Title: The genetics of the mood disorder spectrum: genome-wide association analyses of over 185,000 cases and 439,000 controls

Authors: Jonathan R. I. Coleman[1;2], Héléna A. Gaspar[1;2], Julien Bryois[3], Bipolar Disorder Working Group of the Psychiatric Genomics Consortium[4], Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium[4], Gerome Breen[1;2]

Affiliations:

1. Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
2. NIHR Maudsley Biomedical Research Centre, King's College London, London, United Kingdom
3. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
4. Full consortium authorship listed in Article Information

Correspondence to: Gerome Breen, Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, London, SE5 8AF, UK, gerome.breen@kcl.ac.uk, +442078480409

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Abstract

Background

Mood disorders (including major depressive disorder and bipolar disorder) affect 10-20% of the population. They range from brief, mild episodes to severe, incapacitating conditions that markedly impact lives. Despite their diagnostic distinction, multiple approaches have shown considerable sharing of risk factors across the mood disorders.

Methods

To clarify their shared molecular genetic basis, and to highlight disorder-specific associations, we meta-analysed data from the latest Psychiatric Genomics Consortium (PGC) genome-wide association studies of major depression (including data from 23andMe) and bipolar disorder, and an additional major depressive disorder cohort from UK Biobank (total: 185,285 cases, 439,741 controls; non-overlapping N = 609,424).

Results

Seventy-three loci reached genome-wide significance in the meta-analysis, including 15 that are novel for mood disorders. More genome-wide significant loci from the PGC analysis of major depression than bipolar disorder reached genome-wide significance. Genetic correlations revealed that type 2 bipolar disorder correlates strongly with recurrent and single episode major depressive disorder. Systems biology analyses highlight both similarities and differences between the mood disorders, particularly in the mouse brain cell-types implicated by the expression

patterns of associated genes. The mood disorders also differ in their genetic correlation with educational attainment – positive in bipolar disorder but negative in major depressive disorder.

Conclusions

The mood disorders share several genetic associations, and can be combined effectively to increase variant discovery. However, we demonstrate several differences between these disorders. Analysing subtypes of major depressive disorder and bipolar disorder provides evidence for a genetic mood disorders spectrum.

Introduction

Mood disorders affect 10-20% of the global population across their lifetime, ranging from brief episodes to incapacitating conditions that markedly impact lives (1–4). Major depressive disorder and bipolar disorder are the most common forms and have been grouped together since the Diagnostic and Statistical Manual of Mental Disorders' third edition (DSM-III) (5). Although given dedicated chapters in DSM5, they remain grouped as mood disorders in the International Classification of Disorders (ICD11) (6, 7).

Depressive episodes are common to major depressive disorder and type 2 bipolar disorder, and are usually present in type 1 bipolar disorder (7). The bipolar disorders are distinguished from major depressive disorder by the presence of mania in type 1 and hypomania in type 2 (7). However, these distinctions are not absolute – some individuals with major depressive disorder develop bipolar disorder, and some endorse (hypo)manic symptoms (8–10). Following their first depressive episode, a non-remitting individual might develop recurrent major depressive disorder or bipolar disorder. Treatment guidelines for these disorders differ (11, 12). Identifying shared and distinct genetic associations for major depressive disorder and bipolar disorder could aid our understanding of these diagnostic trajectories.

Twin studies suggest that 35-45% of variance in risk for major depressive disorder, and 65-70% for bipolar disorder, is accounted for by additive genetic factors (13). These genetic components are partially shared, with a twin genetic correlation (r_g) of ~65%, and a common variant based r_g of 30-35%, derived from genome-wide association study (GWAS) results (14–17). Progress has been made

in identifying specific genetic variants that underlie genetic risk. Recently, the Psychiatric Genomics Consortium (PGC) published a GWAS of bipolar disorder, including over 20,000 cases, with 30 genomic loci reaching genome-wide significance (16). They also performed a GWAS of major depression, including over 135,000 individuals with major depressive disorder and other definitions of depression, with 44 loci reaching genome-wide significance (15). The PGC GWAS of major depression has since been combined with a broad depression GWAS (Supplementary Note).

GWAS have identified statistical associations with major depressive disorder and with bipolar disorder individually, but have not explored the genetic relationship between these disorders. In addition, both disorders exhibit considerable clinical heterogeneity and can be separated into subtypes. For example, the DSM5 includes categories for bipolar disorder type 1 and type 2, and for single episode and recurrent major depressive disorder (7). We use the PGC analyses of major depression and bipolar disorder, along with analyses of formally-defined major depressive disorder from UK Biobank, to explore two aims (18, 19). Firstly, we seek to identify shared and distinct mood disorder genetics by combining studies of major depressive disorder and bipolar disorder. We then explore the genetic relationship of mood disorders to traits from the wider GWAS literature. Secondly, we assess genetic similarities and differences between subtypes of bipolar disorder (from the PGC) and major depressive disorder (from UK Biobank), through comparing genetic correlations and polygenic risk scores.

Materials and Methods

Participants

Our primary aim was to combine analyses of bipolar disorder and major depression to examine the shared and distinct genetics of these disorders. Full descriptions of each study and their composite cohorts are provided in each paper (15, 16, 19). Brief descriptions are provided in the Supplementary Methods. Summary statistics were derived from participants of Western European ancestries, and unless otherwise specified are available (or will be made available) at https://www.med.unc.edu/pgc/results-and-downloads.

Major depression data were drawn from the full cohort (PGC MDD: 135,458 cases, 344,901 controls) from (15). This included data from 23andMe (20), access to which requires a Data Transfer Agreement; consequently, the data analysed here differ from the publicly-available summary statistics. Data for bipolar disorder were drawn from the discovery analysis previously reported (PGC BD: 20,352 cases, 31,358 controls), not including replication results (16).

Secondly, we wished to examine genetic correlations between mood disorder subtypes. Summary statistics were available for the primary bipolar disorder subtypes, type 1 bipolar disorder (BD1: 14,879 cases, 30,992 controls) and type 2 bipolar disorder (BD2: 3,421 cases, 22,155 controls), and for schizoaffective bipolar disorder (SAB: 977 cases, 8,690 controls), a mood disorder including psychotic symptoms. Controls are shared across these subtype analyses.

Subtype GWAS were not available from PGC MDD. Instead, a major depressive disorder cohort was derived from the online mental health questionnaire in the UK Biobank (UKB MDD: 29,475 cases, 63,482 controls; Resource 22 on http://biobank.ctsu.ox.ac.uk) (18). The definition of major depressive disorder in this cohort is based on DSM-5, as described in full elsewhere (18), and in Supplementary Table 1 (7). Individuals meeting criteria for major depressive disorder were classed as "recurrent" if they reported multiple depressed periods across their lifetime (rMDD, N = 17,451), and "single-episode" otherwise (sMDD, N = 12,024, Supplementary Table 1). Individuals reporting depressive symptoms but not meeting case criteria were excluded from UKB MDD but used as a "sub-threshold depression" subtype to examine the continuity of genetic associations with major depressive disorder below clinical thresholds (subMDD, N = 21,596). All subtypes were analysed with all controls. Details on the quality control and analysis of the UK Biobank phenotypes is provided in the Supplementary Methods.

Meta-analysis of GWAS data

We meta-analysed PGC MDD and UKB MDD to obtain a single major depressive disorder GWAS (combined MDD). We meta-analysed combined MDD with PGC BD, comparing mood disorder cases to controls (MOOD). Further meta-analyses were performed between PGC MDD and each mood disorder subtype to assess the relative increase in variant discovery when adding different mood disorder definitions to PGC MDD (Supplementary Results).

Summary statistics were limited to common variants (MAF > 0.05; Supplementary Methods) genotyped or imputed with high confidence (INFO score > 0.6) in all studies. Controls were shared between PGC MDD and PGC BD, and

(because PGC MDD included summary data) the extent of this overlap was unknown. Meta-analyses were therefore performed in METACARPA, which controls for sample overlap of unknown extent between studies using the variance-covariance matrix of the observed effect sizes at each variant, weighted by the sample sizes (21, 22). METACARPA adjusted adequately for known overlap between cohorts (Supplementary Methods). For later analyses (particularly linkage disequilibrium score regression) we used as the sample size a "non-overlapping N" estimated for each meta-analysis (Supplementary Methods). The definition, annotation and visualisation of each meta-analysis is described in the Supplementary Materials.

Sensitivity analysis using down-sampled PGC MDD

Cross-trait meta-analyses may be biased if the power of the composite analyses differs substantially (23, 24). The mean chi-square of combined MDD [1.7] exceeded that of PGC BD [1.39], suggesting this bias may affect our results (Supplementary Table 2). We therefore repeated our analyses, meta-analysing UKB MDD with summary statistics for PGC MDD that did not include participants from 23andMe nor the UK Biobank (mean chi-square = 1.35). All analyses were performed on the full and the down-sampled analyses, with the exception of GSMR analyses. Full results of the down-sampled analyses are described in the Supplementary Materials.

Estimation of SNP-based heritability and genetic correlations with published GWAS

Single nucleotide polymorphism (SNP)-based heritability was assessed using linkage disequilibrium score regression (LDSC) (25). SNP-based heritability estimates were transformed to the liability scale, assuming population prevalences of

15% for combined MDD, 1% for PGC BD, and 16% for MOOD, and lower and upper bounds of these prevalences for comparison (Supplementary Methods). LDSC separates genome-wide inflation into components due to polygenicity and confounding (25). Inflation not due to polygenicity was quantified as (intercept-1)/(mean observed chi-square-1) (26). Genetic correlations were calculated in LDSC between each analysis and 414 traits curated from published GWAS. Local estimates of SNP-based heritability and genetic covariance were obtained using HESS v0.5.3b (Supplementary Methods and Results) (27, 28).

Genetic correlations between subtype analyses

To assess the structure of genetic correlations within the mood disorders, SNP-based heritabilities and genetic correlations were calculated in LDSC between bipolar disorder subtypes (BD1, BD2, SAB), and major depressive disorder subtypes (rMDD, sMDD, subMDD). Putative differences between genetic correlations were identified using a z-test ($p < 0.05$), and formally tested by applying a block-jackknife, with Bonferroni correction for significance ($p < 8.3x10^{-4}$; Supplementary Methods). Differences between the genetic correlations of PGC MDD and each bipolar disorder subtype, and between PGC BD and each major depressive disorder subtype were also tested (Bonferroni correction for significance, $p < 0.0083$). Genetic correlations were hierarchically clustered using the gplots package in R v1.4.1 (29, 30). Hierarchical clustering was performed using just the subtypes, and including results from six external GWAS relevant to mood disorders (Supplementary Methods). To validate our conclusion of a genetic mood disorder spectrum, we performed principal component analysis of the genetic correlation matrix including the six external GWAS (Supplementary Methods and Results).

Association of PGC BD polygenic risk scores with major depressive disorder subtypes

Polygenic risk score analyses were performed using PRSice2 to assess whether rMDD was genetically more similar to PGC BD than were sMDD or subMDD (Supplementary Methods) (36).

Gene-wise, gene-set, and tissue and single-cell enrichment analyses

For all analyses, the p-values of SNPs in gene regions were combined to yield gene-wide p-values, using MAGMA v1.06 (Supplementary Methods and Results) (37). Gene set analysis was performed in MAGMA (Supplementary Methods and Results). Further analyses were performed to assess the enrichment of associated genes with expression-specificity profiles from tissues (Genotype-Tissue Expression project, version 7) and broadly-defined ("level 1") and narrowly-defined ("level 2") mouse brain cell-types (38, 39). Analyses were performed in MAGMA following previously described methods with minor modifications, with Bonferroni-correction for significance (Supplementary Methods) (38). Similar analyses can be performed in LDSC-SEG – we report MAGMA results, which reflect specificity of expression across the range, whereas LDSC-SEG compares the top 10% of the range with the remainder (40). Results using LDSC are included in the Supplementary Tables.

Mendelian randomisation (GSMR)

Bidirectional Mendelian randomisation analyses were performed using the GSMR option in GCTA to allow exploratory inference of the causal direction of known relationships between mood disorder traits and other traits (41, 42).

Specifically, the relationship between the mood disorder analyses (MOOD, combined MDD, PGC BD) and schizophrenia, intelligence, educational attainment, body mass index, and coronary artery disease were explored (Supplementary Methods) (32, 43–46). These traits were previously examined in the PGC major depression GWAS – we additionally tested intelligence following the results of our genetic correlation analyses (15).

Conditional and reversed-effect analyses

Additional analyses were performed to identify shared and distinct mood disorder loci, using mtCOJO, an extension of GSMR (Supplementary Methods) (41, 42). Analyses were performed on combined MDD conditional on PGC BD, and on PGC BD conditional on combined MDD (Supplementary Results). To identify loci with opposite directions of effect between combined MDD and PGC BD, the MOOD meta-analysis was repeated with reversed direction of effects for PGC BD (Supplementary Methods and Results).

Results

Evidence for confounding in meta-analyses

Meta-analysis results were assessed for genome-wide inflation of test statistics using LDSC (25). Generally, the LDSC intercept was significantly >1 (1.00-1.06), which has previously been interpreted as confounding (Supplementary Table 2). However, such inflation can occur in large cohorts without confounding (47). Estimates of inflation not due to polygenicity were small in all meta-analyses (4-7%, Supplementary Table 2).

Combined MOOD meta-analysis

We meta-analysed the PGC MDD, PGC BD and UKB MDD cohorts (MOOD, cases = 185,285, controls = 439,741, non-overlapping N = 609,424). 73 loci reached genome-wide significance, of which 55 were also seen in the meta-analysis of PGC MDD and UKB MDD (combined MDD, Table 1, Supplementary Table 3, Supplementary Figures 1-8). 39 of the 44 PGC MDD loci reached genome-wide significance in MOOD. In comparison, only four of the 19 PGC BD loci reached genome-wide significance in MOOD (Supplementary Table 3). MOOD loci overlapped considerably with previous studies of depression and depressive symptoms (51/73) (20, 23, 48–52), bipolar disorder (3/73) (53–56), neuroticism (32/73) (23, 57–59), and schizophrenia (15/73) (32, 60), although participants overlap between MOOD and many of these studies. Locus 52 (chromosome 12) passed genome-wide significance in a previous meta-analysis of broad depression and bipolar disorder, although the two other loci from this study did not replicate (51). Six of the 73 associations are entirely novel ($p > 5x10^{-8}$ in previous studies of all phenotypes; Table 1, Supplementary Table 4).

Down-sampled MOOD (cases = 95,481, controls = 287,932, non-overlapping N = 280,214) showed increased similarity to PGC BD compared to MOOD, but remained more similar to PGC MDD. Nineteen loci reached genome-wide significance in down-sampled MOOD, including nine (20%) from PGC MDD, compared with two (11%) reported in PGC BD (Supplementary Table 3). 17/19 loci were also observed in MOOD. Of the two loci not observed in MOOD, one passed genome-wide significance in PGC BD.

