Below: Analysis conditional on rs13195402 (lead SNP in this region of chromosome 6). P values are based on logistic regression, are uncorrected and two-sided. Analyses were conducted in 32,749 bipolar disorder cases and 53,370 controls.



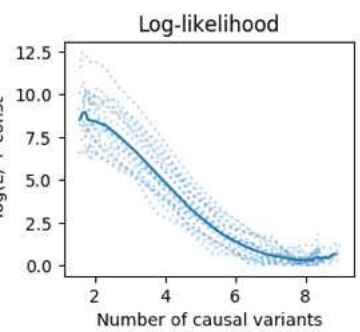
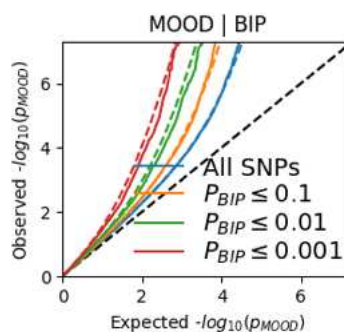
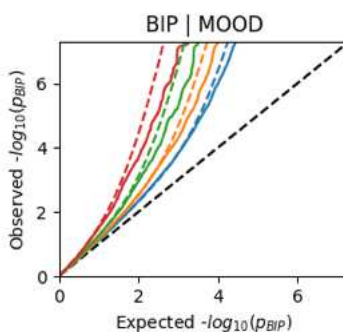
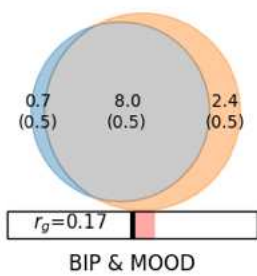
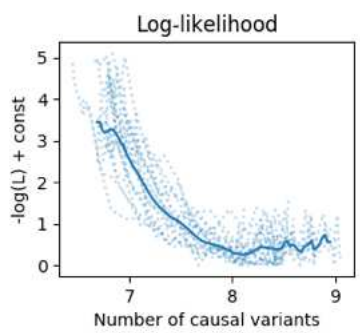
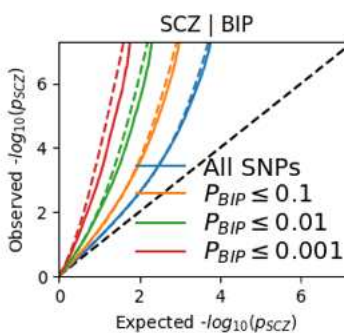
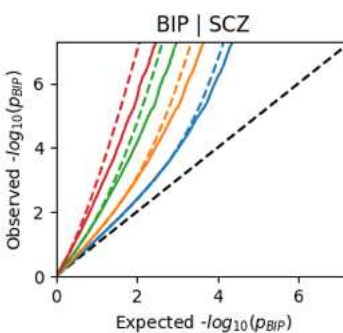
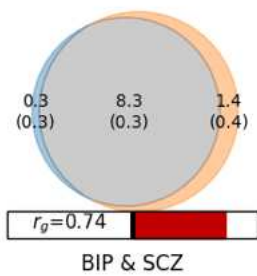
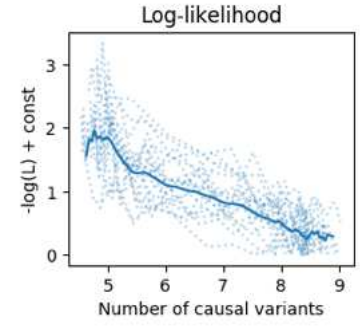
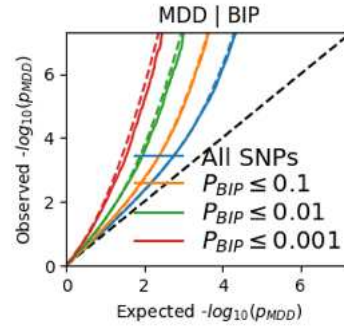
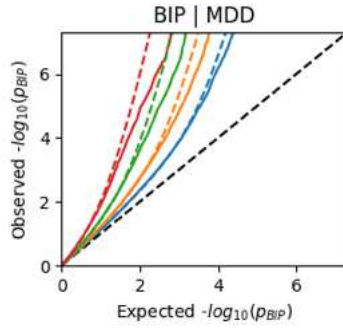
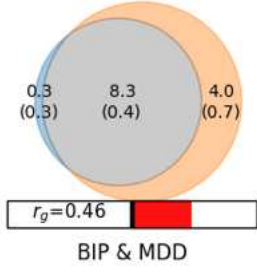
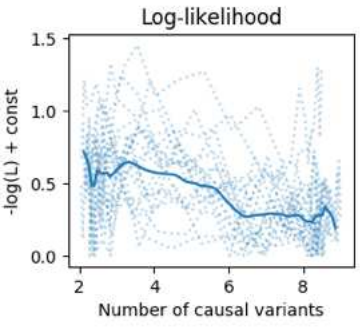
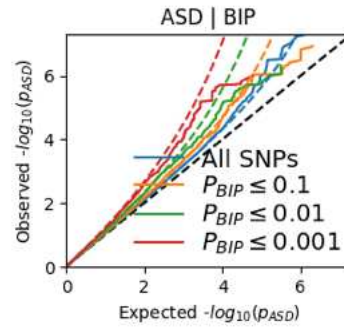
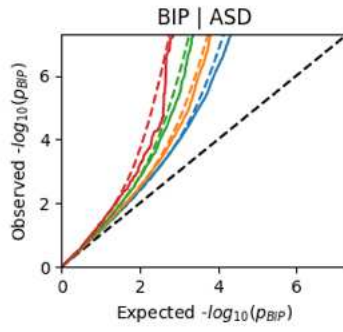
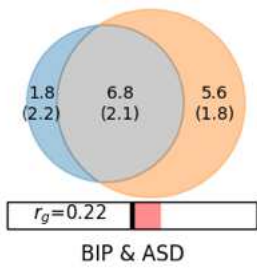
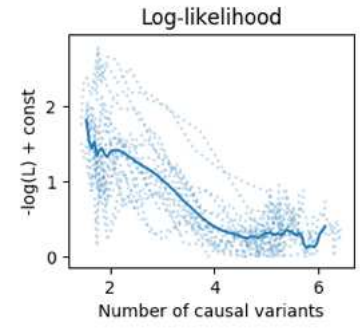
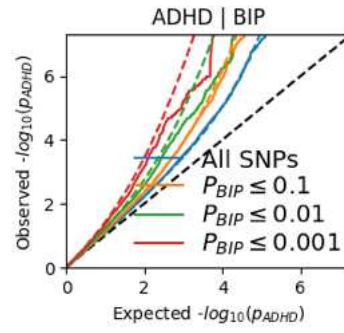
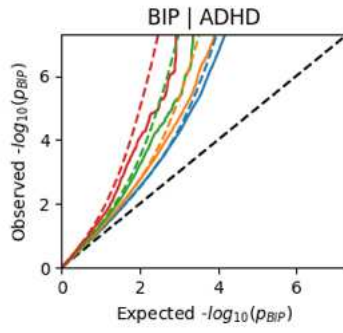
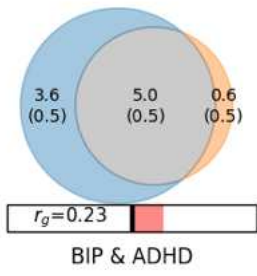
Supplementary Figure 7: Phenotypic variance in bipolar disorder explained by polygenic risk scores per independent wave of ascertainment to the PGC

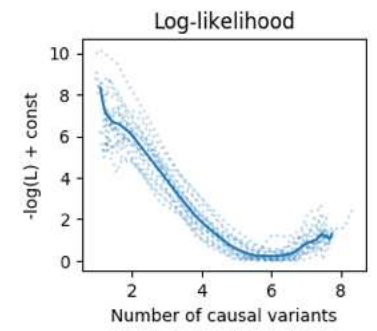
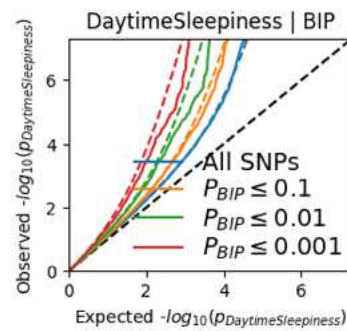
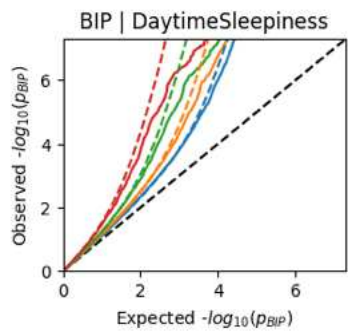
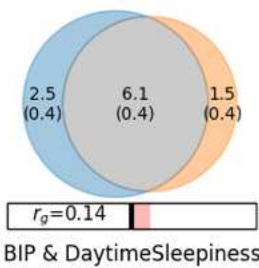
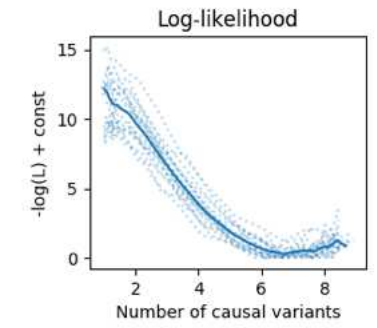
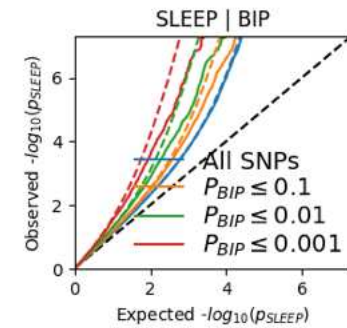
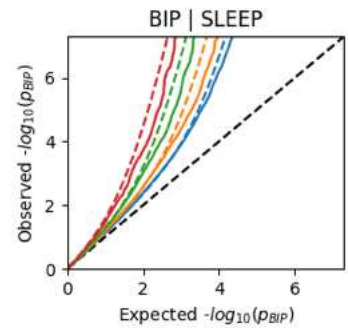
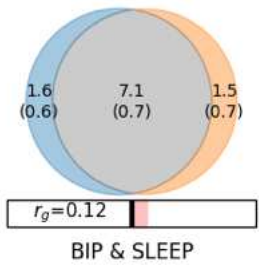
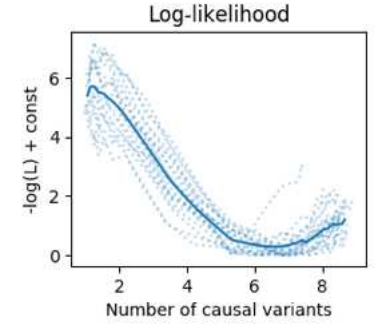
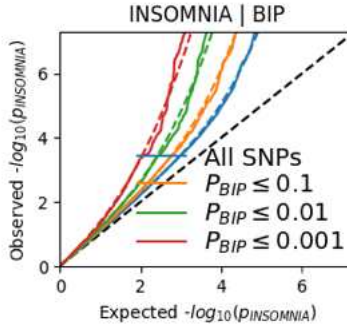
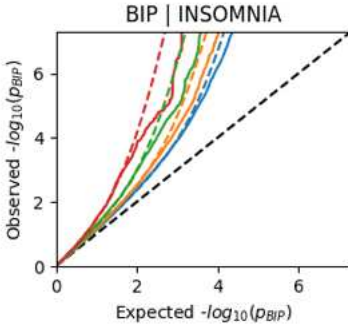
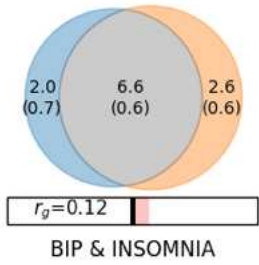
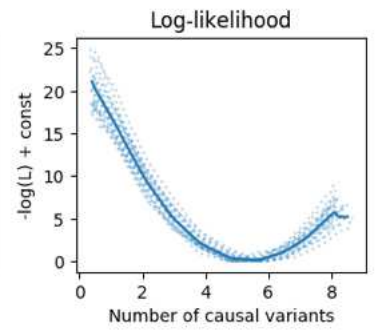
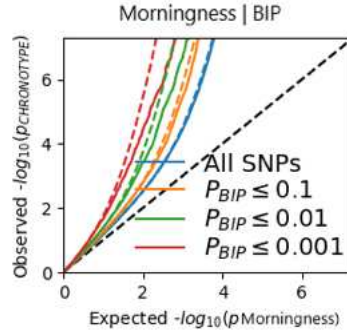
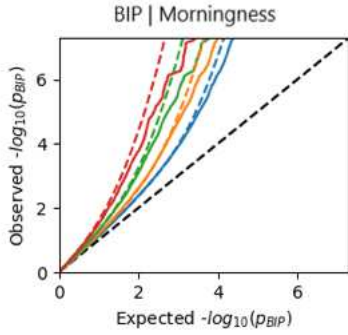
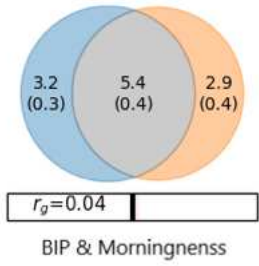
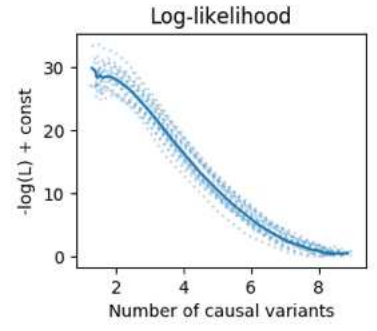
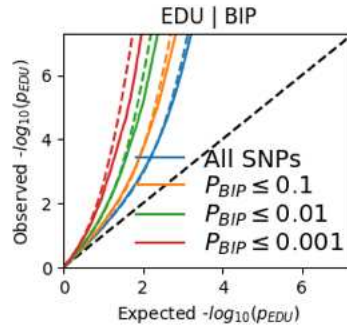
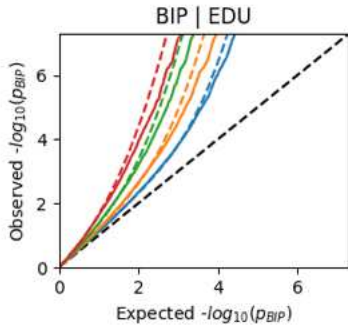
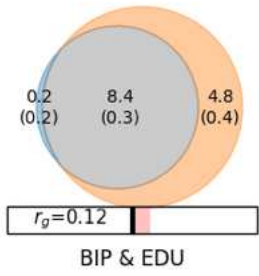
Variance explained is presented on the liability scale, assuming a BD population prevalence of 2%. Results are based on logistic regression. The results shown are the weighted average R^2 values within each wave, calculated weighted by the effective N per cohort. The numbers of cases and controls are shown under the barplot for each wave. The color of the bars represents the P value threshold used to select SNPs from the discovery GWAS. The leftmost barplot (“PGC3 meta”) shows the combined results of all waves (PGC1, PGC2, PGC3, PsychChip, External and follow-up [not shown in plot] datasets) and matches the European ancestry barplot in Figure 2.

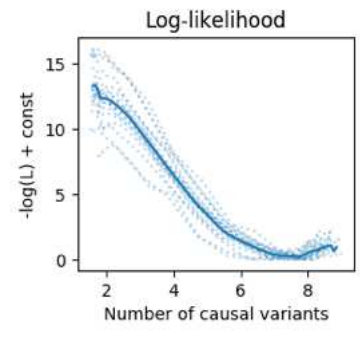
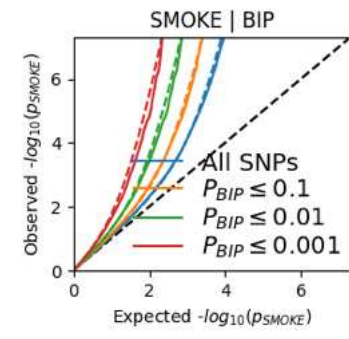
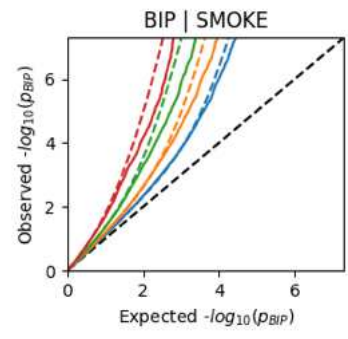
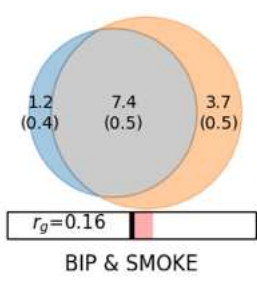
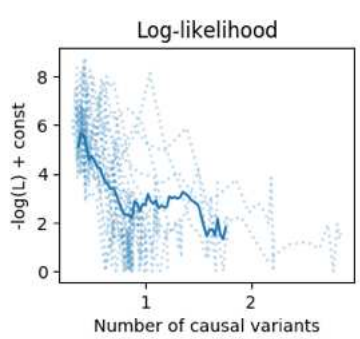
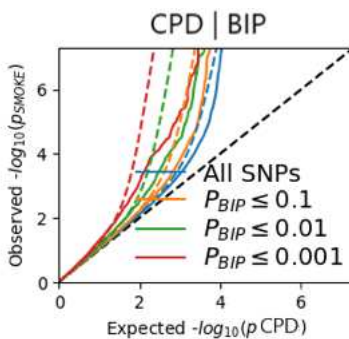
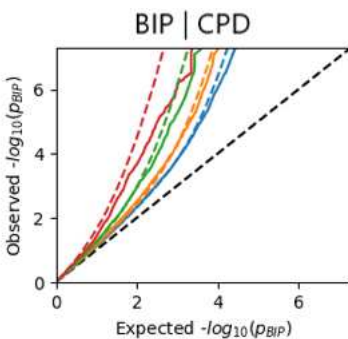
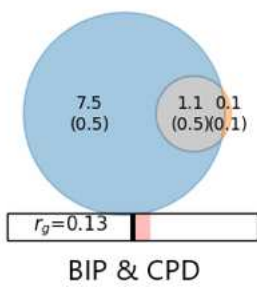
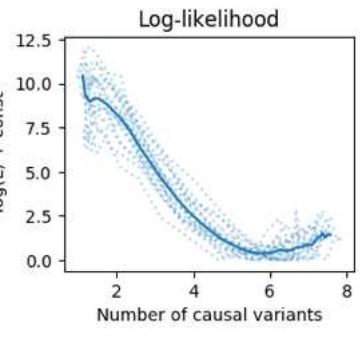
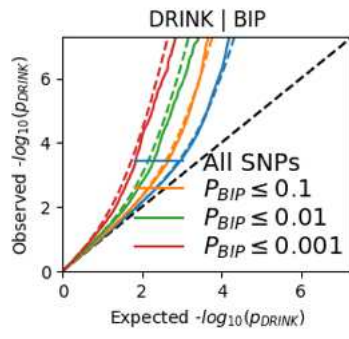
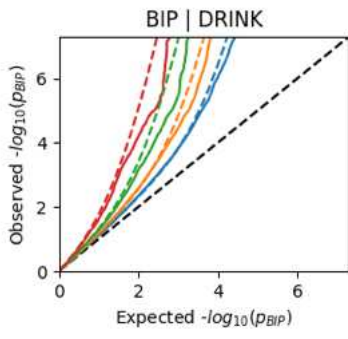
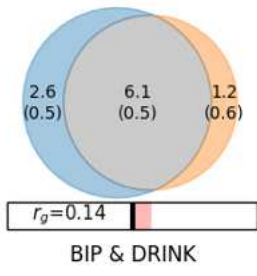
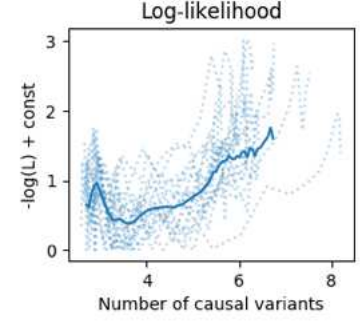
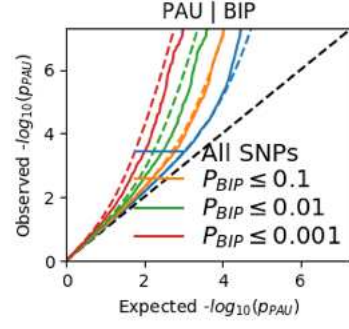
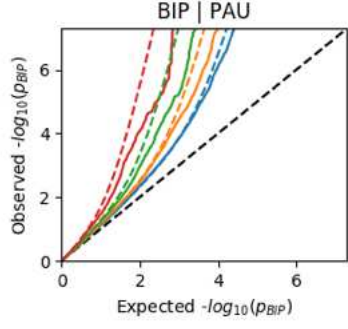
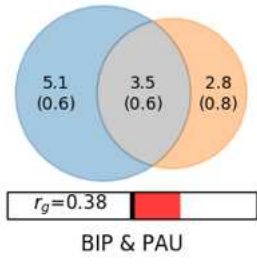
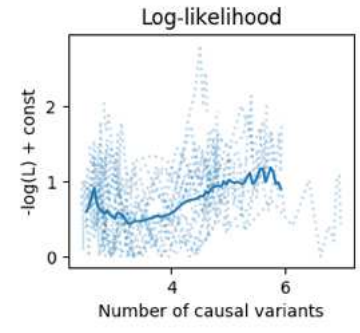
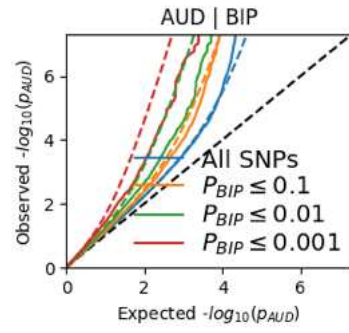
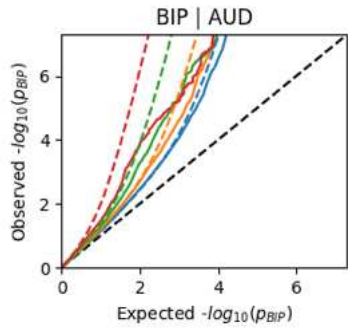
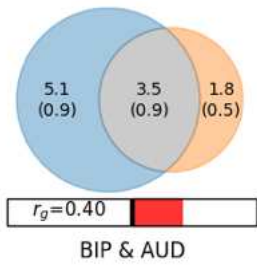


