

## SUPPLEMENTARY MATERIAL

### **Combined analysis of 11 genomewide association studies of bipolar disorder identifies strong evidence for replication of multiple susceptibility loci**

The Psychiatric Genomewide Association Study Consortium Bipolar Disorder Group (PGC-BD)

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## Section S1. Description of individual study sample data contributions, ascertainment and genotyping platforms.

### OVERVIEW

The analyses described in this manuscript use BD case-control GWAS datasets from several major international collections and studies (which we will refer to as the “primary studies”), several of which have already been the subject of published analyses. The details of each sample ascertainment and assessment are provided in the prior publications from the primary studies<sup>1-6</sup>. In each case, standardized semi-structured interviews were used by trained interviewers to collect clinical information about lifetime history of psychiatric illness and operational criteria applied to make lifetime diagnosis according to recognized classifications. All cases have experienced pathologically relevant episodes of elevated mood (mania or hypomania) and meet operational criteria for a BD diagnosis within the primary classification system used in the primary study (variously DSMIV<sup>7</sup> or RDC<sup>8</sup>). The distribution of diagnoses following all QC steps for each sample is shown in Table S1.

Protocols and assessment procedures were approved by the relevant ethical review mechanisms for each study. All participants provided written informed consent prior to participation in the primary study and consent allowed the samples to be used within the current combined analyses. Controls were selected from the same geographical and ethnic populations as cases to have a low probability of having a BD phenotype. Some controls had interviews to allow exclusion of individuals with a personal history of mood disorder, others were not screened (Table S1).

The sample sizes reported in Table S1 and used in the analyses are in several cases smaller than the sample sizes in the primary or published studies because of removal of any sample overlaps across studies. For example, control samples from the NIMH Genetics Repository were used in the STEP-BD, GAIN/BiGS and Pritzker Neuropsychiatric Disorder Research Consortium analyses. There was also an overlap in NIMH repository cases used in the Pritzker Neuropsychiatric Disorders Research Consortium and GAIN/BiGS analyses. There was an overlap in cases used in the GSK and WTCCC analyses. In each case of a sample appearing in more than one dataset, the duplicate in the larger dataset was removed in order that each individual sample appeared only once in any sample used in the analysis. Further details of this procedure are given in the QC sections.

Briefly, the ascertainment procedures used in each primary study were as follows:

*The BOMA-Bipolar Study (uploaded: 681 cases, 1300 controls; post-QC1: 675 cases, 1297 controls).* 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 interviews (SCID-I, SADS-L), medical records, and the family history method. In addition, the OPCRIT system 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). Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent. This includes a clause that all data may be shared with the PGC. However, consents does not include permission for depositing of de-identified individual GWAS genotype and phenotype data into the NIMH genetics initiative repository, although these data may be used in specific collaborations for studies of neuropsychiatric disorders. Case Subjects have been previously reported<sup>9-12</sup>. Control subjects have been previously reported<sup>13</sup>.

*Genetic Association Information Network (GAIN)/ The Bipolar Genome Study (BiGS)* (uploaded: 1001 cases, 1033 controls, post-QC1: 1001 cases, 1032 controls). 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 (systematic ascertainment) and from contacts generated through publicity programs or advocacy groups (nonsystematic ascertainment). Potential cases were evaluated using the Diagnostic Instrument for Genetic Studies, the Family Interview for Genetic Studies, 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 are from the NIMH Genetic Repository sample obtained 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. Case samples have been previously reported<sup>4,5</sup>. Control samples have been previously reported<sup>2-5</sup>.

GlaxoSmithKline (GSK) (uploaded: 899 cases, 904 controls, post-QC1: 892 cases, 902 controls). Cases and controls were recruited from three study sites: the Institute of Psychiatry in London, UK, the Centre for Addiction and Mental Health in Toronto, Canada and the University of Dundee, UK. Cases were recruited through advertisements in hospital, clinics, primary care physician offices, and patient support groups, were  $\geq 18$  years of age at interview, and reported Caucasian ethnicity. They were interviewed using the Schedules for clinical Assessment in Neuropsychiatry (SCAN). BD diagnoses were established according to DSM-IV or ICD-10 criteria using the computerized algorithm, (CATEGO) for the SCAN2.1 interview (WHO). Cases were excluded if they received a diagnosis of intravenous drug dependency or reported intravenous drug use or if they had mood incongruent psychotic symptoms, or if manic episodes only occurred in conjunction with or as a result of alcohol, substance abuse, substance dependence, medical illnesses, or medications. Controls were recruited from the same sites and were  $\geq 18$  years of age, reported

Caucasian ethnicity, and denied the presence of any psychiatric disorders in a questionnaire. Case samples have been previously reported<sup>4</sup>. Control samples have been previously reported<sup>4</sup>.

*Pritzker Neuropsychiatric Disorders Research Consortium (NIMH/Pritzker)* (uploaded: 1130 cases, 772 controls, post-QC1: 1130 cases, 772 controls). The case and controls samples are from the NIMH Genetics Initiative Genetics Initiative Repository. Cases were diagnosed according to DMS-III or DSM-IV criteria using the Diagnostic Interview for Genetic Studies (DIGS) (36) (n=1,081) or Family Interview for Genetic Studies (FIGS) (37) and/or medical record review (n=67), excluding cases with low confidence diagnoses. From each wave 1-5 available non-Ashkenazi European-origin family, two BD I siblings were included when possible and the proband was preferentially included if available (n=946 individuals in 473 sibling pairs); otherwise a single BD I 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 in the DIGS. Case samples have been previously reported<sup>4,5</sup>. Control samples have been previously reported<sup>2-5</sup>.

*Systematic Treatment Enhancement Program for Bipolar Disorder (STEP1)* (uploaded: 954 cases, 1498 controls, post-QC1: 927 cases, 1468 controls; STEP2 uploaded: 665 cases, 192 controls, post-QC1: 659 cases, 192 controls). 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 bipolar I, bipolar II, bipolar 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 BD-I and BD-II diagnoses consented to the collection of blood samples for DNA, under IRB-approved protocols at each site with written informed consent that did not prohibit sharing of genotypic data with other scientists. Of the 2,089 STEP-GRP participants 62% had a consensus diagnosis of BDI on both the ADE and MINI. 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. Case samples have been previously reported<sup>2,3</sup>. Control samples have been previously reported<sup>2-5</sup>.

*Thematically Organized Psychoses (TOP) Study (Oslo, Norway)* (uploaded: 232 cases, 394 controls, post-QC1: 205 cases, 367 controls). Subjects participated in a large ongoing study on schizophrenia and BD and were recruited from out-patient and in-patient psychiatric units in Norway, from May, 2003 through July, 2008. All participants gave written informed consent, and the study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. Diagnosis was established using the Structured Clinical Interview for DSM-IV-TR-axis I disorders (SCID-I) supplemented by case note review and follow up interviews where available. The healthy controls subjects were randomly selected from statistical records of persons from the same catchment areas as the patient groups. The control subjects

were screened by interview and with the Primary Care Evaluation of Mental Disorders (PRIME-MD). 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. Case samples have been previously reported<sup>6</sup> Control samples have been previously reported<sup>14</sup>.

*Trinity College Dublin* (uploaded: 150 cases, 799 controls, post-QC1: 150 cases, 797 controls). 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 Structured Clinical Interview for DSM. 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. Case samples have been previously reported<sup>3</sup>, control samples have been previously reported<sup>3,15,16</sup>.

*University College London (UCL)* (uploaded: 506 cases, 509 controls, post-QC1: 490 cases, 495 controls). The UCL sample comprised Caucasian individuals who were ascertained and received clinical diagnoses of BD 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. Case samples have been previously reported<sup>2,3</sup>. Control samples have been previously reported<sup>2,3</sup>.

*University of Edinburgh* (uploaded: 283 cases, 275 controls, post-QC1: 282 cases, 275 controls). This sample comprised Caucasian individuals contacted through the inpatient and outpatient services of hospitals in South East Scotland. A BDI 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 care givers. 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. Case samples have been previously reported<sup>2</sup>. Control samples have been previously reported<sup>2,3,15,16</sup>.

*Wellcome Trust Case Control Consortium* (uploaded: 1868 cases, 2938 controls, post-QC1: 1864 cases, 2935 controls). BD cases were all over the age of 16 years, living in mainland UK and of

European descent. Recruitment was undertaken by teams based in Aberdeen (8% cases), Birmingham (35% cases), Cardiff (33% cases), London (15% cases) and Newcastle (9% cases), to recruit individuals throughout the UK who had been in contact with mental health services. All subjects were recruited under protocols approved by the appropriate IRBs, and gave written informed consent permitting storage and sharing of de-identified clinical and genotypic data by the WTCCC repository (these genotypes will not be deposited into the NIMH repository). All subjects were interviewed by a trained psychologist or psychiatrist using the SCAN. Best-estimate ratings were made based on interview and medical records information, and lifetime diagnoses assigned according to RDC. Cases have diagnoses of BD-I, BD-II or SA-BD disorders. Controls were recruited from two sources: the 1958 Birth Cohort study and the UK Blood Service (blood donors). Controls (who were not screened to exclude personal or family history of psychiatric illness) were recruited under protocols approved by the appropriate IRBS, and gave written informed consent permitting storage and sharing of de-identified demographic and genotypic data by the WTCCC repository. Case samples have been previously reported<sup>1,3,4,11,17</sup>. Control samples have been previously reported<sup>1</sup>.

Description of the handling of overlapping samples is described in section S3a.

**Table S1: Summary of samples and methods in primary studies used in combined analysis following all QC steps.**

| Sample  | Ancestry                  | Case (n) | Control (n) | BD1         | BD2       | SAB                 | BD-NOS <sup>a</sup> | Diagnosis   | Interview | Controls screened | $\lambda$ |
|---|---------------------------|----------|-------------|-------------|-----------|---------------------|---------------------|-------------|-----------|-------------------|-----------|
| <i>COMBINED ANALYSIS SAMPLES</i>  |                           |          |             |             |           |                     |                     |             |           |                   |           |
| BOMA-Bipolar Study  | German                    | 675      | 1297        | 673 (99.7%) | 2 (0.3%)  | 0                   | 0                   | DSMIV       | SCID      | N                 | 1.04      |
| Genetic Association Information Network (GAIN) & Bipolar Genome Study (BiGS)  | European-American         | 542      | 649         | 516 (95%)   | 0         | 26 (5%)             | 0                   | DSMIIR & IV | DIGS      | Y                 | 1.03      |
| GlaxoSmithKline (GSK) Pritzker Neuropsychiatric Disorders Research Consortium (NIMH/Pritzker) Systematic Treatment Enhancement Program for Bipolar Disorder (STEP1) | British/Canadian/Scottish | 890      | 902         | 632 (71%)   | 80 (9%)   | 134 (15%)           | 44 (5%)             | DSMIV       | SCAN      | N                 | 1.03      |
| Systematic Treatment Enhancement Program for Bipolar Disorder (STEP2)   | European-American         | 1130     | 718         | 1130 (100%) | 0         | 0                   | 0                   | DSMIIR & IV | DIGS      | Y                 | 1.02      |
| Thematically Organized Psychosis (TOP) Study  | European-American         | 922      | 645         | 922 (100%)  | 0         | 0                   | 0                   | DSMIV       | MINI      | Y                 | 1.03      |
| Trinity College Dublin  | European-American         | 659      | 192         | 108 (16%)   | 551 (84%) | 0                   | 0                   | DSMIV       | MINI      | Y                 | 1.02      |
| University College London   | Norwegian                 | 203      | 349         | 119 (59%)   | 58 (29%)  | 6 <sup>b</sup> (3%) | 19 (9%)             | DSMIV       | SCID      | Y                 | 1.03      |
| University of Edinburgh   | Irish                     | 150      | 797         | 150 (100%)  | 0         | 0                   | 0                   | DSMIV       | SCID      | N                 | 1.02      |
|   | British                   | 457      | 495         | 457 (100%)  | 0         | 0                   | 0                   | DSMIV       | SADS-L    | Y                 | 1.01      |
|   | Scottish                  | 282      | 275         | 282 (100%)  | 0         | 0                   | 0                   | DSMIV       | SADS      | N                 | 1.03      |

|   |         |             |             |                       |                      |                     |                     |     |      |   |      |
|---|---------|-------------|-------------|-----------------------|----------------------|---------------------|---------------------|-----|------|---|------|
| Wellcome Trust<br>Case-Control<br>Consortium<br>(WTCCC) | British | 1571        | 2931        | 1300<br>(83%)         | 133<br>(8%)          | 97<br>(6%)          | 41<br>(3%)          | RDC | SCAN | N | 1.08 |
| <b>COMBINED<br/>ANALYSIS TOTAL</b>                      |         | <b>7481</b> | <b>9250</b> | <b>6289<br/>(84%)</b> | <b>824<br/>(11%)</b> | <b>263<br/>(4%)</b> | <b>104<br/>(1%)</b> |     |      |   |      |

<sup>a</sup>BD-NOS includes manic disorder; <sup>b</sup>Includes psychotic depression n=3. SCID<sup>8,18</sup>; DIGS<sup>19</sup>; SCAN<sup>20</sup>; MINI<sup>21</sup>; SADS-L<sup>8</sup>;  $\lambda$ =genomic control lambda

## Section S2. Psychiatric GWAS Consortium Central Pipeline QC (QC1)

All genotype data were deposited by individual investigators directly to the Genetic Cluster Computer (<http://www.geneticcluster.org>) hosted by Dutch National Computing and Networking Services. Data were generated using 4 different genotyping platforms (Affymetrix 500K, 5.0, 6.0 and Illumina HumanHap 500).

