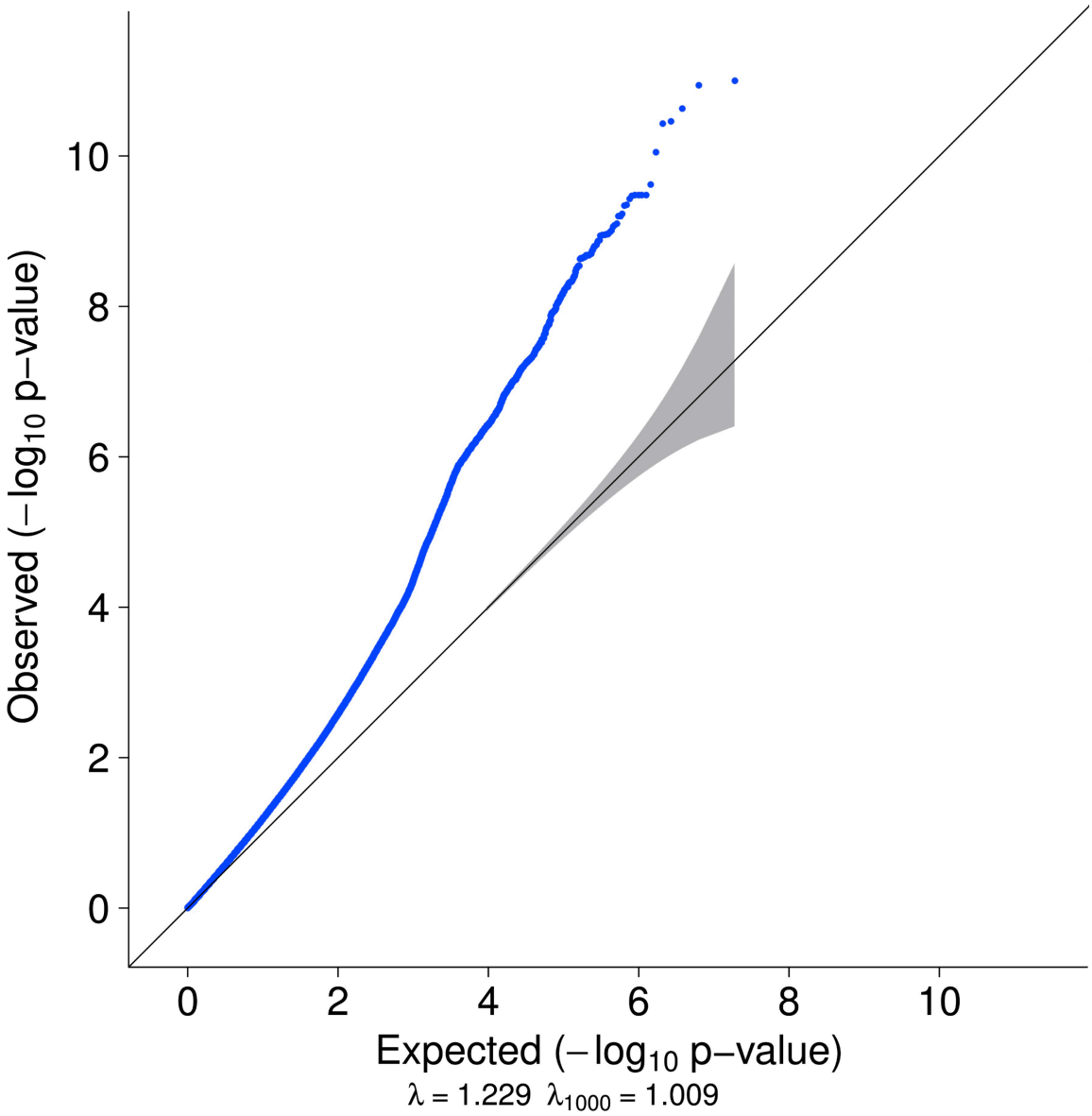
Supplementary PDF for:

Genome-wide association study identifies 30 Loci Associated with Bipolar Disorder.
Eli A. Stahl et al., for the PGC Bipolar Disorder working group.

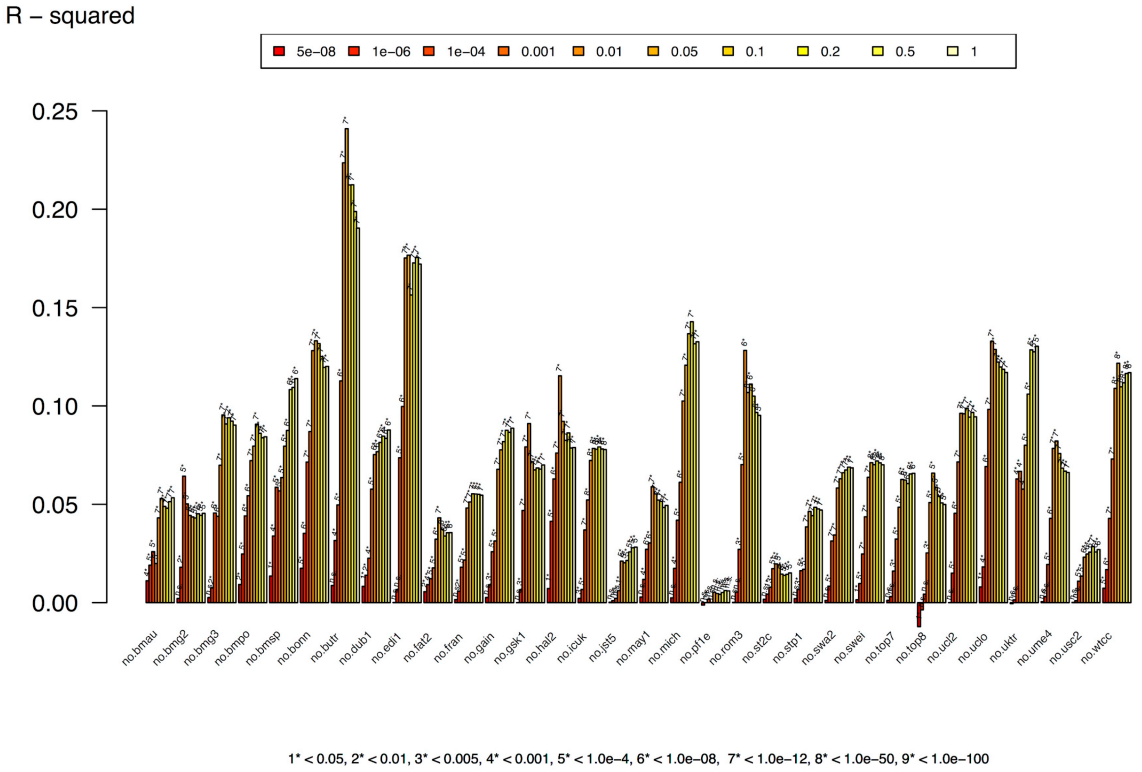
Contents:

Supplemental Figure 1. QQ-plot of primary GWAS.