SNP-based heritability and genetic correlations

The estimate of SNP-based heritability for MOOD (8.8%) was closer to PGC MDD (8.8%) than to PGC BD (20%). Significant genetic correlations between MOOD and other traits included psychiatric and behavioural, reproductive, cardiometabolic, and sociodemographic traits (Figure 1, Supplementary Table 5). Genetic correlations with psychiatric and behavioural traits are consistently observed across psychiatric traits (17, 61). The genetic correlation between MOOD and educational attainment was -0.06 (p=0.004), intermediate between the results of combined MDD (r_g = -0.11) and of PGC BD (r_g = 0.19; Supplementary Table 6). Notably, the genetic correlation with intelligence was not significant in any of the three analyses ($p>1.27x10^{-4}$). However, sensitivity analyses (see below), indicated that including 23andMe in PGC MDD obscured a negative genetic correlation with intelligence.

The SNP-based heritability of down-sampled MOOD from LDSC was 11%, closer to PGC MDD than to PGC BD (Supplementary Table 2). Genetic correlations varied (Supplementary Tables 5 and 7) with some more similar to PGC BD (schizophrenia: down-sampled r_g = 0.61, combined MDD r_g = 0.35, PGC BD r_g = 0.7), and others more similar to combined MDD (ADHD: down-sampled r_g = 0.48, combined MDD r_g = 0.45, PGC BD r_g = 0.14). The genetic correlation with intelligence was significant (r_g = -0.13, $p = 5x10^{-7}$), because the excluded 23andMe depression cohort has a positive genetic correlation with intelligence (r_g = 0.06, p = 0.01). The greater genetic correlation of MOOD with combined MDD (r_g = 0.98) compared to PGC BD (r_g = 0.55) persisted when comparing down-sampled MOOD to combined MDD (r_g = 0.85) and PGC BD (r_g = 0.75; Supplementary Table 6).

Relationship between mood disorder subtypes

Analyses were performed using GWAS data from subtypes of bipolar disorder (BD1, BD2, SAB) and major depressive disorder (rMDD, sMDD, subMDD). SNP-based heritability for the subtypes ranged from subMDD and sMDD (8%), through BD2 and rMDD (10% and 12%, respectively) to BD1 and SAB (22% and 29% respectively, Figure 2, Supplementary Table 2).

The major depressive disorder subtypes were strongly and significantly genetically correlated (r_g = 0.9-0.94, $p_{rg = 0} < 8.3x10^{-4}$). These correlations did not differ significantly from 1 (all $p_{rg = 1} > 0.3$), nor from each other (all $p_{\Delta rg = 0} > 0.5$, Figure 2, Supplementary Table 8). BD1 and SAB were strongly correlated (r_g = 0.77, $p_{rg = 0}$ = $6x10^{-13}$, $p_{rg = 1}$ = 0.03), as were BD1 and BD2 (r_g = 0.86, $p_{rg = 0}$ = $3x10^{-16}$, $p_{rg = 1}$ = 0.2). However, BD2 was not significantly correlated with SAB (r_g = 0.22, $p_{rg = 0}$ = 0.02).

In hierarchical clustering, BD2 clustered with the major depressive disorder subtypes rather than the bipolar disorder subtypes. The strength of correlation between BD2 and BD1 did not differ from that between BD2 and rMDD (r_g = 0.68, $p_{rg = 0}$ = $3x10^{-8}$, $p_{rg = 1}$ = 0.01), following multiple testing correction (Δr_g = 0.18, p = 0.02). Overall, these results suggest a spectrum of genetic relationships between major depressive disorder and bipolar disorder, with BD2 bridging the two disorders (Figure 3; Supplementary Figure 9). This spectrum remained when six external phenotypes were added, and was supported by results from principal component analysis (Supplementary Results, Supplementary Figure 10).

Polygenic risk score analyses showed that individuals with high polygenic risk scores for PGC BD were more likely to report rMDD than sMDD, and more likely to report sMDD than subMDD (Supplementary Results).

Tissue and cell-type specificity analyses

The results of gene-wise and gene set analyses are described in the Supplementary Results. The tissue-specificity of associated genes differed minimally between the analyses (Supplementary Table 9). All brain regions were significantly enriched in all analyses, and the pituitary was also enriched in combined MDD and PGC BD ($p < 9.43x10^{-4}$, Bonferroni correction for 53 regions, Supplementary Table 9). Results from down-sampled MOOD and down-sampled MDD were generally consistent with the main analyses, except spinal cord was not enriched in either, nor was the cordate in the down-sampled MDD analysis.

In contrast, cell-type enrichments differed between combined MDD and PGC BD (Figure 4, Supplementary Tables 10 and 11). Genes associated with PGC BD were enriched for expression in pyramidal cells from the CA1 region of the hippocampus and the somatosensory cortex, and in striatal interneurons. None of these enrichments were significant in combined MDD. Genes only associated with combined MDD were significantly enriched for expression in neuroblasts and dopaminergic neurons from adult mice. Further cell-types (dopaminergic neuroblasts; dopaminergic, GABAergic and midbrain nucleus neurons from embryonic mice; interneurons; and medium spiny neurons) were enriched for both combined MDD and PGC BD, but the rank and strength of enrichment differed, most notably for medium spiny neurons. The general pattern of differences persisted when comparing PGC BD with down-sampled MDD, although genes associated with

down-sampled MDD were not enriched for expression in adult dopaminergic neurons, embryonic midbrain nucleus neurons, interneurons, nor medium spiny neurons (Supplementary Figure 11).

Shared and distinct relationships with mood disorders and inferred causality

Bidirectional Mendelian randomisation was used to investigate previously-described relationships between mood disorder phenotypes (combined MDD, PGC BD) and external traits: schizophrenia, educational attainment, intelligence, body mass index (BMI) and coronary artery disease (CAD; Figure 5, Supplementary Table 12).

Positive bidirectional relationships were observed between combined MDD, PGC BD, and schizophrenia. This is consistent with psychiatric disorders causing further psychiatric disorders, or being correlated with other causal risk factors, including (but not limited to) a shared genetic basis.

There was a negative bidirectional relationship between educational years and combined MDD, but a positive bidirectional relationship with PGC BD (albeit with only nominal significance from PGC BD to educational years). In contrast, no significant relationship was observed between mood phenotypes and intelligence. This is consistent with differing causal roles of education (or its correlates) on the mood disorders, with a weaker reciprocal effect of the mood disorders altering the length of education.

A positive association was seen from BMI to combined MDD, but not from combined MDD to BMI. In contrast, only a nominally significant negative relationship

was seen from PGC BD to BMI. A positive association was observed from combined MDD to CAD; no relationship was observed between CAD and PGC BD.

Discussion

We identified 73 genetic loci by meta-analysing cohorts of major depression and bipolar disorder, including 15 loci novel to mood disorders. Our mood disorders meta-analysis results (MOOD) are more like our major depressive disorder analysis (combined MDD) than our bipolar disorder analysis (PGC BD). Partly, this results from the greater power of the major depressive disorder analysis compared to the bipolar disorder analysis. Nevertheless, genetic associations from our sensitivity analysis with equivalently powered cohorts (using down-sampled MDD instead of combined MDD) still showed a greater similarity to those from major depressive disorder rather than bipolar disorder.

This may reflect a complex genetic architecture in bipolar disorder, wherein one set of variants may be associated more with manic symptoms and another set with depressive symptoms. Variants associated more with mania may have higher effect sizes, detectable at current bipolar disorder GWAS sample sizes, and may not be strongly associated with major depressive disorder. This could contribute to the higher heritability of bipolar disorder compared to major depressive disorder, and agrees with reports that most of the genetic variance for mania is not shared with depression (13, 14). Meta-analysis of bipolar disorder and major depressive disorder cohorts would support variants associated more with depression, but not those associated with mania. This is consistent with our findings, and with depressive symptoms being both the unifying feature of the mood disorders and the core feature of major depressive disorder.

We examined the genetic relationship between mood disorder subtypes, including adding relevant external traits for context (Supplementary Results). Bipolar

disorder type 2 showed greater genetic similarity to major depressive disorder compared to type 1, mirroring similar findings from polygenic risk scores analyses (16, 56). Individuals with high polygenic risk scores for PGC BD were more likely to report recurrent than single-episode major depressive disorder. However, the genetic correlation of PGC BD with recurrent major depressive disorder was not significantly greater than that with single-episode major depressive disorder. This might reflect the difference in power between these methods. Genetic correlations between mood disorder subtypes support a genetic mood spectrum, with the schizophrenia-like bipolar disorder type 1 and schizoaffective disorder at one pole, and the depressive disorders at the other, with bipolar disorder type 2 occupying an intermediate position.

Conditional and reversed-effect analyses (Supplementary Results) suggest that few of the loci we identified are disorder-specific. Nonetheless we observed some genetic differences between the mood disorders. The expression specificity of associated genes in mouse brain cell-types differed between bipolar disorder and major depressive disorder. Cell-types more associated with bipolar disorder (pyramidal neurons and striatal interneurons) were also enriched in analyses of schizophrenia (38). Cell-types more associated in major depressive disorder (neuroblasts, adult dopaminergic neurons, embryonic GABAergic neurons) had weaker enrichments in schizophrenia, but were enriched in analyses of neuroticism (57). The higher rank of serotonergic neurons in major depressive disorder compared to bipolar disorder is striking given the use of drugs targeting the serotonergic system in treating depression (63). Nevertheless, cell-type enrichment analyses require cautious interpretation, especially given the use of non-human reference data (38, 64).

We explored potential causal relationships between the mood disorders and other traits using Mendelian randomisation. Interpreting these analyses is challenging, especially for complex traits, when the ascertainment of cases varies, and when few (< 20) variants are used as instruments (as in the PGC BD and down-sampled analyses presented) (41, 67, 68). Mood disorders demonstrate considerable heterogeneity, potentially confounding the results of Mendelian randomisation. That said, our results are consistent with a bidirectional influence of educational attainment on risk for mood disorders (and vice versa), with different directions of effect in the two mood disorders. We found no significant relationship between intelligence and either mood disorder. We also find results consistent with major depressive disorder increasing the risk for coronary artery disease in a relatively well powered analysis. This mirrors epidemiological findings, although the mechanism remains unclear (69).

Despite the presence of depressive episodes, the mood disorders are diagnostically distinct, with differing epidemiology – for example, more women than men suffer from major depressive disorder, whereas diagnoses of bipolar disorder are roughly equal between the sexes (3). Differences in our genetic results between major depressive disorder and bipolar disorder may result from epidemiological heterogeneity, rather than distinct biological mechanisms (70). Deeper phenotyping of GWAS datasets is ongoing, and will enable the effect of such confounding factors to be estimated in future studies (71).

We extend previous findings showing genetic continuity across the mood disorders (15–17, 56). Combined mood disorder analyses may increase variant discovery, as well as the discovery of shared and distinct neurobiological gene sets and cell-types. Our results indicate some genetic differences between major

depressive disorder and bipolar disorder, including opposite bidirectional relationships of each with educational attainment, a possible influence of major depressive disorder on coronary artery disease risk, and differing mouse brain cell-types implicated by the enrichment patterns of associated genes in each disorder. Finally, our data are consistent with a genetic mood disorder spectrum with separate clusters for bipolar disorder type 1 and depressive disorders, linked by bipolar disorder type 2, and with depression as the common symptom. The identification of specific sets of genetic variants differentially associated with depression and with mania remains an aim for future research.

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The Bipolar Disorder and Major Depressive Disorder Working Groups of the Psychiatric Genomics Consortium are collaborative co-authors for this article. The individual authors are (numbers refer to affiliations listed in the Supplement): Enda M. Byrne[4], Andreas J. Forstner[5;6;7;8;9], Peter A. Holmans[10], Christiaan A. de Leeuw[11], Manuel Mattheisen[12;13;14;15;16], Andrew McQuillin[17], Jennifer M. Whitehead Pavlides[18], Tune H. Pers[19;20], Stephan Ripke[21;22;23], Eli A. Stahl[19;24;25], Stacy Steinberg[26], Vassily Trubetskoy[22], Maciej Trzaskowski[4], Yunpeng Wang[27;28], Liam Abbott[21], Abdel Abdellaoui[29], Mark J. Adams[30], Annelie Nordin Adolfsson[31], Esben Agerbo[16;32;33], Huda Akil[34], Diego Albani[35], Ney Alliey-Rodriguez[36], Thomas D. Als[12;13;16], Till F. M. Andlauer[37;38], Adebayo Anjorin[39], Verneri Antilla[23], Sandra Van der Auwera[40], Swapnil Awasthi[22], Silviu-Alin Bacanu[41], Judith A Badner[42], Marie Bækvad-Hansen[16;43], Jack D. Barchas[44], Nicholas Bass[17], Michael Bauer[45], Aartjan T. F. Beekman[46], Richard Belliveau[21], Sarah E. Bergen[3], Tim B. Bigdeli[41;47], Elisabeth B. Binder[37;48], Erlend Bøen[49], Marco Boks[50], James Boocock[51], Monika Budde[52], William Bunney[53], Margit Burmeister[54], Henriette N. Buttenschøn[3;12;55], Jonas Bybjerg-Grauholm[16;43], William Byerley[56], Na Cai[57;58], Miquel Casas[59;60;61;62], Enrique Castelao[63], Felecia Cerrato[21], Pablo Cervantes[64], Kimberly Chambert[21], Alexander W. Charney[25], Danfeng Chen[21], Jane Hvarregaard Christensen[12;13;55], Claire Churchhouse[21;23], David St Clair[65], Toni-Kim Clarke[30], Lucía Colodro-Conde[66], William Coryell[67], Baptiste Couvy-Duchesne[18;68], David W. Craig[69], Gregory E. Crawford[70;71], Cristiana Cruceanu[37;64], Piotr M. Czerski[72], Anders M. Dale[73;74;75;76], Gail Davies[77], Ian J. Deary[77], Franziska Degenhardt[7;8], Jurgen Del-Favero[78], J Raymond DePaulo[79], Eske M. Derks[66], Nese Direk[80;81], Srdjan Djurovic[82;83], Amanda

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Figure Legends

Figure 1: Selected genetic correlations of a) psychiatric traits and b) other traits with the main meta-analysis (MOOD), the separate mood disorder analyses (combined MDD and PGC BD), and the down-sampled analyses (down-sampled MOOD, down-sampled MDD). Full genetic correlation results are provided in Supplementary Table 5.

Figure 2: SNP-based heritability estimates for the subtypes of bipolar disorder and subtypes of major depressive disorder. Points = SNP-based heritability estimates. Lines = 95% confidence intervals. Full SNP-based heritability results are provided in Supplementary Table 2.