Data were processed by a pipeline established by the central analysis committee of the PGC. The pipeline performs semi-automated data-formatting, data quality-testing, inter and intra-study relatedness checks and imputation.

Within each study the goal was to create a set of genotyped SNPs of high and uniform quality maximizing the number of individuals retained. Initial QC checks were performed separately for each of the BD datasets. We first harmonized the SNP names, position, and strand.

Considering only SNPs with <5% missing data, individuals were retained if:

- missing genotype rate per individual < 0.02

For retained individuals, SNPs were retained if:

- missing genotype rate per SNP < 0.02,
- missing genotype rate between cases and controls per SNP < 0.02 (absolute difference)
- Hardy-Weinberg in controls  $P > 1 \times 10^{-06}$
- frequency difference to Hapmap-reference < 0.15.

At this stage no threshold for minor allele frequency was applied. This removed 380,959 SNPs and 177 individuals from the 11 BD studies. After these filtering steps, there were 10,926 controls and 8,338 cases in the dataset.

Next, the data were imputed using BEAGLE 3.0<sup>22</sup> with phased HapMap Phase 2 as reference. Each dataset was imputed separately, splitting the datasets into imputation batches of 300 individuals. Imputation batches were created randomly, keeping the case-control ratio balanced.

## Section S3. BD Working Group specific QC (QC2)

*Section S3a. Strategy for handling cases and controls that appeared in more than one dataset*

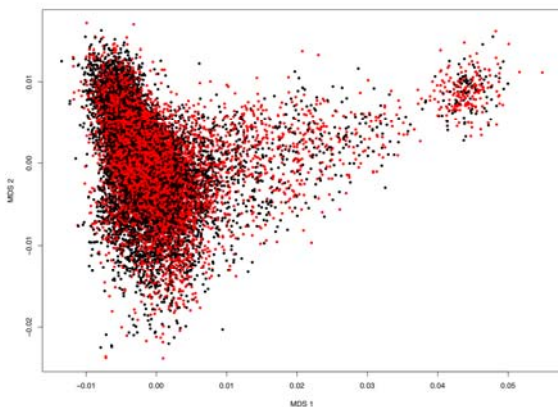
Using PLINK, we first found absolute sample duplicates, defined as pairs with an estimated probability of genome-wide IBD2 sharing above 90%. We found 3,714 individuals in 2,316 pairs were duplicated.

To remove duplicates, in order a) to preserve case/control ratios as close to 50:50 as possible, and b) favor data generated using more recent platforms, we preferentially kept samples from duplicate pairs in the order as follows: BOMA-bipolar study, TOP, STEP2, NIMH/PRITZKER, GAIN/BigS, STEP1, TRINITY COLLEGE, UEDINBURGH, GSK, UCL and then WTCCC. As such, the final dataset contained only unique individuals, with each individual belonging to exactly one sample.

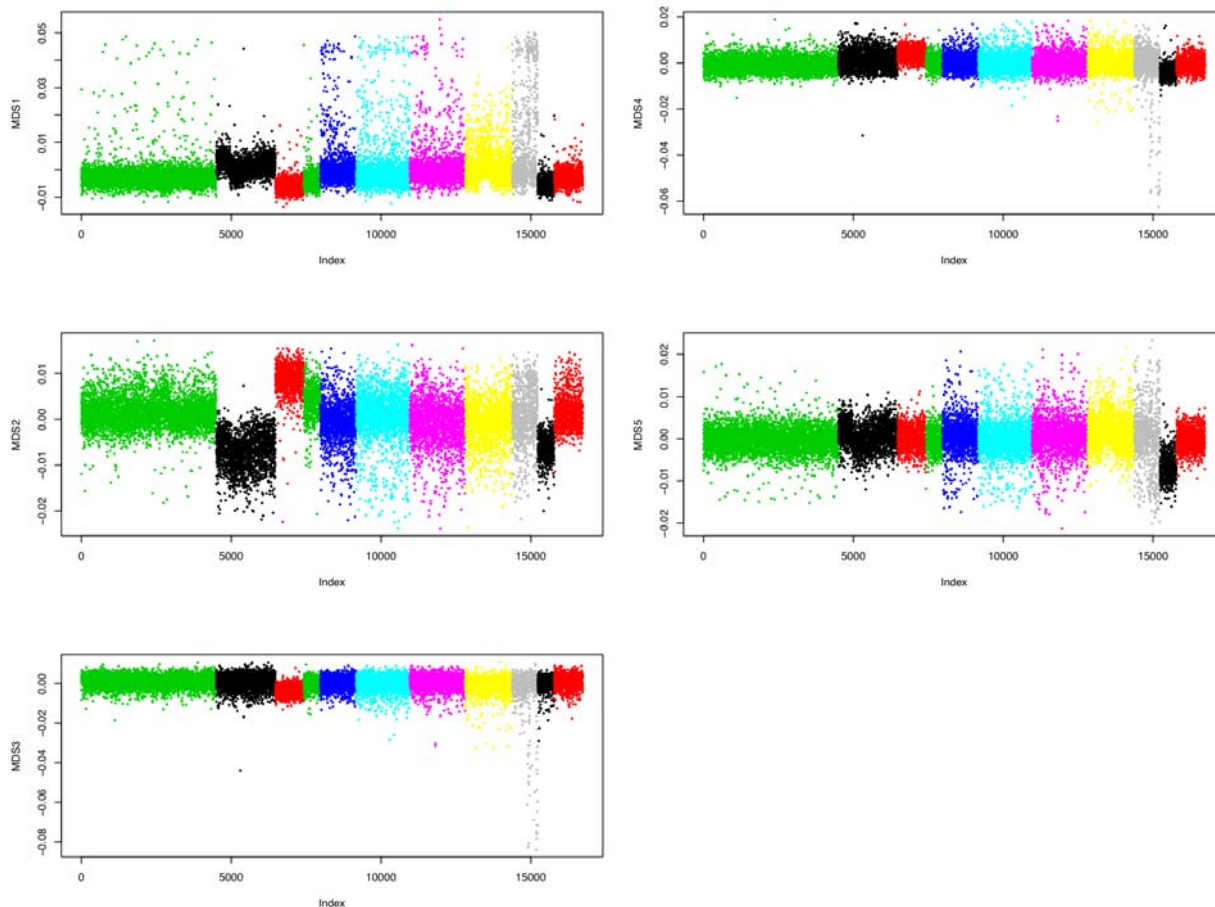
Not including the known sibling pairs in the NIMH/PRITZKER sample, we further detected all instances of previously unknown close relatedness. After removing a small number of parent-offspring, full-sibling and half-sibling pairs, we were left with N=16,731 individuals in 16,254 families (i.e. including 477 sibling pairs from NIMH/PRITZKER).

### *Section S3b. Ancestry Evaluation and Matching*

We used the WTCCC control sample to select a set of SNPs in approximate linkage equilibrium in order to calculate MDS components to assess and correct for population stratification, over-and-above differences captured by the sample indicator variable. This yielded N=21,134 autosomal SNPs that were genotyped on all platforms, which is sufficient for the purpose of MDS analysis. We calculated the top 20 MDS components. Based on inspection of between and within sample correlation with the phenotype, we retained the top 5, which were used as covariates along with 10 binary dummy variables to control for differences between the 11 samples.







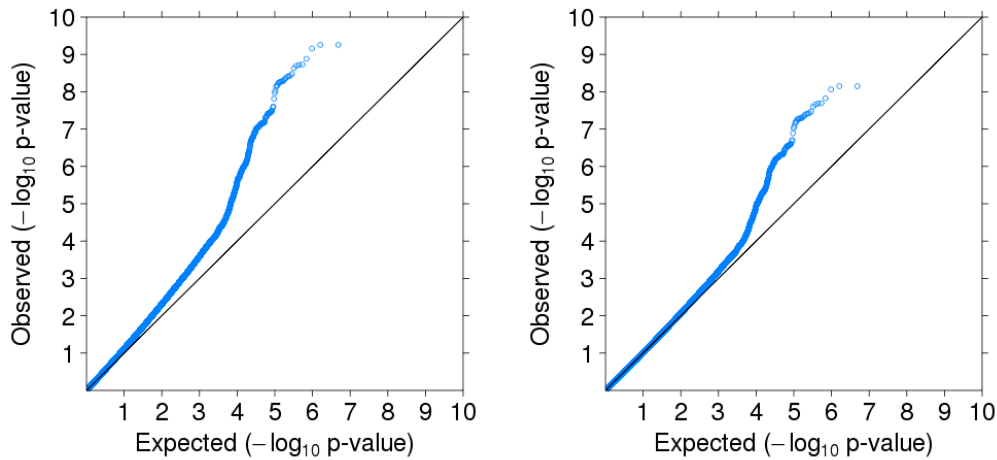
**Figure S1.** *Multidimensional scaling plot of identity-by state distances*

a) Plot of first two MDS components (black=control, red=case). b) All five components, plotted individually against order in sample (x-axis). Samples organized in batches, as follows: Green, WTCCC; Black, BOMA-bipolar study; Red, TRINITY COLLEGE; Green, UEDINBURGH; Blue, GAIN/BiGS; Light-blue, GSK; Pink, NIMH/PRITZKER; Yellow, STEP1; Gray, STEP2; Black, TOP; Red, UCL.

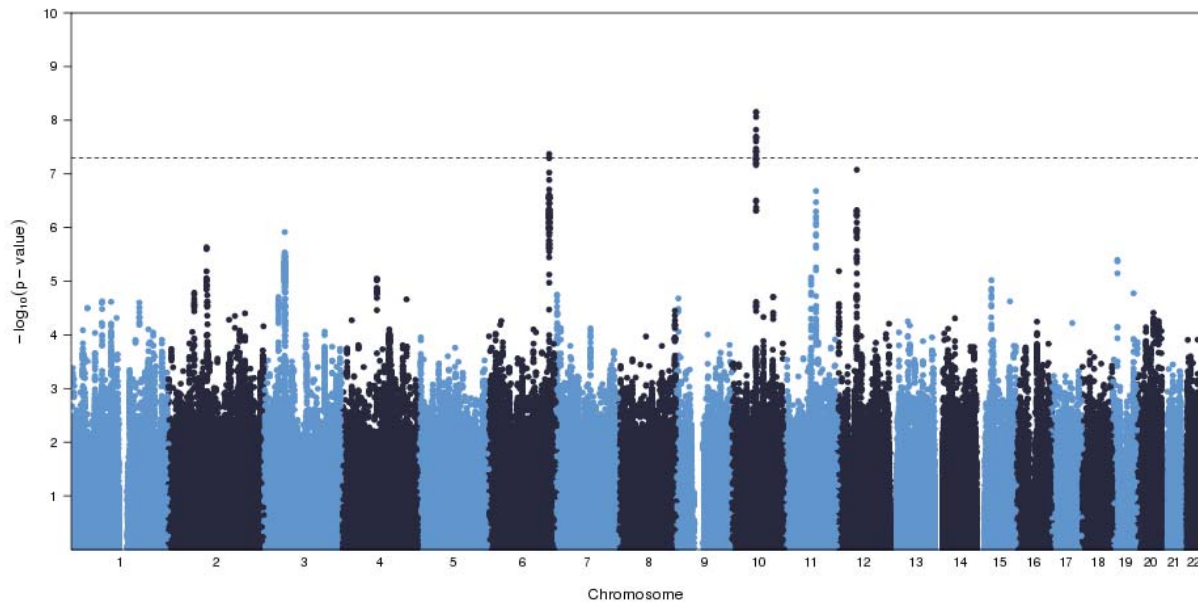
#### Section S4. Association analysis

Following QC1 and QC2 there were 16,731 individuals and 2,541,952 SNPs. Analyses are based on the 2,415,422 SNPs with minor allele frequency  $\geq 1\%$  and imputation  $R^2 > 0.3$  with a HapMap SNP. The primary analysis was a logistic regression of disease state on single SNP allele dosage, including covariates to account for site as well as the first 5 quantitative indices of ancestry based on multi-dimensional scaling analyses. To adjust for the relatedness between the siblings in the sample, we used a robust Huber-White sandwich variance estimator for cluster-correlated observations. All association analyses were performed using PLINK v1.07. No clinical variables were included as covariates. The genomic inflation factor ( $\lambda$ ) was calculated as the ratio

between the observed and expected median chi-square statistics<sup>23</sup>. The genomic inflation factor was 1.148 and was used to correct for the degree of inflation.