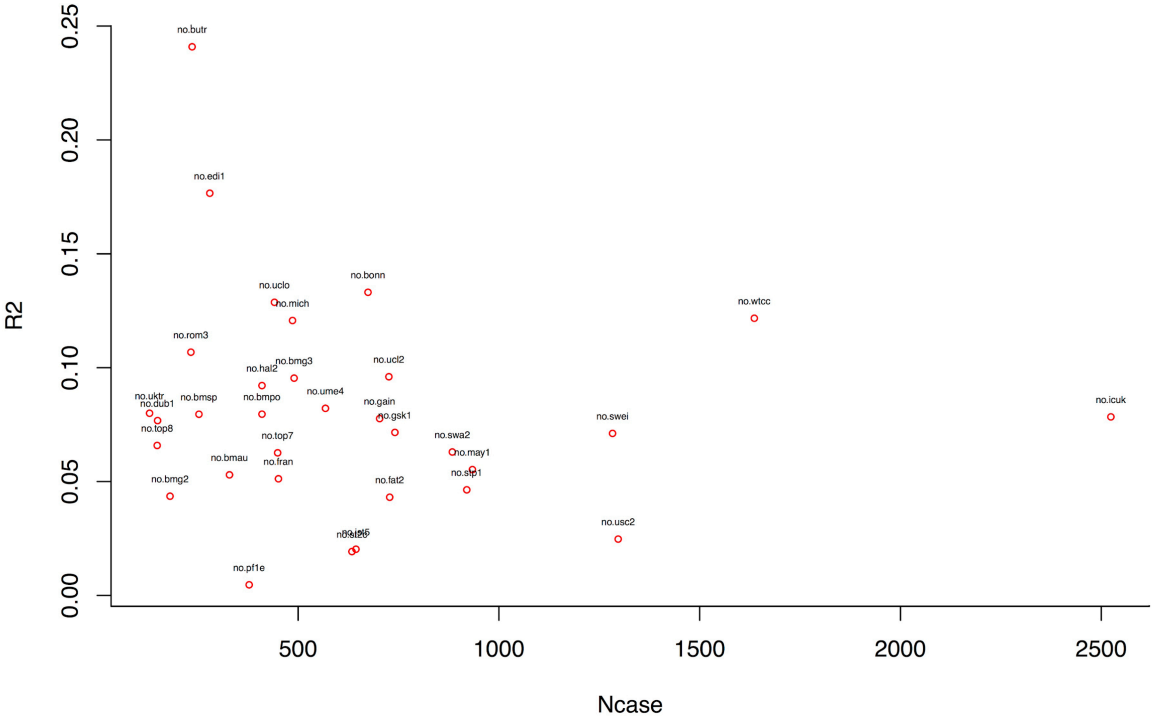


Supplementary Figure 2. Leave one out polygenic risk score analysis.

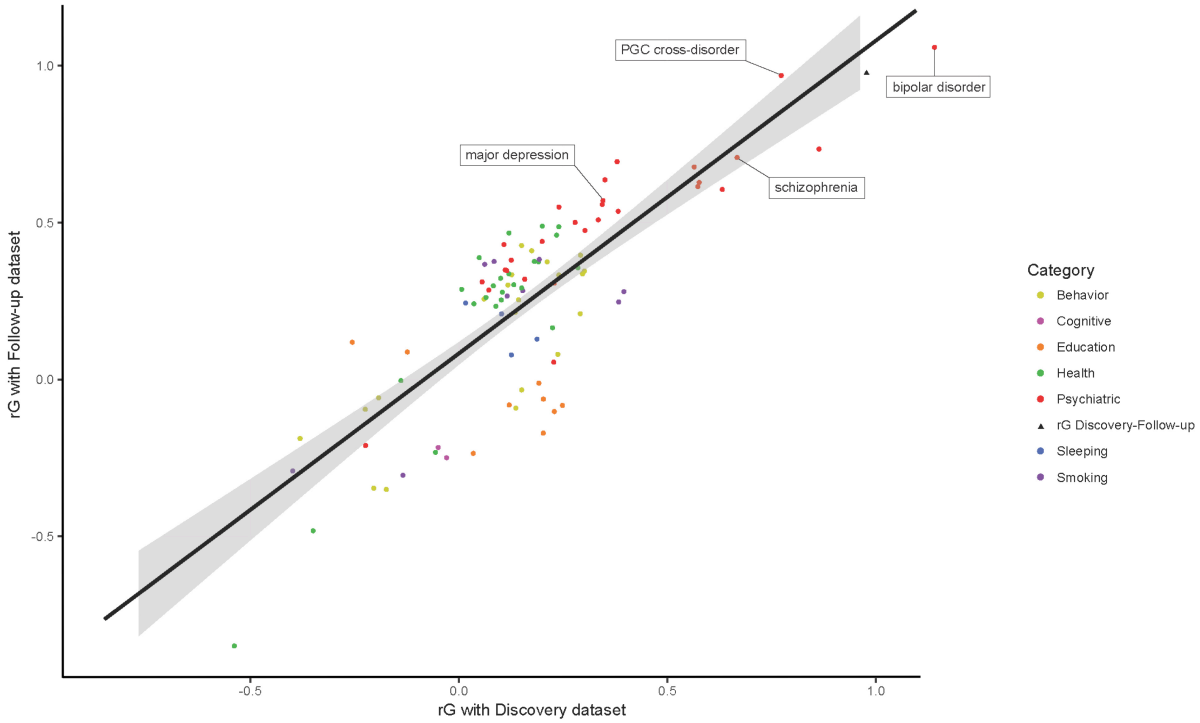
A. Nagelkerke's R2 barplot across datasets



B. Scatterplot of Nagelkerke's R2 vs sample size (number of cases). PRS here are based on discovery GWAS P-threshold 0.05.