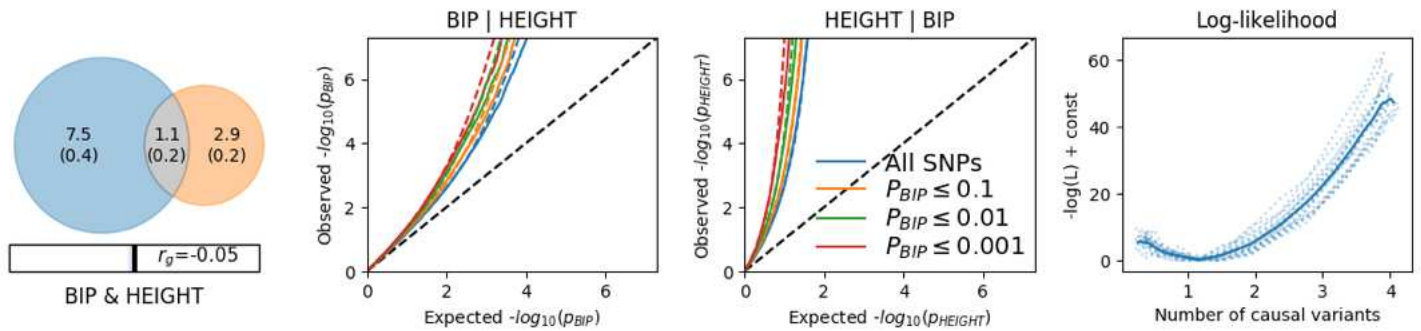
Supplementary Figure 8: Increase of phenotypic variance in bipolar disorder explained by polygenic risk scores in independent non-European datasets as European discovery sample size increases

Variance explained is presented on the liability scale, assuming a BD population prevalence of 2%. Results are based on logistic regression. The numbers of cases and controls are shown under the name of each test dataset. For each target dataset, we plot prediction performance as the PGC BD sample size has increased across freezes of the data. Top panel: Optimization of p-value threshold in each dataset while setting the LD-clumping threshold to 0.1. The color of the bars represents the P value threshold used to select SNPs from the discovery GWAS. Bottom panel: Optimization of LD-clumping threshold in each dataset while setting the p-value threshold to the optimal for each dataset selected in the top panel. The color of the bars represents the LD threshold used to clump SNPs from the discovery GWAS. P-values for association of BD-PRS with case-control status are shown for the best setting above each set of results.









Supplementary Figure 9: Bivariate MiXeR results comparing bipolar disorder (BD) to other traits of interest

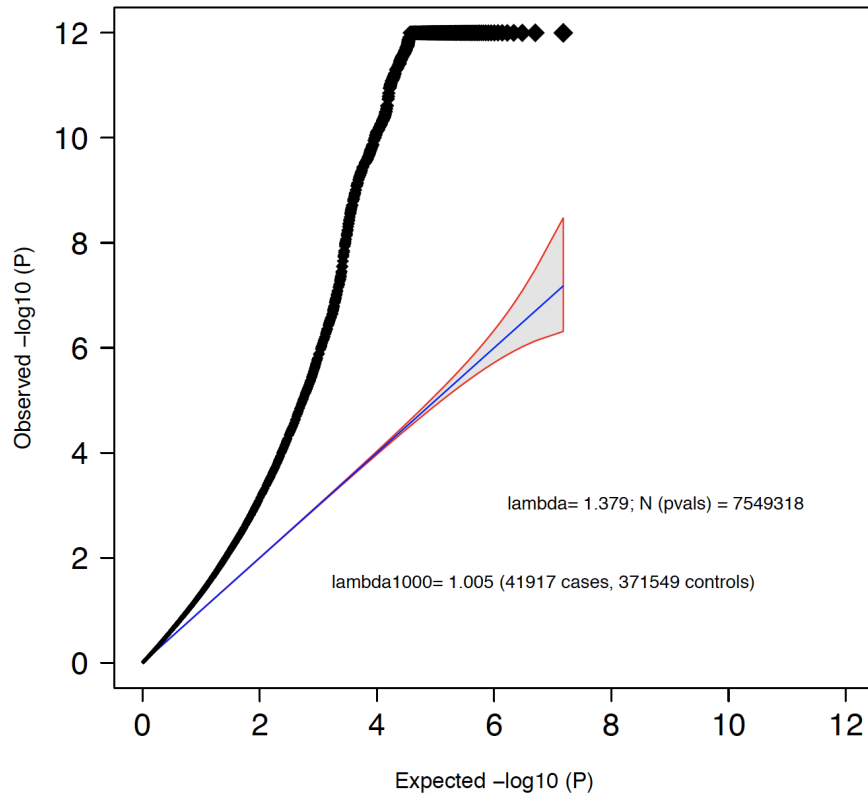
Venn diagrams depict the estimated number of influencing variants shared (grey) between BD and each trait of interest and unique (colors) to either of them. The number of causal variants in thousands is shown. The size of the circles reflects the polygenicity of each trait, with larger circles corresponding to greater polygenicity and vice versa. The estimated genetic correlation (r_g) for each pair is also shown below the corresponding Venn diagram, with an accompanying scale (negative; blue shades, positive; red shades). Conditional quantile-quantile (Q-Q) plots are shown of observed versus expected $-\log_{10}$ P-values in the primary trait (e.g. BD) as a function of significance of association with a secondary trait (e.g. ADHD) at the level of $P \leq 0.1$ (orange lines), $P \leq 0.01$ (green lines), $P \leq 0.001$ (red lines). P values are two-sided and based on logistic or linear regressions. Blue line indicates all SNPs. Dotted lines in blue, orange, green, and red indicate model predictions for each stratum. Black dotted line is the expected Q-Q plot under null (no SNPs associated with the phenotype). Log-likelihood curves highlight the goodness of model fit, by plotting the negative log-likelihood function (lower values correspond to better model fit) against the π_{12} parameter (number of influencing variants shared between two traits). The remaining parameters of the model were constrained to their fitted values. The π_{12} range on the log-likelihood plots goes from the smallest possible value $\pi_{12} = r_g * \sqrt{\pi_1^u, \pi_2^u}$ that is still compatible with the estimated genetic correlation, up to the largest possible value $\pi_{12} = \min(\pi_1^u, \pi_2^u)$ that corresponds to the minimum total polygenicity among the two traits. The minimum point indicates the best-fitting model estimate of the number of influencing variants shared between two traits. ASD, autism spectrum disorder. EDU, educational attainment. AUD, alcohol use disorder. PAU, problematic alcohol use. DRINK, drinks per week. CPD, cigarettes per day, . MOOD, mood instability. SLEEP, sleep duration. SMOKE, smoking initiation.

Supplementary Note: Genome-wide association study of over 40,000 bipolar disorder cases provides new insights into the underlying biology

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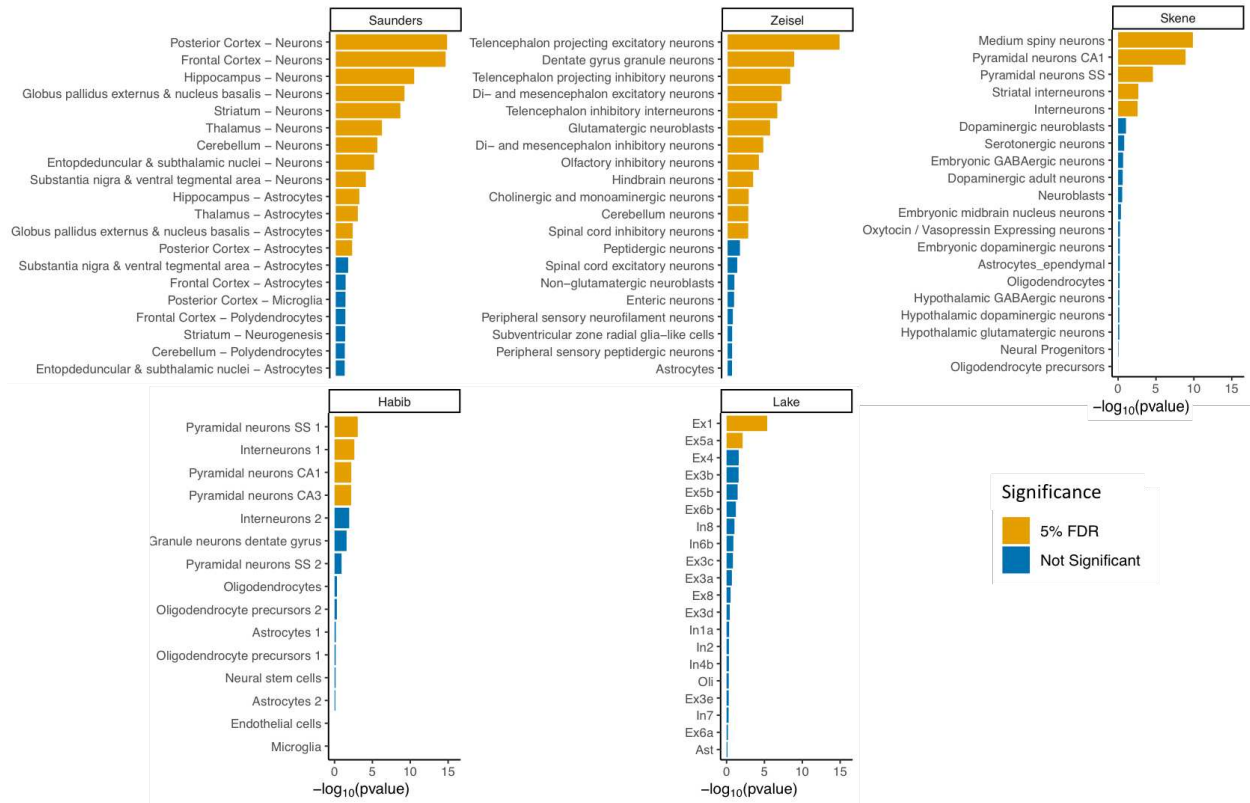
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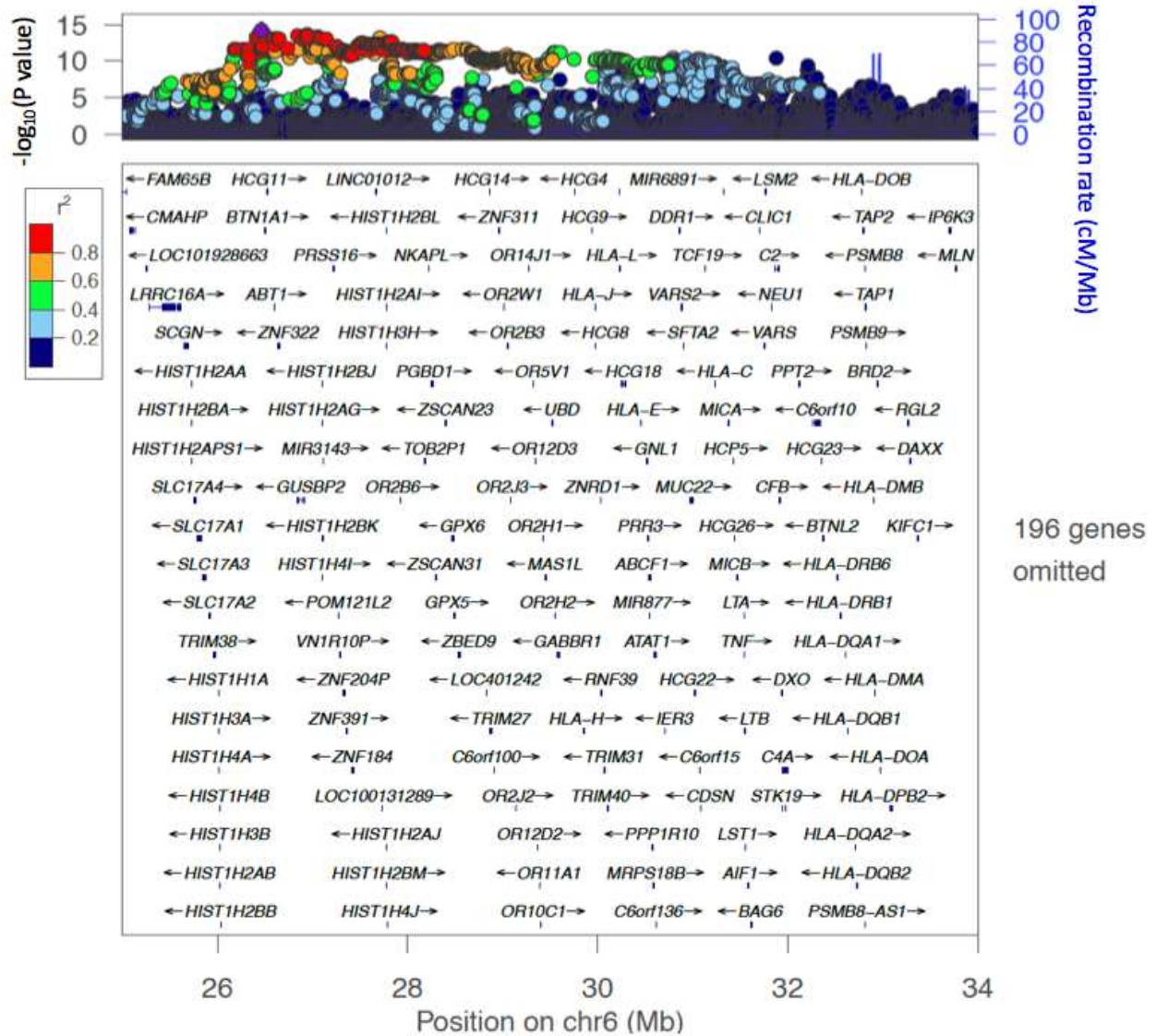
Supplementary Figure 1: Quantile-quantile plot of association test results from genome-wide association meta-analysis of bipolar disorder

The y axis is truncated at $P=1E-12$. SNPs plotted have a minor allele frequency $\geq 1\%$ and an imputation INFO score ≥ 0.6 . Observed results are based on an inverse variance weighted fixed effects meta-analysis of 41,917 bipolar disorder cases and 371,549 controls. P values are uncorrected and two-sided.



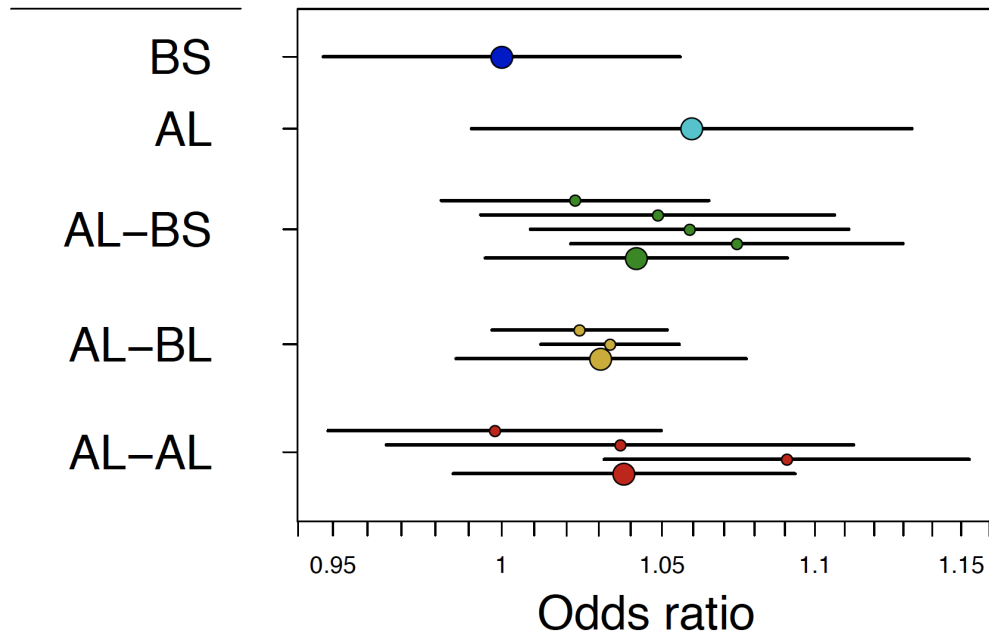
Supplementary Figure 2: Top brain cell types enriched for bipolar disorder association signal

The significance level ($-\log_{10}(p \text{ value})$) of MAGMA is shown for the top 20 most associated cell types in diverse datasets. The genes tested for each cell type are the top 10% of genes most specifically expressed in that cell type compared with all other cell types in the dataset. The color indicates whether the cell type is enriched for BD association signal at a 5% false discovery rate (FDR) across datasets. P values are based on a linear regression and are uncorrected and one-sided. The Zeisel, Saunders and Skene datasets are derived from mouse samples, while the Habib and Lake datasets are derived from human samples. SS - somato-sensory cortex, Ex - excitatory, In - inhibitory, Oli - oligodendrocyte. The numbers after the cell types refer to the cluster of cells with a similar gene expression profile, defined using clustering algorithms in the original publications.