**Figure S2:** Q-Q plot of single SNP statistics, based on SNP allele dosage including covariates described above. Left plot: non-GC corrected; right plot: post-GC correction



**Figure S3:** Manhattan plot of single SNP test statistics including covariates described above

Table S2 contains the associated regions,  $P < 5 \times 10^{-5}$ . To present these results in terms of associated LD-based intervals, rather than a long list of individual, redundant SNPs, we used the clumping approach implemented in PLINK. Specifically, we take all SNPs significant at  $P < 5 \times 10^{-5}$  that have not already been clumped (denoting these as index SNPs) and forms clumps of all other SNPs that are a) within 1 Mb of the index SNP, b) in LD with the index SNP ( $R^2 > 0.2$ ), c) and nominally associated with disease ( $P < 0.05$ ). The approach groups SNPs in LD-space rather than physical distance: as such clumps could overlap spatially either completely or partially and may in some cases represent independent associations. This clumping approach results in 38 SNP with  $P < 5 \times 10^{-5}$ . Analyses described below in sections S6 and S8 use different criteria to identify completely independent association signals.





**Table S3. Meta-analysis of direct genotypes only for Table 2 SNPs**

| SNP        | CHR | Position  | N <sub>S</sub> | N <sub>G</sub> | P <sub>raw</sub> | P <sub>Random</sub> | OR   | OR <sub>Random</sub> | P <sub>het</sub> | I <sub>het</sub> |
|------------|-----|-----------|----------------|----------------|------------------|---------------------|------|----------------------|------------------|------------------|
| rs9371601  | 6   | 152832266 | 8              | 11114          | 0.00004          | 0.00004             | 1.13 | 1.13                 | 0.88             | 0.00             |
| rs10994397 | 10  | 61949130  | 3              | 5611           | 0.00311          | 0.00311             | 1.27 | 1.27                 | 0.71             | 0.00             |
| rs12576775 | 11  | 78754841  | 3              | 5611           | 0.00015          | 0.00290             | 1.22 | 1.22                 | 0.20             | 38.13            |
| rs7296288  | 12  | 47766235  | 8              | 11115          | 0.00013          | 0.00013             | 1.12 | 1.12                 | 0.46             | 0.00             |

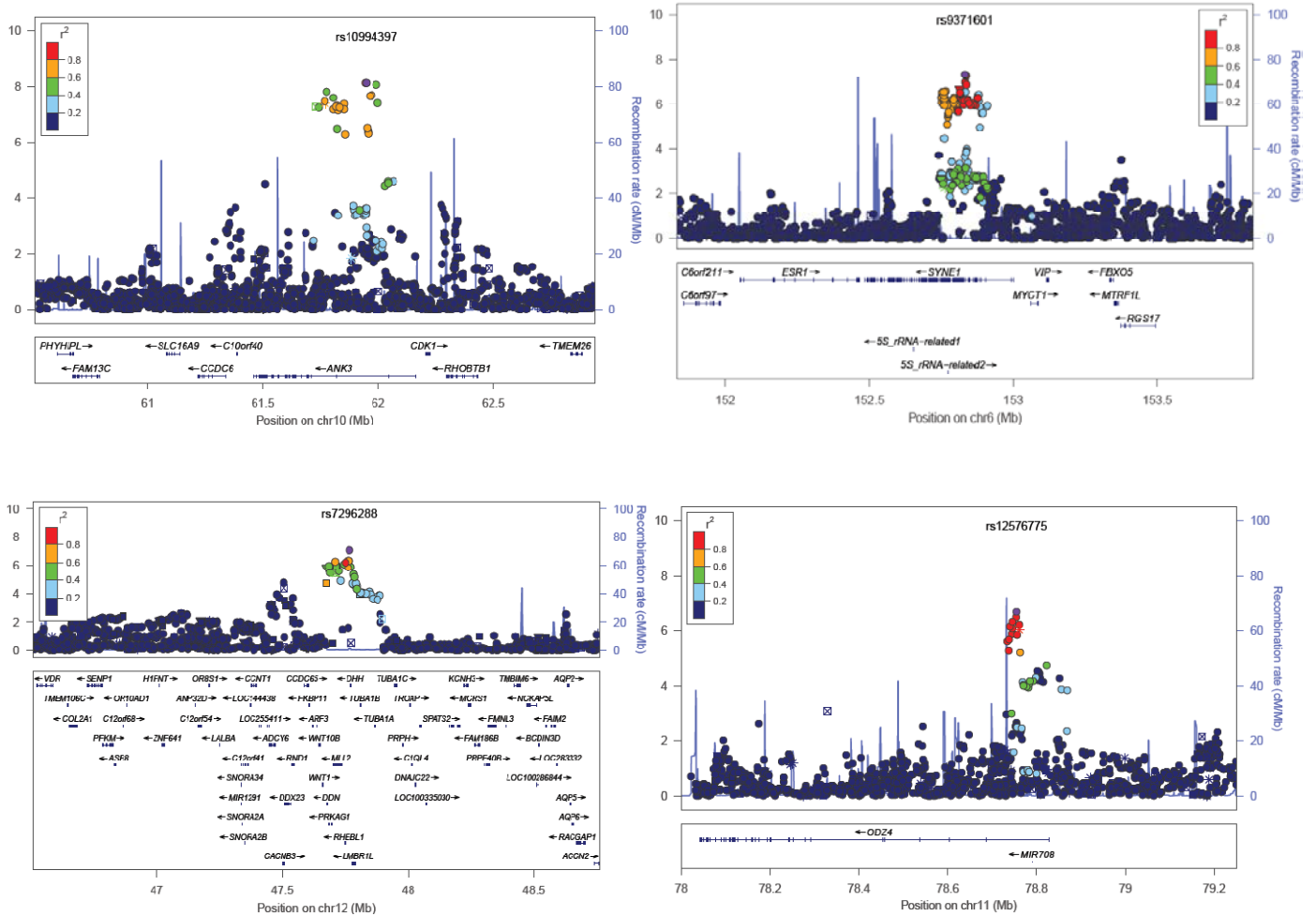
N<sub>S</sub>=number of studies in which SNP was genotyped; rs9371601 and rs7296288 are genotyped in all Affymetrix data; rs10994397 and rs12576775 are genotyped in all Illumina data. N<sub>G</sub>=number of genotypes. P<sub>raw</sub>=Fixed-effects meta-analysis P value; P<sub>Random</sub>=Random-effects meta-analysis P value; OR<sub>Random</sub>=Fixed-effects summary odds ratio for the minor allele; OR(R)=Random-effects summary odds ratio; P<sub>het</sub>=Cochrane's Q P value; I<sub>het</sub>=I<sup>2</sup> heterogeneity index (0-100).

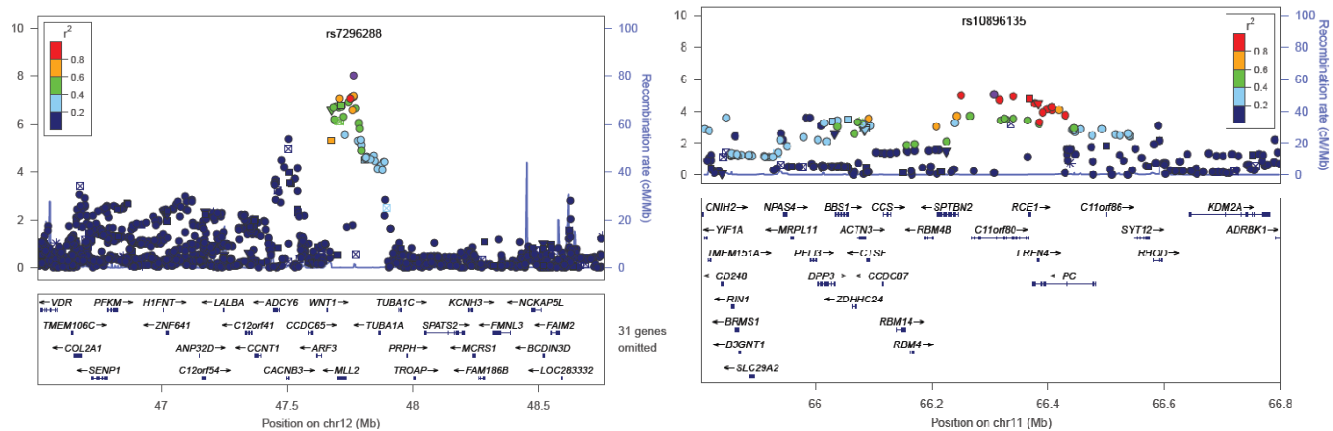
**Table S4: Fixed effects meta-analysis of Table 2 SNPs**

| SNP        | CHR | N <sub>S</sub> | P <sub>raw</sub>        | P <sub>gc post</sub>   | P <sub>gc pre</sub>     | P <sub>gc pre post</sub> | P <sub>Random</sub>     | OR   | OR <sub>Random</sub> | P <sub>het</sub> | I <sub>het</sub> |
|------------|-----|----------------|-------------------------|------------------------|-------------------------|--------------------------|-------------------------|------|----------------------|------------------|------------------|
| rs10994397 | 10  | 11             | 2.9 x 10 <sup>-10</sup> | 3.0 x 10 <sup>-9</sup> | 5.4 x 10 <sup>-10</sup> | 2.8 x 10 <sup>-9</sup>   | 2.9 x 10 <sup>-10</sup> | 1.35 | 1.35                 | 0.53             | 0.00             |
| rs9371601  | 6   | 11             | 1.5 x 10 <sup>-8</sup>  | 1.0 x 10 <sup>-7</sup> | 2.5 x 10 <sup>-8</sup>  | 9.4 x 10 <sup>-8</sup>   | 1.5 x 10 <sup>-8</sup>  | 1.15 | 1.15                 | 0.86             | 0.00             |
| rs7296288  | 12  | 11             | 2.6 x 10 <sup>-8</sup>  | 1.6 x 10 <sup>-7</sup> | 5.3 x 10 <sup>-8</sup>  | 1.9 x 10 <sup>-7</sup>   | 2.6 x 10 <sup>-8</sup>  | 1.14 | 1.14                 | 0.47             | 0.00             |
| rs12576775 | 11  | 11             | 7.6 x 10 <sup>-8</sup>  | 4.2 x 10 <sup>-7</sup> | 1.3 x 10 <sup>-7</sup>  | 4.3 x 10 <sup>-7</sup>   | 7.6 x 10 <sup>-8</sup>  | 1.18 | 1.18                 | 0.71             | 0.00             |