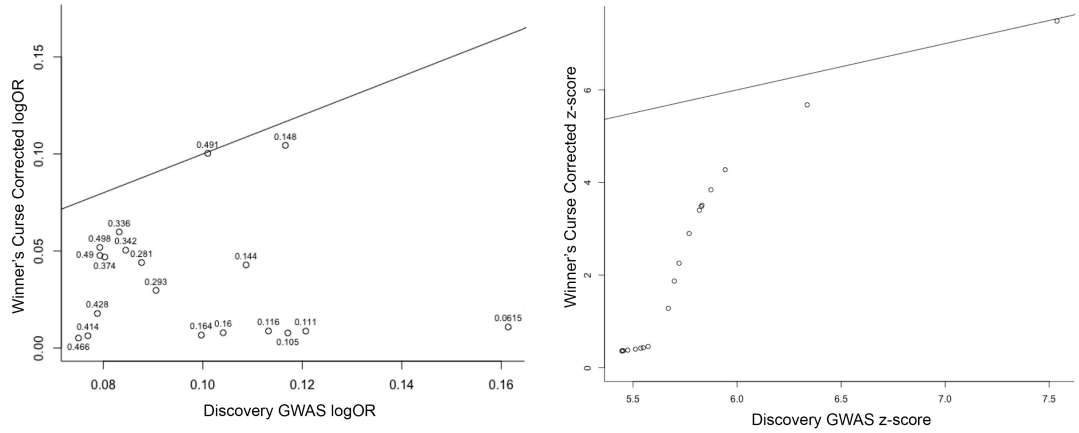


Supplemental Figure 3. Genetic correlations with follow-up sample summary statistics, versus with the BIP32 discovery GWAS. These results are shown in Supplementary Table New1.

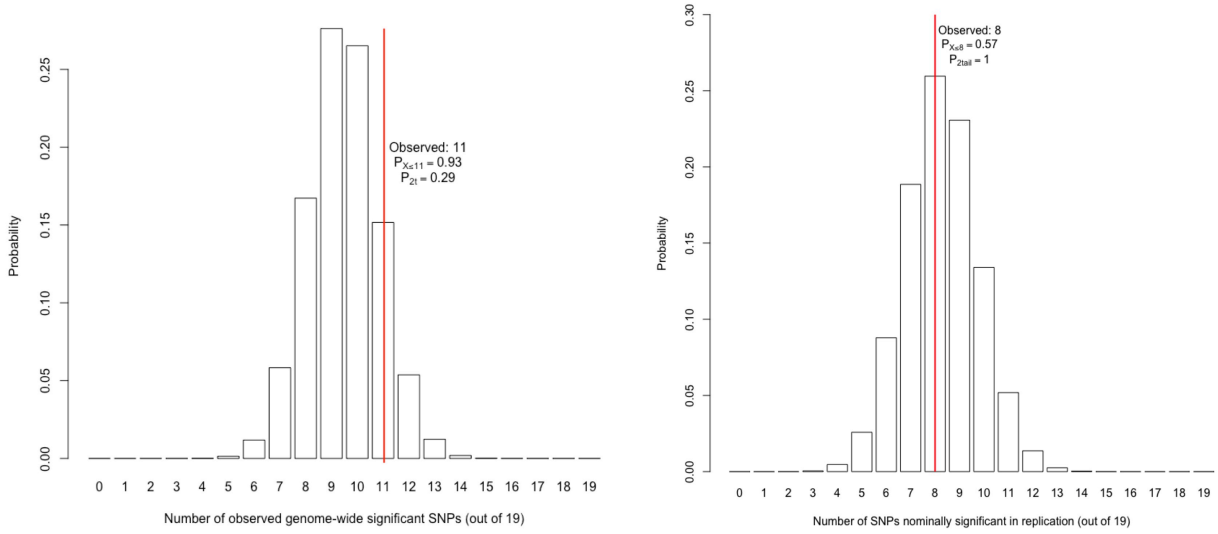


Supplemental Figure 4.

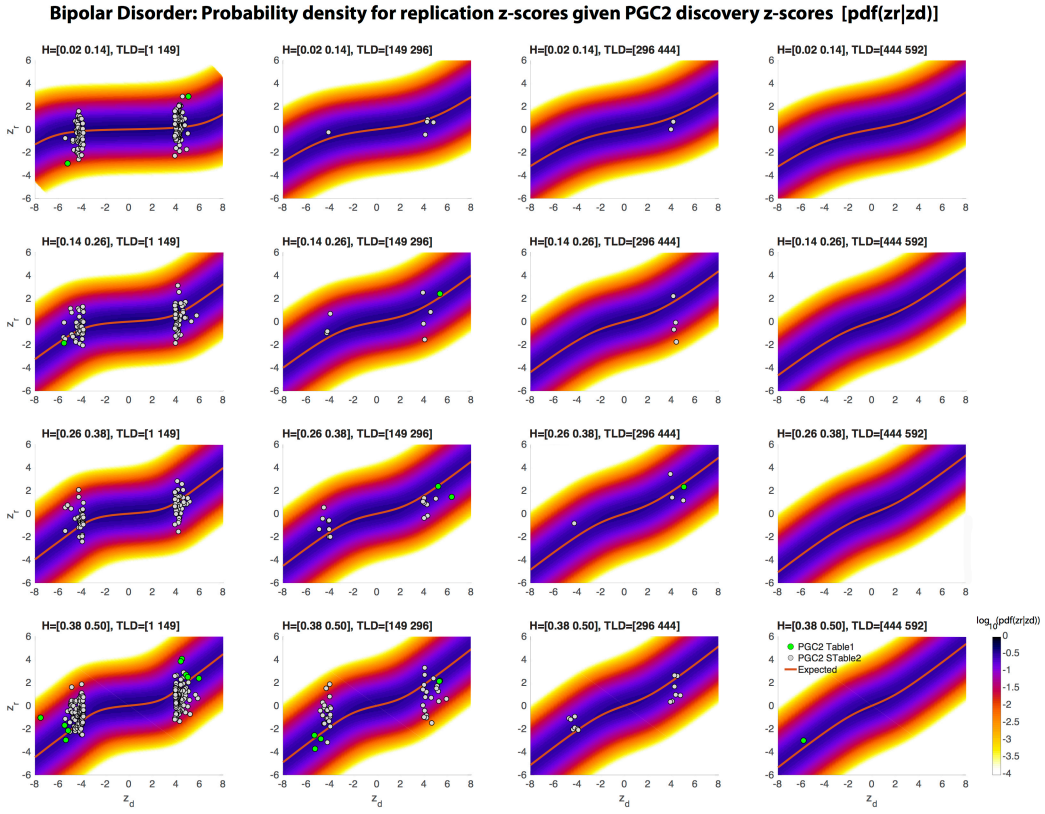
A. Winner's curse corrected effect sizes (y-axis) versus effect sizes observed in our GWAS phase (x-axis). Left panel shows log(OR) values, with points labeled by SNP minor allele frequency. Right panel shows the winner's curse corrected expected GWAS z-score, i.e. log(OR)/SE, versus observed z-score.