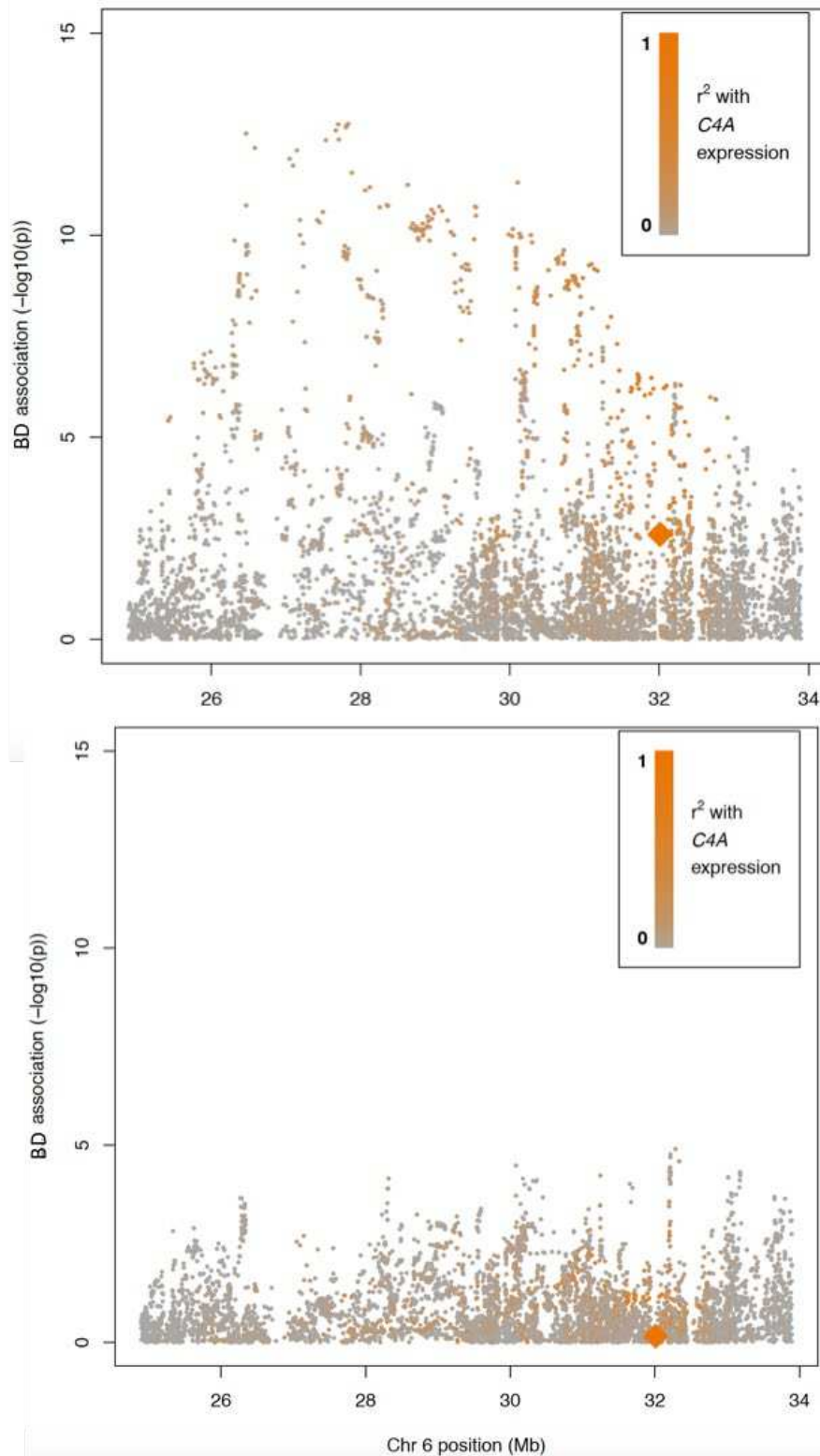
Supplementary Figure 4: Regional plot of bipolar disorder association statistics in the extended major histocompatibility complex (MHC)

The x axis shows genomic position and the y axis shows statistical significance as $-\log_{10}(P \text{ value})$. P values are based on an inverse variance weighted fixed effects meta-analysis of 41,917 bipolar disorder cases and 371,549 controls. P values are uncorrected and two-sided. SNPs are colored by linkage disequilibrium (r^2) to the top lead SNP rs13195402, which is shown as a purple diamond.



Supplementary Figure 5: Odds ratio for bipolar disorder for the five most common *C4* locus structures, in a joint analysis that includes lead SNP rs13195402

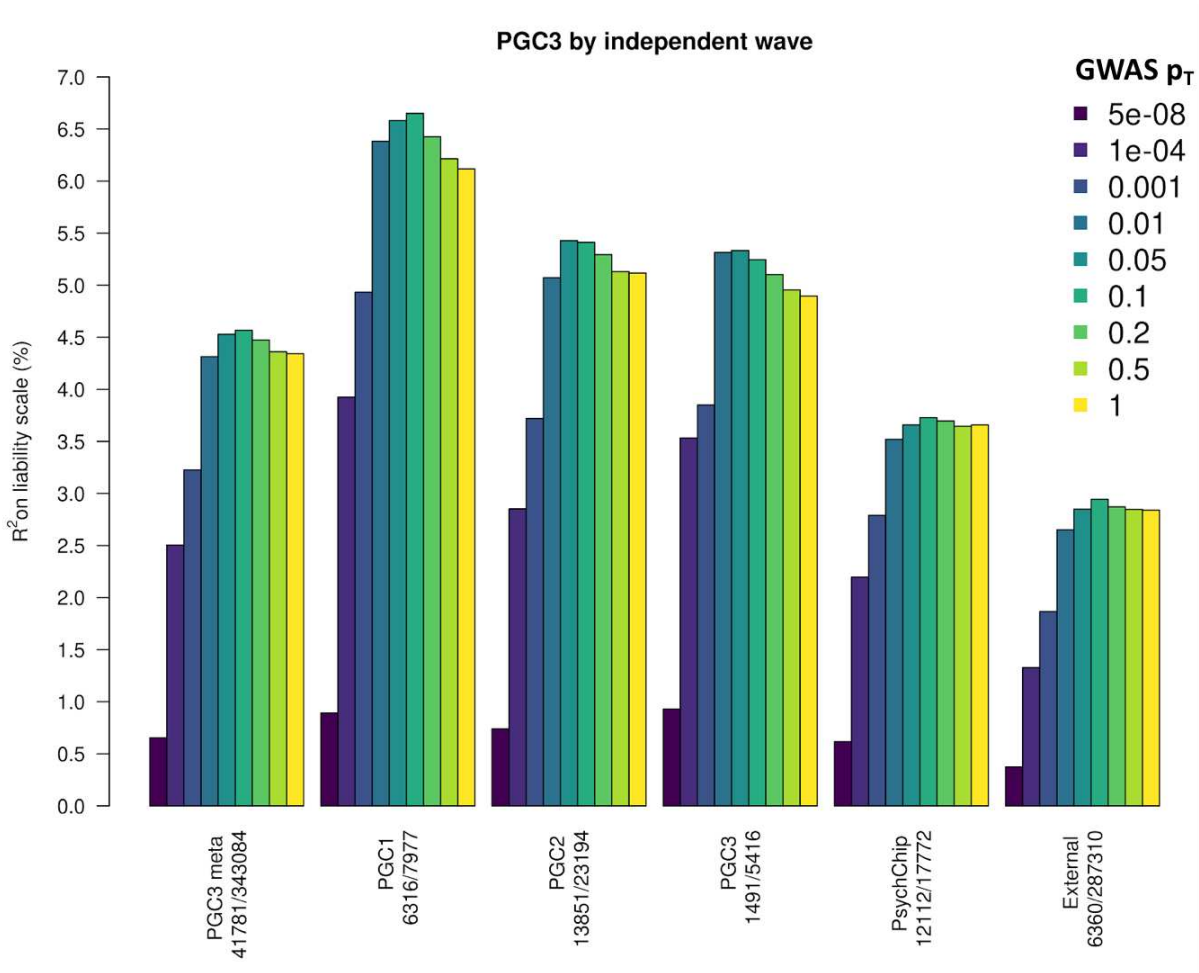
C4 alleles were imputed for 32,749 bipolar disorder cases and 53,370 controls. Odds ratios are calculated relative to the BS haplotype. Error bars represent the 95% confidence interval around the effect size estimate for each allele. Because many *C4* alleles have arisen on multiple SNP haplotype backgrounds, results are shown for each specific haplogroup (small circles) as well as their combined association (large circles). There is no clear difference in bipolar disorder risk levels across these *C4* haplotypes.



Supplementary Figure 6: Association of bipolar disorder to chromosome 6 variation around and within the major histocompatibility complex (MHC) locus, including genetically predicted expression of *C4A*

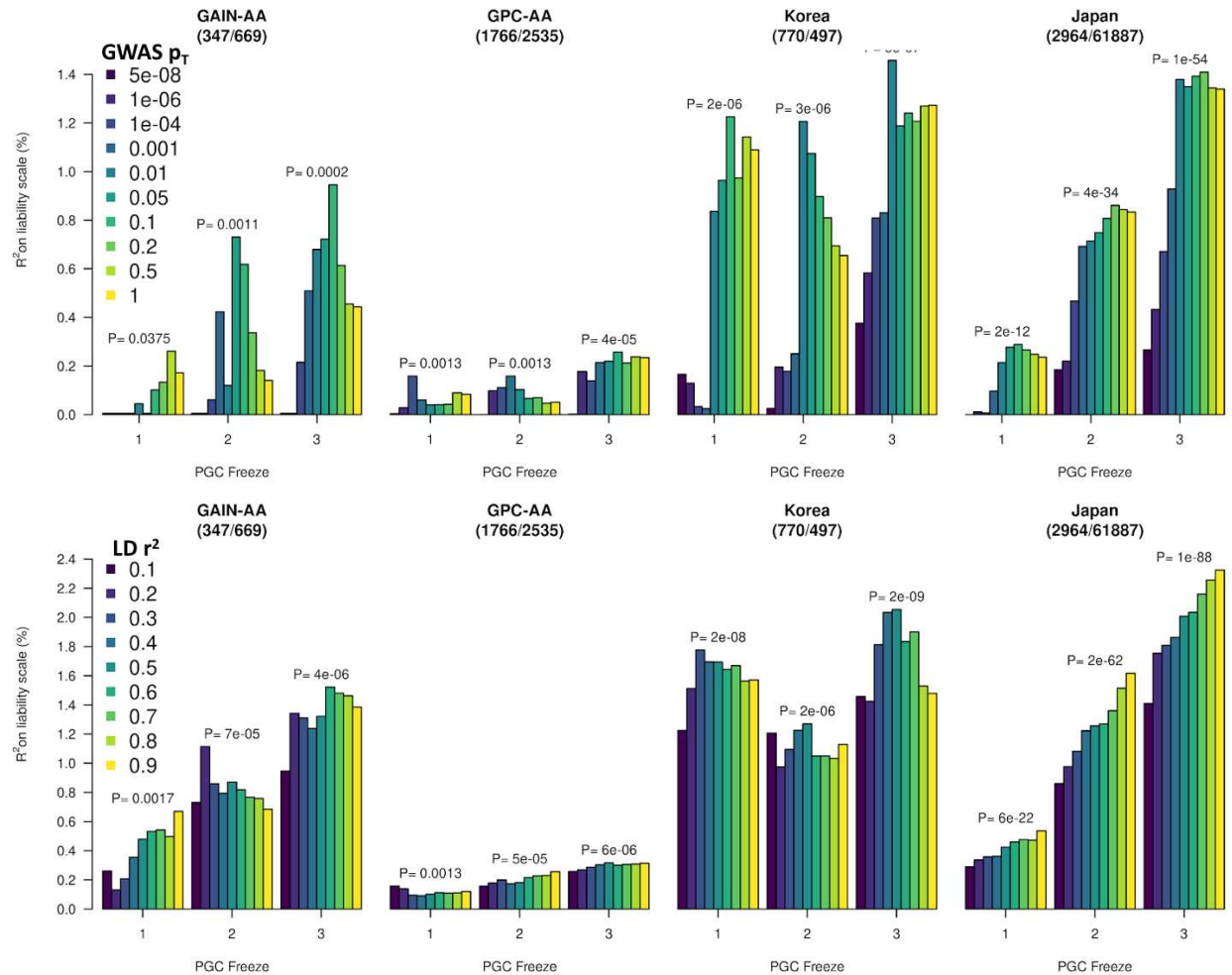
The height of each point represents the statistical strength ($-\log_{10}(P$ value)) of association with bipolar disorder (BD). Genetically predicted *C4A* expression is represented by the orange diamond. SNPs are

colored by their level of correlation to genetically predicted *C4A* expression level. Above: unconditioned analysis. Below: Analysis conditional on rs13195402 (lead SNP in this region of chromosome 6). P values are based on logistic regression, are uncorrected and two-sided. Analyses were conducted in 32,749 bipolar disorder cases and 53,370 controls.



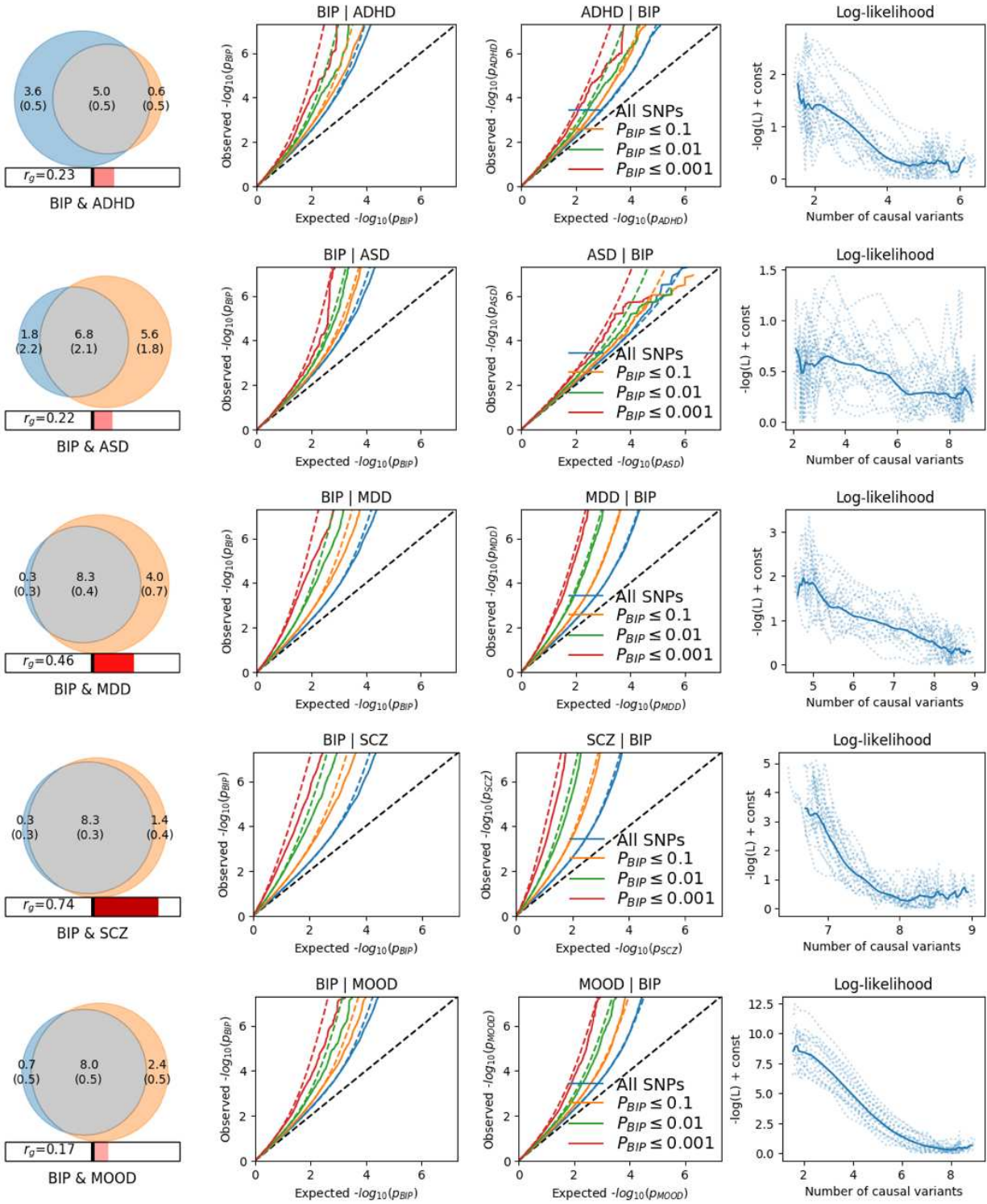
Supplementary Figure 7: Phenotypic variance in bipolar disorder explained by polygenic risk scores per independent wave of ascertainment to the PGC