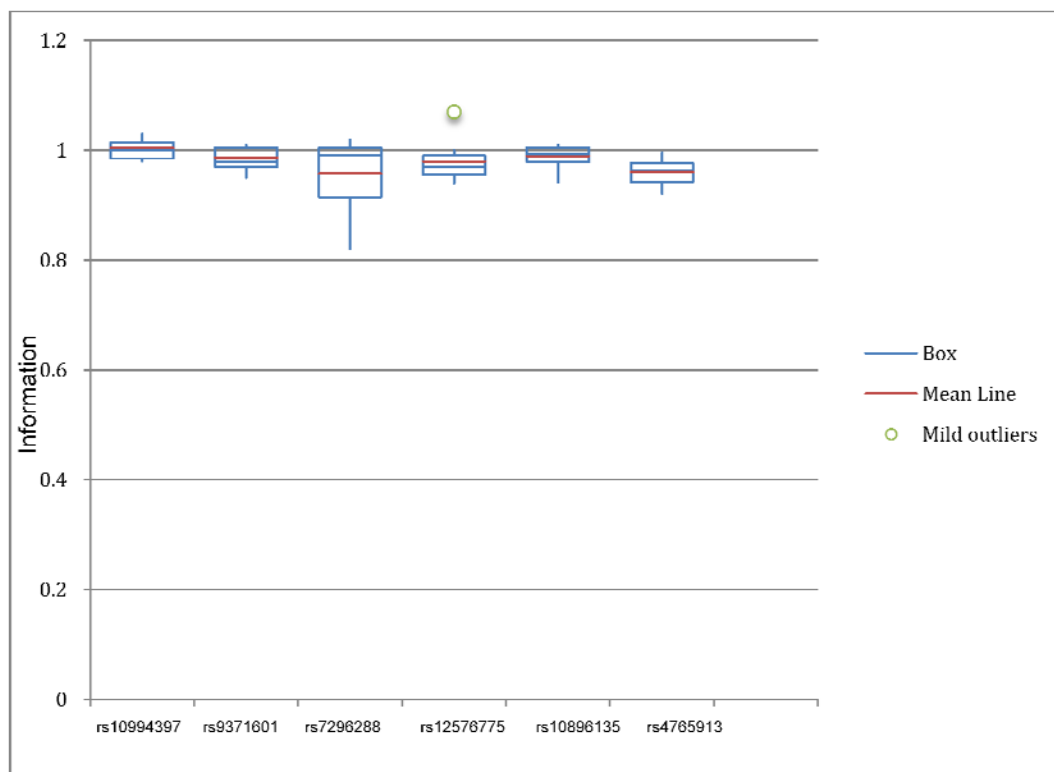
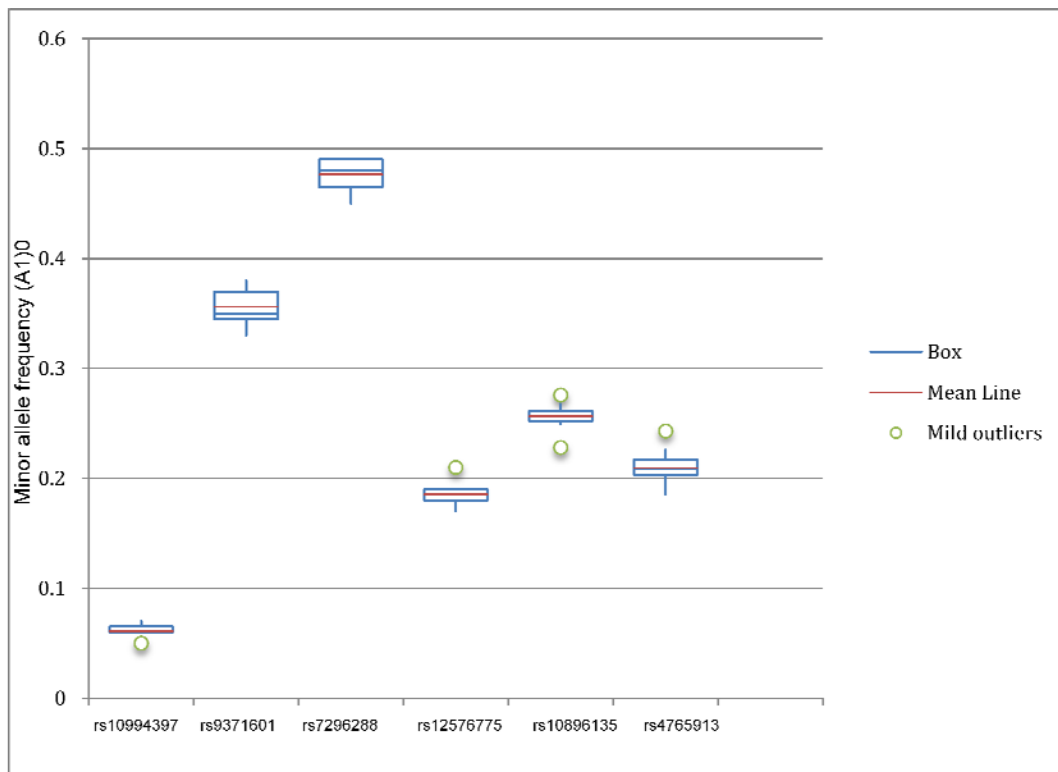
N<sub>S</sub>=equals number of studies with imputed data for the SNP. P<sub>raw</sub>=Fixed-effects meta-analysis P value, λ<sub>gc</sub>=1.13; P<sub>gc post</sub>=Fixed-effects meta-analysis P value, genomic controlled post meta-analysis, λ<sub>gc</sub>=1; P<sub>gc pre</sub>=Fixed-effects meta-analysis P value, each study genomic controlled prior to meta-analysis, λ<sub>gc</sub>= 1.09; P<sub>gc pre post</sub>=Fixed-effects meta-analysis P value,each study genomic controlled prior to meta-analysis and post meta-analysis, λ<sub>gc</sub>=1; P<sub>Random</sub>=Random-effects meta-analysis P value; OR=Fixed-effects summary odds ratio for the minor allele; OR<sub>Random</sub>=Random-effects summary odds ratio; P<sub>het</sub>=Cochrane's Q P value; I<sub>het</sub>=I<sup>2</sup> heterogeneity index (0-100).

**Figure S4: Regional plots.** Results are shown as  $Pgc$  ( $-\log_{10}(P \text{ value})$ ) for genotyped and imputed SNPs. The most associated SNP in the primary analysis is shown as a purple circle. The color of the remaining markers reflects  $r^2$  with the most associated SNP. The recombination rate from CEU HapMap (second y axis) is plotted in light blue.

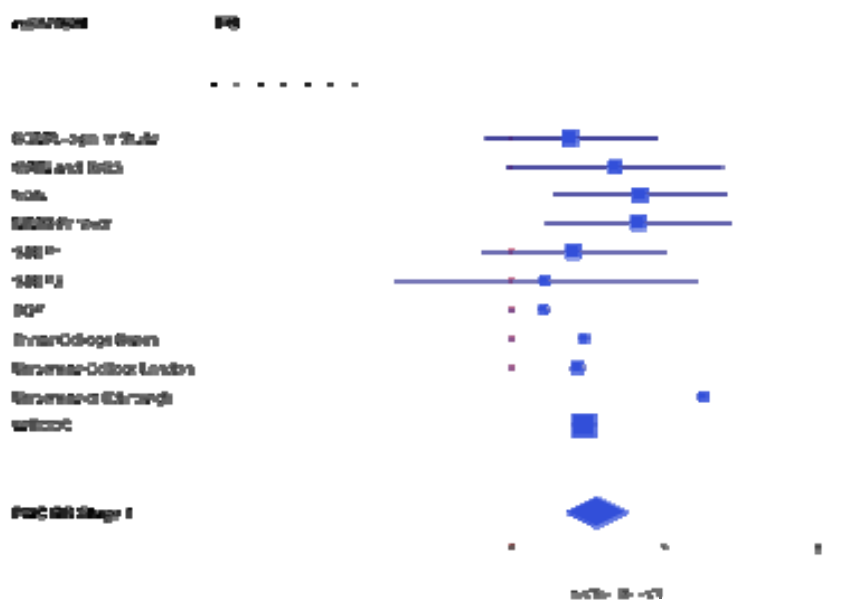
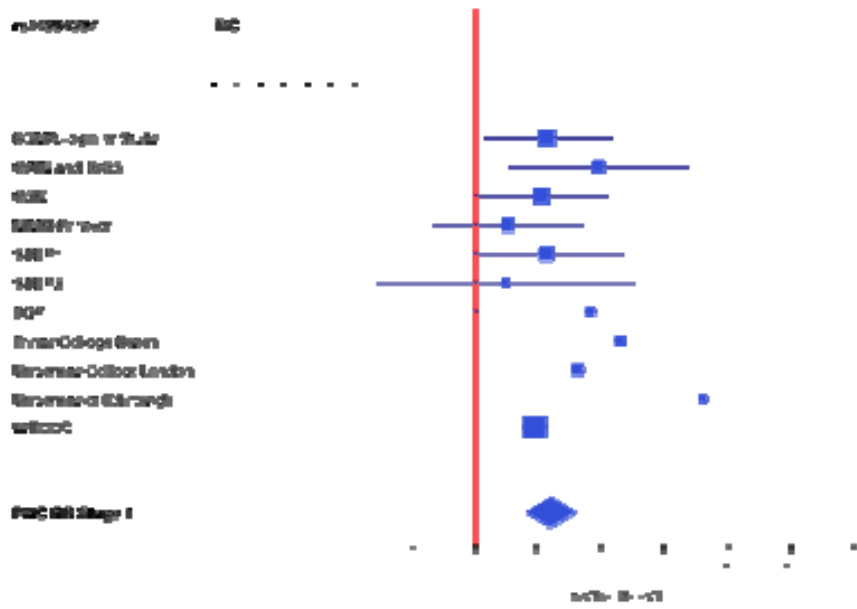




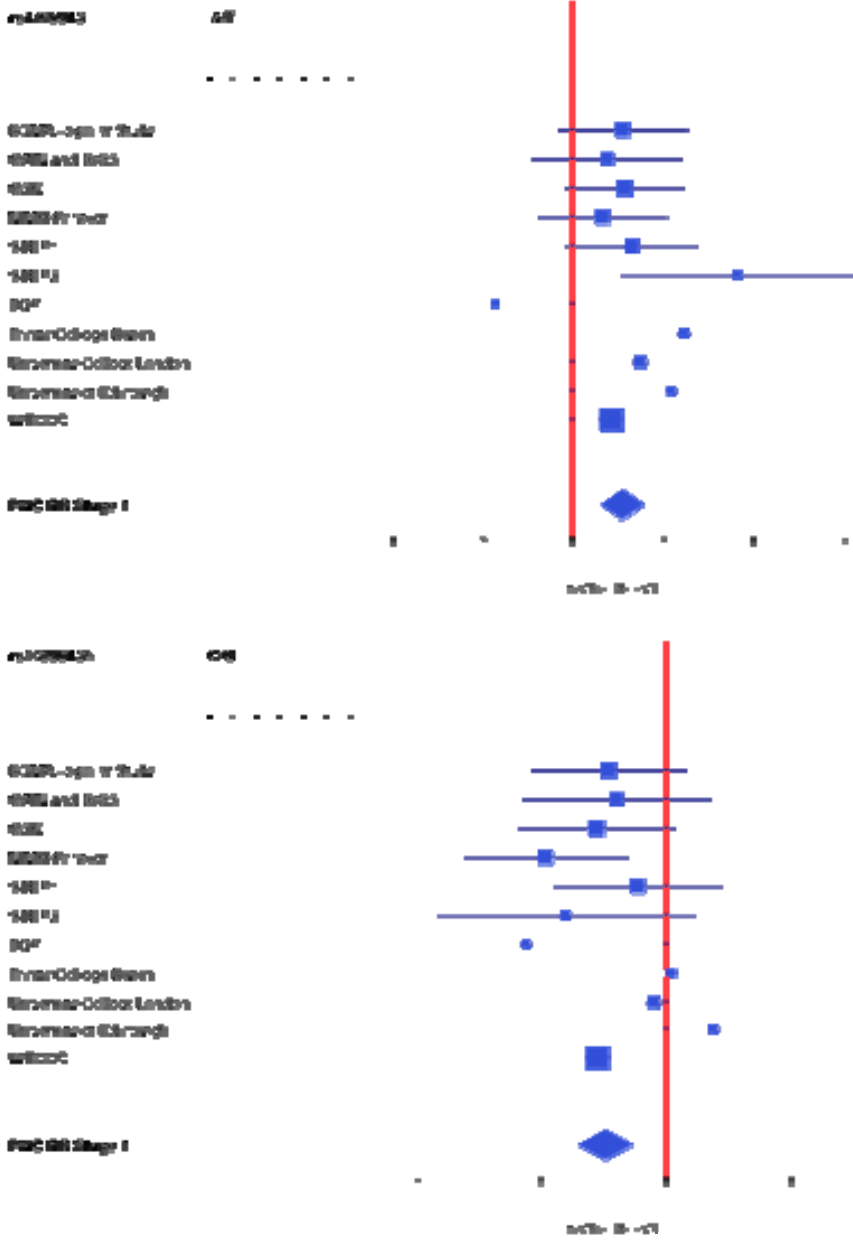
**Figure S5:** Association results by site for imputed SNPs, box plots of information and frequency and forest plots of odds ratios











**Section S5. Description of replication study samples**

*French:* Patients with BD type I or II and controls 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 and have all been assessed by a trained psychiatrist or psychologist with the DIGS and the FIGS. Diagnosis were based on structured interviews supplemented by medical case

notes, mood scales and self rating questionnaire assessing dimensions. Genotyping of controls were provided by the Centre National de Génotypage (M Lathrop, Evry). Patients and controls have been genotyped on the Illumina platform (HumanHap300, HumanHap550, HumanHap 610-quad). Sample QC was performed as described in section S2 (genomic inflation  $\lambda = 1.028$ ). Case and control subjects have not been previously reported.

*Bipolar Genome Study / Translational Genomics Institute 1 (BiGS/TGEN1)*: The TGEN sample is comprised entirely of subjects who were collected as part of wave 5 of the NIMH Genetics Initiative for BD. This collection was conducted at 11 sites where individual unrelated subjects were ascertained for a diagnosis of bipolar I or schizoaffective disorder, bipolar type. All sites were in the United States and varied as to ascertainment method and sites including inpatient and outpatient clinical settings, patient support groups and advertising. Written informed consent was obtained from each subject using consent forms and procedures approved by each site's local human subjects committee. Each consent specifically described the contribution of the subjects data to large repositories in order to facilitate collaborative analyses. Subjects were each individually interviewed using the Diagnostic Interview for Genetics Studies (DIGS). These data and information from medical records and other informants were used to make diagnoses using DSM IV criteria.