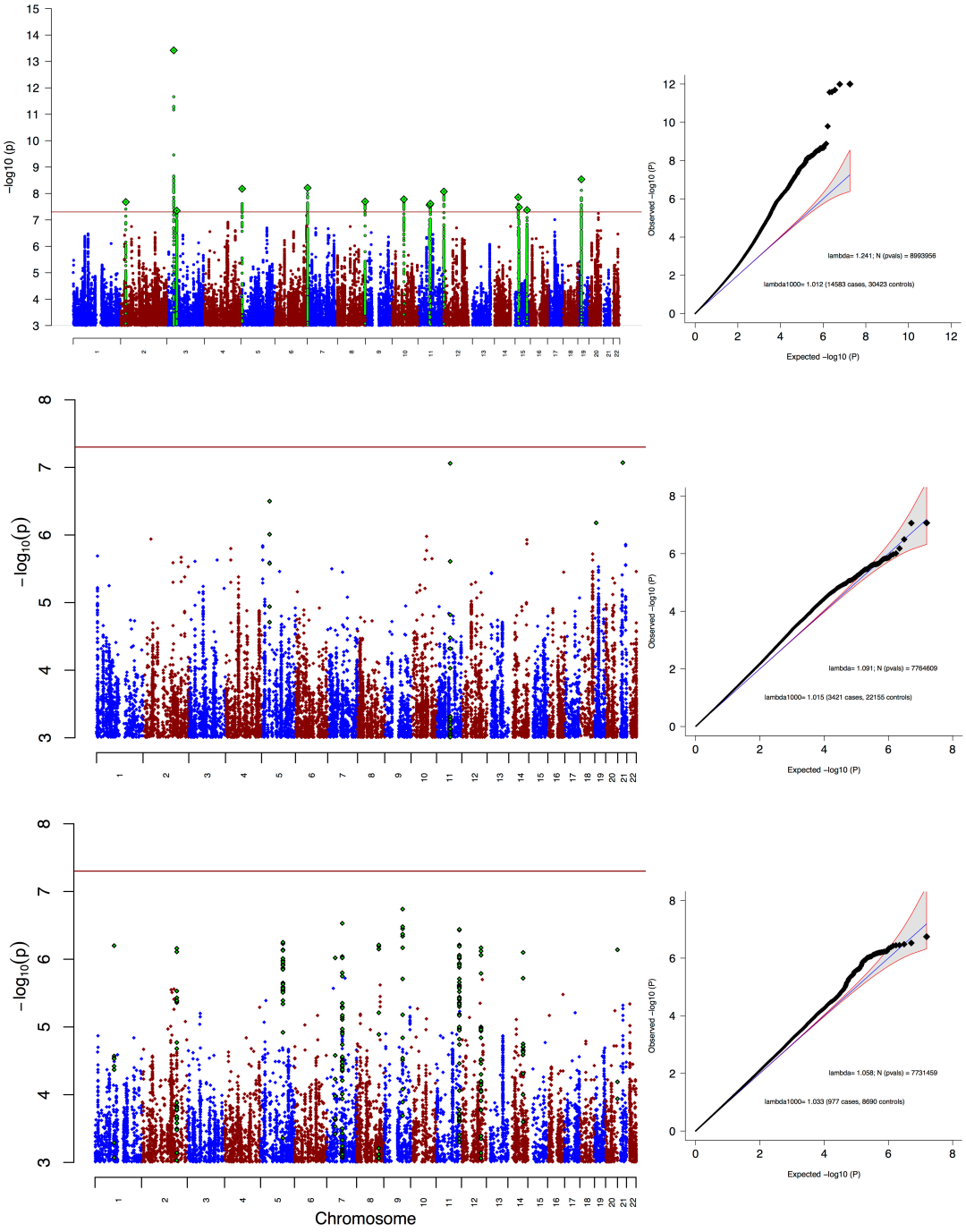
B. Histogram of Poisson binomial distribution of number of combined analysis genome-wide significant (GWS) SNPs out of 19 GWS SNPs in our GWAS phase (left panel), and number nominally significant in follow-up analysis (right). Red lines are the oberved numbers, and P-values are indicated.



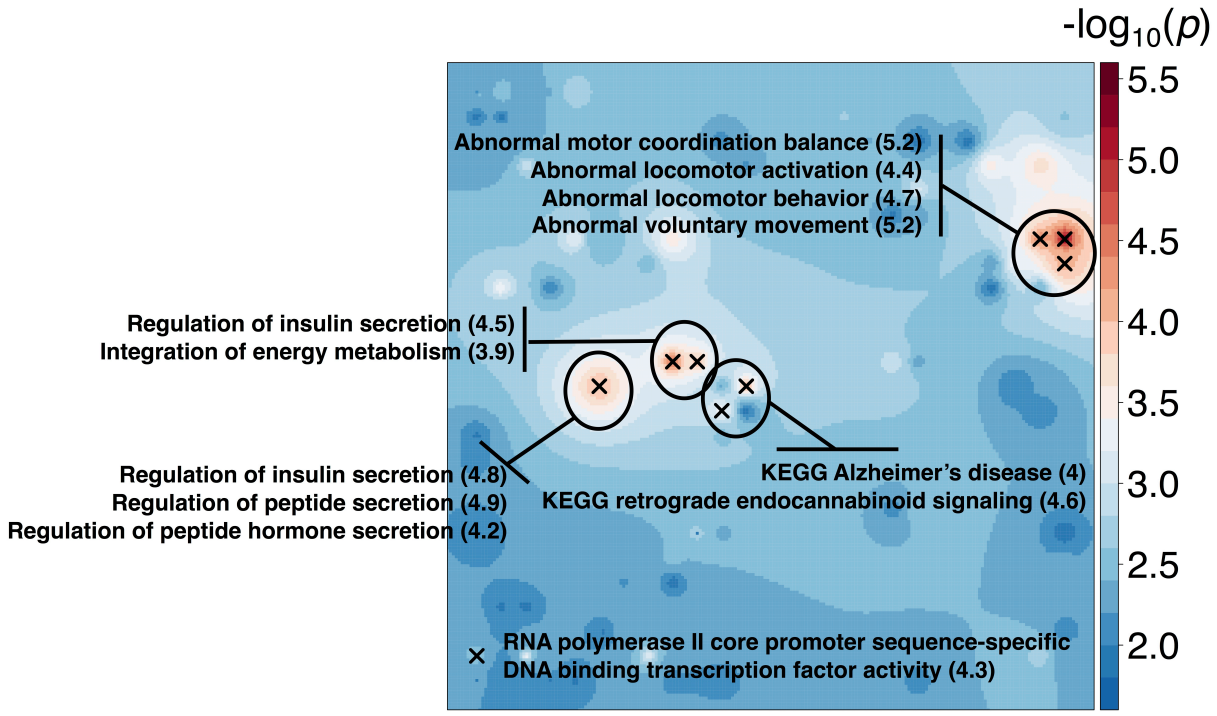
Supplemental Figure 5. Polygenic Inference Analysis of BD GWAS. Plotted as color contours are posterior probability densities of replication z-scores (y-axis) vs discovery z-scores (x-axis). See Supplementary Note Full Methods section, Polygenic inference analysis subsection, for details.