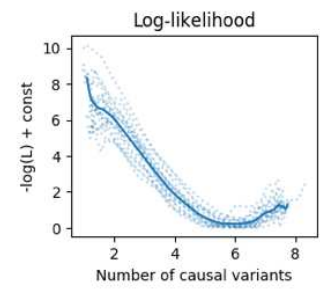
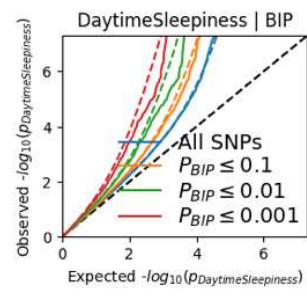
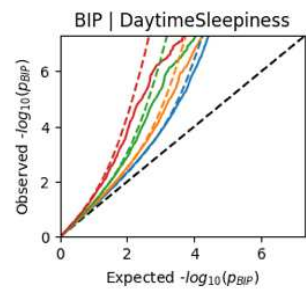
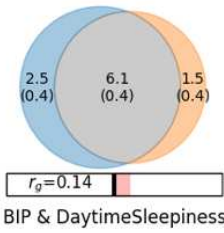
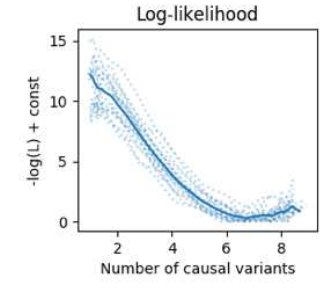
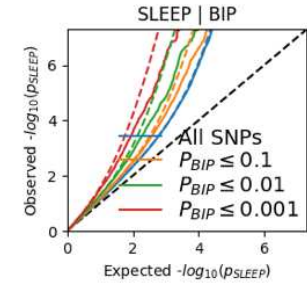
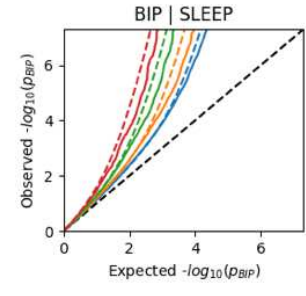
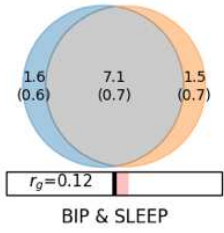
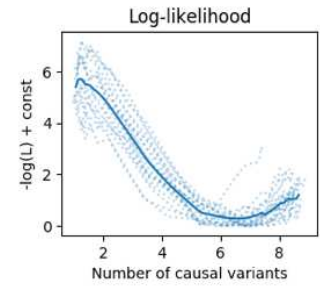
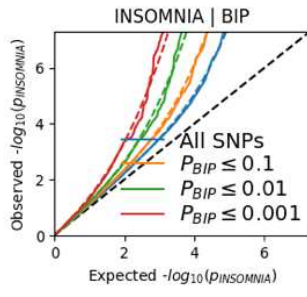
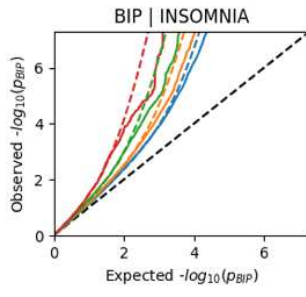
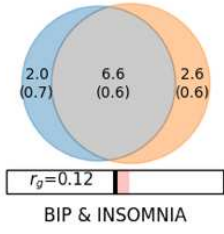
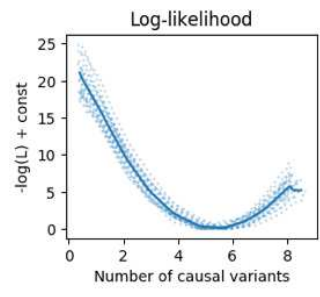
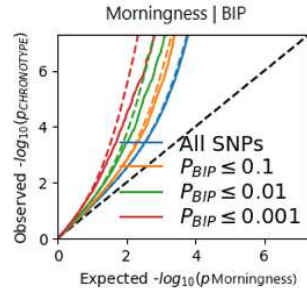
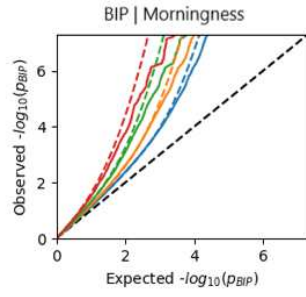
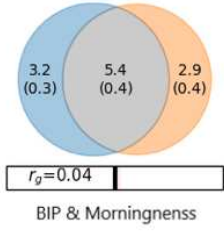
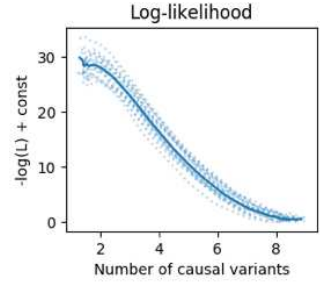
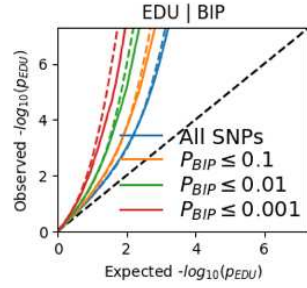
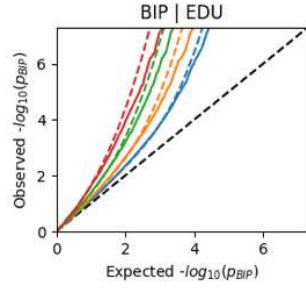
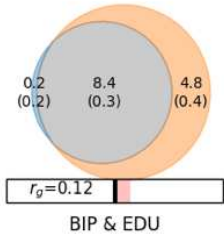
Variance explained is presented on the liability scale, assuming a BD population prevalence of 2%. Results are based on logistic regression. The results shown are the weighted average R^2 values within each wave, calculated weighted by the effective N per cohort. The numbers of cases and controls are shown under the barplot for each wave from left to right. The color of the bars represents the P value threshold used to select SNPs from the discovery GWAS. The leftmost barplot (“PGC3 meta”) shows the combined results of all waves (PGC1, PGC2, PGC3, PsychChip, External and follow-up [not shown in plot] datasets) and matches the European ancestry barplot in Figure 2.

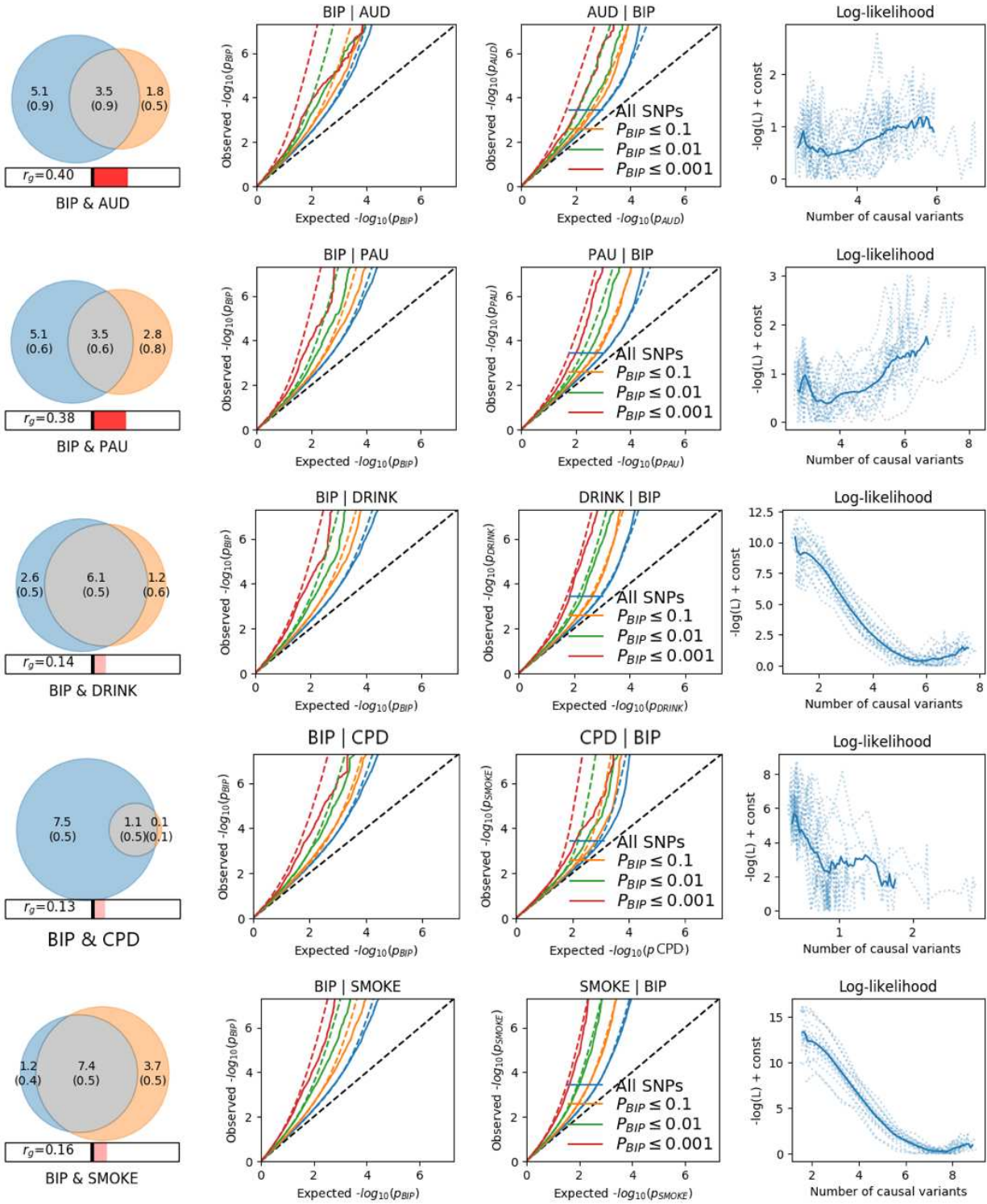


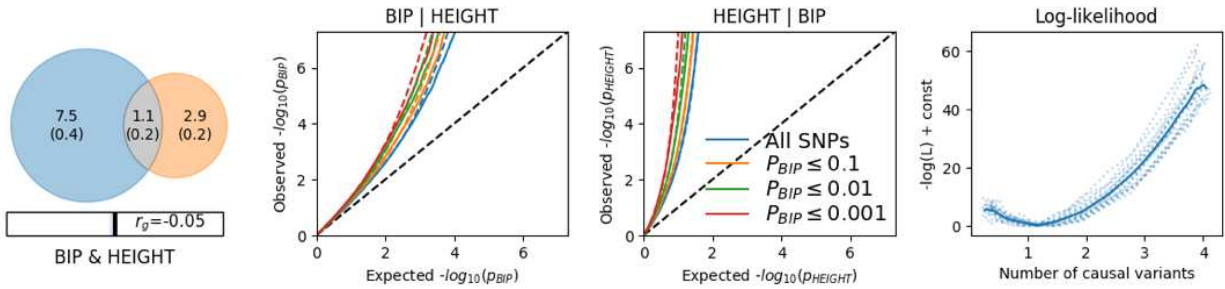
Supplementary Figure 8: Increase of phenotypic variance in bipolar disorder explained by polygenic risk scores in independent non-European datasets, as European discovery sample size increases

Variance explained is presented on the liability scale, assuming a BD population prevalence of 2%. The numbers of cases and controls are shown under the name of each test dataset from left to right. For each test dataset, we plot prediction performance as the PGC BD sample size has increased across freezes of the data. Top panel: Optimization of P value threshold in each dataset while setting the linkage disequilibrium (LD)-clumping threshold to 0.1. The color of the bars represents the P value threshold used to select SNPs from the discovery GWAS. Bottom panel: Optimization of LD-clumping threshold in each dataset while setting the P value threshold to the optimal for each dataset, selected in the top panel. The color of the bars represents the LD threshold used to clump SNPs from the discovery GWAS. P values for association of BD PRS with case-control status are shown for the best setting above each set of results. P values are based on logistic regression, are uncorrected and two-sided.









Supplementary Figure 9: Bivariate MiXeR results comparing bipolar disorder (BD) to other traits of interest

Venn diagrams depict the estimated number of influencing variants shared (grey) between BD and each trait of interest and unique (colors) to either of them. The number of causal variants and standard error in thousands is shown. The size of the circles reflects the polygenicity of each trait, with larger circles corresponding to greater polygenicity and vice versa. The estimated genetic correlation (r_g) for each pair of traits is also shown below the corresponding Venn diagram, with an accompanying scale (negative; blue shades, positive; red shades). Conditional quantile-quantile (Q-Q) plots are shown of observed versus expected $-\log_{10}$ P-values in the primary trait (e.g. BD) as a function of significance of association with a secondary trait (e.g. ADHD) at the level of $P \leq 0.1$ (orange lines), $P \leq 0.01$ (green lines), $P \leq 0.001$ (red lines). P values are two-sided and based on logistic or linear regressions. Blue line indicates all SNPs. Dotted lines in blue, orange, green, and red indicate model predictions for each stratum. Black dotted line is the expected Q-Q plot under null (no SNPs associated with the phenotype). Log-likelihood curves highlight the goodness of model fit, by plotting the negative log-likelihood function (lower values correspond to better model fit) against the π_{12} parameter (number of influencing variants shared between two traits). The remaining parameters of the model were constrained to their fitted values. The π_{12} range on the log-likelihood plots goes from the smallest possible value $\pi_{12} = r_g * \sqrt{\pi_1^u, \pi_2^u}$ that is still compatible with the estimated genetic correlation, up to the largest possible value $\pi_{12} = \min(\pi_1^u, \pi_2^u)$ that corresponds to the minimum total polygenicity among the two traits. The minimum point indicates the best-fitting model estimate of the number of influencing variants shared between two traits. ASD, autism spectrum disorder. EDU, educational attainment. AUD, alcohol use disorder. PAU, problematic alcohol use. DRINK, drinks per week. CPD, cigarettes per day, . MOOD, mood instability. SLEEP, sleep duration. SMOKE, smoking initiation.

Supplementary Note

Sample descriptions

We performed a GWAS meta-analysis of 57 studies from 21 countries in Europe, North America and Australia (**Supplementary Table 1**), totaling 41,917 cases and 371,549 controls of European descent. For 52 cohorts, raw genotype and phenotype data were shared with the Psychiatric Genomics Consortium (PGC). Cases were required to meet international consensus criteria (DSM-IV, ICD-9, or ICD-10) for a lifetime diagnosis of bipolar disorder (BD) established using structured diagnostic instruments from assessments by trained interviewers, clinician-administered checklists, or medical record review. Controls in most samples were screened for the absence of lifetime psychiatric disorders, as indicated. For five external cohorts, GWAS summary statistics for BD were shared with the PGC (iPSYCH, deCODE genetics, Estonian Biobank, HUNT and UK Biobank). Cases in these cohorts were largely defined using ICD codes ascertained from medical records. All samples in previous PGC BD GWAS papers were included, and cohorts were added to the PGC in five waves (PGC1¹, PGC2², PGC PsychChip, PGC3 and External Studies).

Below we describe the ascertainment and diagnosis of the participants in each individual cohort comprising this report. Most cohorts have been published on individually, and the primary report can usually be found using the PubMed identifiers provided. The lead PI of each sample warranted that their protocol was approved by their local Ethical Committee and that all participants provided written informed consent. **Supplementary Table 1** provides additional detail, including sample sizes and genotyping array. As the lifetime prevalence of BD is around 1-2%, some cohorts use controls that are not screened for BD^{3,4}. The boldfaced first line for each sample indicates study PI, PubMed ID if published, country (study name), and the PGC internal tag or study identifier.

===== PGC1 Samples =====

Rietschel, M; Nöthen, MM, Cichon, S | 21926972 [PGC1] | BOMA-Germany I | bip_bonn_eur

Cases for the BOMA-Bipolar Study were ascertained from consecutive admissions to the inpatient units of the Department of Psychiatry and Psychotherapy at the University of Bonn and at the Central Institute for Mental Health in Mannheim, University of Heidelberg, Germany. DSM-IV lifetime diagnoses of bipolar I disorder were assigned using a consensus best-estimate procedure, based on all available information, including a structured interview with the SCID and SADS-L, medical records, and the family history method. In addition, the OPCRIT⁵ checklist was used for the detailed polydiagnostic documentation of symptoms. Controls were ascertained from three population-based studies in Germany (PopGen, KORA, and Heinz-Nixdorf-Recall Study). The control subjects were not screened for mental illness. Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent.

Corvin, A | 18711365 [PGC1] | Ireland | bip_dub1_eur

Samples were collected as part of a larger study of the genetics of psychotic disorders in the Republic of Ireland, under protocols approved by the relevant IRBs and with written informed consent that permitted repository use. Cases were recruited from Hospitals and Community psychiatric facilities in Ireland by a psychiatrist or psychiatric nurse trained to use the SCID. Diagnosis was based on the structured interview supplemented by case note review and collateral history where available. All diagnoses were reviewed by an independent reviewer. Controls were ascertained with informed consent from the Irish GeneBank and represented blood donors who met the same ethnicity criteria as cases. Controls were not specifically screened for psychiatric illness.

Blackwood, D | 18711365 [PGC1] | Edinburgh, UK | bip_edi1_eur

This sample comprised Caucasian individuals contacted through the inpatient and outpatient services of hospitals in South East Scotland. A BD-I diagnosis was based on an interview with the patient using the SADS-L supplemented by case note review and frequently by information from medical staff, relatives and

caregivers. Final diagnoses, based on DSM-IV criteria were reached by consensus between two trained psychiatrists. Ethnically-matched controls from the same region were recruited through the South of Scotland Blood Transfusion Service. Controls were not directly screened to exclude those with a personal or family history of psychiatric illness. The study was approved by the Multi-Centre Research Ethics Committee for Scotland and patients gave written informed consent for the collection of DNA samples for use in genetic studies.

Kelsoe, J | 21926972 [PGC1] | USA (GAIN) | bip_gain_eur

Genetic Association Information Network (GAIN)/ The Bipolar Genome Study (BiGS) The BD sample was collected under the auspices of the NIMH Genetics Initiative for BD (<http://zork.wustl.edu/nimh/>), genotyped as part of GAIN and analyzed as part of a larger GWAS conducted by the BiGS consortium. Approximately half of the GAIN sample was collected as multiplex families or sib pair families (waves 1-4), the remainder were collected as individual cases (wave 5). Subjects were ascertained at 11 sites: Indiana University, John Hopkins University, the NIMH Intramural Research Program, Washington University at St. Louis, University of Pennsylvania, University of Chicago, Rush Medical School, University of Iowa, University of California, San Diego, University of California, San Francisco, and University of Michigan. All investigations were carried out after the review of protocols by the IRB at each participating institution. At all sites, potential cases were identified from screening admissions to local treatment facilities and through publicity programs or advocacy groups. Potential cases were evaluated using the DIGS⁶, FIGS⁷, and information from relatives and medical records. All information was reviewed through a best estimate diagnostic procedure by two independent and non-interviewing clinicians and a consensus best-estimate diagnosis was reached. In the event of a disagreement, a third review was done to break the tie. Controls were from the NIMH Genetic Repository sample obtained by Dr. P. Gejman through a contract to Knowledge Networks, Inc. Only individuals with complete or near-complete psychiatric questionnaire data who did not fulfill diagnostic criteria for major depression and denied a history of psychosis or BD were included as controls for BiGS analyses. Controls were matched for gender and ethnicity to the cases.

Scott, L; Myer, RM; Boehnke, M | 19416921 [PGC1] | Michigan, USA (Pritzker and NIMH) | bip_mich_eur

The Pritzker Neuropsychiatric Disorders Research Consortium (NIMH/Pritzker) case and control samples were from the NIMH Genetics Initiative Genetics Initiative Repository. Cases were diagnosed according to DMS-III or DSM-IV criteria using diagnostic interviews and/or medical record review. Cases with low confidence diagnoses were excluded. From each wave 1-5 available non-Ashkenazi European-origin family, two BD1 siblings were included when possible and the proband was preferentially included if available (n=946 individuals in 473 sibling pairs); otherwise a single BD1 case was included (n=184). The bipolar sibling pairs were retained within the NIMH/Pritzker sample when individuals in more than one study were uniquely assigned to a study set. Controls had non-Ashkenazi European-origin, were aged 20-70 years and reported no diagnosis with or treatment for BD or schizophrenia, and that they had not heard voices that others could not hear. Individuals with suspected major depression were excluded based on answers to questions related to depressive mood. NIMH controls were further selected as the best match(es) to NIMH cases based on self-reported ancestry.

Sklar, P; Smoller, J | 18317468 [PGC1] | USA (STEP1) | bip_stp1_eur

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) was a seven-site, national U.S., longitudinal cohort study designed to examine the effectiveness of treatments and their impact on the course of BD that enrolled 4,361 participants who met DSM-IV criteria for BD1, BD2, bipolar not otherwise specified (NOS), schizoaffective manic or bipolar type, or cyclothymic disorder based on diagnostic interviews. From the parent study, 2,089 individuals who were over 18 years of age with BD1 and BD2 diagnoses consented to the collection of blood samples for DNA. BD samples with a consensus diagnosis of BD1 were selected for inclusion in STEP1. Two groups of controls samples from the NIMH repository were used. One comprised DNA samples derived from US Caucasian anonymous cord blood

donors. The second were controls who completed the online self-administered psychiatric screen and were ascertained as described above, by Knowledge Networks Inc. For the second sample of controls only those without a history of schizophrenia, psychosis, BD or major depression with functional impairment were used.

Sklar, P; Smoller, J | 18711365 [PGC1] | USA (STEP2) | bip_stp2_eur

The STEP2 sample included BD-1 and BD-2 samples from the STEP-BD study described above along with BD-2 subjects from UCL study also described above. The controls samples for this study were from the NIMH repository as described above for the STEP1 study.