*FaST STEP2*: Samples were collected from individuals at 11 U.S.: Massachusetts General Hospital, University of Pittsburgh Western Psychiatric Institute and Clinic, Stanford University School of Medicine, Case University, University of Pennsylvania, University of Massachusetts Medical Center, Baylor College of Medicine, University of Texas Health Science Center at San Antonio, Portland VA Medical Center, University of Colorado Health Sciences Center, University of Oklahoma College of Medicine. Eligible participants were age 18 or older meeting DSM-IV criteria for Bipolar I or II disorder 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), and MH63420 (PI: V Nimgaonkar). Case subjects have not been previously reported.

*Control samples for BiGS/TGEN1 and FaST STEP2*:

The cases of BiGS/TGEN1 and FaST STEP2 were combined with NIMH controls that were independent of those that were included in the primary analyses. The control samples were collected by Pablo Gejman and are described in the GAIN/BiGS primary control sample description. Independence of control samples was confirmed by determining eliminating any individual with PLINK  $\pi\text{-hat} > 0.2$  with another individual in the study. Population stratification was ruled out using principle component analyses. The postimputation  $\lambda_{GC} = 1.03$ .

ICCBD:SBD Bipolar cases were recruited from St. Goran's Hospital in Stockholm, Sweden. All participants gave written informed consent to participate in a genetic study of BD, and the study was approved by the Regional Ethics Committee of Stockholm. Diagnoses were based on physician-administered Affective Disorder Evaluation (ADE) and Mini International Neuropsychiatry Interview (MINI).

ICCBD:BiPolaR1 Bipolar cases were identified from the Swedish Bipolar Quality Assurance Registry (BiPolaR). Patient information in the registry includes disease sub-classification,

psychosis, age at onset, number of manic and depressive episodes, number of hospitalizations and family history. Participants provided written informed consent to participate in a genetic study of psychiatric disease, and the study was approved by the Regional Ethics Committee of Stockholm.

ICCBD:HDR Bipolar cases were identified from the Swedish Hospital Discharge Registry if they 1) have at least two admissions with discharge diagnoses of BD and 2) born in Sweden or another Nordic country. The register contains a nearly complete register of all individuals hospitalized in Sweden since 1973. Diagnoses were established by the attending physician. The study was approved by the Regional Ethics Committee of Stockholm. Controls were collected in a related study of schizophrenia and were identified from the Swedish Hospital Discharge Register. All participants provided written informed consent to participate in genetic studies of psychotic disorders and were interviewed by a research nurse about other medical conditions.

ICCBD:Sweden/Schalling Bipolar cases were recruited from the Stockholm County catchment area. All patients gave written informed consent to participate in a genetic study of BD, and the study was approved by the Regional Ethics Committee of Stockholm. Diagnoses were made according to the DSM-IV criteria. Cases were not reported previously.

Swedish control samples were obtained from the Swedish Hospital Discharge Registry if they had never received discharge diagnoses of BD, schizophrenia and schizoaffective disorder. Sample QC was performed as described in section S2 (genomic inflation  $\lambda = 1.066$ ). Cases have not been previously reported, controls have not previously been reported (but are included in the replication samples being reported by the PGC schizophrenia group)

BOMA-Bipolar Study rep1 and rep2. Cases for BOMA rep1 and rep2 were again 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, as well as at other collaborating psychiatric university hospitals in Germany which have joined the BOMA studies. DSM-IV lifetime diagnoses of BD were assigned using a consensus best-estimate procedure, based on all available information, including structured interviews (SCID-I, SADS-L; rep1) or semi-structured interviews (AMDP; rep2), medical records, and the family history method. In addition, the OPCRIT system, was used for the detailed polydiagnostic documentation of symptoms.

The controls for BOMA rep1 were recruited at the Max Planck Institute of Psychiatry in Munich, Germany, and were selected randomly from a Munich-based community sample. They were collected in the course of genetic studies of major depression, and were therefore screened for the presence of anxiety and affective disorders using the Composite International Diagnostic Screener. Only individuals negative for the above-named disorders were included in the sample. All included controls were Caucasian, 93.04% were of German origin. These subjects thus represent a group of healthy individuals with regard to depression and anxiety. The study was approved by the ethics committee of the Ludwig Maximilians University in Munich, Germany, and written informed consent was obtained from all subjects. These controls were described in detail in the study by Muglia et al. Controls for BOMA rep2 were ascertained from the population-based Heinz Nixdorf Recall Study<sup>24</sup> (additional probands to those used in the BOMA-Bipolar Study

included in the COMBINED ANALYSIS SAMPLES ). Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent. This includes a clause that all data may be shared with collaborating partners such as the PGC. However, consents do not include permission for depositing of de-identified individual GWAS genotype and phenotype data into the NIMH genetics initiative repository, although these data may be used in specific collaborations for studies of neuropsychiatric disorders. All subjects were genotyped using the Illumina platform.

**Australian Samples.** Subjects were ascertained through two studies – i) a BD pedigree sample (described in McAuley et al.<sup>25</sup>) and ii) a specialised Sydney Black Dog Institute BD clinic sample (described in Mitchell et al. 2009<sup>26</sup>). All subjects were interviewed by trained research staff using the DIGS or SCID, using best-estimate DSM-IV diagnoses derived from those instruments, medical records and FIGS. First, for the pedigree sample, only one BD subject per family was included in the case sample. Pedigrees were only included in the original genetic study if there was unilineal inheritance, and at least two BD subjects including at least one with bipolar I disorder. Subjects were ascertained through clinical presentations to the Mood Disorders Unit at Prince of Wales Hospital in Sydney; direct referrals from Australian clinicians; and BD consumer organisations. Second, for the clinic sample, subjects comprised consecutive subjects referred by psychiatrists or general practitioners for specialised clinical review. All patients gave informed consent to participate in this study and the study was approved by the local ethic committee. Patients were included in the BOMA study and genotyped at the Life & Brain Centre in Bonn.

Australian controls were drawn from families participating in the Brisbane Longitudinal Twin Study, an unselected community sample recruited to take part in studies of melanoma risk factors, cognition, and other phenotypes. Subjects were not screened for any phenotype relevant to BD. The study was approved by the ethic committee and all probands gave written informed consent. All were genotyped as a single project by deCODE and have been through an extensive QC process including exclusion for non-european ancestry. The sample is overwhelmingly of northern European origin (mainly British Isles).

**Icelandic Samples.** 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 Research Diagnostic Criteria (RDC) through the use of the Schedule for Affective Disorders and Schizophrenia Lifetime Version (SADS-L) 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.

**Table S5: Summary of samples and methods used in replication analyses**

| Sample | Ancestry | Case (n) | Cont. (n) | BD1 | BD2 | SAB | BD-NOS | Diagnosis | Interview | Cont. screen | $\lambda$ |
|--------|----------|----------|-----------|-----|-----|-----|--------|-----------|-----------|--------------|-----------|
|--------|----------|----------|-----------|-----|-----|-----|--------|-----------|-----------|--------------|-----------|

|   |                       |       |       |                 |                |              |              |               |                               |    |      |
|---|-----------------------|-------|-------|-----------------|----------------|--------------|--------------|---------------|-------------------------------|----|------|
| French  | French                | 451   | 1631  | 341<br>(78%)    | 98<br>(22%)    | 0            | 12           | DSMIV         | DIGS                          | N  | 1.03 |
| Bipolar Genome<br>Study/Translational<br>Genomics Institute<br>(BiGS/TGEN1) | European-<br>American | 1188  | 1112  | 1111<br>(93.5%) | 0              | 77<br>(6.5%) | 0            | DSMIV         | DIGS                          | Y  | 1.03 |
| FaST  | European-<br>American | 494   |       | 383<br>(77.5%)  | 110<br>(22.3%) | 0            | 1<br>(0.2%)  | DSMIV         | MINI<br>ADE                   | Y  |      |
| International Case-<br>Control Cohort-<br>Bipolar Disorder<br>(ICCBD)       | Swedish               | 825a  | 2084  | 489<br>(82%)    | 96<br>(16%)    | 0            | 14b<br>(2%)  | DSMIV         | ADE<br>MINI<br>Hosp<br>record | NA | 1.07 |
| BOMA-Bipolar<br>Study rep1  | German                | 488   | 857   | 289<br>(59.2%)  | 169<br>(34.6%) | 1<br>(0.2%)  | 29<br>(5.9%) | DSMIV         | SCID,<br>SADS-L               | Y  | 1.00 |
| BOMA-Bipolar<br>Study rep2  | German                | 180   | 525   | 175<br>(97.2%)  | 5<br>(2.8%)    | 0            | 0            | DSMIV         | AMDP                          | N  | 1.05 |
| Australian  | Australian            | 326   | 1787  | 253<br>(77.6%)  | 71<br>(21.8%)  | 1<br>(0.3%)  | 1<br>(0.3%)  | DSMIV         | SCID,<br>DIGS                 | N  | 1.00 |
| Icelandic   | Icelandic             | 541c  | 34546 | 314<br>(82%)    | 71<br>(18%)    | 0            | 0            | DSMIV/<br>RDC | SADSL/<br>CITI-<br>Auto       | N  | 1.10 |
| REPLICATION<br>TOTAL  |                       | 4493  | 42542 |                 |                |              |              |               |                               |    |      |
| REPLICATION<br>WITH SUBTYPE<br>AVAILABLE                                    |                       | 4111  |       | 3355<br>(81.6%) | 620<br>(15.1%) | 79<br>(1.9%) | 57<br>(1.4%) |               |                               |    |      |
| GRAND TOTAL   |                       | 11974 | 51792 |                 |                |              |              |               |                               |    |      |

<sup>a</sup>Diagnoses were made from hospital discharge records 226 of the samples, and thus DSMIV subtypes are unavailable, subtypes are given for 599 of the cases, <sup>b</sup>BDNOS included antidepressant induced mania <sup>c</sup>DSMIV diagnoses were not available for 150 subjects who had been collected under earlier diagnostic criteria and described above. DIGS<sup>19</sup>; MINI<sup>21</sup>; ADE; SCID<sup>7</sup>; SADS-L<sup>27</sup>; AMDP; CITI-AUTO;  $\lambda$ =genomic control lambda.

From each replication sample, we obtained information on  $P$  values, odds ratios (OR), standard errors (SE), minor allele frequencies and the associated risk allele for SNPs listed in Table S2. If the specific target SNP listed in Table S2 was not present in the replication dataset, we obtained a proxy SNP in strong LD (based on HapMap Phase 2 data) and weighted the SE to account for the lack of information,  $SE_w = SE / \text{sqrt}(R^2)$ . We then performed a standard meta-analysis, to estimate a common odds ratio weighted by individual study's SEs (Table S8, which shows both fixed and random-effects estimates for the meta-analysis of replication studies.)

$$\frac{\sum \frac{ES_i}{SE_i^2}}{\sum \frac{1}{SE_i^2}}$$

$$\sqrt{\frac{1}{\sum \frac{1}{SE_i^2}}}$$

The primary GWAS results were combined with the replication meta-analysis results using a fixed effects meta-analysis as described above.