Supplemental Figure 6. Paired manhattan plots and qq-plots for BD1 (top row), BD2 (middle row), and SAB (third/bottom row) subtype GWAS.



Supplementary Figure 7. Pathway results, topographical kernel mapping of the principal components of pathway gene membership for the top 50 pathways (FDR<0.1).



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Supplementary Note: Study descriptions and full methods.

Studies

Discovery GWAS samples. We performed GWAS meta-analysis of 32 studies from 14 countries in Europe, North America and Australia (**Supplementary Table 1A**), totaling 20,352 cases and 31,358 controls of European descent. Below we summarize the source and inclusion/exclusion criteria for cases and controls for each sample. All samples in the initial PGC bipolar disorder (BD) paper were included [1]. 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. Controls in most samples were screened for the absence of lifetime psychiatric disorders, as indicated.

Follow-up samples. We tested 881 independent (r^2<0.1) variants that had a $p<10^{-4}$ in the BD GWAS sample GWAS in additional European-ancestry samples (totaling 9,412 cases and 137,760 controls). Below we summarize the source and inclusion/exclusion criteria for cases and controls for each sample.

Details of individual participating studies

We describe below ascertainment and diagnosis of the subjects comprising this report. Most studies have been published, 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 subjects provided written informed consent. **Supplementary Table 1** provides additional detail including sample sizes and genotyping array.

The sections below describe the BD samples that were part of this report. As the lifetime prevalence of BD is around 2%[REF], some studies use controls that are not screened for BD. The boldfaced first line for each sample is study PI, PubMed ID if published, country (study name), and the PGC internal tag or study identifier.

======== GWAS datasets ========

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

Clinical characterization of the patients included the Mini-International Neuropsychiatric Interview (MINI[2]), the Diagnostic Interview for Genetic Studies (DIGS[3]), the Family Interview for Genetic Studies (FIGS[4]) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN[7]). The final diagnoses were made according to the DSM-IV-TR[8] 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'[9].

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)[5] and consensus diagnoses were made according to DSM-IV[6] and Research Diagnostic Criteria (RDC)[7]. 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) project[8]. 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 | PMID:21926972 [PGC1], PMID:20451256 | Norway (TOP) | bip_top7_eur

In the TOP study (Tematisk omrade psykoser), cases of European ancestry, born in Norway, were recruited from psychiatric hospitals in the Oslo region. Patients were diagnosed according to the SCID[9] 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)[10]. 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.

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 Biobank[11]. 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 approval, 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[8] 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 Biobank. Potential controls with ICD9 codes for bipolar disorder, schizophrenia or related diagnoses in their electronic medical record were excluded.

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.

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 cohorts[12]. 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 assessment[13]. 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)[14].

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 cohort[15].

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.

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 OPCRIT[16] 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.

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 Psychiatry[17], 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) Study[18]. 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_eur[19]

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)[20], 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)[21]. 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[11] criteria on the basis of a consensus best-estimate procedure[19] and structured diagnostic interviews using the DIGS[5], FIGS[6], and the SCID[14]. Controls were parents of unselected adolescent twins from the Brisbane Longitudinal Twin Study[25]. 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.

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

Cases were recruited from consecutive admissions to the Obregia Clinical Psychiatric Hospital, Bucharest. Patients were administered the DIGS[5] and FIGS[6] interviews. Information was also obtained from medical records and close relatives. The diagnosis of BP-I was assigned according to DSM-IV[11] criteria using the best estimate procedure[19]. All patients had at least two hospitalized illness episodes. Population-based controls were evaluated using the DIGS[5] 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.

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 RDC[12]. 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.

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 DIGS[5], FIGS[6], 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.

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)[26] and MINI[4]. 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), and MH63420 (PI: V Nimgaonkar). 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 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; Sullivan, PF; Sklar, P | [ICCBD] | Sweden (ICCBD) | bip_swa2_eur

The BD subjects were identified using the Swedish National Quality Register for Bipolar Disorders (BipoläR,) and the Swedish National Patient Register (using a validated algorithm[22] 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; Sullivan, PF; 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 |[23]; [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 were 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.

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 | [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[14], 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 (MINI[2]). 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 described[24]. 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.

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 controls 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 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.

======== Phase 2, Follow up samples========

Andreassen, OA | Not published | Norway (NORMENT) | NORMENT_BIP_morePC

The NORMENT 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.

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 resource[25]. 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 previously [26] 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 as 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 Ncases). 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 Ncontrols = 4 x

Ncases). 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.

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)[27] 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.

Pato, C | Not published | [PGC Psychchip] | mix_gpcw1_eur

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] | mix_germ1_eur

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 2 [28]. 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.

Fullerton, J | Not published | [PGC Psychchip] | mix_neura_eur

The NeuRA sample comprised BD cases and controls from the bipolar high risk study[29] and a clinic sample recruited in Australia. 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.

Serretti, A | Not published | [PGC Psychchip] | mix_span2_eur

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 variant[30]. 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 to 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 features[31]. 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.

Perlis, R; Sklar, P; Smoller, J | Not published | [PGC Psychchip] | bip_usaw1_eur and

Perlis, R; Sklar, P; Smoller, J | Not published | [PGC Psychchip] | bip_usaw0_eur

EHR data were obtained from a health care system of more than 4.6 million patients[32] 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 0.85. Coded classification based on strict filtering achieved a value of 0.79, 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, values 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 | Not published | [PGC Psychchip] | Johns Hopkins University | bip_usaw1_eur

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.[33–35]

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

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.

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

The Icelandic sample consisted of 541 subjects with BD and 34,546 population controls. Patients and controls were Icelandic and were recruited throughout Iceland. Diagnoses were assigned according to RDC[12] through the use of the SADS-L[10] for 303 subjects. DSM-IV BD diagnoses were obtained through the use of the Composite International Diagnostic Interview (CIDI-Auto) for 82 subjects. In addition, there were 150 subjects with ICD-9 or ICD-10 BD diagnoses and 9 subjects with DSM-III BD diagnoses. The 34,546 controls were recruited as a part of various genetic programs at deCODE and were not screened for psychiatric disorders. 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.