Andreassen, OA | PMID:21926972 [PGC1], PMID:20451256 | Norway (TOP) | bip_top7_eur

In the TOP study (Tematisk område psykoser), cases of European ancestry, born in Norway, were recruited from psychiatric hospitals in the Oslo region. Patients were diagnosed according to the SCID⁸ and further ascertainment details have been reported. Healthy control subjects were randomly selected from statistical records of persons from the same catchment area as the patient groups. The control subjects were screened by interview and with the Primary Care Evaluation of Mental Disorders (PRIME-MD)⁹. None of the control subjects had a history of moderate/severe head injury, neurological disorder, mental retardation or an age outside the age range of 18-60 years. Healthy subjects were excluded if they or any of their close relatives had a lifetime history of a severe psychiatric disorder. All participants provided written informed consent and the human subjects protocol was approved by the Norwegian Scientific-Ethical Committee and the Norwegian Data Protection Agency.

McQuillin, A; Gurling, H | 18317468 [PGC1] | UCL (University College London), London, UK | bip_uclo_eur

The UCL sample comprised Caucasian individuals who were ascertained and received clinical diagnoses of bipolar 1 disorder according to UK National Health Service (NHS) psychiatrists at interview using the categories of the International Classification of Disease version 10. In addition bipolar subjects were included only if both parents were of English, Irish, Welsh or Scottish descent and if three out of four grandparents were of the same descent. All volunteers read an information sheet approved by the Metropolitan Medical Research Ethics Committee who also approved the project for all NHS hospitals. Written informed consent was obtained from each volunteer. The UCL control subjects were recruited from London branches of the National Blood Service, from local NHS family doctor clinics and from university student volunteers. All control subjects were interviewed with the SADS-L to exclude all psychiatric disorders.

Craddock, N, Jones, I, Jones, L | 17554300 | WTCCC | bip_wtcc_eur_sr-qc

Cases were all over the age of 17 yr, living in the UK and of European descent. Recruitment was undertaken throughout the UK and included individuals who had been in contact with mental health services and had a lifetime history of high mood. After providing written informed consent, participants were interviewed by a trained psychologist or psychiatrist using a semi-structured lifetime diagnostic psychiatric interview (Schedules for Clinical Assessment in Neuropsychiatry) and available psychiatric medical records were reviewed. Using all available data, best-estimate life-time diagnoses were made according to the RDC¹². In the current study we included cases with a lifetime diagnosis of RDC bipolar 1 disorder, bipolar 2 disorder or schizo-affective disorder, bipolar type.

Controls were recruited from two sources: the 1958 Birth Cohort study and the UK Blood Service (blood donors) and were not screened for history of mental illness.

All cases and controls were recruited under protocols approved by the appropriate IRBs. All subjects gave written informed consent.

===== PGC2 Samples =====

Adolfsson, R | Not published | Umeå, Sweden | bip_ume4_eur

Clinical characterization of the patients included the Mini-International Neuropsychiatric Interview

(MINI¹⁰), the Diagnostic Interview for Genetic Studies (DIGS⁶), the Family Interview for Genetic Studies (FIGS⁷) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)¹¹. The final diagnoses were made according to the DSM-IV-TR and determined by consensus of 2 research psychiatrists. The unrelated Swedish control individuals, consisting of a large population-based sample representative of the general population of the region, were randomly selected from the 'Betula study'.

Alda, M; Smoller, J | Not published | Nova Scotia, Canada; I2B2 controls | bip_hal2_eur

The case samples were recruited from patients longitudinally followed at specialty mood disorders clinics in Halifax and Ottawa (Canada). Cases were interviewed in a blind fashion with the Schedule of Affective Disorders and Schizophrenia-Lifetime version (SADS-L)¹² and consensus diagnoses were made according to DSM-IV¹³ and Research Diagnostic Criteria (RDC)¹⁴. Protocols and procedures were approved by the local Ethics Committees and written informed consent was obtained from all patients before participation in the study. Control subjects were drawn from the I2B2 (Informatics for Integrating Biology and the Bedside) project¹⁵. The study consists of de-identified healthy individuals recruited from a healthcare system in the Boston, MA, US area. The de-identification process meant that the Massachusetts General Hospital Institutional Review Board elected to waive the requirement of seeking informed consent as detailed by US Code of Federal Regulations, Title 45, Part 46, Section 116 (46.116).

Andreassen, OA | Not published | Norway (TOP) | bip_top8_eur

The TOP8 bipolar disorder cases and controls were ascertained in the same way as the bip_top7_eur (TOP7) samples described above, and recruited from hospitals across Norway.

Biernacka, JM; Frye, MA | 27769005 | Mayo Clinic, USA | bip_may1_eur

Bipolar cases were drawn from the Mayo Clinic Bipolar Biobank¹⁶. Enrolment sites included Mayo Clinic, Rochester, Minnesota; Lindner Center of HOPE/University of Cincinnati College of Medicine, Cincinnati, Ohio; and the University of Minnesota, Minneapolis, Minnesota. Enrolment at each site was approved by the local Institutional Review Board, and all participants consented to use of their data for future genetic studies. Participants were identified through routine clinical appointments, from in-patients admitted in mood disorder units, and recruitment advertising. Participants were required to be between 18 and 80 years old and be able to speak English, provide informed consent, and have DSM-IV-TR diagnostic confirmation of type 1 or 2 bipolar disorder or schizoaffective bipolar disorder as determined using the SCID. Controls were selected from the Mayo Clinic Biobank¹⁷. Potential controls with ICD9 codes for bipolar disorder, schizophrenia or related diagnoses in their electronic medical record were excluded.

Breen, G; Vincent, JB | 24387768; 19416921; 21926972 [PGC1] | London, UK; Toronto, Canada [BACC] | bip_bac1_eur

The total case/control cohort (N=1922) includes 871 subjects from Toronto, Canada (N=431 cases (160 male; 271 female); N=440 controls (176 male; 264 female)), 1051 subjects from London, UK (N=538 cases (180 male; 358 female); N=513 controls (192 male; 321 female)). A summary of mean and median age at interview, age of onset (AOO), diagnostic subtypes (BD 1 versus BD 2), presence of psychotic symptoms, suicide attempt and family history of psychiatric disorders has been provided previously for both the Toronto and London cohorts¹⁸. From the Toronto site (Centre for Addiction & Mental Health (CAMH)), BD individuals and unrelated healthy controls matched for age, gender and ethnicity were recruited. Inclusion criteria for patients: a) diagnosed with DSMIV/ICD 10 BD 1 or 2; b) 18 years old or over; c) Caucasian, of Northern and Western European origin, and three out of four grandparents also N.W. European Caucasian. Exclusion criteria include: a) Use of intravenous drugs; b) Evidence of intellectual disability; c) Related to an individual already in the study; d) Manias that only ever occurred in relation to or resulting from alcohol or substance abuse/dependence, or medical illness; e) Manias resulting from non-psychotropic substance usage. The SCAN interview (Schedule for Clinical Assessments in Neuropsychiatry) was used for subject assessment¹⁹. Using the SCAN interview along with case note review, each case was assigned DSM-IV and ICD 10 diagnoses by two independent diagnosticians, according to lifetime consensus best-estimate diagnosis. Lifetime occurrence of psychiatric symptoms was also recorded using

the OPCRIT checklist, modified for use with mood disorders. Similar methods and criteria were also used to collect a sample of 538 BD cases and 513 controls for the London cohort (King's College London; KCL)²⁰. Both studies were approved by respective institutional research ethics committees (the CAMH Research Ethics Board (REB) in Toronto, and the College Research Ethics Committee (CREC) at KCL), and informed written consent was obtained from all participants. GWAS results have previously been published for the entire KCL/CAMH cohort²¹.

Rietschel, M; Nöthen, MM; Schulze, TG; Reif, A; Forstner, AJ | 24618891 | BOMA-Germany II | bip_bmg2_eur

Cases were recruited from consecutive admissions to psychiatric in-patient units at the University Hospital Würzburg. All cases received a lifetime diagnosis of BD according to the DSM-IV criteria using a consensus best-estimate procedure based on all available information, including semi-structured diagnostic interviews using the Association for Methodology and Documentation in Psychiatry²², medical records and the family history method. In addition, the OPCRIT system was used for the detailed polydiagnostic documentation of symptoms.

Control subjects were ascertained from the population-based Heinz Nixdorf Recall (HNR) Study²³. The controls were not screened for a history of mental illness. Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent.

Rietschel, M; Nöthen, MM; Schulze, TG; Bauer, M; Forstner, AJ; Müller-Myhsok, B | 24618891 | BOMA-Germany III | bip_bmg3_eur²⁴

Cases were recruited at the Central Institute of Mental Health in Mannheim, University of Heidelberg, and other collaborating psychiatric hospitals in Germany. All cases received a lifetime diagnosis of BD according to the DSM-IV criteria using a consensus best-estimate procedure based on all available information including structured diagnostic interviews using the AMDP, Composite International Diagnostic Screener (CID-S)²⁵, SADS-L and/or SCID, medical records, and the family history method. In addition, the OPCRIT system was used for the detailed polydiagnostic documentation of symptoms.

Controls were selected randomly from a Munich-based community sample and recruited at the Max-Planck Institute of Psychiatry. They were screened for the presence of anxiety and mood disorders using the CID-S. Only individuals without mood and anxiety disorders were collected as controls. Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent.

Hauser, J; Lissowska, J; Forstner, AJ | 24618891 | BOMA-Poland | bip_bmpo_eur

Cases were recruited at the Department of Psychiatry, Poznan University of Medical Sciences, Poznan, Poland. All cases received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure and structured diagnostic interviews using the SCID. Controls were drawn from a population-based case-control sample recruited by the Cancer-Center and Institute of Oncology, Warsaw, Poland and a hospital-based case-control sample recruited by the Nofer Institute of Occupational Medicine, Lodz, Poland. The Polish controls were produced by the International Agency for Research on Cancer (IARC) and the Centre National de Génotypage (CNG) GWAS Initiative for a study of upper aerodigestive tract cancers. The controls were not screened for a history of mental illness. Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent.

Rietschel, M; Nöthen, MM; Rivas, F; Mayoral, F; Kogevinas, M; others | 24618891 | BOMA-Spain | bip_bmsp_eur

Cases were recruited at the mental health departments of the following five centers in Andalusia, Spain: University Hospital Reina Sofia of Córdoba, Provincial Hospital of Jaen; Hospital of Jerez de la Frontera (Cádiz); Hospital of Puerto Real (Cádiz); Hospital Punta Europa of Algeciras (Cádiz); and Hospital Universitario San Cecilio (Granada). Diagnostic assessment was performed using the SADS-L; the OPCRIT;

a review of medical records; and interviews with first and/or second degree family members using the Family Informant Schedule and Criteria (FISC)²⁶. Consensus best estimate BD diagnoses were assigned by two or more independent senior psychiatrists and/or psychologists, and according to the RDC, and the DSM-IV. Controls were Spanish subjects drawn from a cohort of individuals recruited in the framework of the European Community Respiratory Health Survey (ECRHS, <http://www.ecrhs.org/>). The controls were not screened for a history of mental illness. Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent.

Fullerton, J.M.; Mitchell, P.B.; Schofield, P.R.; Martin N.G.; Cichon, S. | 24618891 | BOMA-Australia | bip_bmau_eur

Cases were recruited at the Mood Disorder Unit, Prince of Wales Hospital in Sydney. All cases received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus best-estimate procedure¹⁹ and structured diagnostic interviews using the DIGS, FIGS, and the SCID. Controls were parents of unselected adolescent twins from the Brisbane Longitudinal Twin Study. The controls were not screened for a history of mental illness. Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent.

Grigoriou-Serbanescu, M; Nöthen, MM | 21353194 | BOMA-Romania | bip_rom3_eur

Cases were recruited from consecutive admissions to the Obregia Clinical Psychiatric Hospital, Bucharest, Romania. Patients were administered the DIGS²⁷ and FIGS⁷ interviews. Information was also obtained from medical records and close relatives. The diagnosis of BP-I was assigned according to DSM-IV criteria using the best estimate procedure. All patients had at least two hospitalized illness episodes. Population-based controls were evaluated using the DIGS to exclude a lifetime history of major affective disorders, schizophrenia, schizoaffective disorders, and other psychoses, obsessive-compulsive disorder, eating disorders, and alcohol or drug addiction.

Kelsoe, J; Sklar, P; Smoller, J | [PGC1 Replication] | USA (FAT2; FaST, BiGS, TGEN) | bip_fat2_eur

Cases were collected from individuals at the 11 U.S. sites described for the GAIN sample. Eligible participants were age 18 or older meeting DSM-IV criteria for BD-I or BD-II by consensus diagnosis based on interviews with the Affective Disorders Evaluation (ADE) and MINI. All participants provided written informed consent and the study protocol was approved by IRBs at each site. Collection of phenotypic data and DNA samples were supported by NIMH grants MH063445 (JW Smoller); MH067288 (PI: P Sklar), MH63420 (PI: V Nimgaonkar) and MH078151, MH92758 (PI: J. Kelsoe). The control samples were NIMH controls that were using the methods described in that section. The case and control samples were independent of those included in the GAIN sample.

Kirov, G | 25055870 | Bulgarian trios | bip_butr_eur

All cases were recruited in Bulgaria from psychiatric inpatient and outpatient services. Each proband had a history of hospitalisation and was interviewed with an abbreviated version of the SCAN. Consensus best-estimate diagnoses were made according to DSM-IV criteria by two researchers. All participants gave written informed consent and the study was approved by local ethics committees at the participating centers.

Kirov, G | 25055870 | UK trios | bip_uktr_eur

The BD subjects were recruited from lithium clinics and interviewed in person by a senior psychiatrist, using the abbreviated version of the SCAN. Consensus best-estimate diagnoses were made based on the interview and hospital notes. Ethics committee approval for the study was obtained from the relevant research ethics committees and all individuals provided written informed consent for participation.

Landén, M; Sklar, P | [ICCBD] | Sweden (ICCBD) | bip_swa2_eur

The BD subjects were identified using the Swedish National Quality Register for Bipolar Disorders (BipolärR) and the Swedish National Patient Register (using a validated algorithm²⁸ requiring at least two

hospitalizations with a BD diagnosis). A confirmatory telephone interview with a diagnostic review was conducted. Additional subjects were recruited from the St. Göran Bipolar Project (Affective Center at Northern Stockholm Psychiatry Clinic, Sweden), enrolling new and ongoing patients diagnosed with BD using structured clinical interviews. Diagnoses were made according to the DSM-IV criteria (Bipolär and St. Göran Bipolar Project) and ICD-10 (National Patient Register). The control subjects used were the same as for the SCZ analyses described above. All ascertainment procedures were approved by the Regional Ethical Committees in Sweden.

Landén, M; Sklar, P | [ICCBD] | Sweden (ICCBD) | bip_swei_eur

The cases and controls in the bip_swei_eur sample were recruited using the same ascertainment methods described for the bip_swa2_eur sample.

Leboyer, M |²⁹; [PGC1 replication] | France | bip_fran_eur

Cases with BD1 or BD2 and control samples were recruited as part of a large study of genetics of BD in France (Paris-Creteil, Bordeaux, Nancy) with a protocol approved by relevant IRBs and with written informed consent. Cases of French descent for more than 3 generations were assessed by a trained psychiatrist or psychologist using structured interviews supplemented by medical case notes, mood scales and self-rating questionnaire assessing dimensions.

Li, Q | 24166486; 27769005 | USA (Janssen), SAGE controls | bip_jst5_eur

The study included unrelated patients with bipolar 1 disorder from 6 clinical trials (IDs: NCT00253162, NCT00257075, NCT00076115, NCT00299715, NCT00309699, and NCT00309686). Participant recruitment was conducted by Janssen Research & Development, LLC (formerly known as Johnson & Johnson Pharmaceutical Research & Development, LLC) to assess the efficacy and safety of risperidone. Bipolar cases were diagnosed according to DSM-IV-TR criteria. The diagnosis of bipolar disorder was confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) in NCT00076115, by the SCID in NCT00257075 and NCT00253162, or by the MINI in NCT00299715 and NCT00309699, and NCT00309686, respectively. Additional detailed descriptions of these clinical trials can be found at ClinicalTrials.gov. Only patients of European ancestry with matching controls were included in the current analysis. Controls subjects were drawn from the Study of Addiction: Genetics and Environment (SAGE, dbGaP Study Accession: phs000092.v1.p1). Control subjects did not have alcohol dependence or drug dependence diagnoses; however, mood disorders were not an exclusion criterion.

Craddock, N; Jones, I; Jones, L | [ICCBD] | Cardiff and Worcester, UK (ICCBD-BDRN) | bip_icuk_eur

Cases were all over the age of 17 yr, living in the UK and of European descent. Cases were recruited via systematic and not systematic methods as part of the Bipolar Disorder Research Network project (www.bdrn.org), provided written informed consent and were interviewed using a semi-structured diagnostic interview, the Schedules for Clinical Assessment in Neuropsychiatry. Based on the information gathered from the interview and case notes review, best-estimate lifetime diagnosis was made according to DSM-IV. Inter-rater reliability was formally assessed using 20 randomly selected cases (mean κ Statistic = 0.85). In the current study we included cases with a lifetime diagnosis of DSM-IV bipolar disorder or schizo-affective disorder, bipolar type. The BDRN study has UK National Health Service (NHS) Research Ethics Committee approval and local Research and Development approval in all participating NHS Trusts/Health Boards. Controls were part of the Wellcome Trust Case Control Consortium common control set, which comprised healthy blood donors recruited from the UK Blood Service and samples from the 1958 British Birth Cohort. Controls were not screened for a history of mental illness. All cases and controls were recruited under protocols approved by the appropriate IRBs. All subjects gave written informed consent.

Ophoff, RA | Not Published | Netherlands | bip_ucla_eur

The case sample consisted of inpatients and outpatients recruited through psychiatric hospitals and institutions throughout the Netherlands. Cases with DSM-IV bipolar disorder, determined after interview

with the SCID, were included in the analysis. Controls were collected in parallel at different sites in the Netherlands and were volunteers with no psychiatric history after screening with the (MINI¹⁰). Ethical approval was provided by UCLA and local ethics committees and all participants gave written informed consent.

Paciga, S | [PGC1] | USA (Pfizer) | bip_pf1e_eur

This sample comprised Caucasian individuals recruited into one of three Geodon (ziprasidone) clinical trials (NCT00141271, NCT00282464, NCT00483548). Subjects were diagnosed by a clinician with a primary diagnosis of Bipolar 1 Disorder, most recent episode depressed, with or without rapid cycling, without psychotic features, as defined in the DSM-IV-TR (296.5x) and confirmed by the MINI (version 5.0.0). Subjects also were assessed as having a HAM-D-17 total score of >20 at the screening visit. The trials were conducted in accordance with the protocols, International Conference on Harmonization of Good Clinical Practice Guidelines, and applicable local regulatory requirements and laws. Patients gave written informed consent for the collection of blood samples for DNA for use in genetic studies.

Pato, C | [ICCBD] | Los Angeles, USA (ICCBD-GPC) | bip_usc2_eur

Genomic Psychiatry Consortium (GPC) cases and controls were collected via the University of Southern California healthcare system, as previously described³⁰. Using a combination of focused, direct interviews and data extraction from medical records, diagnoses were established using the OPCRIT and were based on DSM-IV-TR criteria. Age and gender-matched controls were ascertained from the University of Southern California health system and assessed using a validated screening instrument and medical records.

===== PGC2 Followup Samples =====

Kelsoe, J | [PGC1] | USA (BiGS/TGEN1) | TGEN1_eur

Cases and controls for this sample were ascertained using the same procedures applied for the bip_gain_eur sample described above. These samples formed a distinct PCA cluster from the samples described above and were therefore analysed separately.