**Table S6. Meta-analysis results for SNPs tested in replication**

| SNP         | CHR | POS       | A1 | A2 | FRQ(A1) | PRIMARY GWS     |       |   | REPLICATION META-ANALYSIS |       |                    |                     |                  |                  |
|-------------|-----|-----------|----|----|---------|-----------------|-------|---|---------------------------|-------|--------------------|---------------------|------------------|------------------|
|             |     |           |    |    |         | P <sub>GC</sub> | OR    | N | P <sub>REP</sub>          | OR    | P <sub>FIXED</sub> | OR <sub>FIXED</sub> | P <sub>HET</sub> | I <sub>REP</sub> |
| rs4765913   | 12  | 2290157   | A  | T  | 0.21    | 6.50E-06        | 1.150 | 7 | 0.00032                   | 1.132 | 0.00032            | 1.132               | 0.912            | 0                |
| rs10896135  | 11  | 66307578  | C  | G  | 0.26    | 8.46E-06        | 0.880 | 7 | 0.00294                   | 0.913 | 0.00294            | 0.913               | 0.552            | 0                |
| rs2070615*  | 12  | 47504438  | A  | G  | 0.44    | 4.00E-05        | 0.899 | 7 | 0.00505                   | 0.926 | 0.12140            | 0.938               | 0.049            | 53               |
| rs12576775  | 11  | 78754841  | A  | G  | 0.82    | 2.09E-07        | 0.846 | 7 | 0.01517                   | 0.917 | 0.01517            | 0.917               | 0.653            | 0                |
| rs2175420*  | 11  | 78801531  | C  | T  | 0.82    | 2.90E-05        | 0.870 | 7 | 0.01559                   | 0.917 | 0.01559            | 0.917               | 0.692            | 0                |
| rs3845817   | 2   | 65612029  | C  | T  | 0.61    | 1.65E-05        | 0.895 | 7 | 0.01796                   | 0.936 | 0.04512            | 0.933               | 0.191            | 31               |
| rs2176528   | 2   | 194580428 | C  | G  | 0.68    | 3.98E-05        | 1.147 | 5 | 0.02084                   | 1.092 | 0.02084            | 1.092               | 0.984            | 0                |
| rs4660531   | 1   | 41612409  | G  | T  | 0.64    | 3.16E-05        | 0.892 | 6 | 0.02219                   | 0.933 | 0.02219            | 0.933               | 0.599            | 0                |
| rs7578035   | 2   | 98749324  | G  | T  | 0.50    | 1.83E-05        | 1.115 | 7 | 0.02588                   | 1.063 | 0.04496            | 1.068               | 0.227            | 26               |
| rs2287921   | 19  | 53920084  | C  | T  | 0.53    | 1.68E-05        | 1.122 | 7 | 0.02729                   | 1.064 | 0.02729            | 1.064               | 0.853            | 0                |
| rs11168751* | 12  | 47505405  | C  | G  | 0.85    | 1.80E-05        | 0.841 | 7 | 0.02861                   | 0.901 | 0.02861            | 0.901               | 0.889            | 0                |
| rs7296288   | 12  | 47766235  | A  | C  | 0.52    | 8.39E-08        | 0.872 | 7 | 0.03000                   | 0.942 | 0.04910            | 0.939               | 0.278            | 20               |
| rs7827290   | 8   | 142369497 | G  | T  | 0.33    | 3.54E-05        | 1.134 | 7 | 0.03348                   | 1.065 | 0.03348            | 1.065               | 0.540            | 0                |
| rs12730292  | 1   | 79027350  | C  | G  | 0.64    | 2.37E-05        | 1.125 | 7 | 0.03418                   | 1.064 | 0.05566            | 1.064               | 0.325            | 14               |
| rs12912251  | 15  | 36773660  | G  | T  | 0.70    | 9.57E-06        | 1.130 | 7 | 0.04073                   | 1.061 | 0.19540            | 1.055               | 0.081            | 47               |
| rs4332037   | 7   | 1917335   | C  | T  | 0.82    | 1.78E-05        | 0.867 | 7 | 0.05945                   | 0.934 | 0.19460            | 0.934               | 0.065            | 49               |
| rs6550435   | 3   | 36839493  | G  | T  | 0.36    | 1.97E-05        | 1.118 | 7 | 0.06523                   | 1.053 | 0.11050            | 1.056               | 0.209            | 29               |
| rs17395886  | 4   | 162498835 | A  | C  | 0.16    | 2.18E-05        | 0.860 | 7 | 0.07028                   | 0.933 | 0.07028            | 0.933               | 0.765            | 0                |
| rs6746896   | 2   | 96774676  | A  | G  | 0.68    | 2.33E-06        | 1.136 | 7 | 0.07711                   | 1.052 | 0.11580            | 1.052               | 0.294            | 18               |
| rs736408    | 3   | 52810394  | C  | T  | 0.66    | 1.22E-06        | 1.144 | 7 | 0.09293                   | 1.050 | 0.09293            | 1.050               | 0.698            | 0                |
| rs11162405  | 1   | 78242248  | A  | G  | 0.58    | 2.54E-05        | 0.898 | 7 | 0.09519                   | 0.955 | 0.12310            | 0.953               | 0.285            | 19               |
| rs9804190   | 10  | 61509837  | C  | T  | 0.78    | 3.06E-05        | 1.166 | 7 | 0.19260                   | 1.043 | 0.41780            | 1.033               | 0.174            | 33               |
| rs9371601   | 6   | 152832266 | G  | T  | 0.64    | 4.27E-08        | 0.867 | 7 | 0.20690                   | 0.966 | 0.20690            | 0.966               | 0.560            | 0                |
| rs3774609   | 3   | 53807943  | G  | T  | 0.37    | 1.14E-05        | 0.888 | 7 | 0.21400                   | 0.966 | 0.21400            | 0.966               | 0.874            | 0                |
| rs10994397  | 10  | 61949130  | C  | T  | 0.94    | 7.08E-09        | 0.742 | 7 | 0.23190                   | 0.938 | 0.27150            | 0.938               | 0.331            | 13               |
| rs4668059   | 2   | 168874528 | C  | T  | 0.14    | 4.45E-05        | 1.177 | 7 | 0.31540                   | 1.044 | 0.31540            | 1.044               | 0.687            | 0                |
| rs16966413  | 15  | 36267191  | A  | G  | 0.90    | 4.74E-05        | 0.842 | 4 | 0.31600                   | 0.950 | 0.31600            | 0.950               | 0.575            | 0                |
| rs6102917   | 20  | 40652833  | C  | G  | 0.98    | 3.88E-05        | 1.441 | 7 | 0.32930                   | 1.112 | 0.32930            | 1.112               | 0.820            | 0                |
| rs11085829  | 19  | 13035312  | A  | G  | 0.35    | 4.03E-06        | 0.868 | 7 | 0.34950                   | 0.974 | 0.34950            | 0.974               | 0.586            | 0                |
| rs875326    | 1   | 173556022 | C  | T  | 0.84    | 2.51E-05        | 1.153 | 7 | 0.36680                   | 1.034 | 0.36680            | 1.034               | 0.909            | 0                |
| rs13245097* | 7   | 2307581   | C  | T  | 0.60    | 3.81E-05        | 1.133 | 7 | 0.39240                   | 1.024 | 0.39240            | 1.024               | 0.623            | 0                |
| rs780148    | 10  | 80605089  | C  | G  | 0.51    | 4.66E-05        | 1.122 | 7 | 0.45940                   | 1.027 | 0.84620            | 1.009               | 0.167            | 34               |
| rs2281587   | 10  | 105367339 | C  | T  | 0.65    | 1.96E-05        | 1.120 | 7 | 0.74310                   | 1.009 | 0.74310            | 1.009               | 0.678            | 0                |
| rs10776799  | 1   | 115674570 | G  | T  | 0.18    | 4.84E-05        | 1.147 | 7 | 0.86750                   | 1.006 | 0.86750            | 1.006               | 0.940            | 0                |
| rs263906    | 1   | 101750922 | C  | T  | 0.75    | 2.42E-05        | 1.131 | 7 | 0.88030                   | 1.005 | 0.88030            | 1.005               | 0.607            | 0                |
| rs10028075  | 4   | 87186854  | C  | T  | 0.55    | 8.96E-06        | 0.894 | 7 | 0.51830                   | 1.018 | 0.50510            | 1.024               | 0.150            | 36               |
| rs3968      | 9   | 4931997   | C  | G  | 0.83    | 2.09E-05        | 1.166 | 7 | 0.02554                   | 0.924 | 0.05668            | 0.920               | 0.206            | 29               |
| rs8006348   | 14  | 50595223  | A  | G  | 0.74    | 4.91E-05        | 0.891 | 7 | 0.15070                   | 1.045 | 0.15070            | 1.045               | 0.585            | 0                |

POS= basepair position in Build 36. A1=Allele predicted towards for OR N=number of replication studies where the SNP or a proxy was available. SNPs are listed in the order found in Table 3 (1-tailed replication *P* value). P<sub>REP</sub>=2-tailed *P* value. SNPs marked by an asterisk do not represent independent association signals.

**Table S7. Replication results by site**

This table shows odds ratios for each of the replication datasets. At missing entries, no SNP in the region had a sufficient R2 in that particular dataset. Odds ratios are reported for the allele given in the discovery sample (Table S2)

| SNP         | CHR | POS       | A1 | AUSTRALIAN | BiGS/TGEN/<br>FaST | FRENCH | BOMA<br>rep1 | BOMA<br>rep2 | ICELANDIC | ICCBD-<br>Sweden |
|-------------|-----|-----------|----|------------|--------------------|--------|--------------|--------------|-----------|------------------|
| rs4765913   | 12  | 2290157   | A  | 1.088      | 1.165              | 1.095  | 1.073        | 1.175        | 1.074     | 1.217            |
| rs10896135  | 11  | 66307578  | C  | 0.839      | 0.948              | 0.875  | 0.924        | 1.140        | 0.845     | 0.948            |
| rs2070615*  | 12  | 47504438  | A  | 0.846      | 0.953              | 1.000  | 1.026        | 1.272        | 0.882     | 0.833            |
| rs12576775  | 11  | 78754841  | A  | 0.813      | 0.915              | 0.936  | 0.887        | 1.275        | 0.947     | 0.906            |
| rs2175420*  | 11  | 78801531  | C  | 0.973      | 0.896              | 0.951  | 0.850        | 1.066        | 1.000     | 0.841            |
| rs3845817   | 2   | 65612029  | C  | 1.050      | 0.913              | 0.979  | 0.829        | 0.700        | 0.982     | 0.955            |
| rs2176528   | 2   | 194580428 | C  | NA         | 1.107              | 1.058  | NA           | 1.104        | 1.117     | 1.063            |
| rs4660531   | 1   | 41612409  | G  | 0.913      | 0.974              | 0.814  | NA           | 1.018        | 0.938     | 0.947            |
| rs7578035   | 2   | 98749324  | G  | 1.056      | 1.048              | 1.196  | 1.210        | 1.029        | 1.062     | 0.954            |
| rs2287921   | 19  | 53920084  | C  | 1.030      | 1.123              | 1.043  | 0.967        | 1.034        | 1.103     | 1.045            |
| rs11168751* | 12  | 47505405  | C  | 0.801      | 0.932              | 0.945  | 1.072        | 0.850        | 0.900     | 0.817            |
| rs7296288   | 12  | 47766235  | A  | 0.917      | 1.033              | 0.973  | 0.891        | 0.872        | 0.977     | 0.844            |
| rs7827290   | 8   | 142369497 | G  | 1.143      | 1.064              | 0.957  | 1.057        | 0.893        | 1.155     | 1.058            |
| rs12730292  | 1   | 79027350  | C  | 1.003      | 1.158              | 1.225  | 1.024        | 0.975        | 0.995     | 1.018            |
| rs12912251  | 15  | 36773660  | G  | 1.085      | 1.072              | 0.872  | 1.244        | 0.864        | 1.118     | 1.054            |
| rs4332037   | 7   | 1917335   | C  | 1.031      | 0.977              | 1.024  | 0.966        | 0.819        | 0.731     | 1.004            |
| rs6550435   | 3   | 36839493  | G  | 1.247      | 1.099              | 1.021  | 0.977        | 1.199        | 0.953     | 1.052            |
| rs17395886  | 4   | 162498835 | A  | 1.029      | 0.882              | 0.892  | 0.869        | 0.875        | 1.029     | 0.898            |
| rs6746896   | 2   | 96774676  | A  | 1.028      | 1.101              | 1.186  | 1.024        | 1.034        | 0.921     | 1.090            |
| rs736408    | 3   | 52810394  | C  | 1.103      | 1.028              | 0.989  | 1.053        | 0.919        | 1.145     | 1.029            |
| rs11162405  | 1   | 78242248  | A  | 0.970      | 1.015              | 0.931  | 1.031        | 0.761        | 0.859     | 0.985            |
| rs9804190   | 10  | 61509837  | C  | 0.876      | 1.085              | 0.984  | 1.079        | 0.840        | 1.186     | 1.023            |
| rs9371601   | 6   | 152832266 | G  | 1.082      | 0.967              | 1.008  | 0.856        | 0.897        | 0.929     | 0.997            |
| rs3774609   | 3   | 53807943  | G  | 1.034      | 0.943              | 0.899  | 1.026        | 0.897        | 0.979     | 0.973            |
| rs10994397  | 10  | 61949130  | C  | 0.925      | 1.128              | 1.088  | 0.917        | 0.959        | 0.726     | 0.899            |
| rs4668059   | 2   | 168874528 | C  | 1.031      | 0.959              | 1.140  | 1.163        | 1.057        | 1.143     | 0.947            |
| rs16966413  | 15  | 36267191  | A  | NA         | 0.889              | 1.096  | NA           | NA           | 0.971     | 0.914            |
| rs6102917   | 20  | 40652833  | C  | 1.379      | 1.110              | 1.007  | 1.008        | 0.607        | 1.114     | 1.255            |
| rs11085829  | 19  | 13035312  | A  | 0.979      | 0.982              | 0.865  | 1.015        | 1.181        | 1.005     | 0.947            |
| rs875326    | 1   | 173556022 | C  | 1.106      | 1.026              | 1.061  | 1.075        | 1.065        | 1.080     | 0.944            |
| rs13245097* | 7   | 2307581   | C  | 0.945      | 1.026              | 0.985  | 0.963        | 1.101        | 1.135     | 1.013            |
| rs780148    | 10  | 80605089  | C  | 0.975      | 1.040              | 0.845  | 0.891        | 0.794        | 1.098     | 1.140            |
| rs2281587   | 10  | 105367339 | C  | 0.915      | 1.039              | 1.011  | 1.004        | 1.226        | 1.039     | 0.959            |
| rs10776799  | 1   | 115674570 | G  | 0.962      | 1.014              | 0.914  | 1.015        | 1.065        | 1.062     | 1.006            |
| rs263906    | 1   | 101750922 | C  | 1.070      | 0.963              | 1.164  | 1.089        | 1.025        | 0.928     | 1.012            |
| rs10028075  | 4   | 87186854  | C  | 0.994      | 0.961              | 1.222  | 0.984        | 1.126        | 0.945     | 1.063            |
| rs3968      | 9   | 4931997   | C  | 1.069      | 0.977              | 0.938  | 0.950        | 0.644        | 0.812     | 0.945            |
| rs8006348   | 14  | 50595223  | A  | 0.897      | 1.083              | 1.130  | 1.053        | 0.963        | 0.999     | 1.088            |

POS =basepair position in Build 36, A1= Allele predicted towards for OR, SNPs marked by an asterisk do not represent independent association signals.