Supplementary Note: FULL METHODS

QC and imputation of discovery GWAS samples

Individual genotype data for all GWAS samples were processed using the PGC "ricopili" pipeline (**URLs**) for standardized quality control, imputation, and analysis [36]. The default parameters for retaining genotyped SNPs and subjects were: SNP missingness < 0.05 (before sample removal); subject SNP 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; and SNP Hardy-Weinberg equilibrium ($P > 10^{-6}$ in controls or $P > 10^{-10}$ in cases). Based on visual inspection of PCA plots for each dataset (which were all 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 IMPUTE2 / SHAPEIT (chunk size of 3 Mb and default parameters). SNPs and insertion-deletion polymorphisms were imputed using the 1000 Genomes Project multi-ancestry reference panel (URLs)[37] (30,069,288 variants, release "v3.macGT1"). We retained SNPs with imputation marker INFO score ≥ 0.3 and minor allele frequencies ≥0.01.

For relatedness checks and PCA in our GWAS samples, after imputation, we hard-called genotypes (minimum genotype probability 0.8, otherwise missing) and retained SNPs with high imputation quality (INFO >0.8) and low missingness (<1%). We performed linkage disequilibrium pruning ($r^2 > 0.02$) and frequency filtering (MAF > 0.05), retaining a set of 24,498 autosomal SNPs. Relatedness testing identified pairs of subjects with pi_hat > 0.2 and one member of each pair was removed at random after preferentially retaining cases over controls. For the combined set of GWAS samples, we then derived principal components. [38]

QC and imputation of follow-up samples

The same QC and imputation procedures were used by the collaborating research teams in each of the

follow-up studies except for DeCODE. QC, imputation and association analyses were performed in the DeCODE sample as previously described [39].

Statistical analysis

BD association analysis in discovery GWAS samples. To determine which principal components to include in each the individual discovery study analyses, we tested the first 20 principal components for phenotype association in the combined discovery GWAS samples using logistic regression with study indicator variables included as covariates. The first six principal components and PCA19 showed significant correlation with the main phenotype and were therefore included in the individual study association analysis. For autosomal chromosomes, logistic regression association tests in each study were conducted for BD case status against the imputed marker dosage including the seven jointly derived PC's identified above to control for population stratification [40]. For chromosome X, we performed logistic regression analysis (as above) separately in males and females, with males coded as 0,2 for 0 or 1 copies of the risk allele. Association results for males and females were combined using a fixed effects meta-analysis.

Meta-analysis of discovery GWAS results We combined association results across discovery GWAS studies using an inverse-variance weighted fixed effects model.

BD subtype association analysis in discovery GWAS samples

For BD1, BD2 and SAB subtype-specific GWAS, we performed logistic regression analysis as above, including studies with at least 35 cases. Numbers of cases and controls are shown in **Supplementary Table 1A**. Given small and unbalanced case/control numbers, in order to assure that results were not driven by a single study, particularly for low-frequency variants, we restricted BD2 and SAB analyses to variants with MAF>2% and that were present in ten of the sixteen BD2 studies or four of the six SAB studies.

Polygenic risk score (PRS) analyses. We conducted PRS prediction analyses [41] as in the PGC schizophrenia report [42], to assess the validity of our GWAS results and to compare with other traits. Using pre-specified p-value thresholds, we selected SNPs from the discovery GWAS meta-analysis (from the total discovery GWAS sample, from a leave-one study-out discovery GWAS meta-analysis, or from GWAS summary statistics for another trait). We excluded uncommon SNPs (MAF < 0.05), lower-quality variants (imputation INFO < 0.9), indels, and all but the single most associated variant in the extended MHC region (chr6:25-34 Mb). We LD pruned the remaining SNPs by "clumping" [43,44], discarding variants within 500 kb and in LD $r^2 > 0.1$ with any selected SNP in the region. At each p-value threshold, from BD GWAS meta-analysis summary statistics for the pruned SNPs, we calculated a PRS for each individual as the sum of the count of risk allele counts multiplied by the natural log of the risk allele-oriented odds ratio. The R^2 explained by the PRS was calculated from the difference between full (GWAS-based risk score, principal component and study indicator covariates) and reduced (principal component and study indicator covariates) logistic regression models. The R^2 was converted (for better interpretation) to the liability scale of the population [45] assuming BD prevalence as indicated ranging from 0.5-2%. The liability scale R^2 estimates should then be comparable across target sample cohorts, whatever the proportion of cases in the sample. In the leave-one-out analysis, the target BD discovery GWAS study was excluded from the BD GWAS meta-analysis (**Supplementary Table 14**). To assess the association of SCZ and DEPR PRS with BD subtypes, we regressed subtype case status (BD1 n=8044, BD2 n=3,365, SAB n=977) on the PRS adjusting for ancestry principal components and a cohort indicator using logistic regression, and visualized covariate-adjusted PRS in BD1 and BD2 subtypes (**Figure 2**).

To identify factors that might influence the leave-one-out analysis results, we used separate linear regression models to test for association between the uncorrected R^2 and the proportion of females, proportion of cases with psychosis, proportion of cases with family history, and the median age of onset for BD. No significant results were found.

Linkage disequilibrium (LD) score regression. We used LD score regression on our GWAS summary statistics [46,47] to estimate heritability and bivariate genetic correlations (**Supplementary Table 7**), and to partition SNP-heritability by genomic features [48] (**Supplementary Table 10**) . We used LD score regression to estimate genetic correlation between BD and other psychiatric disorders (PGC-based meta-analyses) and a range of additional disorders, diseases, and human traits [47]. The intent of these comparisons was to evaluate the extent of shared common variant genetic architectures in order to suggest hypotheses about the fundamental genetic basis of BD. When GWAS include overlapping samples, estimation of genetic correlation remains unbiased but the intercept of the LD score regression increases and is an estimate of the correlation between association statistics attributable to sample overlap [49].

For LD score regression, GWAS summary statistics were further QC-filtered for imputation INFO > 0.9 and MAF > 2%. We note that BD2 h^2_{SNP} estimates were lower than expected given estimates from results for LD-score regression h^2_{SNP} for BD2 relative to previous studies [50]. We therefore examined the sensitivity of BD2 h^2_{SNP} to MAF cutoffs (MAF>1%, 2%, 5%) and saw consistent increases in BD2 h^2_{SNP} at higher MAF cutoffs (in contrast to our other GWAS analyses, which showed slight decreases in h^2_{SNP} with higher MAF cutoffs, as observed for other common traits [51, 48] and consistent with minor contributions of low-frequency SNPs to h^2_{SNP}). BD subtype SNP-heritability and genetic correlation results are shown for all three MAF cut-offs in **Supplementary Table 8A**, with the primary MAF>2% results at top and reported in the main text.