Figure 3: Genetic correlations across the mood disorder spectrum. Labelled arrows show genetic correlations significantly different from 0. Solid arrows represent genetic correlations not significantly different from 1 ($p < 0.00333$, Bonferroni correction for 15 tests). Full results are provided in Supplementary Table 8.

Figure 4: Cell-type expression specificity of genes associated with bipolar disorder (PGC BIP, left) and major depressive disorder (combined MDD, right). Black vertical lines = significant enrichment ($p < 2x10^{-3}$, Bonferroni correction for 24 cell-types). See Supplementary Table 10 for full results.

Figure 5: GSMR results from analyses with the main meta-analysis (MOOD), and the major depression and bipolar disorder analyses (combined MDD, PGC BD). External traits are coronary artery disease (CAD), educational attainment (EDU), body mass index (BMI), and schizophrenia (SCZ). Betas are on the scale of the outcome GWAS

(logit for binary traits, phenotype scale for continuous). * p < 0.004 (Bonferroni correction for two-way comparisons with six external traits). For figure data, including the number of non-pleiotropic SNPs included in each instrument, see Supplementary Table 12.

Data availability

GWAS results from analyses including 23andMe are restricted by a data transfer agreement with 23andMe. For these analyses, LD-independent sets of 10,000 SNPs will be made available via the Psychiatric Genetics Consortium (https://www.med.unc.edu/pgc/results-and-downloads). Summary statistics not including 23andMe will be made available via the Psychiatric Genetics Consortium (https://www.med.unc.edu/pgc/results-and-downloads).

Tables

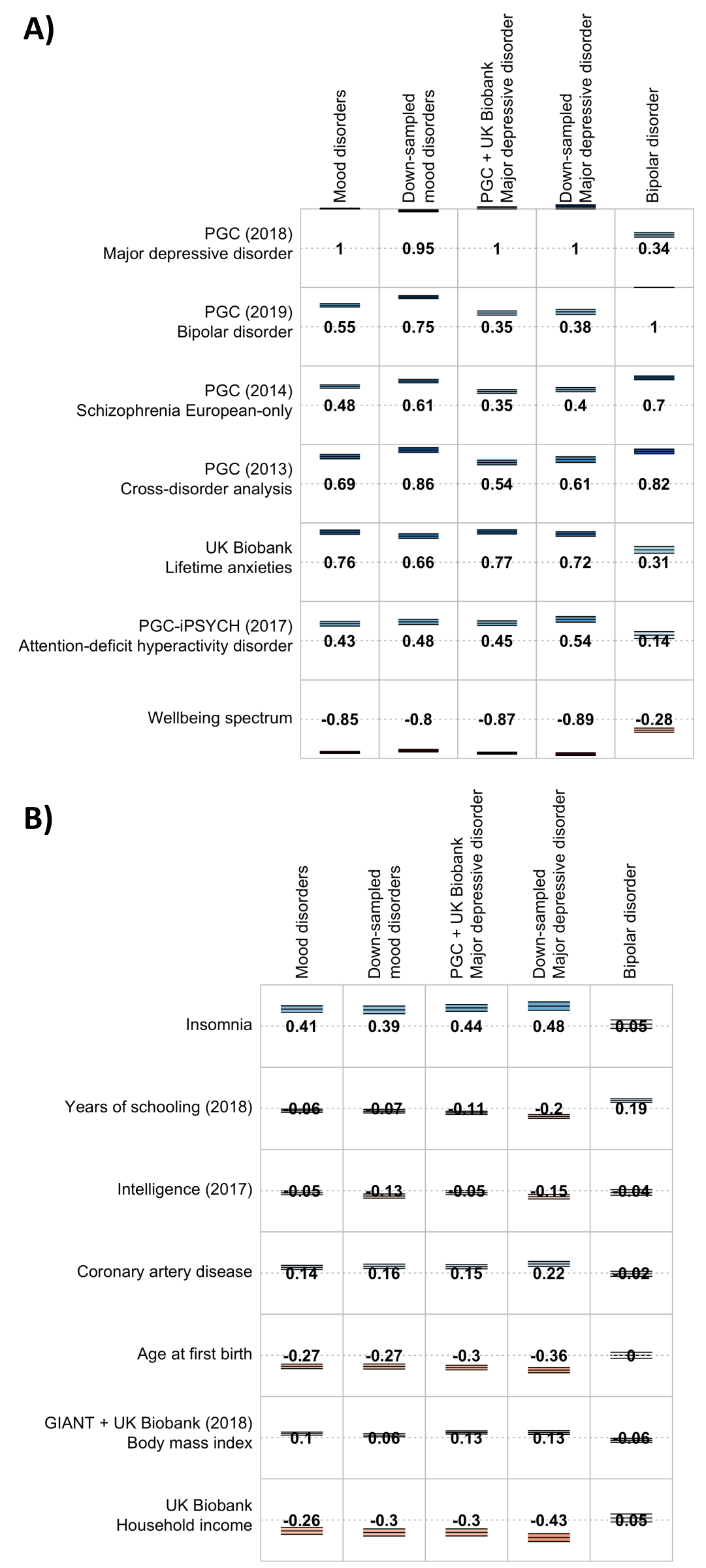
Locus	Chr	BP	Index SNP	A1	A2	OR	SE	p	Previous report
1	1	37192741	rs1002656	T	C	0.97	0.005	$2.71x10^{-11}$	DO, N
2	1	72837239	rs7531118	T	C	0.96	0.004	$1.05x10^{-16}$	D, DO, S, O
4	1	80795989	rs6667297	A	G	0.97	0.005	$5.86x10^{-11}$	D, DO
5	1	90796053	rs4261101	A	G	0.97	0.005	$1.78x10^{-8}$	D
6	1	175913828	rs10913112	T	C	0.97	0.005	$1.46x10^{-10}$	DO, O
7	1	177370033	rs16851203	T	C	0.96	0.007	$2.38x10^{-9}$	DO, S, O
9	2	22582968	rs61533748	T	C	0.97	0.004	$3.84x10^{-11}$	DO, N
10	2	57987593	rs11682175	T	C	0.97	0.004	$2.18x10^{-11}$	D, DO, BS, N, S, O
11	2	157111313	rs1226412	T	C	1.03	0.005	$1.27x10^{-8}$	D, DO, N, O
12	2	198807015	rs1518367	A	T	0.97	0.005	$1.18x10^{-8}$	BS, S, O
13	3	108148557	rs1531188	T	C	0.96	0.006	$1.61x10^{-9}$	O
14	3	158107180	rs7430565	A	G	0.97	0.004	$2.30x10^{-11}$	D, DO, N, O
16	4	42047778	rs34215985	C	G	0.97	0.006	$1.72x10^{-10}$	D, DO, N
17	5	77709430	rs4529173	T	C	0.97	0.005	$4.29x10^{-9}$	O
18	5	88002653	rs447801	T	C	1.03	0.004	$2.29x10^{-10}$	D, DO, N, O
19	5	92995013	rs71639293	A	G	1.03	0.005	$5.85x10^{-9}$	DO, N
20	5	103904226	rs12658032	A	G	1.04	0.005	$2.19x10^{-16}$	D, DO, N, O
21	5	106603482	rs55993664	A	C	0.97	0.006	$1.87x10^{-8}$	NOVEL LOCUS
22	5	124251883	rs116755193	T	C	0.97	0.005	$1.47x10^{-10}$	D, O
23	5	164523472	rs11135349	A	C	0.97	0.004	$2.96x10^{-11}$	D, DO, N
24	5	166992078	rs4869056	A	G	0.97	0.005	$5.21x10^{-9}$	D
25	6	28673998	rs145410455	A	G	0.94	0.007	$7.17x10^{-18}$	D, DO, BO, BS, DS, N, S, O
26	6	101339400	rs7771570	T	C	0.97	0.004	$9.68x10^{-10}$	DO, N, O
27	6	105365891	rs1933802	C	G	0.98	0.004	$1.05x10^{-8}$	DO, S, O
28	7	12267221	rs4721057	A	G	0.97	0.004	$7.31x10^{-11}$	D, DO, N, O

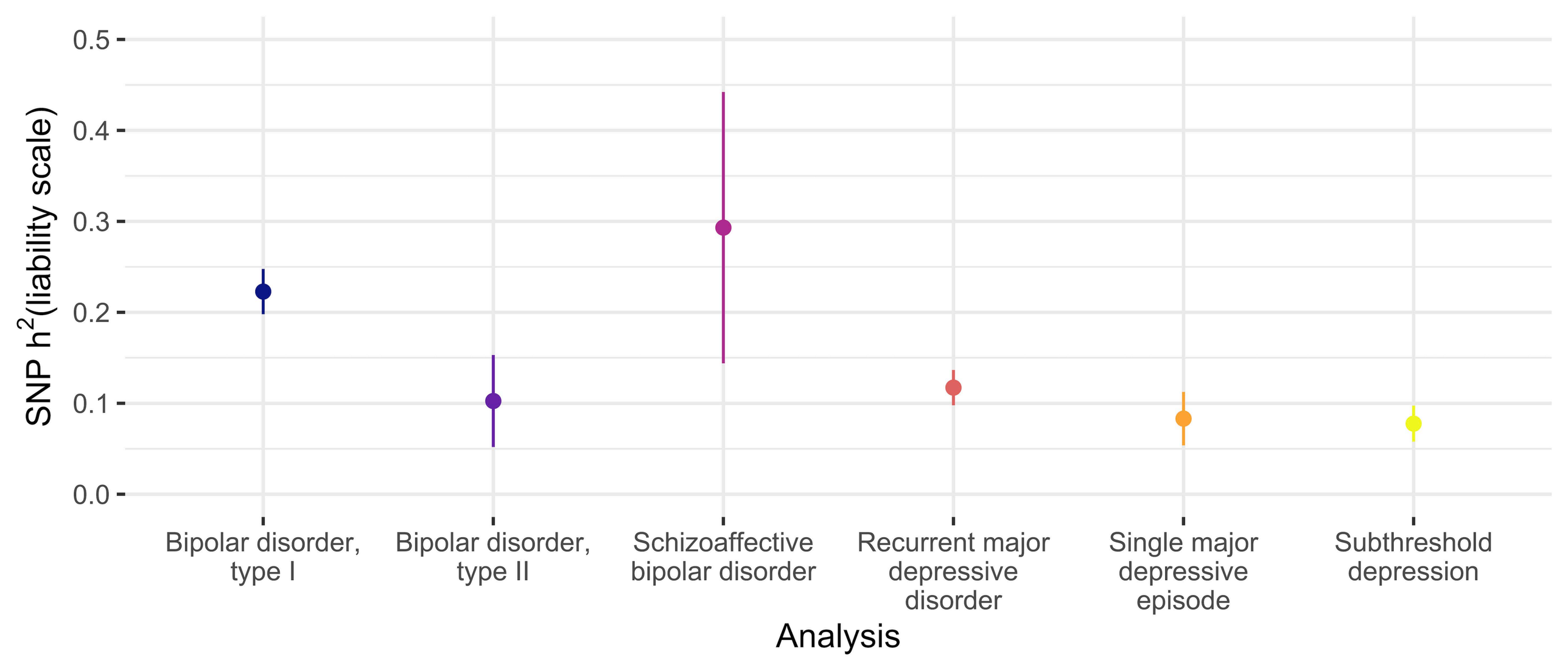
29	7	24826589	rs79879286	C	G	1.04	0.006	$1.97x10^{-11}$	B, BS, DO, S
30	7	82514089	rs34866621	T	C	1.03	0.005	$2.21x10^{-8}$	DO, O
31	7	109099919	rs58104186	A	G	1.03	0.004	$7.12x10^{-9}$	D, DO
34	9	11379630	rs10959753	T	C	0.96	0.005	$1.45x10^{-13}$	D, DO, N, O
35	9	37207269	rs4526442	T	C	0.96	0.006	$7.97x10^{-11}$	DO, O
36	9	81413414	rs11137850	A	G	1.03	0.005	$1.25x10^{-8}$	NOVEL LOCUS
38	9	119733380	rs10759881	A	C	1.03	0.005	$8.56x10^{-9}$	D, DO
40	9	122664468	rs10818400	T	G	0.98	0.004	$1.29x10^{-8}$	N
41	9	126682068	rs7029033	T	C	1.04	0.008	$2.61x10^{-8}$	D, DO, O
42	10	104684544	rs78821730	A	G	0.96	0.007	$2.95x10^{-8}$	N, BS, S, O
43	10	106563924	rs61867293	T	C	0.96	0.005	$5.64x10^{-12}$	D, DO, N, O
44	11	16293680	rs977509	T	C	0.97	0.005	$1.19x10^{-8}$	DO, N, O
45	11	31850105	rs1806153	T	G	1.03	0.005	$2.81x10^{-9}$	D, DO, N, O
46	11	32765866	rs143864773	T	C	1.04	0.008	$1.70x10^{-8}$	NOVEL LOCUS
47	11	61557803	rs102275	T	C	0.97	0.005	$5.04x10^{-11}$	B, DO, BO, O
48	11	63632673	rs10792422	T	G	0.98	0.004	$2.18x10^{-8}$	O
49	11	88743208	rs4753209	A	T	0.97	0.004	$4.15x10^{-9}$	DO, N, O
50	11	99268617	rs1504721	A	C	0.98	0.004	$2.24x10^{-8}$	O
51	11	113392994	rs2514218	T	C	0.97	0.005	$3.22x10^{-10}$	DO, BS, N, S, O
52	12	2344644	rs769087	A	G	1.03	0.005	$3.27x10^{-8}$	B, BD, BO, DS, BS, S, O
53	12	23947737	rs4074723	A	C	0.97	0.004	$3.18x10^{-9}$	D, DO, N, O
54	12	121186246	rs58235352	A	G	0.95	0.009	$1.64x10^{-10}$	DO, O
55	12	121907336	rs7962128	A	G	1.02	0.004	$3.63x10^{-8}$	NOVEL LOCUS
56	13	44327799	rs4143229	A	C	0.95	0.008	$2.73x10^{-10}$	D
57	13	53625781	rs12552	A	G	1.04	0.004	$1.25x10^{-23}$	D, DO, O
58	14	42074726	rs61990288	A	G	0.97	0.004	$2.29x10^{-10}$	D, DO, O
60	14	64686207	rs915057	A	G	0.98	0.004	$1.92x10^{-8}$	D, DO, O
61	14	75130235	rs1045430	T	G	0.97	0.004	$9.83x10^{-11}$	D, DO, N, O
62	14	104017953	rs10149470	A	G	0.97	0.004	$1.15x10^{-10}$	D, DS, DO, BS, S, O