**Table S8. Simulation of effects of winner’s curse on estimated ORs and replication power**

| True GRR    | Estimated OR (mean) |              |              | OR fold-inflation |
|-------------|---------------------|--------------|--------------|-------------------|
|             | All                 | n.s.         | p<5e-8       |                   |
| 1.50        | 1.508               | -            | 1.508        | 1.00              |
| 1.30        | 1.304               | -            | 1.304        | 1.00              |
| 1.20        | 1.203               | 1.146        | 1.209        | 1.03              |
| 1.10        | 1.101               | 1.100        | 1.174        | 1.66              |
| 1.08        | 1.081               | 1.081        | 1.172        | 2.03              |
| <b>1.05</b> | <b>1.051</b>        | <b>1.051</b> | <b>1.170</b> | <b>3.16</b>       |
| 1.02        | 1.021               | 1.021        | -            | -                 |

| True GRR    | Power in replication sample<br>Assuming true mean OR |           |          |
|-------------|--|-----------|----------|
|             | a=0.05   | a=0.01    | a=0.001  |
| 1.50        | 100  | 100       | 100      |
| 1.30        | 100  | 100       | 100      |
| 1.20        | 100  | 100       | 99       |
| 1.10        | 82   | 62        | 34       |
| 1.08        | 65   | 41        | 17       |
| <b>1.05</b> | <b>31</b>  | <b>13</b> | <b>3</b> |
| 1.02        | 9  | 2         | 0        |

### Section S7. Gene Ontology (GO) enrichment analyses.

We looked for specific Gene Ontology (GO) terms that are enriched for the genes in the most highly associated intervals. We based this analysis on the 38 intervals described above (LD-defined intervals around SNPs with  $P < 5 \times 10^{-5}$  after GC-correction). For this analysis 34 regions were analyzed by collapsing any regions that a) physically-overlapped, b) spanned the same gene or c) did not show conditionally independent association signals. Three regions contains SNPs that had low pairwise  $R^2$  but did not show independent association when covarying for the neighboring SNP – reflecting high LD measured in terms of  $D'$  and not indicative of truly independent signals (see Section S9 below). The enrichment analysis described below critically depends on the assumption of independence between intervals, so as not to “double-count” genes. The final list contained 34 independent regions (merging intervals with index SNPs at: chr7:1917335 and chr7:2307581; chr11:78754841 and chr11:78801531; chr12:47504438, chr12:47505405 and chr12:47766235).

We accessed the gene2go dataset from NCBI (<ftp.ncbi.nlm.nih.gov/gene/DATA/gene2go.gz>) and mapped the Entrez GeneIDs to gene symbols and hg18 genomic co-ordinates via the UCSC Genome Browser database. Of 9834 total GO terms, we restricted the analysis to terms with at least 2 human genes and not more than 200, leaving 6482 GO terms (“targets”). For each target, we counted the number of association intervals that contained at least 1 target gene; we required that at least 2 intervals contained at least 1 gene from each target. We then evaluated for each target, the probability of observing the number of intersecting intervals by chance alone, via a permutation procedure (implemented In the INRICH software, Lee *et al*, in prep.). Specifically, we

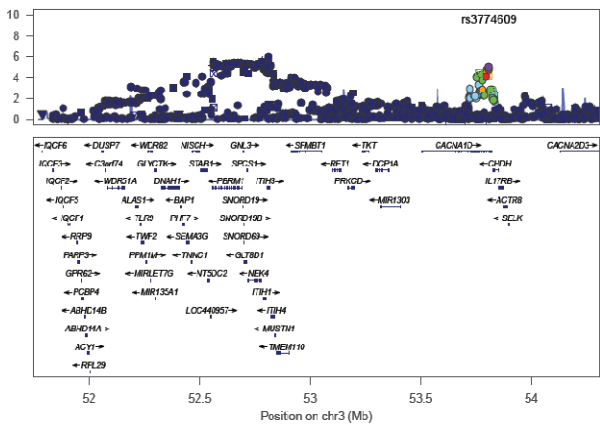
randomly placed each independent interval in an alternate position on genome, but matching for the total number of SNPs and implied new size of the interval (such that the distance in base-pairs is within a factor of 0.8 to 1.2 of the original) and also the total number of genes within each interval. In this manner, we control for potential biases due to SNP and gene density, and gene size. We repeated the permutation 100,000 times. We corrected for multiple testing by evaluating the distribution of minimum empirical p-values under the null hypothesis, given 6482 targets were tested. The corrected empirical  $P$  values implicitly take the non-independence of GO terms into account. We observed a single target that was enriched in the top  $P < 5 \times 10^{-5}$  regions the association analysis that also withstood experiment-wide correction for multiple testing: GO:0015270, dihydropyridine-sensitive calcium channel activity. This target contains 8 genes, 3 of which are present in independent association-intervals. The probability of this enrichment (controlling for the total SNP and gene-density in the association-intervals) is  $P = 0.00002$ ; the probability of observing an empirical p-value this small, given all the targets tested, is  $P = 0.0205$ . The three genes are *CACNA1C*, *CACNA1D* and *CACNB3*.

## S8. CONDITIONAL ANALYSES

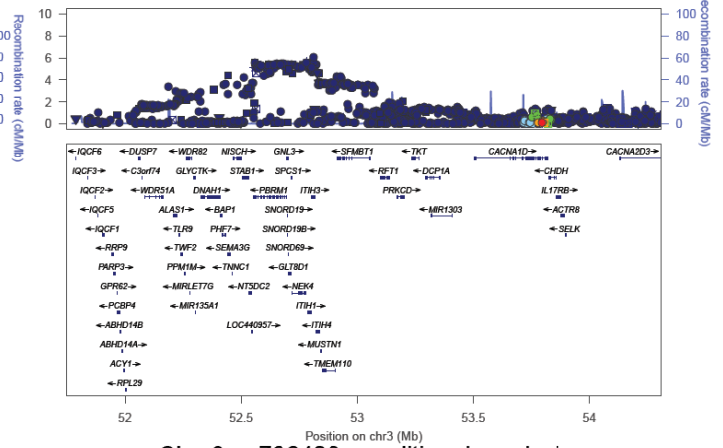
To identify additional signals after accounting for the effects of the initial GWAS signals we performed conditional analysis including the most strongly associated SNPs in the analysis of each SNP. In regions in which we detected a potential secondary signal(s) ( $P_{gc} < 10^{-4}$ ) we performed separate conditional analyses using the initial GWAS identified SNP or the potential secondary signal SNP(s). The  $P$  values are genomic-control corrected.

**Figure S6. Conditional analyses**

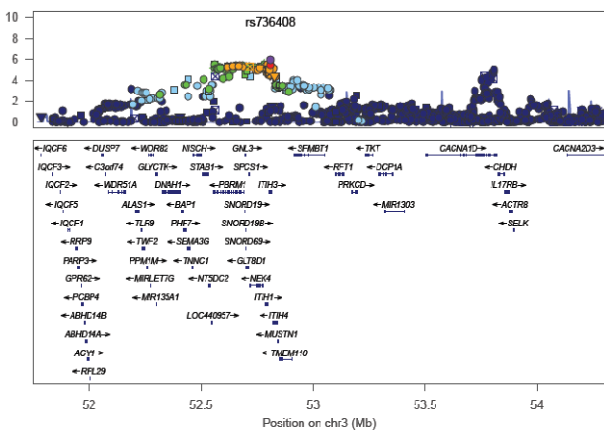
Chr\_3\_rs3774609



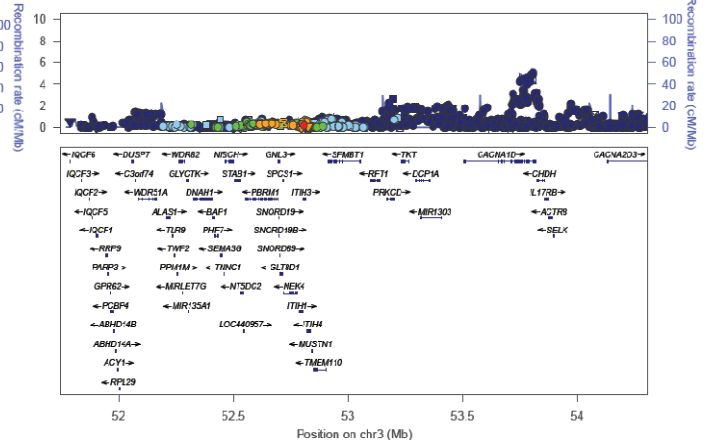
Chr\_3\_rs3774609\_conditional\_analysis



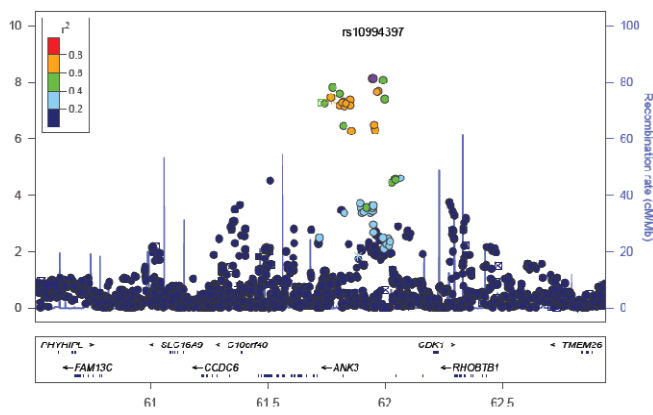
Chr\_3\_rs736408



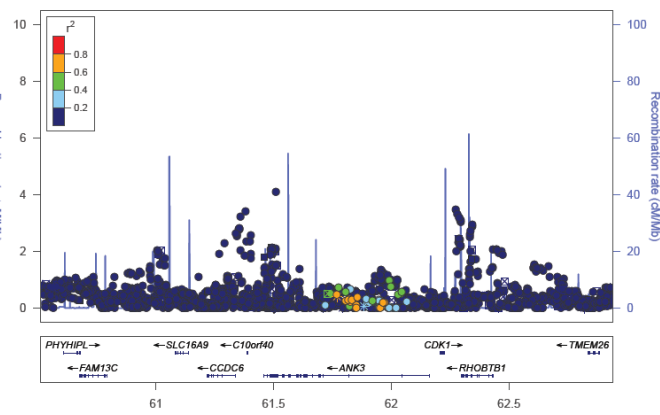
Chr\_3\_rs736408\_conditional\_analysis



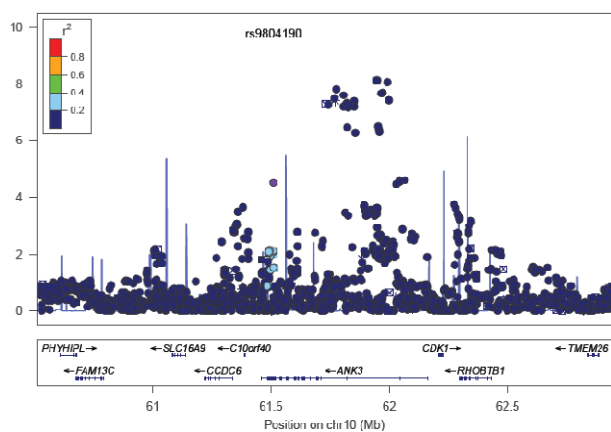
Chr\_10\_rs10994397



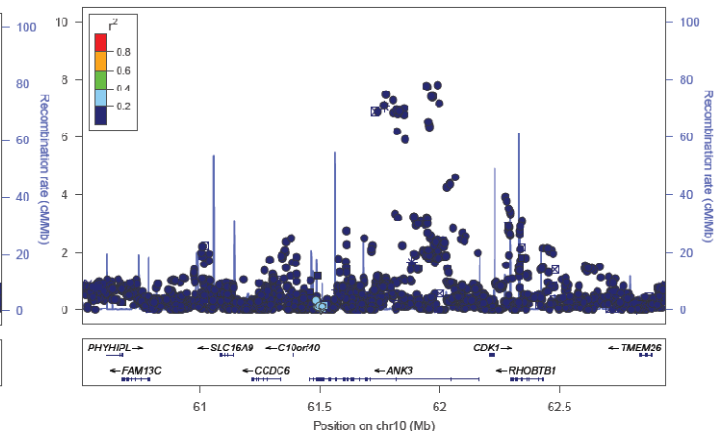
Chr\_10\_rs10994397\_conditional\_analysis