Li, Q | 24166486 | various Eastern Europe, shared T. Esku controls | JJ_EAST_eur

The cases were drawn from the same six clinical studies described for bip_jst5_eur except that only patients of east European ancestry with matching controls were included in this cohort. Most of the Eastern European controls were from the Estonian Biobank project (EGCUT)³¹ and were ancestrally matched with cases.

Schulze, T | [ConLiGen] | Germany | BIP_KFO_eur

The KFO sample was derived from the Clinical Research Group 241 (KFO241 consortium; www.kfo241.de) and the PsyCourse consortium (www.psycourse.de). The samples form part of a multi-site German/Austrian longitudinal study. Diagnoses were made according to DSM-IV. German Red Cross controls were collected by the Central Institute for Mental Health in Mannheim, University of Heidelberg, Germany. Volunteers who gave blood to the Red Cross were asked whether they would be willing to participate in genetic studies of psychiatric disorders. Control subjects were not selected on the basis of mental health screening.

===== External studies =====

Mortensen, P; Borglum, A | Not published | [iPsych] | NA

The iPSYCH bipolar disorder sample is a nationwide population based case-cohort sample derived from the Danish Bloodspot resource³². In 1981, Denmark began storing neonatal bloodspots and collected samples have been subsequently linked to the Danish Psychiatric Central Research Register (DPCRR). The iPSYCH sample includes practically all individuals diagnosed with bipolar disorder who were born in Denmark between 1981 and 2005. Cases were diagnosed clinically by a psychiatrist at in- or out-patient psychiatric hospitals according to ICD10 as recorded in DPCRR (ICD10 codes F30-F31). Diagnoses were

given in 2013 or earlier for persons not less than 10 years old. Controls were randomly selected from the same national birth cohort and not diagnosed with bipolar disorder.

DNA was prepared as described previously³³ and genotyping was done using the PsychChip array from Illumina (CA, San Diego, USA) according to the manufacturer's protocols. Genotypes were processed using the Ricopili pipeline and imputation using the 1000 genomes phase 3 reference panel. Genetic outliers were excluded based on principal component analysis. Due to the large number of study subjects in the overall iPSYCH cohort, the sample was genotyped and processed in 23 waves with each wave treated as a separate sample. Only waves with at least 100 bipolar cases were included in the analysis, and controls were down-sampled from each included wave (Ncontrols = 4 x N cases). After this processing, genotypes from 839 cases and 2938 controls were included for analysis. Due to the nature of the analyses and the overall lower number of cases we decided to relax the per wave sample size requirement for the sex-specific analysis and the analysis of chromosome X data. At least 50 female or male bipolar cases were required for a wave in order to be included in the analyses (with N controls = 4 x N cases). Please note that this still resulted in a nominal "loss of waves" that were included in the analyses when compared to the analysis of the full dataset. A total of 697 female cases and 1867 female controls as well as 111 male cases and 512 male controls were included, respectively. Processing and analysis of genotype data were performed at the secured, national high performance-computing cluster *GenomeDK* (<http://genome.au.dk>). The study was approved by the Danish Data Protection Agency and the Scientific Ethics Committee in Denmark.

Stefánsson, H | [PGC1 replication] | Iceland (deCODE genetics) | deCODE

The Icelandic sample consisted of 2,908 subjects with BD (1661 SNP typed) and 344,848 controls (141,854 SNP typed). DNA was isolated from blood samples provided by patients and controls that were recruited throughout Iceland. Approval for the study was granted by the National Bioethics Committee of Iceland and the Icelandic Data Protection Authority and informed consent was obtained for all participants providing a sample for the study. Diagnoses were assigned according to Research Diagnostic Criteria³⁴ through the use of the SADS-L³⁵ for 303 subjects. DSM-IV BD diagnoses were obtained through the use of the Composite International Diagnostic Interview (CIDI-Auto) for 82 subjects. The remaining BD subjects were diagnosed by ICD 9 or ICD 10 at Landspítali University Hospital in the years 1987-2018. Controls were recruited as a part of various genetic programs at deCODE and were not screened for psychiatric disorders. Whole genome sequencing was performed on samples from 541 BD cases and 26,014 controls. Two types of imputations were performed; into SNP-typed individuals based on long-range phasing, followed by a familial imputation step into un-typed relatives of SNP-typed individuals³⁶. Cases of bipolar I disorder were defined using ICD-10 codes 31.1 and 31.2 and ICD-9 codes 296.0 and 296.2. Cases of bipolar II disorder were defined using the ICD-10 code 31.0 in the absence of ICD-10 codes F31.1 and F31.2 and ICD-9 codes 296.0 and 296.2.

Milani L | 24518929 | Estonia (Estonian Biobank) | EstonianBiobank

The Estonian Biobank (EstBB) is a population-based cohort of 200,000 participants with a rich variety of phenotypic and health-related information collected for each individual³¹. At recruitment, all participants signed a consent to allow follow-up linkage of their electronic health records (EHR), thereby providing a longitudinal collection of phenotypic information. Health records have been extracted from the national Health Insurance Fund Treatment Bills (from 2004), Tartu University Hospital (from 2008), and North Estonia Medical Center (from 2005). The diagnoses are coded in ICD-10 format and drug dispensing data include drug ATC codes, prescription status and purchase date (if available). For the current study, cases of bipolar disease were determined by searching the EHRs for data on F31* ICD-10 diagnosis. All remaining participants who did not have any ICD-10 F* group diagnoses were defined as controls. Cases with bipolar I disorder were those with ICD codes of F31.1 and F31.2.

Zwart JA | Unpublished | Norway (the Nord-Trøndelag Health Study) | HUNT

The HUNT sample consisted of 905 subjects with BD and 41,914 population controls³⁷. Patients and

controls were of European ancestry and were recruited from the Nord-Trøndelag County, Norway. Diagnoses were assigned according to ICD-9 or ICD-10. The controls included individuals not diagnosed with substance use disorders, schizophrenia, bipolar disorder, major depressive disorder, anxiety disorders, eating disorders, personality disorders, or ADHD in hospitals (ICD-9 or ICD-10) or general practice (ICPC2). They also were >40 years of age, had low self-reported levels of anxiety and depression (HADS-A and HADS-D ≤ 11), and reported no use of antidepressants, anxiolytics, or hypnotics. Approval for the study was granted by the Data Inspectorate of Norway, the Health Directorate and the Regional Committee for Medical and Health Research Ethics. Cases of bipolar I disorder were those with ICD codes of F31.1, F31.2 or F31.6 and individuals with an ICD-9 code of 295 or ICD-10 codes F20-F29 were excluded. Cases of bipolar II disorder were those with ICD codes of F31.8 and individuals with an ICD-9 code of 295 or ICD-10 codes F20-F29, F31.1-.2 or F31.6 were excluded.

Breen G | 30305743 | UK (UK Biobank) | UKBiobank

The UK Biobank is a prospective cohort study of 501,726 individuals, recruited at 23 centres across the United Kingdom³⁸. Extensive phenotypic data are available for UK Biobank participants from health records and questionnaires. Participants were classified as having bipolar disorder if they had a reported clinical diagnosis of bipolar disorder (all primary and secondary ICD10 F31 code diagnoses in hospital inpatient records data; UK Biobank category 2002; <http://biobank.ctsu.ox.ac.uk/showcase/label.cgi?id=2002>; N = 777) or if they self-reported bipolar disorder during an interview with a nurse at baseline recruitment (UK Biobank data-field 20002; <http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=20002>; N = 1,116; union N = 1,454). The selection of control participants has been described previously³⁹. Control participants did not meet case criteria, did not report the use of any psychiatric medication at baseline (UK Biobank data-field 20003; <http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=20003>), and did not self-report any history of mental health disorder in the online mental health questionnaire (UK Biobank category 136; <http://biobank.ctsu.ox.ac.uk/showcase/label.cgi?id=136>; N = 58113).

===== PGC PsychChip Samples =====

Pato, C | Not published | [PGC Psychchip] | gpcw1

The cases and controls in this study were ascertained in the same manner as those described above for bip_usc2_eur.

Reif, A | Not published | [PGC Psychchip] | germ1

Cases were recruited in the same manner as those described above for BOMA-Germany II | bip_bmg2_eur. Control subjects were healthy participants who were recruited from the community of the same region as cases. They were of Caucasian descent and fluent in German. Exclusion criteria were manifest or lifetime DSM-IV axis I disorder, severe medical conditions, intake of psychoactive medication as well as alcohol abuse or abuse of illicit drugs. Absence of DSM-IV axis I disorder was ascertained using the German versions of the Mini International Psychiatric Interview. IQ was above 85 as ascertained by the German version of the Culture Fair Intelligence Test 2⁴⁰. Study protocols were reviewed and approved by the ethical committee of the Medical Faculty of the University of Würzburg. All subjects provided written informed consent.

Serretti, A, Ribases M | Not published | [PGC Psychchip] | spsp3

The sample includes 267 BD subjects (Spanish Wave2 Serretti PsychChip QC Summary), of which 180 Spanish and 87 Italian. Spanish sample: 180 subjects were enrolled in a naturalistic cohort study, consecutively admitted to the out-patient Bipolar Disorders Unit, Hospital Clinic, University of Barcelona. This is a systematic cross-sectional analysis deeply described in a previous paper on the same sample investigating rs10997870 SIRT1 gene variant⁴¹. Inclusion criteria were a diagnosis of Bipolar Disorder (type 1 or 2) according to DSM-IV TR criteria and age of 18 years or older. The study was approved by the local ethical committee and carried out in accordance with the ethical standards laid down in the Declaration

of Helsinki. Signed informed consent was obtained from all participants after a detailed and extensive description of the study and patient's confidentiality was preserved. The current and lifetime diagnoses of mental disorders were formulated by independent senior psychiatrists (diagnostic concordance: Kappa=0.80) according to DSM-IV TR clinical criteria and confirmed through the semi-structured interviews for Axis I disorders according to DSM IV TR criteria (SCID I). Furthermore, all available clinical data coming from follow-up at our unit and collateral information concerning illness history were cross-referred in order to ensure accuracy and obtain complete clinical information. Specific psychopathological dimensions were assessed by means of rating scales and clinical questionnaires administered by clinicians, adequately trained to enhance inter-rater reliability. Mood episodes were defined according to DSM-IV TR criteria and their severity was measured through the administration of the 21-item Hamilton Depression Rating Scale (HDRS-21, Spanish version). The most severe depressive episode was defined on the basis of the severity at the HDRS (total score > 14) and clinical judgment. Italian sample: 87 subjects with bipolar depression were enrolled into the study when admitted at the Department of Psychiatry, University of Bologna, Italy. A description of the subjects has been previously reported when analyzing clinical features⁴². Inclusion criteria were: a diagnosis of bipolar disorder, most recent episode depressive as assessed by DSM-IV-TR criteria; Young Mania Rating Scale (YMRS) score <12; Hamilton Depression Rating Scale (HAM-D) <12. Exclusion criteria were: presence of a bipolar disorder, most recent episode manic or hypomanic; presence of severe medical conditions; presence of moderate to severe dementia (Mini Mental State Examination score <20). The following scales were administered biweekly during the hospitalization: HAM-D, Hamilton Anxiety Rating Scale (HAM-A), YMRS and Dosage Record and Treatment Emergent Symptom Scale (DOTES). Written informed consent was obtained for each patient recruited. The study protocol was approved by the local Ethical Committee and it has been performed in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki.

The Spanish controls were part of the Mental-Cat clinical sample or the INSchool population-based cohort. A total of 1,774 controls from the Mental-Cat cohort (60.5% males) were evaluated and recruited prospectively from a restricted geographic area at the Hospital Universitari Vall d'Hebron of Barcelona (Spain) and consisted of unrelated healthy blood donors. The INSchool sample consisting of 771 children (76.2% males) from schools in Catalonia were involved for screening using the Achenbach System of Empirically Based Assessment (ASEBA) with the Child Behavior Checklist CBCL/4-18 (completed by parents or surrogates), the Teacher Report Form TRF/5-18 (completed by teachers and other school staff) and the Youth Self-Report YSR/11-18 (completed by youths); the Strengths and Difficulties Questionnaire (SDQ) and the Conner's ADHD Rating Scales (Parents and Teachers). Genomic DNA samples were obtained either from peripheral blood lymphocytes by the salting out procedure or from saliva using the Oragene DNA Self-Collection Kit (DNA Genotek, Kanata, Ontario Canada). DNA concentrations were determined using the Pico-Green dsDNA Quantitation Kit (Molecular Probes, Eugene, OR) and genotyped with the Illumina Infinium PsychArray-24 v1.1 at the Genomics Platform of the Broad Institute. The study was approved by the Clinical Research Ethics Committee (CREC) of Hospital Universitari Vall d'Hebron, all methods were performed in accordance with the relevant guidelines and regulations and written informed consent was obtained from participant parents before inclusion into the study. Detailed information has been published previously⁴³.

Perlis, R; Sklar, P; Smoller, J, Goes F, Mathews CA, Waldman I | Not published | [PGC Psychchip] | usaw4
Perlis, R; Sklar, P; Smoller, J: EHR data were obtained from a health care system of more than 4.6 million patients⁴⁴ spanning more than 20 years. Experienced clinicians reviewed charts to identify text features and coded data consistent or inconsistent with a diagnosis of bipolar disorder. Natural language processing was used to train a diagnostic algorithm with 95% specificity for classifying bipolar disorder. Filtered coded data were used to derive three additional classification rules for case subjects and one for control subjects. The positive predictive value (PPV) of EHR-based bipolar disorder and subphenotype diagnoses was calculated against diagnoses from direct semistructured interviews of 190 patients by

trained clinicians blind to EHR diagnosis. The PPV of bipolar disorder defined by natural language processing was 0.86. Coded classification based on strict filtering achieved a value of 0.84, but classifications based on less stringent criteria performed less well. No EHR-classified control subject received a diagnosis of bipolar disorder on the basis of direct interview (PPV=1.0). For most subphenotypes, PPV exceeded 0.80. The EHR-based classifications were used to accrue bipolar disorder cases and controls for genetic analyses. Samples were genotyped on the Psychchip array.

Goes, FS: Cases represented independent probands from a European-American family sample that was collected at Johns Hopkins University from 1988-2010. Families had at least 2 additional relatives with a major mood disorder (defined as bipolar disorder type 1, bipolar type 2 or recurrent major depressive disorder). Diagnostic interviews were performed using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (N=81) and the Diagnostic Instrument for Genetics Studies (N=161). All cases underwent best-estimate diagnostic procedures. After genotyping quality control there were 242 cases, of which 240 were diagnosed as Bipolar Disorder type 1 and 2 as Schizoaffective Disorder, bipolar type. Diagnoses were based on DSM-III and DSM-IV criteria. Probands from this sample have been previously studied in family based linkage and exome studies.⁴⁵⁻⁴⁷

Mathews CA: Control samples were ascertained as part of ongoing genetic and neurophysiological studies of hoarding, obsessive compulsive and tic disorders. Controls reported no current or lifetime history of mania or hypomania at the time of ascertainment. Sixty-two of the 104 controls were screened for psychiatric illness using the Structured Clinical Interview for DSM-IV TR diagnoses and diagnoses of bipolar disorder, lifetime or current, were ruled out through a best estimate consensus diagnosis. Other psychiatric diagnoses were not excluded. The remaining 42 participants were not formally screened, but reported no lifetime or current history of bipolar disorder, obsessive compulsive, hoarding, or tic disorders. Samples were genotyped on the Psychchip array. Ethical approvals were obtained from the University of Florida Human Subjects Review Board.

Waldman I: Control samples were ascertained as part of an ongoing genetic study of ADHD and other Externalizing disorders (i.e., Oppositional Defiant Disorder and Conduct Disorder). Controls reported no current diagnoses of Externalizing or Internalizing disorders at the time of ascertainment. Controls were assessed for psychiatric conditions using the Emory Diagnostic Rating Scale (EDRS)⁴⁸, a questionnaire that assessed parent ratings of symptoms of common DSM-IV Externalizing and Internalizing disorders (e.g., Major Depressive Disorder and various anxiety disorders). Samples were genotyped on the Psychchip array. Ethical approvals were obtained from the Emory University and University of Arizona Human Subjects Review Boards.

Baune, BT; Dannlowski, U | Not published | [PGC Psychchip] | bdtres

The Bipolar Disorder treatment response Study (BP-TRS) comprises BD inpatient cases and screened controls of Caucasian background. Psychiatric diagnosis of Bipolar Disorders was ascertained using SCID or MINI 6.0 using DSM-IV criteria in a face-to-face interview by a trained psychologist / psychiatrist for both cases and controls. Healthy controls were included if no current or lifetime psychiatric diagnosis was identified. Cases were included if current or lifetime diagnosis of bipolar disorder was ascertained by structured diagnostic interview. Cases and controls are of similar age range (≥ 18 yrs of age) and were collected from the same geographical areas. Other assessments including symptom ratings, psychiatric history, treatment history, treatment response were based on interview, and carried out by trained psychologists/psychiatrists. Samples were genotyped on the Psychchip array. Ethical approval was obtained from the University of Münster Human Ethics Committee, Münster, Germany.

Ophoff R, Posthuma D, Lochner C, Franke B | Not published | [PGC Psychchip] | dutch

Ophoff R: Cases and controls were collected using the same protocol as described above for the "ucla" sample.

Lochner C: Controls include population based-controls ascertained from blood banks and controls recruited through university campuses and newspaper advertisements, who underwent a psychiatric

interview and had no current or lifetime psychiatric disorder^{49,50}.

Franke B: The controls included are healthy individuals from the Dutch part of the International Multicenter ADHD Genetics (IMAGE) project^{51,52}.

Posthuma D: Data were provided for 960 unscreened Dutch population controls from the Netherlands Study of Cognition, Environment and Genes (NESCOG)⁵³. The study was approved by the institutional review board of Vrije Universiteit Amsterdam and participants provided informed consent.

Gawlik M | Not published | [PGC Psychchip] | gawli

Patients were recruited at the Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Germany. Diagnosis according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-fourth edition) was made by the best estimate lifetime diagnosis method, based on all available information, including medical records, and the family history method.

Fullerton J, Mitchell PB, Schofield PR, Green MJ, Weickert CS, Weickert TW, The Australian Schizophrenia Research Bank | Not published | [PGC Psychchip] | neuc1

The NeuRA collection comprised BD cases from three cohorts ascertained in Australia: the bipolar high risk study⁵⁴ (n=97), the Imaging Genetics in Psychosis Study (IGP; n=47)⁵⁵ and a clinic sample (n=109) recruited via the Sydney Bipolar Disorders Clinic⁵⁶. The clinic sample used the same ascertainment procedures as described for the bip_bmau_eur sample. The bipolar high risk study is a collaborative study with 4 US and one Australian groups, with young participants aged 12-30. The IGP sample was recruited from outpatient services of the South Eastern Sydney-Illawarra Area Health Service (SESAHS), the Sydney Bipolar Disorders Clinic and the Australian Schizophrenia Research Bank. Healthy controls were sourced from the high risk, IGP and the Cognitive and Affective Symptoms of Schizophrenia Intervention (CASSI) trial⁵⁷ studies, and were recruited from the community, had no personal lifetime history of a DSM-IV Axis-I diagnosis as determined by psychiatric interview, and no history of psychotic disorders among first-degree biological relatives. Additional controls were recruited as part of the strategy to develop an Australian Schizophrenia Research Biobank for studies into the genetics of this disease. The ascertainment of these controls has been previously described⁵⁸.