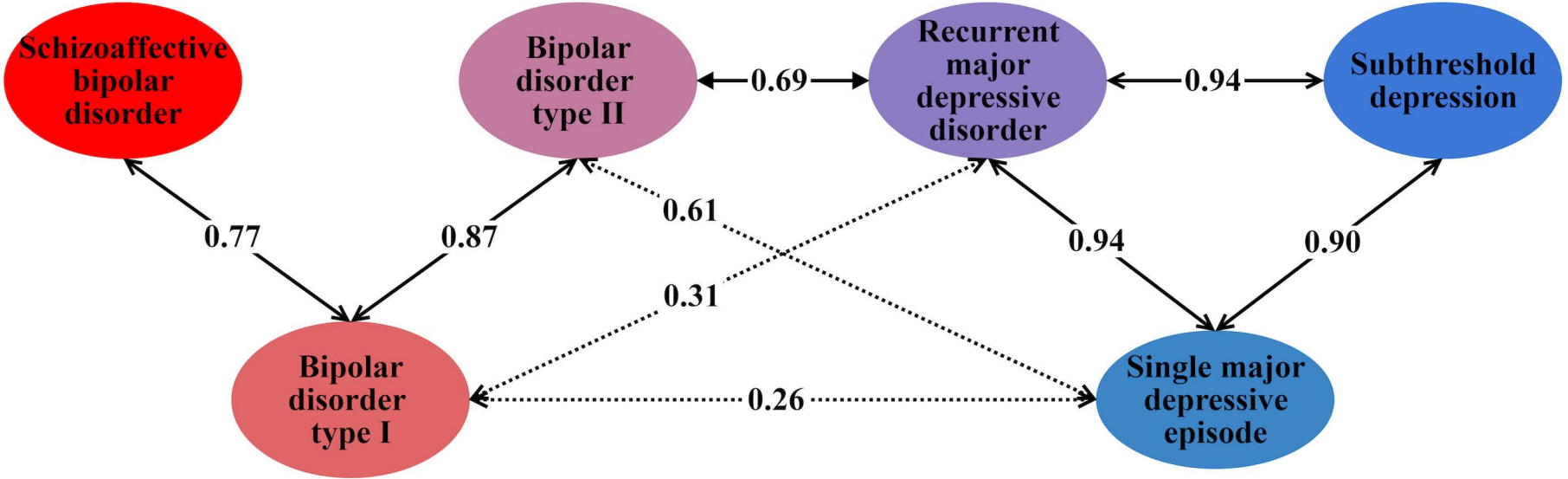
63	15	36355868	rs1828385	A	C	0.97	0.004	$1.15x10^{-8}$	NOVEL LOCUS
64	15	37643831	rs8037355	T	C	0.97	0.004	$4.09x10^{-15}$	D, DO, O
65	16	6310645	rs8063603	A	G	0.97	0.005	$5.36x10^{-11}$	D, DO
66	16	7667332	rs11077206	C	G	1.03	0.004	$5.49x10^{-10}$	D, DO, N, O
67	16	13038723	rs12935276	T	G	0.97	0.005	$4.75x10^{-10}$	D, DO, N, O
68	16	13750257	rs7403810	T	G	1.03	0.005	$7.52x10^{-11}$	DO, BS, S, O
69	16	72214276	rs11643192	A	C	1.03	0.004	$1.46x10^{-11}$	D, O
70	17	27363750	rs75581564	A	G	1.04	0.006	$2.47x10^{-10}$	D, DO, O
71	18	31349072	rs4534926	C	G	1.03	0.004	$9.14x10^{-9}$	DO, N
72	18	36883737	rs62099069	A	T	0.97	0.004	$9.52x10^{-10}$	D, O
73	18	42260348	rs117763335	T	C	0.97	0.005	$1.33x10^{-8}$	O
74	18	50614732	rs11663393	A	G	1.03	0.004	$1.56x10^{-10}$	D, DO, N, O
75	18	52517906	rs1833288	A	G	1.03	0.005	$4.54x10^{-8}$	D, DS, DO, N, S, O
76	18	53101598	rs12958048	A	G	1.04	0.005	$4.86x10^{-14}$	D, DO, BS, N, S, O
77	19	30939989	rs33431	T	C	1.02	0.004	$4.04x10^{-8}$	DO, O
78	20	45841052	rs910187	A	G	0.97	0.005	$3.09x10^{-9}$	DO, O
79	22	41621714	rs2179744	A	G	1.03	0.005	$3.83x10^{-12}$	D, B, DO, BS, N, S, O
80	22	42815358	rs7288411	A	G	1.03	0.005	$3.86x10^{-8}$	NOVEL LOCUS
81	22	50679436	rs113872034	A	G	0.96	0.006	$1.10x10^{-9}$	O

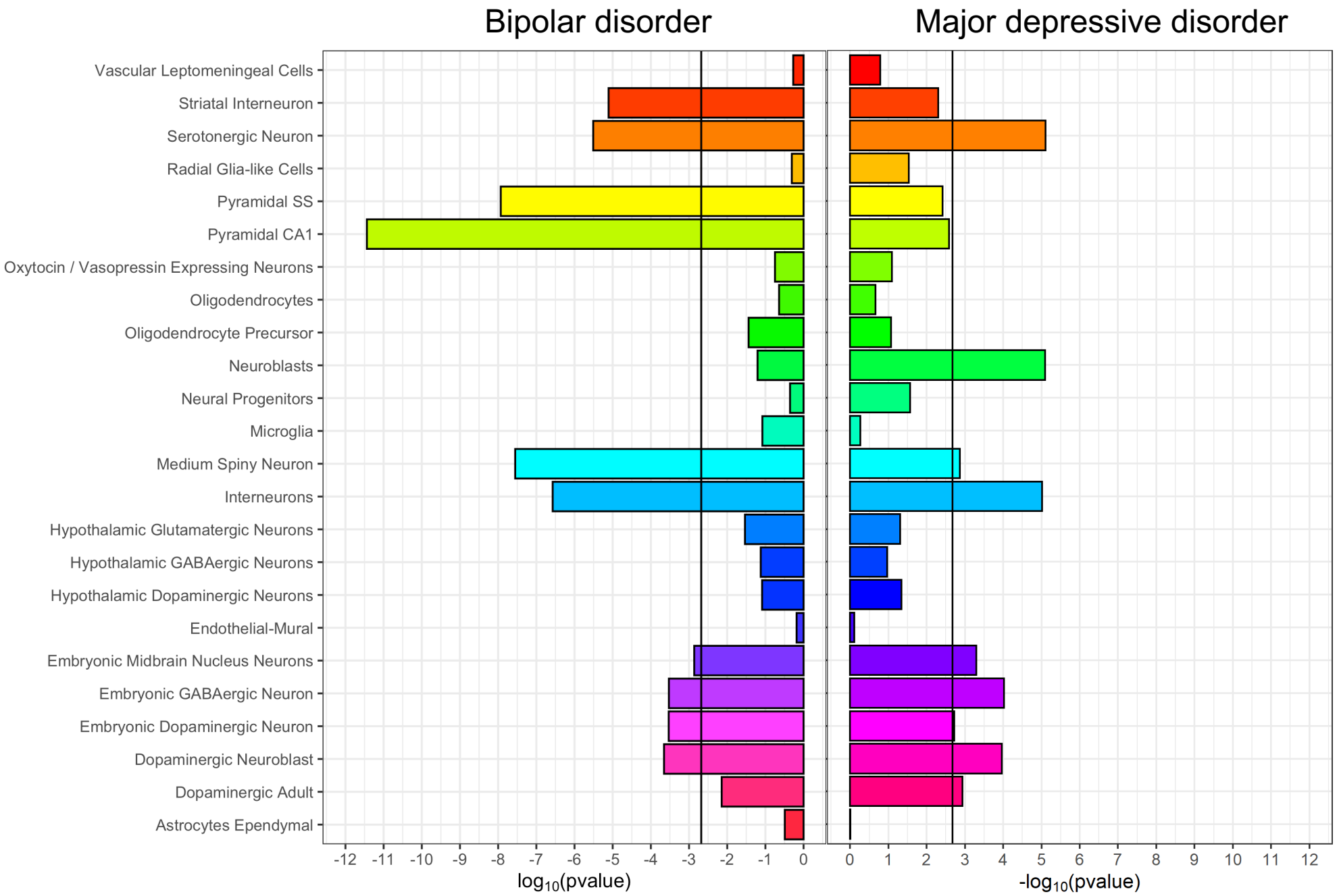
Table 1: Loci genome-wide significant ($p < 5x10^{-8}$) in the MOOD meta-analysis.

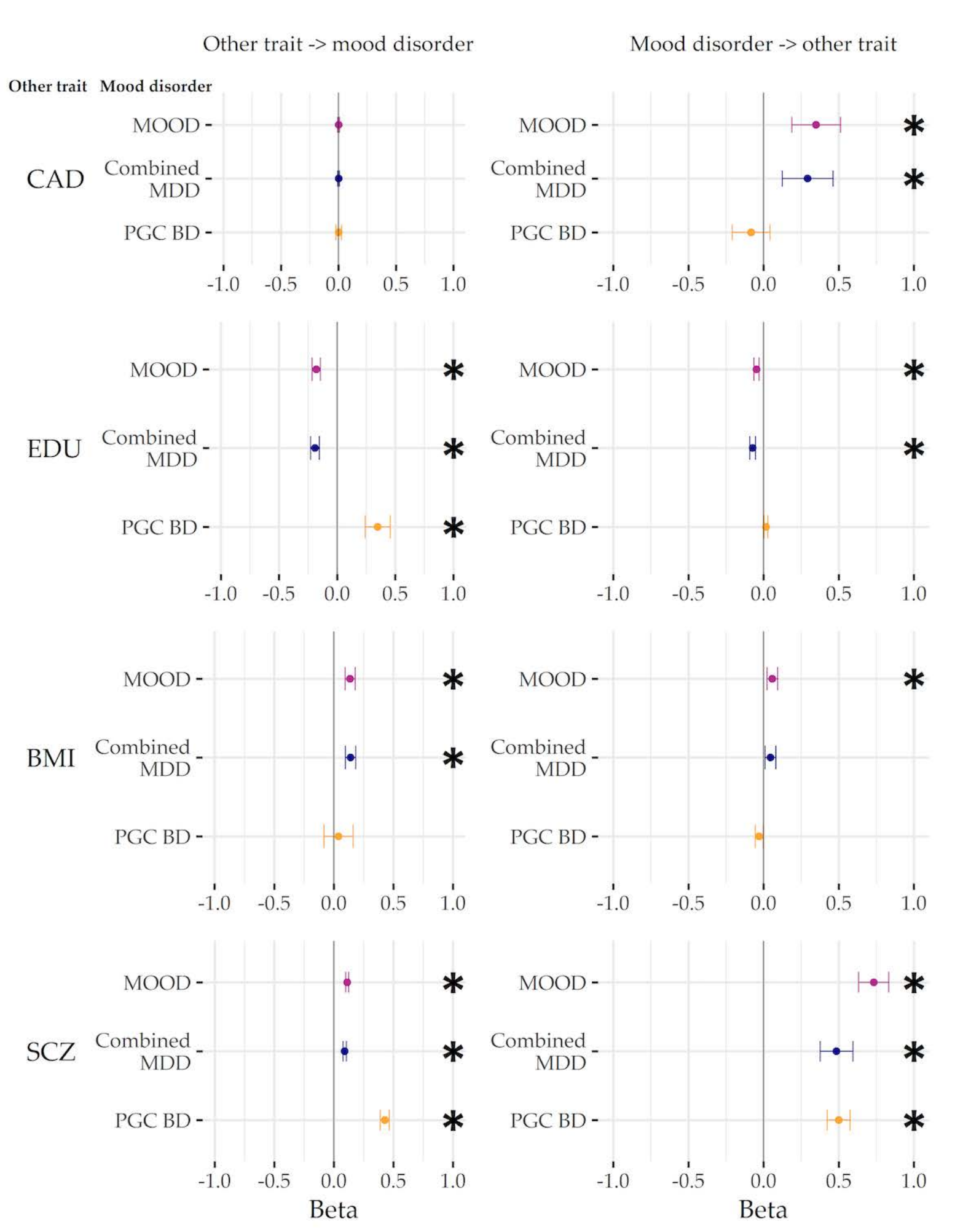
Locus – shared locus number for annotation (Supplementary Table 3), Chr – chromosome, BP – base position, A1 – effect allele, A2 – non-effect allele, Previous report – locus previously implicated in PGC MDD (D), PGC BD (B), previous combined studies of bipolar disorder and major depressive disorder (BD), other studies of major depressive disorder or depressive symptoms (DO), other studies of bipolar disorder (BO), previous combined studies of bipolar disorder and schizophrenia (BS), previous combined studies of major depressive disorder and schizophrenia (DS), neuroticism (N), schizophrenia (S), or other studies (O – see Supplementary Table 4).


A)
Mood disorders
Down-sampled mood disorders
PGC + UK Biobank Major depressive disorder
Down-sampled Major depressive disorder
Bipolar disorder
PGC (2018) Major depressive disorder
1
0.95
1
1
0.34
PGC (2019) Bipolar disorder
0.55
0.75
0.35
0.38
1
PGC (2014) Schizophrenia European-only
0.48
0.61
0.35
0.4
0.7
PGC (2013) Cross-disorder analysis
0.69
0.86
0.54
0.61
0.82
UK Biobank Lifetime anxieties
0.76
0.66
0.77
0.72
0.31
PGC-iPSYCH (2017) Attention-deficit hyperactivity disorder
0.43
0.48
0.45
0.54
0.14
Wellbeing spectrum
-0.85
-0.8
-0.87
-0.89
-0.28
B)
Mood disorders
Down-sampled mood disorders
PGC + UK Biobank Major depressive disorder
Down-sampled Major depressive disorder
Bipolar disorder
Insomnia
0.41
0.39
0.44
0.48
0.05
Years of schooling (2018)
-0.06
-0.07
-0.11
-0.2
0.19
Intelligence (2017)
-0.05
-0.13
-0.05
-0.15
-0.04
Coronary artery disease
0.14
0.16
0.15
0.22
0.02
Age at first birth
-0.27
-0.27
-0.3
-0.36
0
GIANT + UK Biobank (2018) Body mass index
0.1
0.06
0.13
0.13
0.06
UK Biobank Household income
-0.26
-0.3
-0.3
-0.43
0.05


SNP h2(liability scale)
0.5
0.4
0.3
0.2
0.1
0.0
Bipolar disorder, type I
Bipolar disorder, type II
Schizoaffective bipolar disorder
Recurrent major depressive disorder
Single major depressive episode
Subthreshold depression
Analysis


Schizoaffective bipolar disorder
Bipolar disorder type II
Recurrent major depressive disorder
Subthreshold depression
Bipolar disorder type I
Single major depressive episode
0.69
0.94
0.77
0.87
0.61
0.94
0.90
0.31
0.26