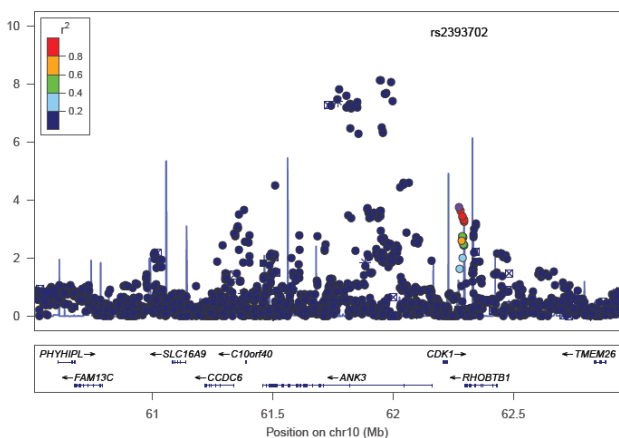
Chr\_10\_rs9804190



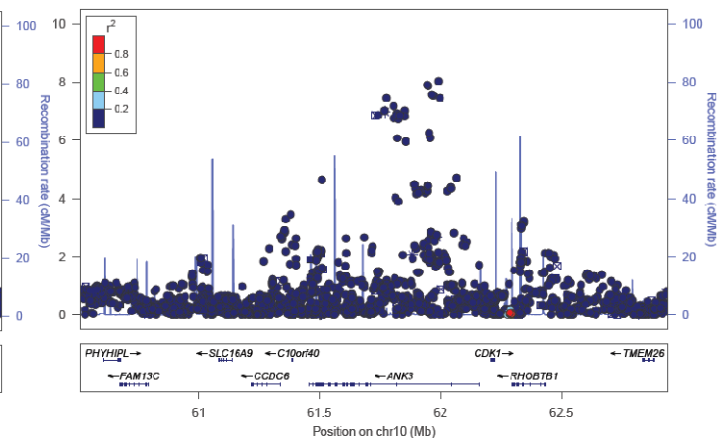
Chr\_10\_rs9804190\_conditional\_analysis

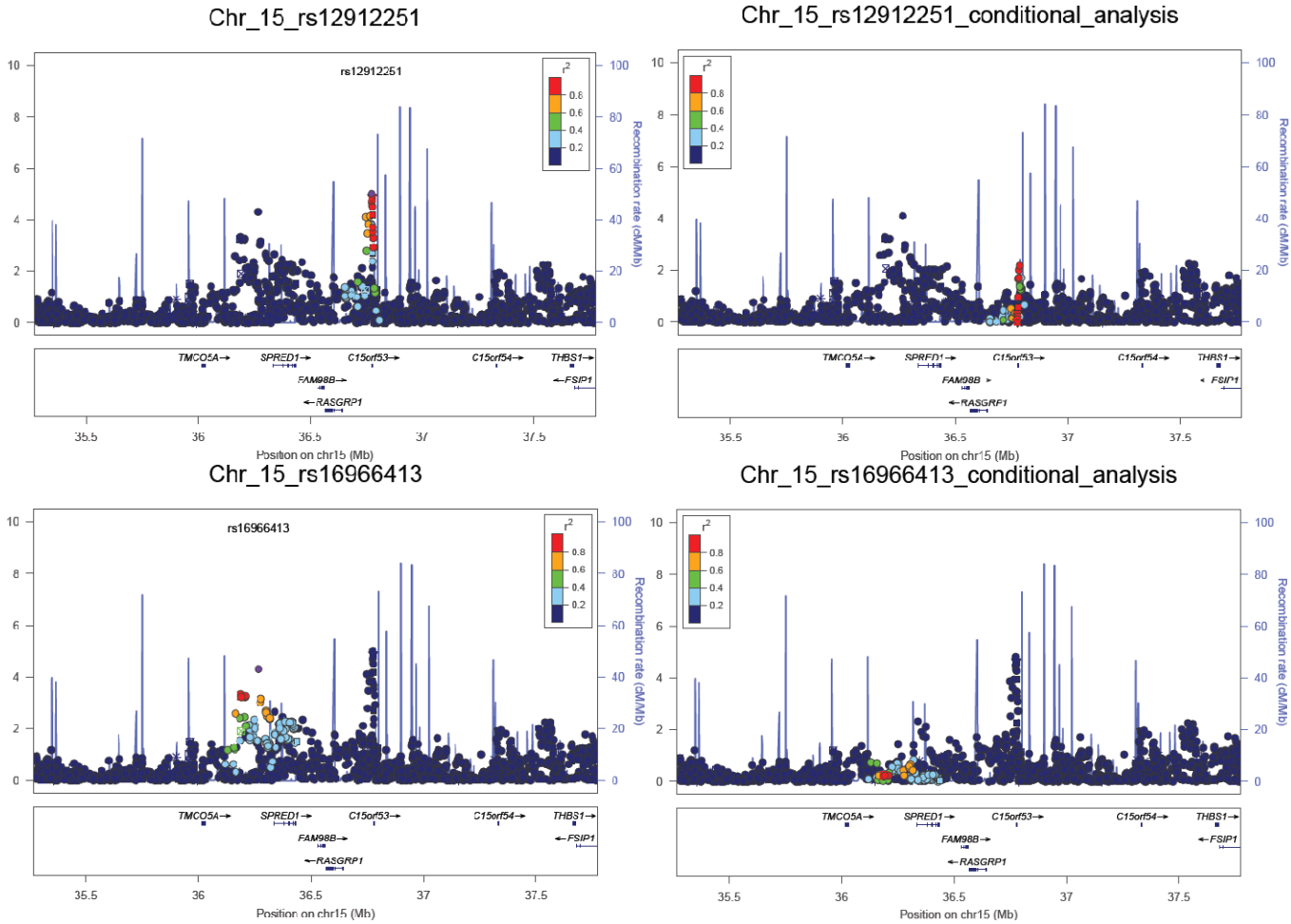


Chr\_10\_rs2393702



Chr\_10\_rs10994397\_conditional\_analysis





**Section S9. Polygene analyses**

We used the PGC bipolar dataset to perform an independent replication of the previously reported polygenic analysis of the International Schizophrenia Consortium (2009), which implied a shared component of risk between schizophrenia and BD that is driven by a large number of common risk

variants of small effect. This result implies a substantial polygenic basis to bipolar, and would predict that a well-powered analysis using independent BD samples for both “discovery” and “target” samples (following the approach outlined by the ISC) should also be expected to yield evidence for polygenicity.

Briefly, to address this question we partitioned the PGC sample into a target (the German sample) and discovery (all other samples). We used only genotyped SNPs that are common to all platforms and in linkage equilibrium, yielding approximately 20,000 SNPs. We estimated the odds ratios from the 10 sites, excluding the German sample, by fixed-effect meta-analysis and took the log of these odds ratios as weights to calculate the scores in the target sample. Following the ISC, we selected discovery sample p-value thresholds of  $P < 0.01, 0.05, 0.1, 0.2, 0.3, 0.4$  and  $0.5$ . For each threshold, we performed a logistic regression of disease state in the target sample on the polygenic score from the remaining, independent samples, covarying for the rate of genotyping failure and also the MDS components to adjust for potential technical and population stratification confounds. As shown below, we observed a significant enrichment of putatively-associated “score alleles” in target sample cases compared to controls ( $P$  values and pseudo- $R^2$  presented, but all effects were in the expected direction, with a higher score in cases compared to controls). A more comprehensive analysis of the polygenic component of risk within and across the five different PGC diseases (ADHD, autism, BD, major depression and schizophrenia) is underway.

**Table S9. Variance explained in BD target samples using a BD discovery sample**

| Discovery $P$ value threshold | $R^2$  | Target $P$ value       |
|-------------------------------|--------|------------------------|
| 0.01                          | 0.0062 | 0.003206               |
| 0.05                          | 0.0164 | $4.68 \times 10^{-06}$ |
| 0.10                          | 0.0189 | $1.48 \times 10^{-06}$ |
| 0.20                          | 0.0213 | $1.58 \times 10^{-07}$ |
| 0.30                          | 0.0210 | $2.33 \times 10^{-07}$ |
| 0.40                          | 0.0237 | $4.11 \times 10^{-08}$ |
| 0.50                          | 0.0283 | $1.71 \times 10^{-09}$ |

### Section S10. Combined analysis of top BD findings with schizophrenia

In order to identify whether our most strongly BD associated signals were independently associated with schizophrenia, we investigated the top 5 signals (nominal uncorrected  $P_{raw} < 5 \times 10^{-7}$  from our primary bipolar dataset to a similar set of data prepared from the PGC schizophrenia group. Following our analysis in the replication dataset a 6th signal representing the calcium channel region was added. Because there was substantial overlap in the controls used in the two studies a strategy was employed to randomly assign each control to either the bipolar or schizophrenia dataset to construct fully independent groups of cases and controls. Briefly, for the 14,044 controls samples in both datasets, a PLINK pi-hat  $> 0.9$  was used to identify identical controls. Only one individual was retained for analysis and randomly assigned to either BD or SCZ. The primary analysis was a logistic regression of disease state on single SNP allele dosage similar to those described above for our primary GWAS sample association. We include



covariates to account for site as well as the quantitative indices (the first 5 plus 3 additional that showed some correlation with phenotype) of ancestry based on multi-dimensional scaling.

*Table S10. Association analysis of BD loci in schizophrenia and BD and SCZ combined*

| SNP original | SNP proxy  | R2   | CHR | Base Pair | A1 | A2 | Freq A1 | Freq A2 | COMBINED P value | COMBINED OR |
|--------------|------------|------|-----|-----------|----|----|---------|---------|------------------|-------------|
| rs4765913    | -          |      | 12  | 2219845   | C  | G  | 0.35    | 0.33    | 7.70E-08         | 1.110       |
| rs736408     | rs2535629  | 0.88 | 3   | 52808259  | A  | G  | 0.33    | 0.35    | 8.41E-09         | 0.898       |
| rs10994397   | rs10994359 | 0.86 | 10  | 61892113  | T  | C  | 0.93    | 0.94    | 2.45E-08         | 0.820       |
| rs12576775   | rs17138230 | 1.00 | 11  | 78753500  | A  | T  | 0.81    | 0.83    | 3.90E-06         | 0.902       |
| rs9371601    | -          |      | 6   | 152832266 | T  | G  | 0.36    | 0.35    | 1.41E-05         | 1.081       |
| rs7296288    | rs2117028  | 0.52 | 12  | 47767215  | A  | G  | 0.43    | 0.42    | 1.94E-05         | 1.108       |

Base Pair=hg18; SCZ cases = 9375;

Combined cases = 16374; Combined controls = 14044

R2 calculated using Hapmap2: rs736408, rs12576775 and HapMap3: rs10994397, rs7296288

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From 2003-2006, the Principal Investigators and Co-Investigators were: NorthShore University HealthSystem, Evanston, IL, R01 MH59571, Pablo V. Gejman, M.D. (Collaboration Coordinator; PI), Alan R. Sanders, M.D.; Emory University School of Medicine, Atlanta, GA, R01 MH59587, Farooq Amin, M.D. (PI); University of California, San Francisco, CA, R01 MH60870, William F. Byerley, M.D. (PI); University of Iowa, IA, R01 MH59566, Donald W. Black, M.D. (PI), Raymond R. Crowe, M.D.; Washington University, St. Louis, MO, R01 MH60879, C. Robert Cloninger, M.D. (PI); University of Colorado, Denver, CO, R01 MH59565, Robert Freedman, M.D. (PI), Ann Olincy, M.D.; Stanford University, Palo Alto, CA, R01 MH61675, Douglas F. Levinson, M.D. (PI); Louisiana State University, New Orleans, LA, R01 MH67257, Nancy G. Buccola, APRN, BC, MSN (PI); University of Queensland, Brisbane, Queensland, Australia, R01 MH59588, Bryan J. Mowry, M.D. (PI); Mt. Sinai School of Medicine, New York, NY, R01 MH59586, Jeremy M. Silverman, Ph.D. (PI).

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From 1991-98, the Principal Investigators and Co-Investigators were: Indiana University, Indianapolis, IN, U01 MH46282, John I. Nurnberger, Jr., M.D., Ph.D., Marvin Miller, M.D., and Elizabeth Bowman, M.D.; Washington University, St. Louis, MO, U01 MH46280, Theodore Reich, M.D., Allison Goate, Ph.D., and John Rice, Ph.D.; Johns Hopkins University, Baltimore, MD, U01 MH46274, J. Raymond DePaulo, Jr., M.D., Sylvia Simpson, M.D., MPH, and Colin Stine, Ph.D.; NIMH Intramural Research Program, Clinical Neurogenetics Branch, Bethesda, MD, Elliot Gershon, M.D., Diane Kazuba, B.A., and Elizabeth Maxwell, M.S.W.

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### **University College London**

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## University of Edinburgh

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## Wellcome Trust Case-Control Consortium

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