We tested for enrichment of genomic annotation partitioning relative to the proportion of the genome proportional to bp length represented by each annotation. We used a baseline model consisting of 53 functional categories. The categories are fully described elsewhere [48], and included conserved regions [52], UCSC gene models (exons, introns, promoters, UTRs), and functional genomic annotations constructed using data from ENCODE [53] and the Roadmap Epigenomics Consortium [54].

Selection of discovery GWAS SNPs for follow-up study genotyping. We used PLINK [43,44] "clumping" to identify an LD-pruned set of discovery GWAS meta-analysis BD-associated SNPs ($P < 0.0001$) within associated regions. To do this we identified an index SNP with the smallest *P*-value and retained SNPs with association $P < 0.0001$ and $r^2 < 0.1$ within a genomic window of 500 Kb, using PLINK (flags "--clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.1 --clump-kb 500"). We further combined any SNPs within 3 Mb windows (1.5Mb on either side of index SNPs), and confirmed conditionally independent associations of reported SNPs within windows.

Association analysis in follow-up studies and combined analysis For each available autosomal SNP from the SNPs chosen for follow-up ($P<10^{-4}$, see above), each follow-up study performed logistic regression analysis of BD against imputed dosages using study-specific covariates. We performed fixed-effects meta-analysis of the follow-up studies and then of the combined GWAS and follow-up studies.

Defining combined discovery and follow-up meta-analysis significant loci and lead SNPs We defined genome-wide significance as $P < 5x10^{-8}$ in our combined GWAS+follow-up analysis. We also report loci variants with $P < 5x10^{-8}$ in our GWAS, as we believe that these are very likely to be true associations and to achieve genome-wide significance in larger samples in the future. For all reported associations and loci, we reviewed forest plots and tests for heterogeneity of effects (**Supplementary Figure 3**), and confirmed that association signals arose from the majority of the cohorts. To identify independent associations within the $r^2>0.1$ LD-defined region around each lead SNP, we conducted conditional analyses in each discovery GWAS sample and combined the results using a fixed effects meta-analysis (**Supplementary Table 5**). For assessing association of all SNPs in the regions in a joint logistic regression analysis with the primary lead variant, a multiple test corrected significance level of $P=1.01x10^{-5}$ was obtained by dividing 0.05 by the effective number of independent SNPs across loci following Gao et al. [55], by conducting PCA on the genotype matrix at each locus and counting the number of eigenvalues required to exceed 99.9% variance explained, and summing across loci. Additional conditional analyses

were conducted assessing our lead variants in joint logistic regression analyses with previously published associations for bipolar (**Supplementary Table 5B**) or other traits (**Supplementary Table 6**).

Power analysis given winner's curse corrected effect sizes For each of the 19 SNPs with $P_{GWAS} < 5x10^{-8}$, we calculated the power using the naive winner's curse corrected effect size [56,57]. Winner's curse corrected effect sizes β_{WC} were calculated numerically in R as the solution for β of: $\widehat{\beta} = \beta + s\frac{\phi(\beta/s-c)-\phi(-\beta/s-c)}{\Phi(\beta/s-c)+\Phi(-\beta/s-c)}$, where $\widehat{\beta}$ and s are the observed GWAS effect size and standard error respectively, β is the true effect size, $\phi()$ and $\Phi()$ are the standard normal pdf and cdf respectively, and c is the positive standard normal critical value for genome-wide significance *i.e.* $c = \Phi^{-1}(1 - 2.5 \times 10^{-8})$. For each SNP, we calculated the probability of $P_{followup} < 0.05$, and we calculated the probability of combined analysis genome-wide significance as the probability of the estimated follow-up sample effect size $\widehat{\beta}_{followup}$ being more extreme than the positive and negative values required to achieve $P_{combined} < 5x10^{-8}$ in inverse-variance weighted meta-analysis of GWAS and follow-up samples, given our observed values for $\widehat{\beta}_{GWAS}$, s_{GWAS} and $s_{followup}$, and with $\widehat{\beta}_{followup} \sim N(\beta_{WC}, s_{followup})$. We then used the Poisson binomial distribution to calculate probabilities of the number of the 19 top GWAS SNPs reaching $P_{followup} < 0.05$ or $P_{combined} < 5x10^{-8}$. Corrected effect sizes are plotted against observed GWAS odds ratios and *z*-scores, and the distribution of the number of significant SNPs out of the 19 SNPs genome-wide significant in GWAS is illustrated with the observed number and Poisson binomial p-values indicated, in **Supplementary Figure 4**.

Polygenic Inference analysis of BD GWAS effect sizes. A discovery z-score from sample size N_d is the sum of two random components

$$z_d = \delta_d + \epsilon_d. \qquad (1)$$

A replication z-score from sample size N_r similarly is

$$z_r = \delta_r + \epsilon_r \tag{2}$$

where δ is the genetic fixed effect (causal for the SNP in question, or LD-mediated from one or more neighboring causal SNPs), and ε is the environmental contribution and noise, modeled as a normal distribution, $N(0, \sigma_0^2)$, with mean 0 and variance σ_{0d}^2 or σ_{0r}^2 (both approximately equal to 1 for BIP data). Effect sizes are related by

$$\delta_r = \sqrt{\frac{N_r}{N_d}}\delta_d. \tag{3}$$

The posterior distribution pdf(z_r|z_d) is the convolution of pdf(δ_d|z_d) with $N(0, \sigma_r^2)$, where

$$\mathrm{pdf}(\delta_d|z_d) = \frac{\mathrm{pdf}(z_d|\delta_d)}{\mathrm{pdf}(z_d)}\mathrm{pdf}(\delta_d) \tag{4}$$

which, using Eq. 3, gives pdf(δ_r|z_d);

$$\mathrm{pdf}(z_d|\delta_d) = \phi(z_d; \delta_d, \sigma_{0d}^2), \tag{5}$$

where $\phi\left(z_d; \delta_d, \sigma_{0d}^2\right)$ is the Gaussian for z with mean δ and variance σ_r^2; pdf(z_d) and pdf(δ_d) are calculated using a Gaussian mixture model (https://www.biorxiv.org/content/early/2018/06/07/133132). It should be noted that these probability densities are SNP-specific in that they depend on the SNP's heterozygosity and LD structure, i.e., the distributions of heterozygosity and LD r^2 of its neighbors. The convolution can be written as

$$\begin{aligned}\mathrm{pdf}(z_r|z_d) &= \int_{-\infty}^{\infty} \mathrm{pdf}(\sqrt{\frac{N_d}{N_r}}\delta_r|z_d)\phi(z_r - \delta_r; 0, \sigma_{0r}^2)d\delta_r \\ &= \int_{-\infty}^{\infty} \mathrm{pdf}(\delta_d|z_d)\phi(z_r - \sqrt{\frac{N_r}{N_d}}\delta_d; 0, \sigma_{0r}^2)d\delta_d. \end{aligned} \tag{6}$$

This can be reexpressed using fast Fourier transforms without the need to perform explicit integration.