Landen M, Hillert J, Alfredsson L | Not published | [PGC Psychchip] | swed1

The cases in the swed1 sample were recruited using the same ascertainment methods described for the bip_swa2_eur sample. Population-based healthy controls, randomly selected from the Swedish national population register, were collected as part of two case-control studies of multiple sclerosis: GEMS (Genes and Environment in Multiple Sclerosis) and EIMS (Epidemiological Investigation of Multiple Sclerosis)⁵⁹.

Di Florio A, McQuillin A, McIntosh A, Breen G | Not published | [PGC Psychchip] | ukwa1

McQuillin A: BD cases were recruited using the same protocol as the bip_uclo_eur described above. A subset (n=448) of the control subjects were random UK blood donors obtained from the ECACC DNA Panels (<https://www.phe-culturecollections.org.uk/products/dna/hrcdna/hrcdna.jsp>). The remaining control subjects (n=814) had been screened for an absence of mental illness in using the same protocol as the bip_uclo_eur described above.

Di Florio A: Cases were recruited across the United Kingdom in the same manner as described for the bip_wtcc_eur and bip_icuk_eur samples.

McIntosh AM: BD cases were recruited from the clinical case loads of treating psychiatrists from Edinburgh and across the central belt of Scotland. Controls were identified from non-genetic family members and from the extended networks of the participants themselves. All participants were of European ancestry and diagnosis was confirmed using an established battery developed for ICCBD. Breen G: Controls were drawn from blood donors to the UK Motor Neuron Disease Association DNA Biobank⁶⁰

Perlis, R; Sklar, P; Smoller, J, Nievergelt C, Kelsoe J | Not published | [PGC Psychchip] | usaw5

Kelsoe, J: The Pharmacogenomics of Bipolar Disorder (PGBD) study was a prospective assessment of lithium response in BDI patients. The goal was to identify genes for lithium response. Subjects were

recruited from clinics at 11 international sites and followed for up to 2.5 years. Diagnosis was obtained by DIGS interview and medical records reviewed by blind experienced clinicians. As the comparison was between lithium responders and non-responders, no controls were collected. All subjects provided written informed consent.

Perlis R: Cases of bipolar disorder were Individuals treated with lithium drawn from the Partners Healthcare electronic health record (EHR) database, which spans two large academic medical centers, Massachusetts General Hospital and Brigham and Women's Hospital in addition to community and specialty outpatient clinics⁶¹. Any patients aged 18 years or older with at least one lithium prescription between 2006 and 2013 based on e-prescribing data were included. The Partners Institutional Review Board approved all aspects of this study. Individuals with a diagnosis of schizophrenia based on ICD9 codes were excluded.

Smoller J: Cases and controls were recruited in the same manner as described above for "usaw4".

===== PGC3 Samples =====

Rietschel M, Nöthen MM, Forstner AJ, Streit F, Babadjanova G | 24618891 | Russia (BOMA-Russia) | bmrus

Patients were recruited from consecutive admissions to the psychiatric inpatient units of the Russian State Medical University, Moscow. Unrelated controls were recruited from the general population. All protocols and procedures were approved by the respective local Ethics Committees. Written informed consent was obtained from all study participants before the study participation. All patients were assigned a lifetime diagnosis of BPAD type I or type II. This was based on Diagnostic and Statistical Manual of Mental Disorders-IV criteria and a consensus best-estimate procedure, including a structured interview-I, review of medical records, the family history method and the Operational Criteria Checklist for Psychotic Illness OPCRIT system.

Ferentinos P, Dikeos D, Patrinos G | Not published | Greece (Attikon General Hospital) | greek

All adult patients with a DSM-IV-TR/DSM-5 diagnosis of Bipolar Disorder hospitalized at the inpatient unit or followed-up at the specialized 'Affective disorders and Suicide' outpatient clinic of the 2nd Department of Psychiatry, National and Kapodistrian University of Athens, Attikon General Hospital, Athens, Greece from 2012 to 2017 were recruited for the current study. Patients were referred to the specialized 'Affective disorders and Suicide' outpatient clinic either from the inpatient unit after hospitalization or from the community. Diagnosis was established and demographic (age, gender, family status, profession, employment status, education) and relevant clinical features (e.g. age at onset, polarity of first and most recent episode, number of lifetime depressive and manic/hypomanic episodes, number of hospitalizations, lifetime suicidality, lifetime psychosis) were extracted through a M.I.N.I.-5.0.0-based semi-structured diagnostic interview, which was administered during patients' initial clinical assessment and regularly updated ever since, interviews of primary caregivers and inspection of medical records. Lifetime presence of any DSM-IV-TR axis I psychiatric comorbidities (dysthymia, panic disorder, agoraphobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, alcohol and substance abuse and dependence, anorexia nervosa, bulimia nervosa) was similarly extracted. Family history of major psychiatric disorders and suicidality in first and second degree relatives was recorded with a specific questionnaire based on the Family Interview for Genetic Studies. Medical comorbidities were recorded with the Cumulative Illness Rating Scale, completed on the basis of interview with patient and primary caregivers, inspection of patient's medical records and laboratory exams (basic or specific, if considered necessary). Presence of selected medical diseases was specifically recorded.

Control (unaffected) participants were a convenient sample drawn from the same geographic area as case participants, either within health care facilities or as community volunteers. All of them went through a brief clinical interview including items on psychiatric and medical history, psychiatric family history, past

and current medical or psychiatric therapies, and a brief mental state examination. Only participants found to be free of lifetime major mental disorders (MDD, BD, schizophrenia, or other psychotic disorders) and with no family history of major mental disorder in their first-degree relatives were recruited as controls.

All cases and controls were native Greek speakers. All participants provided written informed consent before being included in the study and the study protocol was approved by the Research Ethics Committee of Attikon General Hospital.

Andreassen, OA | Not published | Norway (TOP) | norgs

The NORGS bipolar disorder cases and controls were ascertained in the same way as the bip_top7_eur (TOP7) samples described above, and recruited from hospitals across Norway.

Andreassen, OA | Not published | Norway (TOP) | noroe

The NOROE bipolar disorder cases and controls were ascertained in the same way as the bip_top7_eur (TOP7) samples described above, and recruited from hospitals across Norway.

Reininghaus E | Not published | Austria (Medical University of Graz) | graza

Assoz.Prof. DDr. Eva Reininghaus, Priv.Do. DDr. Susanne Bengesser, Priv.Do. Dr. Nina Dalkner, Priv.Do. Armin Birner and further team members of the special outpatients department for bipolar affective disorders at the Department of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz, Austria: Cases with bipolar affective disorder (type I and II) and healthy controls were recruited at the Department of Psychiatry and Psychotherapeutic Medicine at the Medical University of Graz (MUG), Austria. Study protocols were approved by the ethics committee of the Medical University of Graz. Patients and healthy controls gave written informed consent and the study was conducted according to the declaration of Helsinki. All patients received a clinical interview by a psychiatrist or psychologist and a diagnosis according to DSM-IV with the SCID-I (Structured clinical interview). Healthy controls did not have a history of a psychiatric disorder. Furthermore, healthy controls did not have any first or second degree relatives with a psychiatric disorder. The PGC-Graz sample (n= 244; 114 males, 130 females) includes 167 cases with bipolar disorder and 77 healthy controls genotyped with Omniexpress 1.2 by Illumina.

Grigoriou-Serbanescu M | 31791676; 26806518 | Romania (BOMA-Romania) | bmrom

This sample includes the BOMA-Romania sample and additional cases from the ConLiGen-Romania sample. For the BOMA-Romania sample, unrelated BP-I patients were recruited from consecutive admissions in the Obregia Psychiatric Hospital of Bucharest, Romania. All participants provided written informed consent following a detailed explanation of the study aims and procedures. The study was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants were of Romanian descent according to self-reported ancestry. Genealogical information about parents and all four grandparents was obtained through direct interview of the subjects.

The patients were investigated with the Diagnostic Interview for Genetic Studies (DIGS)²⁷ and the Family Interview for Genetic Studies (FIGS)⁷ The diagnosis of BP-I was assigned according to DSM-IV criteria on the basis of both the DIGS and medical records. Patients were included in the sample if they had at least two documented hospitalized illness episodes (one manic/mixed and one depressive or two manic episodes) and no residual mood incongruent psychotic symptoms during remissions. This information was also confirmed by first degree relatives for 64% of the cases. The illness age-of-onset was defined as the age at which the proband first met DSM-IV criteria for a manic, mixed, or major depressive episode. Family history of psychiatric illness was obtained with FIGS administered both to the patients and to all available relatives.

Cases in the ConLiGen-Romania study were ascertained in the same manner as for BOMA-Romania. Cases were required to have taken lithium for at least two years and lithium treatment response was evaluated with the Alda scale⁶².

Population-based controls were evaluated using the DIGS and FIGS to screen for a lifetime history of major

affective disorders, schizoaffective disorders, SCZ and other psychoses, obsessive-compulsive disorder, eating disorders, and alcohol or drug addiction. Unaffected individuals were included as controls in the present study.

Quality control, imputation and analysis of cohorts external to the PGC

For external cohorts, quality control (QC), imputation and GWAS were conducted by the collaborating research teams using comparable procedures as used for the PGC cohorts. These are outlined below. SNPs were retained in the GWAS summary statistics using the filtering method described for the PGC cohorts.

iPSYCH

For the iPSYCH cohort, QC, imputation and GWAS was performed using RICOPILI, as described for the PGC cohorts⁶³.

deCODE genetics

QC, imputation and association analyses were performed in the deCODE sample as previously described^{36,64}.

Estonian Biobank

A more detailed description of the genotyping, quality control and imputation procedures for the Estonian Biobank (EstBB) is reported elsewhere^{65,66}. As a short description, of all the studied EstBB participants at the time of this study, 33,277 have been genotyped using the Global Screening Array v1, 8137 on the HumanOmniExpress beadchip, 2641 on the HumanCNV370-Duo BeadChips and 7,832 on the Infinium CoreExome-24 BeadChips from Illumina. Furthermore, 2,056 individuals' whole genomes have been sequenced at the Genomics Platform of the Broad Institute. Sequenced reads were aligned against the GRCh37/hg19 version of the human genome reference using BWA-MEM1 v0.7.7. The genotype data was phased using Eagle2 (v. 2.3) and imputed using BEAGLE (v. 4.1) software, implementing a joint Estonian and Finnish reference panel (described in⁶⁵).

The GWAS was performed among 17,616 unrelated individuals (PiHat < 0.2) of whom 408 were cases of bipolar disorder and 17,209 were controls. The GWAS was run with the EFACTS software on variants with an allele frequency of at least 0.01% using an additive genetic logistic model (b.wald). To minimize the effects of population admixture and stratification, the analyses only included samples with European ancestry based on principal component analysis (PCA) and were adjusted for the first ten principal components (PCs) of the genotype matrix, as well as for birth year, birth year squared, gender and genotyping array. By the time of the analysis of the BDI phenotype, all 200,000 EstBB participants had been genotyped with the Global Screening Array and imputed using the Estonian reference panel. The BDI GWAS with 147 cases and 65,952 controls was performed using SAIGE, including related individuals and adjusting for the first ten PCs, as well as for birth year, birth year squared and sex.

HUNT

Participants were genotyped with Illumina HumanCoreExome arrays (HumanCoreExome12 v1.0, HumanCoreExome12 v1.1, or UM HUNT Biobank v1.0). In quality control, genotypes with call rates <99%, contamination >2.5%, large CNVs, lower call rate of technical duplicate pair or twins, uncommon sex chromosome constellations, and discrepancies with reported sex were removed. Variants with call rates <99%, higher call rates genotyped in another assay, probe sequences not mapping to the reference genome, cluster separation <0.3, genrain score < 0.15, or HWE deviation from unrelated samples of European ancestry (p<0.0001) were also removed. Imputation was performed against a customized merged reference panel of 2,201 low-coverage whole-genome sequenced samples from the HUNT study and the Haplotype Reference consortium release 1.1 (excluding 1,023 samples from the HUNT study). The Scalable and Accurate Implementation of GEneralized mixed model (SAIGE) was used for association testing to account for case-control imbalance and relatedness⁶⁷.

UK Biobank

Genotypic data were available for 488,380 individuals and were imputed to the HRC, UK10K and 1,000 Genomes Phase 3 reference panels using IMPUTE4 to identify $\approx 93\text{M}$ variants for 487,409 individuals⁶⁸. Variants for analysis were limited to those with minor allele frequency ≥ 0.01 , imputation INFO-score ≥ 0.4 , and which were either genotyped or imputed to the HRC reference panel, leaving a total of 7794483 SNPs for analysis. Using the genotyped SNPs, individuals were removed if: recommended by the UK Biobank core analysis team for unusual levels of missingness or heterozygosity; SNP genotype call rate $< 98\%$; related to another individual in the dataset (KING $r < 0.044$, equivalent to removing up to third-degree relatives inclusive); phenotypic and genotypic gender information was discordant (X-chromosome homozygosity (FX) < 0.9 for phenotypic males, FX > 0.5 for phenotypic females). Removal of relatives was performed using a greedy algorithm, which minimises exclusions (for example, by excluding the child in a mother-father-child trio). All analyses were limited to individuals of White Western European ancestry, as defined by 4-means clustering on the first two genetic principal components provided by the UK Biobank⁶⁸. Principal component analysis was also performed on the European-only subset of the data using the software flashpca2⁶⁹. A genome-wide association study was performed using BGenie v.1.2⁶⁸, covarying for 6 PCs, and factors capturing site of recruitment and genotyping batch.

Sample descriptions and polygenic risk scoring in non-European cohorts

Polygenic risk scores (PRS) generated from the GWAS meta-analysis were tested for association with BD in four non-European cohorts, to investigate the cross-ancestry utility of PRS. The BD PRS were computed using summary statistics from the PGC1¹, PGC2², and PGC3 GWAS of BD to assess prediction performance in diverse ancestry samples, as the size of the European ancestry training sample increased. Analyses were conducted using PRSice-2⁷⁰, with P value informed clumping based on the LD structure of the target dataset. Following the PRS strategy of Bigdeli *et al*⁷¹, subsets of SNPs were selected from the results at nine increasingly liberal P value thresholds (P_T) ($P_T < 5\text{E-}08$, $P_T < 1\text{E-}04$, $P_T < 1\text{E-}03$, $P_T < 0.01$, $P_T < 0.05$, $P_T < 0.1$, $P_T < 0.2$, $P_T < 0.5$, $P_T < 1$) as well as eight different LD-clumping r^2 parameters (clump- $r^2 = 0.1, 0.2, 0.3, \dots, 0.8$). The phenotypic variance explained by the PRS (R^2) was calculated on the liability scale using a BD population prevalence of both 1% and 2%. Each of the non-European samples are described below.

Japan (advanced COSMO and Biobank Japan) | PMID: 28115744

A detailed description of the sample information, genotyping, quality control and imputation procedures is reported elsewhere⁷². In brief, 2,964 BD and 61,887 comparison subjects from the Japanese population were included in this dataset (genotyped by Illumina OmniExpressExome v1.0 or v1.2 BeadChips). After the imputation and stringent QC, a total of 6,195,093 imputed SNPs were analysed for the association analysis. The diagnosis for each case subject followed the DSM-IV-TR criteria for BD and schizoaffective disorder and was reached by the consensus of at least two experienced psychiatrists, based on unstructured interviews with the subject and their family, as well as a review of the subject's medical records. For the comparison subjects, we used GWAS data for subjects in the BioBank Japan project collected as case subjects for non-psychiatric disorders. These subjects were not psychiatrically evaluated.

Korea

We genotyped 807 patients with bipolar disorder, 726 patients with schizophrenia and 497 healthy control subjects using the Affymetrix Axiom[®]Korea Biobank Array 1.0 (K-CHIP). K-CHIP was designed by the Center for Genome Science at the Korea National Institute of Health, including 833K SNPs. A more detailed description of the genotyping procedure is reported elsewhere⁷³. We performed sample-level and variant-level QC of genotype data. We excluded variants with missing rate $> 1\%$, Hardy-Weinberg equilibrium $P < 10^{-6}$, or minor allele frequency $< 1\%$, and samples with missing rate $> 5\%$, relatedness among the sample, mismatch between self-reported and inferred sex, or deviated heterozygosity rate. We confirmed homogeneity of the samples based on visual inspection of principal component analysis plots. Genotype imputation was conducted using the Haplotype Reference Consortium (HRC) reference panel. After the

imputation and additional post-QC ($R^2 > 0.8$ and minor allele frequency $> 1\%$), a total of 770 bipolar cases and 497 controls and 5,483,856 variants were analysed for polygenic risk score. All the patients met the DSM-IV-TR diagnostic criteria for bipolar I disorder and bipolar II disorder. For clinical diagnosis, a structured interview using the Korean version of the Diagnostic Interview for Genetic Studies (DIGS) or the Structured Clinical Interview for DSM-IV (SCID) was performed. The control group consisted of volunteers from the community who were free of any history of clinically significant psychiatric symptoms. Detailed assessment processes are described elsewhere⁷⁴.

GAIN (admixed African American) (USA)

Genetic Association Information Network (GAIN)/ The Bipolar Genome Study (BiGS) Data from the existing National Institutes of Health Genetic Association Information Network (GAIN) study of bipolar disorder was obtained through dbGap: phs000017.v3.p1. The GAIN study was multi-site and informed consent and institutional review board approval were obtained and details are described above for the GAIN-European data. Bipolar I diagnosis was confirmed with the structured Diagnostic Interview for Genetic Studies (DIGS) for the assessment of major mood and psychotic disorders and their spectrum conditions. The admixed African American (AA) bipolar patient data used in this study were from unrelated individuals in multiplex families and assessed with DIGS version 4. The genotyping has been described previously⁷⁵. Briefly, genotyping of AA samples (347 BD cases; 669 controls) was carried out separately from European American (EA) samples, using the Affymetrix Genome-Wide Human SNP Array 6.0. Further quality controls were carried out to remove samples with low call rate (below 98.5% for EA and 97.8% for AA), excessively high or low heterozygosity (between 0.344 and 0.363 for EA and between 0.29 and 0.324 for AA), or incompatibility between reported gender and genetically determined gender. Samples were also checked for unexpected familial relationships using pairwise IBD estimation in PLINK. The total number of SNPs passing all initial QC tests was 845,814 for AA. Genotype imputation was conducted using the Consortium on Asthma among African ancestry Populations in the Americas (CAAPA) reference panel. After the imputation and additional post-QC (dosage $R^2 > 0.7$), a total of 347 bipolar cases and 669 controls and 10,762,719 variants were analysed for polygenic risk score.

Genomic Psychiatry Cohort (GPC) (admixed African American) (USA)

Details of ascertainment and diagnosis, genotyping and quality control have been described in detail previously⁷¹. Briefly, cases were ascertained using the Diagnostic Interview for Psychosis and Affective Disorders (DI-PAD), a semi-structured clinical interview administered by mental health professionals, which was developed specifically for the GPC study. Individuals reporting no lifetime symptoms indicative of psychosis or mania and who have no first-degree relatives with these symptoms are included as control participants. Genotyping of the AA-GPC was performed in 7 ‘batches’ using Illumina Infinium arrays (Omni2.5, Multi-Ethnic Global Array, and Global Screening Array). Typed variants were aligned to the human reference genome (GRCh37), and within each genotyping batch, variants with missingness greater than 2% or Hardy-Weinberg Equilibrium P -value $< 10^{-6}$ were excluded; all scripts for pre-processing GWAS array data are downloadable from <https://github.com/freeseek/gwaspipeline>. Computational phasing and statistical genotype imputation were performed for each genotyping batch using Eagle (v2.3.5)⁷⁶ and Minimac3 (v2.0.1)⁷⁷, respectively, with default parameters and using publicly available reference haplotypes from the 1000 Genomes Project (1KGP) Phase 3⁷⁸. Principal components analysis (PCA) was performed with GCTA (v1.2.4)⁷⁹, using a genome-wide genetic relatedness matrix (GRM) estimated for the full GPC dataset and reference samples from the 1KGP Phase 3 data based on 34,918 genotyped SNPs. For each individual, we estimated genome-wide average proportions of African (AFR), European (EUR), Admixed American (AMR), East Asian (EAS), and South Asian (SAS) ancestry from global ancestry PCs using a simple linear mixed model. PRS for BD were tested in two groups of cases and controls: 1766 cases and 2535 controls with $\geq 25\%$ African ancestry and 1636 cases and 2357 controls with $\geq 50\%$ African ancestry. Associations between polygenic scores and case-control status were evaluated by logistic regression, with the first six global ancestry PCs and a batch indicator included as covariates.