Bipolar disorder
Major depressive disorder
Vascular Leptomeningeal Cells
Striatal Interneuron
Serotonergic Neuron
Radial Glia-like Cells
Pyramidal SS
Pyramidal CA1
Oxytocin / Vasopressin Expressing Neurons
Oligodendrocytes
Oligodendrocyte Precursor
Neuroblasts
Neural Progenitors
Microglia
Medium Spiny Neuron
Interneurons
Hypothalamic Glutamatergic Neurons
Hypothalamic GABAergic Neurons
Hypothalamic Dopaminergic Neurons
Endothelial-Mural
Embryonic Midbrain Nucleus Neurons
Embryonic GABAergic Neuron
Embryonic Dopaminergic Neuron
Dopaminergic Neuroblast
Dopaminergic Adult
Astrocytes Ependymal
-12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0
log10(pvalue)
0 1 2 3 4 5 6 7 8 9 10 11 12
-log10(pvalue)


Other trait -> mood disorder
Mood disorder -> other trait
Other trait
Mood disorder
CAD
EDU
BMI
SCZ
MOOD
Combined MDD
PGC BD
-1.0
-0.5
0.0
0.5
1.0
Beta

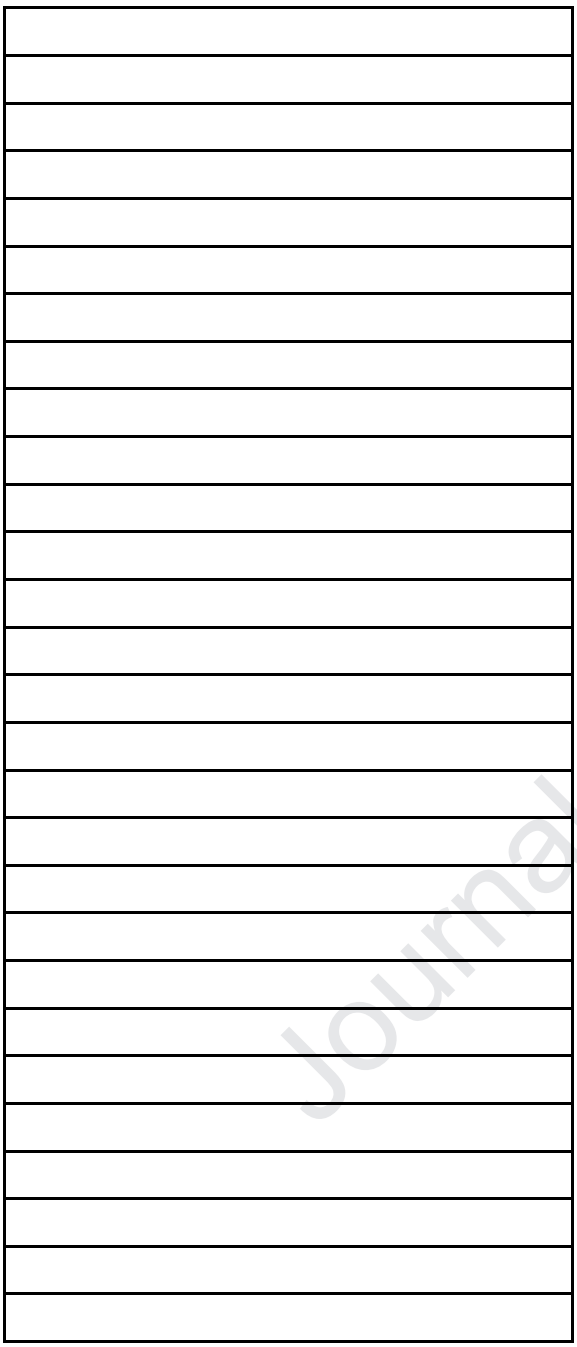
Resource Type	Specific Reagent or Resource
Add additional rows as needed for each resource type	Include species and sex when applicable.
Deposited Data; Public Database	Human DNA samples and data
Deposited Data; Public Database	Human DNA samples and data
Software; Algorithm	miscellaeous scripts for the handling of GWAS data
Software; Algorithm	RICOPILI; the primary software pipeline used by the
Software; Algorithm	METACARPA; the primary metaanalyis sofware used
Software; Algorithm	LD score software

KEY RESOURCES TABLE

Source or Reference	Identifiers
Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.
https://www.ukbiobank.ac.uk/register-apply/	
https://www.med.unc.edu/pgc/shared-	
https://github.com/JoniColeman	
https://github.com/Ripkelab/ricopili	
https://github.com/hmgu-itg/metacarpa	
https://github.com/bulik/ldsc	

S TABLE

Additional Information
Include any additional information or notes if necessary.



Key Resource Table

The journals of the Society of Biological Psychiatry support efforts in the biomedical research community to improve transparency and reproducibility in published research. Thus, *Biological Psychiatry* and *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* are pleased to participate in the initiative to include a Key Resources Table in published articles.

Authors are asked to submit this table at first revision, which may be uploaded using the "Key Resources Table" item type. This table will then be published as supplemental information.

The Key Resources Table is designed to promote reproducibility and thus, should include the resources and relevant details necessary to reproduce the study's results. It does not need to be exhaustive. Extensive lists (e.g., oligonucleotides, etc.) may be supplied in a supplementary table and the table referenced here. We strongly encourage the use of RRID identifiers that provide persistent, unique identifiers to key study resources. Search

Resource categories

Note: For all categories, indicate sex and species when applicable

- **Antibody** - include host organism common name and clonality (e.g., “mouse mon
- **Biological sample** - any other biological entity, ranging from isolated tissue to def
- **Cell line** - if a primary cell line, describe in Additional Information
- **Chemical compound, drug -** commercially available reagents
- **Commercial assay/kit -** detection assays; labeling and sample preparation kits
- **Deposited data or public database** - include both raw data from this paper deposited into a repository and public repository databases (postmortem tissue; genetic consortia data; etc.)
- **Genetic reagent** - applies to mutations and variants in whole organism, including
- **Peptide, recombinant protein -** commercially available reagents
- **Recombinant DNA reagent -** traditional cultured clones, plasmids, cDNAs, etc., i
- **Sequence-based reagent -** oligonucleotides, primers, etc.; indicate sequence
- **Software, algorithm -** include version number and URL for download
- **Organism/Strain** - applies to whole organism in cell line; indicate species of cell line or construct comp

oclonal")

fined population

transgenically introduced constructs

ncluding recombinant DNA libraries

ponent

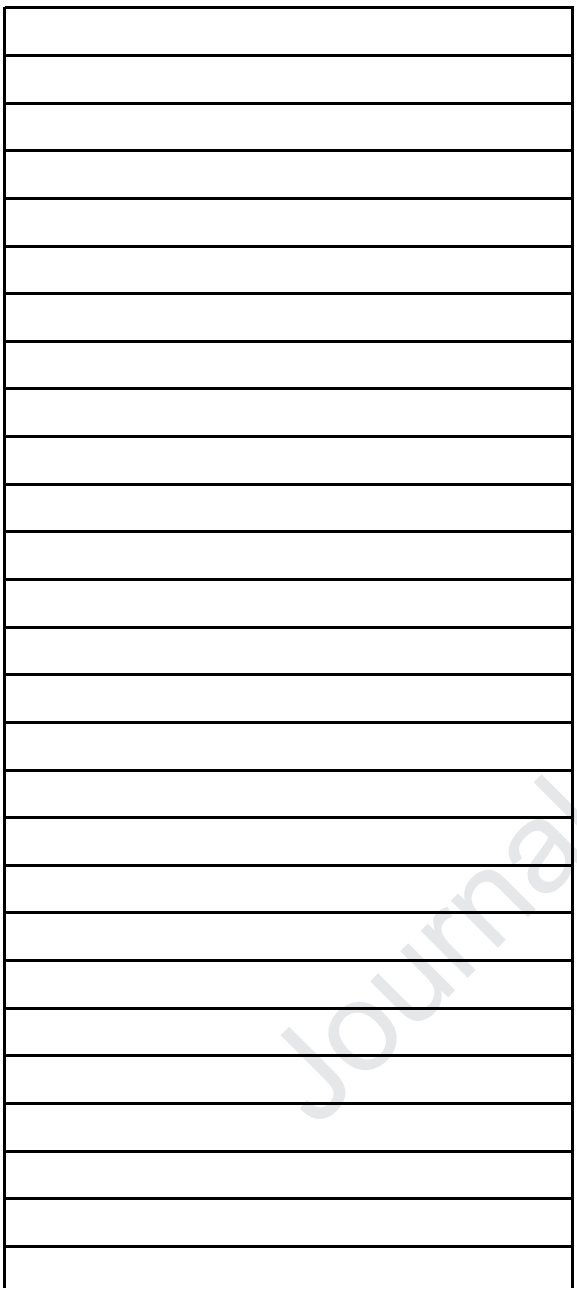
Resource Type	Specific Reagent or Resource
Add additional rows as needed for each resource type	Include species and sex when applicable.
Antibody	rabbit anti-E2F2
Antibody	total actin
Antibody	E2F3
Bacterial or Viral Strain	AAV-hSyn-DIO-hM3D(Gq)-mCherry
Bacterial or Viral Strain	HSV-*wtSmurf1*
Biological Sample	postmortem brain tissue
Cell Line	control 03231 iPSC line
Chemical Compound, Drug	Terazosin
Commercial Assay Or Kit	Bio-Rad DC Protein Assay
Commercial Assay Or Kit	TruSeq Stranded mRNA Sample Prep Kit v2
Deposited Data; Public Database	GSE13564, GSE80655, and GSE25219
Organism/Strain	Mouse: C57BL/6J, male
Sequence-Based Reagent	Primers for RT-qPCR, see Table S1
Software; Algorithm	HTSeq Python package
Software; Algorithm	MATLAB v9.1

EXAMPLE KEY RESOURCES TABLE

Source or Reference	Identifiers
Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.
Abcam	Abcam Cat# ab50917, RRID:AB_869541
MP Biomedicals	Cat#8691002, RRID:AB_2335304
Santa Cruz	C-18, Cat#SC-878, RRID:AB_2096807
University of North Carolina Vector Core	N/A
PMID: 10458166	Addgene plasmid # 11752
Harvard Brain Tissue Resource Center	RRID:SCR_003316
National Institute of Neurological Disorders and Stroke repository	NINDS # ND03231; RRID:SCR_004520
Sigma-Aldrich	N/A
Bio-Rad Laboratories, Inc.	# 5000111
Illumina, Inc.	Cat. No. RS-122-2101
NCBI GEO DataSets	https://www.ncbi.nlm.nih.gov/gds
The Jackson Laboratory	RRID:IMSR_JAX:000664
This paper	N/A
https://doi.org/10.1093/bioinformatics/btp120; https://doi.org/10.1093/bioinformatics/btu638	RRID:SCR_005514
Mathworks	RRID:SCR_001622

)URCES TABLE

Additional Information
Include any additional information or notes if necessary.



The Genetics of the Mood Disorder Spectrum: Genome-wide Association Analyses of Over 185,000 Cases and 439,000 Controls

Supplement 1

Contents

Affiliations of Individual Authors from the Bipolar Disorder and Major Depressive Disorder Working Groups of the Psychiatric Genomics Consortium

1 Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
2 NIHR Maudsley Biomedical Research Centre, King's College London, London, United Kingdom
3 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
4 Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia
5 Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, Switzerland
6 Department of Psychiatry (UPK), University of Basel, Basel, Switzerland
7 Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany
8 Department of Genomics, Life&Brain Center, University of Bonn, Bonn, Germany
9 Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland
10 Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, United Kingdom
11 Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, Netherlands
12 iSEQ, Center for Integrative Sequencing, Aarhus University, Aarhus, Denmark
13 Department of Biomedicine - Human Genetics, Aarhus University, Aarhus, Denmark
14 Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden
15 Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg, Würzburg, Germany
16 iPSYCH, The Lundbeck Foundation Initiative for Psychiatric Research, Copenhagen, Denmark
17 Division of Psychiatry, University College London, London, United Kingdom
18 Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia
19 Medical and Population Genetics, Broad Institute, Cambridge, MA, USA
20 Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children’s Hospital, Boston, MA, USA
21 Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, USA
22 Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, Germany
23 Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA
24 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

25 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA
26 deCODE Genetics / Amgen, Reykjavik, Iceland
27 Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Copenhagen, Denmark
28 Institute of Clinical Medicine, University of Oslo, Oslo, Norway
29 Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, Netherlands
30 Division of Psychiatry, University of Edinburgh, Edinburgh, United Kingdom
31 Department of Clinical Sciences, Psychiatry, Umeå University Medical Faculty, Umeå, Sweden
32 National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark
33 Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark
34 Molecular & Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI, USA
35 Neuroscience, Istituto Di Ricerche Farmacologiche Mario Negri, Milano, Italy
36 Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA
37 Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany
38 Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
39 Psychiatry, Berkshire Healthcare NHS Foundation Trust, Bracknell, United Kingdom
40 Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany
41 Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA
42 Psychiatry, Rush University Medical Center, Chicago, IL, USA
43 Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark
44 Department of Psychiatry, Weill Cornell Medical College, New York, NY, USA
45 Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
46 Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, Netherlands
47 Virginia Institute for Psychiatric and Behavior Genetics, Richmond, VA, USA
48 Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA
49 Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway
50 Psychiatry, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, Netherlands
51 Human Genetics, University of California Los Angeles, Los Angeles, CA, USA
52 Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany
53 Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, USA

54 Molecular & Behavioral Neuroscience Institute and Department of Computational Medicine & Bioinformatics, University of Michigan, Ann Arbor, MI, USA
55 iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark
56 Psychiatry, University of California San Francisco, San Francisco, CA, USA
57 Human Genetics, Wellcome Trust Sanger Institute, Cambridge, United Kingdom
58 Statistical genomics and systems genetics, European Bioinformatics Institute (EMBL-EBI), Cambridge, United Kingdom
59 Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health (CIBERSAM), Madrid, Spain
60 Department of Psychiatry, Hospital Universitari Vall d´Hebron, Barcelona, Spain
61 Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
62 Psychiatric Genetics Unit, Group of Psychiatry Mental Health and Addictions, Vall d´Hebron Research Institut (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain
63 Department of Psychiatry, University Hospital of Lausanne, Prilly, Vaud, Switzerland
64 Department of Psychiatry, Mood Disorders Program, McGill University Health Center, Montreal, QC, Canada
65 Institute for Medical Sciences, University of Aberdeen, Aberdeen, United Kingdom
66 Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia
67 University of Iowa Hospitals and Clinics, Iowa City, IA, USA
68 Centre for Advanced Imaging, The University of Queensland, Brisbane, QLD, Australia
69 Translational Genomics, USC, Phoenix, AZ, USA
70 Center for Genomic and Computational Biology, Duke University, Durham, NC, USA
71 Department of Pediatrics, Division of Medical Genetics, Duke University, Durham, NC, USA
72 Department of Psychiatry, Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland
73 Department of Neurosciences, University of California San Diego, La Jolla, CA, USA
74 Department of Radiology, University of California San Diego, La Jolla, CA, USA
75 Department of Psychiatry, University of California San Diego, La Jolla, CA, USA
76 Department of Cognitive Science, University of California San Diego, La Jolla, CA, USA
77 Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, United Kingdom
78 Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium

79 Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA
80 Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, Netherlands
81 Psychiatry, Dokuz Eylul University School Of Medicine, Izmir, Turkey
82 Department of Medical Genetics, Oslo University Hospital Ullevål, Oslo, Norway
83 NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, Bergen, Norway
84 Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
85 Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, USA
86 Department of Neurology, Oslo University Hospital, Oslo, Norway
87 NORMENT, KG Jebsen Centre for Psychosis Research, Oslo University Hospital, Oslo, Norway
88 Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
89 Department of Mathematics, Massachusetts Institute of Technology, Cambridge, MA, USA
90 Center for Statistical Genetics and Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA
91 Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
92 Department of Medical & Molecular Genetics, Indiana University, Indianapolis, IN, USA
93 Center for Neurobehavioral Genetics, University of California Los Angeles, Los Angeles, CA, USA
94 Department of Molecular Medicine and Surgery, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden
95 Department of Clinical Neuroscience, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden
96 Child and Adolescent Psychiatry Research Center, Stockholm, Sweden
97 Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany
98 Department of Psychiatry, Dalhousie University, Halifax, NS, Canada
99 Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA
100 Department of Psychological Medicine, University of Worcester, Worcester, United Kingdom
101 School of Biomedical and Healthcare Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, United Kingdom
102 School of Psychiatry, University of New South Wales, Sydney, NSW, Australia
103 Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark
104 Biostatistics, University of Minnesota System, Minneapolis, MN, USA
105 Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom
106 Danish Headache Centre, Department of Neurology, Rigshospitalet, Glostrup, Denmark

107 Institute of Biological Psychiatry, MHC Sct. Hans, Mental Health Services Copenhagen, Roskilde, Denmark
108 Department of Psychology, Eberhard Karls Universität Tübingen, Tubingen, Germany
109 Department of Psychiatry, Leiden University Medical Center, Leiden, Netherlands
110 Brain and Mind Centre, University of Sydney, Sydney, NSW, Australia
111 Department of Psychiatry and Behavioral Sciences, Howard University Hospital, Washington, DC, USA
112 Center for Multimodal Imaging and Genetics, University of California San Diego, La Jolla, CA, USA
113 Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany
114 Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland
115 Max Planck Institute of Psychiatry, Munich, Germany
116 Psychiatrie Translationnelle, Inserm U955, Créteil, France
117 Faculté de Médecine, Université Paris Est, Créteil, France
118 Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA
119 Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada
120 Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, ON, Canada
121 Department of Psychiatry, University of Toronto, Toronto, ON, Canada
122 Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada
123 Bioinformatics, University of British Columbia, Vancouver, BC, Canada
124 Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany
125 Cell Biology, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA
126 Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA
127 Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
128 Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA
129 Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
130 Informatics Program, Boston Children's Hospital, Boston, MA, USA
131 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom
132 Department of Endocrinology at Herlev University Hospital, University of Copenhagen, Copenhagen, Denmark
133 Psychiatry, Altrecht, Utrecht, Netherlands
134 Institute of Social and Preventive Medicine (IUMSP), University Hospital of Lausanne, Lausanne, VD, Switzerland
135 Swiss Institute of Bioinformatics, Lausanne, VD, Switzerland
136 Psychiatry, North East London NHS Foundation Trust, Ilford, United Kingdom

137 Clinic for Psychiatry and Psychotherapy, University Hospital Cologne, Cologne, Germany
138 Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, USA
139 HudsonAlpha Institute for Biotechnology, Huntsville, AL, USA
140 Department of Human Genetics, University of Michigan, Ann Arbor, MI, USA
141 Psychiatry, University of Illinois at Chicago College of Medicine, Chicago, IL, USA
142 Mental Health, NHS 24, Glasgow, United Kingdom
143 Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom
144 Psychiatry, Brigham and Women's Hospital, Boston, MA, USA
145 Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany
146 Statistics, University of Oxford, Oxford, United Kingdom
147 Department of Genetics, Harvard Medical School, Boston, MA, USA
148 Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA
149 Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA
150 Genetic Cancer Susceptibility Group, International Agency for Research on Cancer, Lyon, France
151 School of Psychology and Counseling, Queensland University of Technology, Brisbane, QLD, Australia
152 Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, South Brisbane, QLD, Australia
153 Child Health Research Centre, University of Queensland, Brisbane, QLD, Australia
154 Estonian Genome Center, University of Tartu, Tartu, Estonia
155 Discipline of Biochemistry, Neuroimaging and Cognitive Genomics (NICOG) Centre, National University of Ireland, Galway, Galway, Ireland
156 Neuropsychiatric Genetics Research Group, Dept of Psychiatry and Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland
157 Medical Genetics, University of British Columbia, Vancouver, BC, Canada
158 Statistics, University of British Columbia, Vancouver, BC, Canada
159 Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany
160 DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany
161 Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany
162 Research/Psychiatry, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA
163 Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, Australia
164 Department of Clinical Psychiatry, Psychiatry Clinic, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
165 Department of Neurobiology, Care sciences, and Society, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden

166 Humus, Reykjavik, Iceland
167 Mental Health Department, University Regional Hospital, Biomedicine Institute (IBIMA), Málaga, Spain
168 Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA
169 Solid Biosciences, Boston, MA, USA
170 Outpatient Clinic for Bipolar Disorder, Altrecht, Utrecht, Netherlands
171 Department of Psychiatry, Washington University in Saint Louis, Saint Louis, MO, USA
172 Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, Spain
173 Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA
174 Medicine, Psychiatry, Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA
175 Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA
176 Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA
177 Rush University Medical Center, Chicago, IL, USA
178 Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
179 Scripps Translational Science Institute, La Jolla, CA, USA
180 Department of Psychiatry and Psychotherapy, Medical Center of the University of Munich, Campus Innenstadt, Munich, Germany
181 Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA
182 Behavioral Health Services, Kaiser Permanente Washington, Seattle, WA, USA
183 Faculty of Medicine, Department of Psychiatry, School of Health Sciences, University of Iceland, Reykjavik, Iceland
184 Div Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
185 NORMENT, University of Oslo, Oslo, Norway
186 Institute of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom
187 Psychiatry and the Behavioral Sciences, University of Southern California, Los Angeles, CA, USA
188 Mood Disorders, PsyQ, Rotterdam, Netherlands
189 Research Division, Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany
190 Centre for Addiction and Mental Health, Toronto, ON, Canada
191 Neurogenomics, TGen, Los Angeles, AZ, USA
192 College of Biomedical and Life Sciences, Cardiff University, Cardiff, United Kingdom
193 Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, Germany
194 Institute for Community Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany
195 Medical Genetics Section, CGEM, IGMM, University of Edinburgh, Edinburgh, United Kingdom

196 Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom
197 Internal Medicine, Erasmus MC, Rotterdam, Zuid-Holland, Netherlands
198 Roche Pharmaceutical Research and Early Development, Neuroscience, Ophthalmology and Rare Diseases Discovery & Translational Medicine Area, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, Switzerland
199 Psychiatry, Psychiatrisches Zentrum Nordbaden, Wiesloch, Germany
200 Neuroscience Research Australia, Sydney, NSW, Australia
201 Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, USA
202 Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, Canada
203 Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
204 Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
205 Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA
206 Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
207 NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Institute of Clinical Medicine and Diakonhjemmet Hospital, University of Oslo, Oslo, Norway
208 National Institute of Mental Health, Klecany, Czechia
209 Department of Psychiatry, University of Münster, Münster, Germany
210 Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia
211 Department of Psychiatry and Addiction Medicine, Assistance Publique - Hôpitaux de Paris, Paris, France
212 Paris Bipolar and TRD Expert Centres, FondaMental Foundation, Paris, France
213 UMR-S1144 Team 1: Biomarkers of relapse and therapeutic response in addiction and mood disorders, INSERM, Paris, France
214 Psychiatry, Université Paris Diderot, Paris, France
215 Psychiatry, University of Pennsylvania, Philadelphia, PA, USA
216 Centre for Integrative Biology, Università degli Studi di Trento, Trento, Trentino-Alto Adige, Italy
217 Department of Psychiatry and Psychotherapy, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
218 Division of Endocrinology, Children's Hospital Boston, Boston, MA, USA
219 Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, London, United Kingdom
220 Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, USA
221 School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia
222 Department of Human Genetics, University of Chicago, Chicago, IL, USA
223 Amsterdam Public Health Institute, Vrije Universiteit Medical Center, Amsterdam, Netherlands
224 Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania
225 Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, USA

226 Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, United Kingdom
227 Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden
228 INSERM, Paris, France
229 Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, USA
230 Cancer Epidemiology and Prevention, M. Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland
231 School of Psychology, The University of Queensland, Brisbane, QLD, Australia
232 Research Institute, Lindner Center of HOPE, Mason, OH, USA
233 Human Genetics Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA
234 Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
235 Division of Mental Health and Addiction, University of Oslo, Institute of Clinical Medicine, Oslo, Norway
236 Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia
237 Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology - NTNU, Trondheim, Norway
238 Psychiatry, St Olavs University Hospital, Trondheim, Norway
239 Psychosis Research Unit, Aarhus University Hospital, Risskov, Denmark
240 Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
241 University of Liverpool, Liverpool, United Kingdom
242 Psychiatry and Human Genetics, University of Pittsburgh, Pittsburgh, PA, USA
243 Mental Health Services in the Capital Region of Denmark, Mental Health Center Copenhagen, University of Copenhagen, Copenhagen, Denmark
244 Division of Psychiatry, Haukeland Universitetssjukehus, Bergen, Norway
245 Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway
246 Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, USA
247 College of Medicine Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, USA
248 Psychiatry, Harvard Medical School, Boston, MA, USA
249 Division of Clinical Research, Massachusetts General Hospital, Boston, MA, USA
250 Department of Clinical Genetics, Amsterdam Neuroscience, Vrije Universiteit Medical Center, Amsterdam, Netherlands
251 Department of Neurology and Neurosurgery, McGill University, Faculty of Medicine, Montreal, QC, Canada
252 Montreal Neurological Institute and Hospital, Montreal, QC, Canada
253 Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy
254 Faculty of Medicine, University of Iceland, Reykjavik, Iceland
255 Department of Psychiatry, Hospital Namsos, Namsos, Norway
256 Department of Neuroscience, Norges Teknisk Naturvitenskapelige Universitet Fakultet for naturvitenskap og teknologi, Trondheim, Norway

257 Child and Adolescent Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, Netherlands
258 Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, Netherlands
259 Department of Psychiatry, McGill University, Montreal, QC, Canada
260 Dept of Psychiatry, Sankt Olavs Hospital Universitetssykehuset i Trondheim, Trondheim, Norway
261 Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain
262 Division of Epidemiology, New York State Psychiatric Institute, New York, NY, USA
263 Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
264 Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, USA
265 Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
266 Department of Medical & Molecular Genetics, King's College London, London, United Kingdom
267 Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA
268 Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

† Deceased

Supplementary Note

Relationship between these analyses and recent depression analyses from the UK Biobank

The PGC GWAS of major depression included data from the first 150,000 UK Biobank individuals whose genotypic data was released (1). Depression GWAS in the full UK Biobank cohort have since been published, including both broad and narrow definitions (2). The broad depression GWAS was meta-analysed with data from the PGC publication (3). We conducted a further meta-analysis of PGC and UK Biobank major depressive disorder data, using data from the online mental health phenotyping, including questions derived from the Composite International Diagnostic Interview – Short Form (4, 5). This phenotype has good concordance with direct clinical assessments of major depressive disorder and can be considered a major depressive disorder phenotype, compared to the less specific broad depression phenotype used by Howard et al (3, 6, 7). The effects on GWAS of using different depression phenotypes from the UK Biobank is investigated in depth elsewhere (8). We compare our results with those from Howard et al where appropriate (3).

Supplementary Methods

Participants

The PGC MDD cohort consists of an anchor set of 29 cohorts (16,823 cases and 25,632 controls), with case individuals meeting international consensus criteria (DSM-IV, ICD-9, or ICD-10) for a lifetime diagnosis of major depressive disorder using structured diagnostic instruments. Six additional cohorts (118,635 cases and

319,269 controls) were drawn from broader population-based studies, and cases met criteria through self-report or responses to structured diagnostic instruments. Controls in most samples were screened for the absence of lifetime psychiatric disorders. All participants were of Western European ancestries. Individuals from the anchor cohort meet criteria for major depressive disorder. However, the additional cohorts include individuals who self-reported their diagnosis, and might not have met criteria for major depressive disorder in a clinical setting. In particular, these additional cohorts included data from 23andMe, where case participants were defined by a positive endorsement of a single question "Have you ever been diagnosed with clinical depression?" (or a different version of this question with similar phrasing) (9). These participants self-reported a professional diagnosis of depression, rather than being ascertained via a direct examination of all criteria for major depressive disorder. As such, it was considered more appropriate to refer to these individuals as having major depression, rather than major depressive disorder (1).

The PGC BD cohort consists of 32 studies (20,352 cases and 31,358 controls) of Western European ancestries. Case individuals were required to meet international consensus criteria for a lifetime diagnosis of bipolar disorder using structured diagnostic instruments. Controls in most samples were screened for the absence of lifetime psychiatric disorders.

In the UKB MDD cohort, participants were defined as cases if they met criteria based on questions derived from the Composite International Diagnostic Interview (CIDI). Participants were excluded if they self-reported previous diagnoses of schizophrenia (or other psychoses) or bipolar disorder. Controls were excluded if they self-reported any mental illness, reported taking any drug with an

antidepressant indication, had previously been hospitalised with a mood disorder or met previously-defined criteria for a mood disorder (Supplementary Table 1) (10).

Quality control and imputation of UK Biobank data was performed centrally and is described elsewhere (11). Additional quality control was performed and is described in full elsewhere (5). In brief, participants were limited to unrelated individuals (KING correlation coefficient < 0.044 with all pairs, equivalent to removing all third degree-or-closer relatives) from probable Western European ancestries with good quality genotype data (passed Affymetrix and central UK Biobank quality assurance processes, genotyping call rate > 98%, concordant genotypic and phenotypic sex). Genome-wide association analyses (GWAS) of each UKB cohort were performed in BGenie v1.2, limited to variants with minor allele frequency (MAF) > 0.01 that were genotyped or imputed with confidence (IMPUTE2 INFO score > 0.4) (11, 12). All GWAS included six genotypic principal components (derived from the Western European ancestries subset of the UKBiobank using flashpca2) (13) and factors of genotyping batch and assessment centre as covariates to control for batch effects and population stratification. BGenie performs linear regressions on phenotypes residualised for covariates - as such, the resulting beta effect sizes (for all UKB analyses) were converted to odds ratios for meta-analysis using LMOR (14). Standard errors for the odds ratios were calculated by transforming the BGenie p-value to a Z score and dividing log(odds ratio) by Z (15).