Thus, using Eqs. 4 and 6 (or the FFT version of it), for any z_d, pdf($\delta_r | z_d$) and pdf($z_r | z_d$) can be calculated for finely-spaced vectors with elements δ_r and z_r respectively over a range such that the pdfs start at 0, increase, and then ultimately decrease to 0 again). See Supplementary Figure 5, calculated for our discovery and follow-up data, where the data (SNPs) are divided up into a 4 x 4 grid of heterozygosity (H) x total LD (TLD).

To assess whether observed replication z-scores, z_{rObs}, are statistically consistent with the observed discovery z-scores, z_{dObs}, for a given SNP (explicitly taking into account its H and TLD structure) one can claculate the probability of obtaining a replication z-score, z_r, that is ``more extreme'' that the observed value as follows: if $z_{dObs} > 0$, calculate $p(z_r < z_{rObs})$ by integrating the pdf thus

$$\mathrm{p}(z_r < z_{rObs} | z_{dObs}) = \int_{-a_{lim}}^{z_{rObs}} \mathrm{pdf}(z_r | z_{dObs}) dz_r, \qquad (7)$$

and if $z_{dObs} < 0$, calculate $p(z_r > z_{rObs})$ from

$$\mathrm{p}(z_r > z_{rObs} | z_{dObs}) = \int_{z_{rObs}}^{a_{lim}} \mathrm{pdf}(z_r | z_{dObs}) dz_r. \qquad (8)$$

These probabilities were calculated for 623 SNPs with discovery GWAS $p < 10^{-4}$ and having rs# IDs and LD values from 1000 Genomes phase 3.

Relation of BD GWAS findings to tissue and cellular gene expression. To investigate if the effects of any variants are mediated through changes in gene expression or DNA methylation, we applied the summary-based Mendelian randomisation (SMR) approach [58] to the BD summary statistics and large eQTL and mQTL datasets from blood and brain. To test for effects on gene expression in brain, we used results from a meta-analysis of eQTL data from brain tissue from the GTEx study [59], the Common Mind Consortium (CMC) [60] and the Religious Orders Study and Memory and Aging Project (ROSMAP) [61]. The effective sample size was 1,194 individuals. The details of the meta-analysis have been described in

detail elsewhere [62]. Using meta-analysis results across brain regions and studies is justified owing to the high correlation in effect sizes between them [62]. For analysis of eQTLs in blood, we used eQTL summary data from the eQTLGen Consortium (n > 31,000 in blood). We also performed the SMR analysis to detect associations between DNAm sites and the BD using brain mQTL data from Jaffe et al. (n = 526) [63] and blood cis-mQTL data from a meta-analysis of results from the Lothian Birth Cohort and the Brisbane Systems Genetics Study (n = 1,980) [64].

Only genes with a cis-eQTL with $p_{eQTL} < 5x10^{-8}$ were included in the analysis. Probes that passed the tissue-wide significance threshold accounting for testing multiple SNPs and showed no evidence of heterogeneity due to pleiotropy ($p_{HET} > 0.01$) were considered to be associated. Individual-level genotypes from the ARIC data (n = 7,762 unrelated individuals) [65] were used to estimate LD for the HEIDI test. Results are shown in **Supplementary Table 11**.

Gene-wise and pathway analysis. Our approach was guided by rigorous method comparisons conducted by PGC members [66,67]. *P*-values quantifying the degree of association of genes and gene sets with BD were generated using MAGMA (v1.06) [67]. The gene window used was 35 kb upstream and 10 kb downstream to include regulatory elements, and multi-SNP LD adjusted p-values were calculated for each gene (MAGMA P_JOINT). We used European-ancestry subjects from 1,000 Genomes Project (Phase 3 v5a, MAF ≥ 0.01) [37] for the LD reference. We used ENSEMBL gene models for 18,172 genes giving a Bonferroni corrected *P*-value threshold of $2.8x10^{-6}$. Gene set *P*-values were obtained using a competitive analysis that tests whether genes in a gene set are more strongly associated with the phenotype than other gene sets.

We included gene sets from MSigDB (v5.2) [68] which includes canonical pathways and Gene Ontology gene sets. Canonical pathways were curated from BioCarta, KEGG, Matrisome, Pathway Interaction Database, Reactome, Sigma-Aldrich, Signaling Gateway, Signal Transduction KE, and SuperArray. Pathways containing between 10 and 10,000 genes were included.

The pathway map (**Supplemental Figure 5**) was constructed using the kernel generative topographic mapping algorithm (k-GTM) as described by [69]. GTM is a probabilistic alternative to Kohonen maps: the kernel variant is used when the input is a similarity matrix. The GTM and k-GTM algorithms are implemented in GTMapTool (URLs). We used the Jaccard similarity matrix of FDR-significant pathways as input for the algorithm. Parameters for the k-GTM algorithm are the square root of the number of grid points (k), the square root of the number of RBF functions (m), the regularization coefficient (l), the RBF width factor (w), and the number of feature space dimensions for the kernel algorithm (b). We set k=square root of the number of pathways, m=square root of k, l=1 (default), w=1 (default), and b=the number of principal components explaining 99.5% of the variance in the kernel matrix. The output of the program is a set of coordinates representing the average positions of pathways on a 2D map. The x and y axes represent the dimensions of a 2D latent space. The pathway coordinates and corresponding MAGMA *P*-values were used to build the pathway activity landscape using the kriging interpolation algorithm implemented in the R gstat package.

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

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

Supplementary Note URLs

1000 Genomes Project multi-ancestry imputation panel,

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

Bedtools, https://bedtools.readthedocs.io

Genotype-based checksums for relatedness determination,

http://www.broadinstitute.org/~sripke/share_links/checksums_download

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

CommonMind Consortium, https://www.synapse.org//#!Synapse:syn2759792/wiki/69613

GTMapTool, http://infochim.u-strasbg.fr/mobyle-cgi/portal.py#forms::gtmaptool

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

PGC website, https://pgc.unc.edu

NIH NeuroBiobank, https://neurobiobank.nih.gov

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

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