Selection of traits for Mendelian randomization

BD has been linked to a range of other psychiatric, cognitive and behavioral phenotypes by clinical and epidemiological studies. On the basis of such studies, we selected 17 traits of interest for investigation of their genetic and potential causal relationships with BD. Traits were selected by a team of clinicians and biostatisticians, considering key clinical questions and the availability of GWAS summary statistics for the traits. Below we list the traits initially selected and the rationale for their inclusion. Only traits with at least 10 genome-wide significant loci were sufficiently powered to be investigated using Mendelian randomization, resulting in 10 traits tested (Supplementary Table 18).

Sleep traits

Reduced sleep duration is a diagnostic criterion for mania¹⁰² and has been implicated both as a prodromal symptom¹⁰³ and trigger of illness episodes¹⁰⁴. Hypersomnia and insomnia are commonly reported during major depressive episodes in bipolar disorder^{105–107} and have been identified as residual symptoms associated with impairment^{107–109}. Near-24-hour (circadian) oscillations are found in almost every human physiological process, including sleep-wake cycles¹¹⁰. Robust evidence associates bipolar disorder with a delayed sleep phase (i.e. evening chronotype)^{111–113}. Interventions targeting sleep are common for the treatment of bipolar disorder, ranging from the use of sedating medication for the treatment of acute mania^{114,115} to circadian manipulation^{114,116} to prevent recurrences and improve outcomes. Until recently, there was no clear evidence supporting a genetic relationship between sleep and bipolar disorder. However, a recent study on over 20,000 participants found that the polygenic association between sleep and bipolar disorder differs across sleep traits and bipolar subtypes¹¹⁷, with sleep duration associated to bipolar I disorder and insomnia to bipolar II disorder, but not vice versa. The study also did not find any evidence to support a causal relationship between sleep and bipolar phenotypes.

Alcohol and substance use and misuse

Of all psychotic and affective disorders, bipolar disorder has been reported to be the most strongly linked with alcohol or drug abuse. Compared to other primary psychiatric diagnoses, mania and hypomania may have one of the highest associations with alcohol use disorders, with a pooled lifetime prevalence around 35%¹¹⁸. Even when criteria for alcohol use disorders are not met, increased levels of alcohol use in bipolar disorder are associated with a less favourable illness course¹¹⁹. Lifetime co-occurrence rates for other substances are also high in bipolar disorder, with mean rates of 20% for cannabis use and 17% of any drug use disorders, according to a meta-analysis of clinical studies¹²⁰. Conversely, individuals with substance use disorders have higher rates of bipolar disorder compared to non-users, with significant pooled odds ratios for both lifetime (OR 4.68, 95% CI 3.39–6.47) and 12 months drug use disorders (OR 6.49, 95% CI 4.30–9.80), according to a meta-analysis of national surveys of general populations¹²¹. In our research, we particularly focussed on cigarette smoking, as a recent Mendelian randomization study has suggested a causal link between smoking behaviors and bipolar disorder¹²².

Educational attainment and measures of intelligence

The link between bipolar disorders and measures of intelligence or educational attainment is controversial. Evidence from a longitudinal whole population cohort study suggested that the association between educational attainment and risk of subsequent bipolar disorder follows a non-linear distribution: individuals with excellent school performance had the highest increased risk of later bipolar disorder compared with those with average grades (hazard ratio HR = 3.79, 95% CI 2.11–6.82). Yet, at the other

end of the distribution, individuals with the poorest grades had also an increased risk of bipolar disorder (HR = 1.86, 95% CI 1.06–3.28), but the risk for them was not as high as for excellent students¹²³.

The association of bipolar disorder with educational attainment may differ from that with measures of intelligence. A Dutch study corroborated this hypothesis by finding associations in opposite directions for educational attainment (positive association with bipolar disorder) and measures of intelligence quotient (negative association with bipolar disorder)¹²⁴. Moreover, it found that the association with educational attainment was specific for bipolar disorder and did not extend to schizophrenia.

Molecular genetic studies have also found an association between bipolar disorder and educational attainment ($r:0.25$; $r_{LD}:0.28$)¹²⁵, but results for intelligence are equivocal^{126–128}. Evidence from a population-based longitudinal study has suggested that the polygenic burden for bipolar disorder manifests as impaired cognitive performance in 8-year-old children from the general population¹²⁹. The association, however, seemed to be driven by genetic variants shared with schizophrenia.

Such distinction between bipolar disorder and schizophrenia has also been supported by conditional false discovery rate genome-wide analyses¹²⁸. Here, the majority of bipolar disorder risk alleles were associated with better cognitive performance, while the association was in the opposite direction (i.e. impaired cognitive performance) for schizophrenia. Among BD risk alleles identified at a lower significance threshold there was a balanced mix of bipolar disorder risk alleles associated with better or poorer cognitive performance¹²⁸. This is in line with the non-significant genetic correlation between BD and intelligence², and the non-linear association between risk of bipolar disorder and school performance¹²³.

Mood instability

Mood instability does not have a shared, agreed definition^{130,131}. Although it is present in many psychiatric phenotypes, the association with bipolar disorder is particularly striking. Chronic mood instability is present between illness episodes, with longitudinal studies suggesting that it is actually more common than discrete episodes^{132–135}. Mood instability in bipolar disorder is of clinical relevance as it is associated with poor prognosis^{132–134,136–139}. Although the mechanisms linking mood instability and bipolar disorder are not clear, a neurocomputational model has suggested that mood bias observed in bipolar disorder affects the striatal response to rewards, increasing reward prediction errors, and, in turn, causing expectations and mood to oscillate¹⁴⁰. A recent UK biobank genome wide association study of mood instability has, however, found only a weak genetic association between bipolar disorder and mood instability ($r_g=0.09$; $s.e.=0.037$)¹⁴¹. Authors have suggested that the “mood instability” construct elicited in the general population by the question “Does your mood often go up and down?” is different from that experienced in the context of bipolar disorder, supporting the importance of phenotype definitions and the heterogeneity of mood instability.

Brain volumes

Neuroimaging research in bipolar disorder has been hindered by the lack of statistical power of small studies. The ENIGMA Bipolar Disorder Working Group¹⁴² has overcome the problem by integrating data from 28 international cohorts in the largest brain magnetic resonance imaging study of bipolar disorder to date. They compared cortical grey matter thickness and surface in 1837 BD individuals and 2582 controls and found significant associations between reduced cortical surface area and history of psychosis (but not mood state at the time of scanning) and between cortical thickness and duration of illness. They also found an age-by-diagnosis interaction and an association with medication use.

Physical activity

Guidelines suggest physical activity for patients with bipolar disorder, especially for those taking antipsychotics and long-term medication¹⁴³. In a systematic review of 15,587 patients with bipolar disorder, the prevalence of sedentary lifestyle varied from 40% to 64.9%¹⁴⁴. Despite the high burden, the review concluded that the evidence was “insufficient to establish a cause-effect relationship between mood and physical exercise”. A recent 2 sample Mendelian randomization study on 5 SNPs associated with overall physical activity was also inconclusive¹⁴⁵. One of the methods employed, however, suggested a protective causal association from overall physical activity to BD (OR, 0.491; 95% CI: 0.314–0.767; p=0.002).

Childhood-onset psychiatric disorders

Youths with BD have higher rates of attention deficit/hyperactivity disorder (ADHD)¹⁴⁶ and childhood ADHD has been found to prospectively predict later BD¹⁴⁷. It has been reported that a clinically significant proportion of youth with bipolar I disorder also suffer from comorbid autism spectrum disorder¹⁴⁸

Full acknowledgements

We thank the participants who donated their time, life experiences and DNA to this research, and the clinical and scientific teams that worked with them. We are deeply indebted to the investigators who comprise the PGC. 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 and the Mount Sinai high performance computing cluster (<http://hpc.mssm.edu>), which is supported by the Office of Research Infrastructure of the National Institutes of Health under award numbers S10OD018522 and S10OD026880. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Cohort acknowledgements:

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).

BACCS-Canada: This work was supported through funding from the Canadian Institutes of Health Research, MOP-172013, to JBV at the Centre for Addiction & Mental Health, Toronto. The ascertainment of the case control cohorts was also supported by funding from GlaxoSmithKline to JBV.

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: This work was supported by the Australian National Health and Medical Research Council, grant numbers: 1037196 (PBM, PRS), 1066177 (JMF, JIN), 1063960 (JMF, PRS); and the Lansdowne Foundation. 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. AJF received support from the BONFOR Programme of the University of Bonn, Germany. MH was supported by the Deutsche Forschungsgemeinschaft.

Fran (France): This research was supported by Assistance Publique des Hôpitaux de Paris (APHP Grant PHRC GAN12), by Institut National de la Santé et de la Recherche Médicale (INSERM grant C0829), by the Fondation FondaMental and by the Investissements d’Avenir Programs managed by the Agence nationale pour la Recherche (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 (grant #166098), Genome Canada and from Dalhousie Medical Research Foundation.

HUNT: The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. The genotyping was financed by the National Institute of health (NIH), University of Michigan, The Norwegian Research council, and Central Norway Regional Health Authority and the Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU). The genotype quality control and imputation has been conducted by the 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 (NTNU).

iPSYCH BP group: ADB and the iPSYCH team acknowledges funding from The Lundbeck Foundation (grant no R102-A9118, R155-2014-1724 and R248-2017-2003), the Stanley Medical Research Institute, NIMH (1U01MH109514-01), an Advanced Grant from the European Research Council (project no: 294838), and grants from Aarhus University to the iSEQ, CGPM (GenomeDK HPC facility) and CIRRAU centers. The Danish National Biobank resource was supported by the Novo Nordisk Foundation.

The Mayo Bipolar Disorder Biobank was funded by the Marriot Foundation and the Mayo Clinic Center for Individualized Medicine.

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.

Neuc1 (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).

Neuc1 (NeuRA-IGP-Australia): MJG was supported by a NHMRC Career Development Fellowship (1061875).

Neuc1 (NeuRA-BDHR-Australia): This work was supported by the Australian National Health and Medical Research Council, grant numbers: 1037196 (PBM, PRS), 1066177 (JMF, JIN), 1063960 (JMF, PRS); and the Lansdowne Foundation. JMF would like to thank Janette M O'Neil and Betty C Lynch for their support.

Neuc1/ASGC1/ASRB: This study used samples and data from the Australian Schizophrenia Research Bank (ASRB), which is supported by the National Health and Medical Research Council of Australia, the Pratt Foundation, Ramsay Health Care, the Viertel Charitable Foundation and the Schizophrenia Research Institute. We thank and acknowledge the contribution of the ASRB Chief Investigators: V. Carr, U. Schall, R. Scott, A. Jablensky, B. Mowry, P. Michie, S. Catts, F. Henskens and C. Pantelis.

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

Span2: CSM was 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 was 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 (PI14/01700, PI15/01789, PI16/01505, PI17/00289, PI18/01788, PI19/00721, and P19/01224), and cofinanced by the European Regional Development Fund (ERDF), "la Marató de TV3" (092330/31), the Agència de Gestió d'Ajuts Universitaris i de Recerca-AGAUR, Generalitat de Catalunya (2014SGR1357 and 2017SGR1461) and the Pla estratègic de recerca i innovació en salut (PERIS), Generalitat de Catalunya (MENTAL-Cat; SLT006/17/287). This project has also received funding from the European Union's Horizon 2020 Research and Innovation Programme under the grant agreements No 667302 (CoCA) and 728018 (Eat2beNICE).

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.

Sweden: This work was funded by the Swedish Research Council (M. Schalling, C. Lavebratt), the Stockholm County Council (M. Schalling, C. Lavebratt, L. Backlund, L. Frisé, U. Ösby) and the Söderström Foundation (L. Backlund) and the Swedish Brain Foundation (T. Olsson).

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: The principal funder of this project was the Wellcome Trust. For the 1958 Birth Cohort, venous blood collection was funded by the UK Medical Research Council.

EstBB: This study has been supported by grants from the Estonian Research Council (grant numbers PRG184, PRG687, IUT20-60 and IUT24-6), and the CoMorMent project within the EU H2020 Framework Program (agreement no. 847776).

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

This work was supported in part by the Million Veteran Program Merit Review Award #I01 BX003341 from the U.S. Department of Veterans Affairs, Biomedical Laboratory Research and Development Service and the VISN 4 Mental Illness Research, Education and Clinical Center. The views expressed in this article are those of the authors and do not necessarily represent the position or policy of the Department of Veterans Affairs or the U.S. Government.

Funding Sources

Study	Lead investigator	Country, Funder, Award number
PGC	P Sullivan; EA Stahl	USA, NIMH MH109528; NIMH U01 MH109536
PGC	D Posthuma	Netherlands, Scientific Organization Netherlands, 480-05-003
PGC	D Posthuma	Dutch Brain Foundation and the VU University Amsterdam Netherlands

UK - BDRN (Cardiff)	PA Holmans	Medical Research Council (MRC) Centre (G0801418) and Program Grants (G0800509)
Analysis	NR Wray	NHMRC 1078901,108788
ASRB	V Carr	Australia, National Health and Medical Research Council, grant number: (86500).
ASRB	M Cairns	Australia, National Health and Medical Research Council, grant numbers: (1121474, 1147644).
ASRB	C Pantelis	Australia, National Health and Medical Research Council, grant numbers: (628386, 1105825).
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, NIMH	FJ McMahon	US, NIMH, R01 MH061613, ZIA MH002843
BiGS, GAIN, UCSD	J Kelsoe	US, NIMH, MH078151, MH081804, MH59567
BOMA-Australia	JM Fullerton	Australia, National Health and Medical Research Council, grant numbers: 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; 1063960
Romania (BOMA-Romania) bip_rom3_eur and bmrom	M Grigoriu- Serbanescu	Multiple grants from UEFISCDI, Romania
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 3429/3-2

BOMA-Germany I, II, III, BOMA-Spain	M Rietschel	Germany, Deutsche Forschungsgemeinschaft, RI 908/11-1
BOMA-Germany I, II, III, BOMA-Spain	M Rietschel	Germany, BMBF, ERA-Net Neuron "EMBED", 01EW1904
BOMA-Germany I, II, III, BOMA-Spain	M Rietschel	Germany, BMBF, ERA-Net Neuron "Synschiz", 01EW1810
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)
Bulgarian Trios (Cardiff)	G Kirov	The recruitment was funded by the Janssen Research Foundation. Genotyping was funded by multiple grants to the Stanley Center for Psychiatric Research at the Broad Institute from the Stanley Medical Research Institute, The Merck Genome Research Foundation, and the Herman Foundation.
EstBB	L Milani	Estonia, Estonian Research Council (grant numbers PRG184, PRG687, IUT20-60 and IUT24-6), European Commission EU H2020 (CoMorMent project, agreement no. 847776).
France	M Leboyer, F Bellivier, B Etain, S Jamain	France, APHP, INSERM, ANR, Fondation Fondamental
Halifax	M Alda	CIHR grant #166098 and Dalhousie Medical Research Foundation

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
Mayo Bipolar Disorder Biobank	JM Biernacka, MA Frye	Marriot Foundation and the Mayo Clinic Center for Individualized Medicine
Michigan	M Boehnke	US, NIMH, R01 MH09414501A1; US, NIMH, MH105653
Million Veteran Program	H Kranzler	I01 BX003341 from the U.S. Department of Veterans Affairs, Biomedical Laboratory Research and Development Service and the VISN 4 Mental Illness Research, Education, and Clinical Center.
Mount Sinai	EA Stahl	NARSAD Young Investigator Award
Mount Sinai, STEP-BD, FAST	P Sklar, EA Stahl	US NIH R01MH106531, R01MH109536
NeuRA-CASSI-Australia (neuc1)	C Shannon Weickert	Australia, National Health and Medical Research Council, grant number: 568807
NeuRA-CASSI-Australia (neuc1)	TW Weickert	Australia, National Health and Medical Research Council, grant number: 568807
NeuRA-IGP-Australia (neuc1)	MJ Green	Australia, National Health and Medical Research Council, grant numbers: 630471, 1081603
NeuRA-BDHR-Australia (neuc1)	PB Mitchell, PR Schofield, JM Fullerton	Australia, National Health and Medical Research Council, grant numbers: 1037196; 1066177; 1063960, & The Lansdowne Foundation

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)	C Pato, MT Pato, JA Knowles, H Medeiros	US, National Institutes of Health, R01MH085542

SWEBIC	M Landén	The Stanley Center for Psychiatric Research, Broad Institute from a grant from Stanley Medical Research Institute; NIMH MH077139 (PFS), The Swedish Research Council: 2018-02653 (ML), the Swedish foundation for Strategic Research (KF10-0039), the Brain foundation (FO2020-0261), and the Swedish Federal Government under the LUA/ALF agreement (ALF 20170019, ALFGBG-716801).
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)	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 (Cardiff)	N Craddock, I Jones, LA Jones	UK, Wellcome Trust, 078901; USA, Stanley Medical Research Institute, 5710002223-01
UK - BDRN (Cardiff)	A Di Florio	European Commission Marie Curie Fellowship, grant number 623932.
UNIBO / University of Barcelona, Hospital Clinic, IDIBAPS, CIBERSAM	E Vieta	Grants PI15/00283 (Spain) and 2014 SGR 398 (Catalonia)

University of Pittsburgh	V Nimgaonkar	US, NIMH MH63480
USC	JL Sobell	USA, National Institutes of Health, R01MH085542
WTCCC	N Craddock; AH Young	Wellcome Trust. For the 1958 Birth Cohort, venous blood collection was funded by the UK Medical Research Council. AHY was funded by 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)
Greece	G.P.Patrinios	European Commission (H2020-668353; Ubiquitous Pharmacogenomics (U-PGx); Greek General Secretariat of Research and Technology (MIS 5002550)
University of California, Irvine	MP Vawter	USA, National Institutes of Health, MH113177, MH074307, MH085801, MH099440, RR000827, MH060068, MH060870. Pritzker Neuropsychiatric Disorders Research Fund L.L.C.
Korea	HJ Lee	National Research Foundation of Korea (2019R1A2C2084158, 2017M3A9F1031220). Ministry of Health & Welfare of Korea (HM14C2606)
BIPGRAZ, Austria	EZ Reininghaus	Funding from the government of Styria, Austria.
BIPGRAZ, Austria	SA Bengesser	MEFO funding of the Medical University of Graz.
Korea	KS Hong	National Research Foundation of Korea (2019R1A2C1005346, 2019M3C7A1030617)
Japan	N Iwata, M Ikeda	Japan Agency for Medical Research and Development (JP20dm0107097, JP20km0405201, JP20km0405208)

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Named authors and their affiliations appear in the main manuscript.

HUNT All-In Psychiatry

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