Use of MAF > 0.05 as a cutoff

All summary statistics were limited to variants with MAF > 0.05. This was chosen because previous analyses of the BD2 subtype suggested that including lower MAF variants may bias SNP-based heritability estimates (16). Specifically, the

BD2 subtype comprises multiple small cohorts, some with unbalanced case/control numbers. Consequently, potentially spurious effects in a single study can drive results for low-frequency variants. We therefore chose to remove lower frequency variants from all analyses in this paper.

Population prevalences

SNP-based heritability estimates were transformed to the liability scale assuming that the combined population prevalence between major depressive disorder and bipolar disorder is the sum of the disorder prevalences. Specifically, we assumed a population prevalence of 15% for combined MDD, 1% for PGC BD, and thus 16% for MOOD. Further estimates were made for the lower bounds of prevalence and upper bounds of prevalence for comparison. Namely, we set lower bounds of population prevalence at 10% for combined MDD, 0.5% for PGC BD and 10.5% for MOOD, and upper bounds at 20%, 2% and 22% for combined MDD, PGC BD and MOOD respectively.

Definition of non-overlapping N

As some analyses (particularly LD score regression) use the total number of subjects in the analysis for calculations, a "non-overlapping N" was estimated for each meta-analysis, using the following equation (derived from the equation describing the genetic covariance intercept in LD Score) (17):

$$\text{Non-overlapping N} = N1 + (N2 - (g_{cov\_int} * \sqrt{N1N2}))$$

where N1 is the cohort size of the larger component part of the meta-analysis, N2 is the same for the smaller cohort and g_{cov_int} is the genetic covariance intercept from the calculation of genetic correlation between the component parts in LD Score. This

method can be extended to the meta-analysis of three cohorts in a two-step process (calculating a non-overlapping N for cohorts one and two, and then the non-overlapping N for the meta-analysis of the combined one-two cohort with cohort three). In the case of MOOD herein, the non-overlapping N was calculated as if meta-analysing PGC MDD and PGC BD followed by UKB MDD; and as if meta-analysing PGC MDD and UKB MDD followed by PGC BD. The average of the two results was taken as the non-overlapping N. Note that this equation implicitly assumes that the phenotypic correlation between the traits of interest in the overlapping samples is 1 (which is reasonable in this instance). Note also that the resulting non-overlapping N is underestimated in the presence of shared confounding between the cohorts (such as through population stratification) (18).

Comparison of METACARPA with meta-analysis of independent cohorts

We contributed individuals from the UK Biobank to PGC MDD, and so were able to define the overlap between PGC MDD and UKB MDD (3,087 cases and 5,128 controls, representing 10% and 8% of UKB MDD respectively). To examine the robustness of meta-analysis using overlapping cohorts in METACARPA, we re-ran UKB MDD excluding these overlapping individuals and then meta-analysed the results with PGC MDD using inverse variance weighted meta-analysis in METAL. We calculated genetic correlations between the results using LDSC, and calculated Pearson's correlations between the betas and p-values of the two analyses. Results of these analyses were highly consistent (betas r = 0.99, p-values r = 0.98, LDSC r_g = 1), suggesting METACARPA can adjust adequately for overlap between cohorts.

Definition of GWAS loci

GWAS results were clumped using PLINK1.9, assigning nominally-significant ($p < 10^{-4}$) variants to a clump if they were in linkage disequilibrium ($r^2 > 0.1$ in unrelated non-Finnish European participants from 1000 Genomes project) with a variant with a lower p-value lying within 3Mb (19, 20). Non-Finnish Europeans were used for the LD reference panel because they were the best match for the participants included in this analysis, who were of predominantly Western European ancestries. Loci were declared genome-wide significant if a variant in the locus reached the conventional threshold for genome-wide significance ($p = 5 \times 10^{-8}$). Results were visualised using FUMA, including mapping the loci to potentially affected genes through expression quantitative trait loci (eQTLs) and chromatin contact sites in brain tissues or neural progenitor cells (21).

All genomic loci reaching genome-wide significance in at least one analysis were combined for annotation. Where loci from different GWAS overlapped, they were combined into a single locus ranging from the minimum base position from any of the constituent loci to the maximum. Annotation was performed using RegionAnnotator version 1.63 (https://github.com/ivankosmos/RegionAnnotator), which includes data from: the NHGRI-EBI GWAS Catalog; OMIM; GENCODE genes; genes previously implicated in autism and in intellectual disability; copy-number variants previously implicated in psychiatric disorders; and mouse knockout phenotypes. Results from the GWAS Catalog module of RegionAnnotator were filtered to include only variants reaching genome-wide significance. Where multiple variants are listed as significant from a previous GWAS of a specific phenotype, only the variant with the lowest p-value is reported. Results from the GWAS Catalog module were supplemented by direct query of the NHGRI-EBI GWAS Catalog for

each region (data from 2018-11-05), lookup of top SNPs in http://atlas.ctglab.nl, and manual assessment of psychiatric and behavioural GWAS not yet listed in the NHGRI-EBI GWAS Catalog.

Relationship between meta-analyses (hierarchical clustering)

The relationship between the loci identified in the meta-analyses (MOOD, combined MDD) and the constituent analyses (PGC MDD, UKB MDD, PGC BD) was assessed using a hierarchically-clustered heatmap, with the 2014 PGC schizophrenia analysis (SCZ) included for comparison (22). For the purpose of this comparison, an index SNP was selected for each locus (the variant with the lowest p-value that was common to all four analyses) to obtain the direction of effect in each analysis. Index SNP p-values were converted to $-\log_{10}$(p-value). If the $OR_{index} < 1$ in a given analysis, the $\log_{10}$(p-value) was used in place of the $-\log_{10}$(p-value). A hierarchically-clustered heatmap was then generated using the default options of the heatmap.2 function of the gplots package in R v1.4.1 (complete clustering on the Euclidean distance between vectors) with clustering performed separately for rows and for columns (23, 24).

Hierarchical clustering of genetic correlations between subtypes, and extension to examine relationships with related traits

Genetic correlations between the major depressive disorder and bipolar disorder subtypes were hierarchically clustered using the method described above. In addition, we included results from six external GWAS relevant to mood disorders. We examined relationships with anxiety disorders (correlated with depressive phenotypes), schizophrenia (correlated with bipolar disorder), and ADHD (showed differing genetic correlations with PGC MDD and PGC BD) (22, 25, 26). We also

examined subjective wellbeing, which may reflect positive mood, and included measures of specific aspects of wellbeing, namely eudaimonic wellbeing (feeling life has meaning) and hedonic wellbeing (feeling happy) (27, 28). For hierarchical clustering only, the sign of genetic correlations with the three wellbeing phenotypes were reversed so that positive effect sizes meant poor outcomes for all phenotypes.

We concluded that the genetic correlations between subtypes of major depressive disorder and bipolar disorder were indicative of a genetic mood disorder spectrum. To validate this conclusion, we performed a principal component analysis of the genetic correlation matrix as used for hierarchical clustering above (that is, including the six external GWAS with correlations with the wellbeing phenotypes reversed). Principal component analysis was performed using the prcomp function from base R, and using plot3D (https://cran.r-project.org/package=plot3D) for visualisation (23).

Conditional and reversed-effect analyses

Analyses were performed to understand which genomic loci are shared or distinct between the disorders, using mtCOJO, an extension of the GSMR method implemented in GCTA (29, 30). mtCOJO adjusts the results of a genome-wide association analysis, conditioning on the effects of a set of significantly associated, independent variants from a second set of summary statistics (a putative instrumental variable). This putative instrumental variable is also used as a proxy for the trait of interest to infer causal direction in GSMR analyses. The effect size estimated by this method is robust to confounding caused by genetic or environmental effects shared between the studies analysed, assuming these are uncorrelated with the instrumental variable. mtCOJO adjusts for sample overlap (i.e.

the same individuals being present in both datasets) using the genetic covariance intercept from LD score regression (29, 31).

Conditional analyses in mtCOJO were performed on combined MDD conditional on PGC BD (MDDcBD), and on PGC BD conditional on combined MDD (BDcMDD). Variant selection for conditioning was performed with the default settings in mtCOJO, clumping using the UK Biobank dataset, and selecting at least ten variants with $p<5x10^{-8}$, which were not in linkage disequilibrium ($r^2 < 0.05$) with a variant with a lower p-value, and which did not show evidence of pleiotropy (passed the HEIDI-outlier analysis, threshold 0.01) (29). As down-sampled MDD had only eight variants with p<5x10-8, conditional analyses and GSMR were not performed using this meta-analysis. Similarly, BDcMDD had only six variants passing genome-wide significance, so GSMR analyses with BDcMDD as the exposure were not possible. Results were clumped in PLINK using the procedure described above. Genetic correlations were compared between combined MDD and MDDcBD, and between PGC BD and BDcMDD, first using a z-test to identify putative differences ($p < 0.05$), and then formally testing by applying a block-jackknife (described below). A conservative Bonferroni correction was used to determine significance ($p < 1.27x10^{-4}$, approximate correction for 414 tests) (32–34).

A further analysis was performed to identify loci with opposite directions of effect between combined MDD and PGC BD. For this analysis, the direction of effects for the PGC BD analysis was reversed, and the MOOD meta-analysis repeated as described in the main text.

GSMR

GSMR uses the HEIDI test to remove pleiotropic variants from the instrument variable set. All analyses were run using the default settings in GSMR, assuming at least ten linkage-independent ($r^2 < 0.05$) significant ($p<5x10^{-8}$) variants pass the HEIDI test (threshold $p<0.01$).

Comparing two genetic correlations using jackknife and LDSC

Let there be four phenotypes A, B, C, and D. The goal is to compare the genetic correlation between A and B to the genetic correlation between C and D. Global estimates of these correlations can be computed using the LDSC software and will be noted *r(A,B)* and *r(C,D)*. The same software can output jackknife delete values for genetic covariance: G(A,B), G(C,D), as well as for heritability: H(A,B) and H(C,D). These jackknife delete values are estimated by excluding blocks of values (here, number of blocks $n = 200$). The n-dimensional vectors G(A,B), G(C,D), H(A,B) and H(C,D) can be used to generate genetic correlation delete values R(A,B) and R(C,D). The difference between the global estimates *r(A,B)* and *r(C,D)* is *d(AB,CD)*, and the difference between the vectors R(A,B) and R(C,D) is D(AB,CD). The global genetic correlation difference *d(AB,CD)* and the delete values D(AB,CD) are used to compute jackknife pseudovalues. The *i*th pseudovalue is

$$P_i(AB, CD) = n \times d(AB, CD) - (n-1) * D_i(AB, CD)$$

The mean and variance of the jackknife pseudovalues are

$$m(AB, CD) = \frac{1}{n}\sum_{i=1}^{n} P_i(AB, CD)$$

$$v(AB, CD) = \frac{1}{n-1}\sum_{i=1}^{n} (P_i(AB, CD) - m(AB, CD))^2$$

The jackknife estimate of the difference between the two correlations *m(AB,CD)* can then be compared to test $H_0 : \theta = \theta_0$ ($\theta_0 = 0$ for no difference between genetic correlations), and a p-value can be derived from the z statistic:

$$z(AB, CD) = \frac{m(AB, CD) - \theta_0}{\sqrt{(1/n) \times v(AB, CD)}}$$

Estimating local SNP-based heritability and genetic covariance in HESS

Local estimates of SNP-based heritability and genetic correlation were obtained using HESS v0.5.3b (35, 36). All analyses used the reference panel provided with the software (1000 Genomes Project European individuals) and previously defined blocks of the genome in linkage equilibrium, with 50 eigenvectors for inverting the LD matrix and a minimum eigenvalue cutoff of 1 (37, 38). Overlap between cohorts was calculated consistent with the calculation of non-overlapping N (see above), assuming overlapping individuals had a phenotypic correlation of 1 (that is, overlapping individuals were controls in both studies). Local heritability estimates were calculated for all meta-analyses, component GWAS and subtypes. Local genetic covariance was calculated between combined MDD and PGC BD, between MOOD and down-sampled MOOD, and between all of the major depressive disorder and bipolar disorder subtype pairwise.

Gene-wise and gene-set enrichment analyses

For all analyses, gene-wise p-values were calculated as the aggregate of the mean and smallest p-value across all SNPs annotated to Ensembl gene locations using MAGMA v1.06 (using the build 37 reference supplied on the MAGMA website) (39). SNPs were assigned to genes if they lay between 35kb upstream and 10kb downstream of the gene location (40). MAGMA accounts for possible confounders such as gene size, gene density, linkage disequilibrium and minor allele count. The threshold for genome-wide significance was defined at $p < 2.6 \times 10^{-6}$ (Bonferroni correction for the 19,041 genes tested). Genes passing genome-wide significance were defined as coming from the same locus if they lay within 100kb of each other, or if they overlapped a locus from the single variant analysis. Gene set analysis was performed in MAGMA for 13,567 gene sets. Significance was set at a Bonferroni-corrected threshold of $p = 5.34 \times 10^{-6}$ for 9,361 effectively independent tests within each analysis.

Gene set analysis was performed for all analyses. A gene set matrix **P** was generated with elements $P_{g,p} = 1$ if gene *g* was in set *p* and $P_{g,p} = 0$ otherwise. Association between gene set membership and gene-wise z-scores was computed using MAGMA. 13,567 gene sets were drawn from OpenTargets (downloaded January 2017) (41), GO ontologies, canonical gene sets drawn from MSigSB v5.2 C2 and C5 datasets (42), and biological gene sets related to psychiatric disorders described in various scientific publications. There is considerable overlap of genes between gene sets (within and between sources). Gene sets that overlapped entirely were treated as a single gene set in analyses. The effective number of gene sets tested was defined as the number of principal components accounting for 99.5% of explained variance in the gene set similarity matrix, obtained by computing the

Tanimoto similarity between gene sets. This results in a Bonferroni-corrected threshold of $p = 5.34 \times 10^{-6}$ for 9,361 effectively independent tests for each matrix.

Tissue and single-cell enrichment analyses

Further analyses were performed to assess the enrichment of associated genes with expression-specificity profiles from tissues (version 7 data from the Genotype-Tissue Expression project) and broadly-defined ("level 1") and narrowly-defined ("level 2") cell-types (Karolinska Institutet mouse brain single-cell RNA sequencing superset) (43, 44). Analyses were performed in MAGMA following previously described methods with minor modifications (44). Briefly, for the single cell data set (44), gene expression for each cell type was scaled to 1,000,000 unique molecular identifiers prior to computing specificity scores. Specificity scores are defined as the proportion of the total expression of a specific gene found in a given cell type. For the GTEx dataset, transcripts per million (TPM) were transformed to $\log_2(\text{TPM} +1)$ prior to computing specificity scores. For each tissue or cell-type, the specificity scores were then rank-transformed to a standard normal distribution using the *rntranform* function from the GenABEL R package (45). The standard normalised specificity scores were then regressed on gene-wise association in the meta-analysis, defined as the mean p-value across all SNPs assigned to the gene. Multiple-testing correction was applied using Bonferroni-correction within each analysis.

Association with predicted brain tissue gene expression

Variant-level meta-analysis results were used to predict gene expression using S-PrediXcan and genomic and transcriptomic reference data from the thirteen brain regions assayed in the GTEx project (version 7) (43, 46). Associations were

calculated between these predicted gene expression levels and each meta-analysed phenotype. Significance was set at $8.5x10^{-8}$, the Bonferroni correction for 586,469 tests (45,113 genes across 13 tissues) as in the original S-PrediXcan publication (46). Genes were defined as coming from the same locus following the approach described for MAGMA analyses.

Polygenic risk score prediction of UKB subtypes using PGC BD summary statistics

In order to determine if the recurrent major depressive disorder subtype (rMDD) was genetically more similar to PGC BD than were other major depressive disorder subtypes (single episode major depressive disorder, sMDD;and subthreshold depression, subMDD), polygenic risk score analyses were performed using PRSice2 (47). PGC BD results were used as the base analysis to produce polygenic risk scores (PRS) in the genotyped data from the UKB sample, and these were then compared across the major depressive disorder subtypes using logistic regression (including the covariates described above for the UKB GWAS). PRS were derived using linkage-independent ($r^2 < 0.1$, ± 250kb) variants at seven p-value thresholds from the PGC BD data (pT = 0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5). Correction for multiple-thresholding was performed by using 20000 permutations (using the permutation function in PRSice2) to produce an empirical p-value (minimum possible empirical p = $5x10^{-5}$). Variance explained was initially calculated as Nagelkerke pseudo-R^2 (using the fmsb package in R) and was subsequently converted to liability scale using http://cnsgenomics.com/shiny/abc/ (48, 49). Population prevalences for each subtype were set as follows: rMDD = 0.05; sMDD = 0.15; subMDD = 0.2. The population prevalence for each comparison was then calculated as each prevalence divided by the summed prevalence to give the

following: rMDD vs sMDD = 0.25 (that is, 0.05 / [0.05+0.15]); rMDD vs subMDD = 0.2; sMDD vs subMDD = 0.429.

Supplementary Results

Conditional analyses

We performed analyses of combined MDD conditioning on PGC BD (MDDcBD). Diminished effects (shrinkage of the odds ratio shrinkage towards 1) were observed in 51/63 loci reaching genome-wide significance in combined MDD, suggesting most loci significantly associated with combined MDD have the same direction of effect in PGC BD (Supplementary Table 13). Results from the reverse analysis (PGC BD conditioned on combined MDD: BDcMDD) support this conclusion, with 14/19 associated loci from PGC BD showing a diminished effect (Supplementary Table 13).

The SNP-based heritability of the conditional analyses showed reduced estimates compared to the respective main analyses (MDDcBD: 7%, combined MDD: 9%, BDcMDD: 17%, PGC BD: 20%, Supplementary Table 2). Genetic correlations for MDDcBD mirror those for combined MDD, except that genetic correlations with schizophrenia (and related analyses, such as the schizophrenia-bipolar disorder meta-analyses) were significantly smaller (Supplementary Figure 12, Supplementary Tables 5 and 14) (22, 50). The genetic correlations from BDcMDD were similar to PGC BD, with significant reductions only with studies of depression and anxiety (Supplementary Tables 15 and 15) (26, 51, 52).

In addition to conditional analyses, we reversed the observed effects from PGC BD and meta-analysed with combined MDD. 32 loci were significant in the

resulting MOOD BD Reversed analysis (Supplementary Table 3). All loci were strongly associated with combined MDD (max p = $2x10^{-7}$), 27 passing genome-wide significance, compared with only one locus passing significance in PGC BD. 19 loci showed consistent direction of effect between combined MDD and PGC BD, indicating that these loci were driven by strong associations with combined MDD, rather than having a differing effect on major depressive disorder than on bipolar disorder. The smallest p-value observed in PGC BD for any of the 13 loci with differing directions of effect was $p=6x10^{-6}$, for locus Rev2 on chromosome 7. This locus contains the *CTTNBP2* gene, rare variants in which have suggestive evidence for implication in autism spectrum disorder (53).

Down-sampled reversed analyses yielded three loci passing genome-wide significance (Supplementary Table 3). All of these loci passed genome-wide significance in down-sampled MDD and had shared directions of effect between PGC BD and down-sampled MDD, indicating these loci do not have a differing effect on major depressive disorder than on bipolar disorder.

Tissue and cell-type expression specificity analyses showed high consistency between the main and the conditional analyses (Supplementary Tables 9-11). All brain tissues were enriched in both conditional analyses. In cell-type analyses, neuroblasts, adult dopaminergic neurons, embryonic GABAergic and midbrain nucleus neurons were significantly enriched in MDDcBD and not in BDcMDD. Conversely, medium spiny neurons (as well as both sets of pyramidal cells and the striatal interneurons) were significantly enriched in BDcMDD and not in MDDcBD.

GSMR analyses also showed high consistency between the main and the conditional analyses, although these analyses were limited because BDcMDD had

too few variants with $p<5x10^{-8}$ and so could only be used as an outcome, not an exposure, in GSMR analyses (Supplementary Figure 13, Supplementary Tables 12). MDDcBD had no significant relationship with PGC BD (nor BDcMDD with combined MDD), suggesting that conditioning was effective at removing the bidirectional relationship seen between combined MDD and PGC BD. Otherwise, results observed for combined MDD were also observed for MDDcBD, except that the positive association of major depressive disorder on CAD was attenuated and did not pass significance in MDDcBD. Results observed for PGC BD (as an outcome) were also observed for BDcMDD.

Gene-wise and gene set analyses

Gene-wise association analyses in MAGMA identified 361 genes associated with the MOOD phenotype at p < 2.6x10-6 (Supplementary Table 16). Associated genes were distributed across 120 loci, including 47 of the loci identified in MOOD. However, proximity is only a weak indication of the association of a gene with a trait (54). More evidence is provided by the convergence of brain-derived eQTL and chromatin contact data from a locus onto a single gene (Supplementary Figures 14-33 - note no figures are provided for chromosomes 8 or 21, as there are no significant loci on these chromosomes). In MOOD, such evidence suggested significant loci may act on *NEGR1* (loci 2 and 3), *RSRC1* (locus 14), *TMEM161B* (locus 18), *LHX2* (locus 41), *SOX5* (locus 53), *LACC1* (locus 56), *PCDH8* (locus 57) and *ZC2HC1C* (locus 61). However, diverse eQTL and chromatin contacts were observed at many of these loci, suggesting these associations may act through other genes as well.

Results from gene set analysis were generally similar between combined MDD and PGC BD, and in each of the conditional analyses (Supplementary Table 17). Gene sets significantly enriched across all analyses included genes previously implicated in schizophrenia, targets of the RNA splicing proteins *CELF4* and *RBFOX1/RBFOX3*, loss-of-function intolerant (pLI09) genes, and genes with products potentially involved in synaptic processes (Supplementary Table 17). Certain gene sets were enriched in one disorder only - for example, RBFOX2 targets were significantly enriched in combined MDD, but not in PGC BD. In contrast, gene sets annotated as mutation-intolerant (constrained and genic intolerance RVIS) were significantly enriched in PGC BD but not combined MDD. In the conditional analyses, results for combined MDD and MDDcBD were similar, with significantly associated gene sets falling into broad categories of psychiatrically associated, neurodevelopmental, and anthropometric gene sets (Supplementary Table 17). Fewer significant gene sets were observed in BDcMDD than in PGC BD, but included mutation-intolerant gene sets (Supplementary Table 17).

Local SNP-based heritability and genetic covariance

Genome-wide SNP-based heritability estimates on the observed scale were similar between LDSC and HESS for all main meta-analyses (Supplementary Table 18). For both MOOD and combined MDD, local SNP-based heritability was significantly >0 in the region overlapping loci 2 and 3 (near *NEGR1*), and for multiple regions comprising locus 25 (the major histocompatibility locus; $p < 2.94 \times 10^{-5}$, Bonferroni correction for 1703 LD-independent regions). No regions had significant local SNP-based heritability for PGC BD. Combined MDD and PGC BD were significantly genetically correlated (0.29, compare 0.35 from LDSC; Supplementary

Table 19), but no regions had local genetic covariance that significantly differed from 0 ($p > 2.94x10^{-5}$).

The observed SNP-based heritability of down-sampled MOOD from HESS was 11% (compare LDSC 8%; Supplementary Tables 2 and 18). Only one region, part of locus 25, had local SNP-based heritability significantly >0. One region on chromosome 10 had local SNP-based heritability significantly >0 in down-sampled MDD. However, this is probably a false positive, there are no variants significantly associated with down-sampled MDD in the region. In addition, this region encompasses the centromere of chromosome 10, which may result in the LD structure of the region being specified incorrectly.

Genetic correlations of mood disorder subtypes

Genetic correlations between the bipolar disorder and major depressive disorder subtypes suggest a spectrum of genetic relationships between major depressive disorder and bipolar disorder, with BD2 bridging the two disorders (Supplementary Figure 34). Adding in six external phenotypes resulted in two clusters, with two sets of intermediate phenotypes (Supplementary Table 10, Supplementary Figures 35-40). Major depressive disorder subtypes cluster with anxiety disorders and the wellbeing spectrum, albeit with negative genetic correlations with wellbeing. The relationship of the wellbeing spectrum with depressive disorders was captured more effectively by hedonic rather than eudaimonic wellbeing - however, neither of these wellbeing subtypes clustered with depressive disorders, reinforcing previous conclusions that wellbeing is multidimensional (55). In contrast, schizophrenia clusters with schizoaffective bipolar disorder and bipolar disorder type 1, consistent with the greater genetic similarity of

these subtypes to schizophrenia (16, 56). ADHD has a moderate genetic correlation with bipolar disorder type 2, but not with the other bipolar disorder subtypes, arguing that the weaker genetic correlation between ADHD and bipolar disorder (compared to major depressive disorder) is specific to type 1 bipolar disorder.

Principal component analysis identified three principal components accounting for >90% of the variance in the genetic correlation matrix (Supplementary Figure 41). The first principal component accounted for 59% of the variance, and described the spectrum as proposed above, separating the cluster of schizophrenia, schizoaffective bipolar disorder, and bipolar disorder type 1 from the cluster of the depressive disorders, with bipolar disorder type 2 and ADHD intermediate between the two. The second (21% variance explained) principal component separated the eudaimonic and hedonic wellbeing phenotypes from the other phenotypes, and the third principal component (12% variance explained) separated ADHD from the other phenotypes (Supplementary Figure 41).

Estimates of local heritability (Supplementary Table 18) and genetic covariance (Supplementary Table 19) were calculated in HESS to assess whether specific regions of the genome were shared or distinct between subtypes. However, with the exception of BD1 and rMDD, SNP-based heritability estimates on the observed scale from HESS did not differ significantly from 0 (BD1 = 33%; BD2 = 3%; SAB = 0.4%; rMDD = 9%; sMDD = 0%; subMDD = 0.1%). This most likely resulted from the small cohort size of the subtype analyses, which results in a downward bias in SNP-based heritability estimation in HESS (36). No regions had significant local SNP-based heritability for any of the subtypes (all p > 2.94x10-5, Bonferroni correction for 1703 LD-independent regions). BD1 and rMDD were genetically

correlated (0.36, compare 0.31 from LDSC; Supplementary Table 10), but no region had a genetic covariance significantly >0 (all p > 2.94x10-5).

Genetic correlations of PGC MDD and PGC BD with mood disorder subtypes

The genetic correlation of PGC MDD and BD2 was stronger than those with BD1 (Δr_g [difference between r_g estimates] = 0.39, p = $1x10^{-4}$) and with SAB (Δr_g = 0.52, p = $2x10^{-5}$), but the genetic correlations with BD1 and with SAB were not significantly different (Δr_g = 0.14, p = 0.05). PGC BD had a stronger genetic correlation with rMDD than with subMDD (Δr_g = 0.27, p = $3x10^{-5}$), but the genetic correlation between PGC BD and sMDD was not significantly different to those with rMDD (Δr_g = -0.07, p = 0.5) nor with subMDD (Δr_g = 0.20, p = 0.009).

Results from PGC MDD + subtype meta-analyses

Bipolar disorder subtypes

64 loci reached genome-wide significance across the meta-analyses between PGC MDD and the bipolar disorder subtypes (MDD-BD1, MDD-BD2, and MDD-SAB; Supplementary Table 3). Of these, 54 also reached significance in MOOD. The ten remaining loci were significant in MDD-BD2 alone (four loci), in MDD-BD2 and in MDD-SAB (three), in MDD-BD1 and in MDD-BD2 (one), in MDD-BD1 (one), and in MDD-SAB (one). Gene-wise association analyses in MAGMA identified 272 genes associated at p < $2.6x10^{-6}$ in at least one of the meta-analyses (Supplementary Table 16). Associated genes were distributed across 86 loci, including 44 of the loci identified by at least one single variant meta-analysis.

Heritability estimates for the meta-analyses between PGC MDD and the bipolar disorder subtypes were all very similar, ranging from 8-10% (assuming a

lower bound of population prevalence of 10.5%, and an upper bound of 22%; Supplementary Table 2). Genetic correlations with previously-published traits were broadly similar across the different meta-analyses, and mirrored those from the main MOOD meta-analysis (psychiatric and behavioural, reproductive, and sociodemographic traits; Supplementary Table 5).

Major depressive disorder subtypes

65 loci reached genome-wide significance across the meta-analyses between PGC MDD and the major depressive disorder subtypes (MDD-rMDD, MDD-sMDD, and MDD-subMDD; Supplementary Table 3). Of these, 52 also reached significance in the MOOD analysis - the remaining 13 loci were significant in MDD-rMDD alone (four loci), in MDD-subMDD alone (four), in MDD-rMDD and MDD-subMDD (three), in all three analyses (one) and in MDD-sMDD and MDD-subMDD alone (one). Gene-wise association analyses in MAGMA identified 261 genes associated at $p < 2.6x10^{-6}$ in at least one of the meta-analyses (Supplementary Table 16). Associated genes were distributed across 93 loci, including 45 of the loci identified by at least one single variant meta-analysis.

Heritability estimates for the meta-analyses between PGC MDD and the major depressive disorder subtypes were all similar, ranging from 7-10% (assuming a lower bound of population prevalence of 10%, and an upper bound of 20%), although estimates for MDD-rMDD were slightly higher than those for MDD-sMDD and MDD-subMDD (Supplementary Table 2). Genetic correlations with previously-published traits were broadly similar across the different meta-analyses, and mirrored those from the main MOOD meta-analysis (psychiatric and behavioural, reproductive, and sociodemographic traits; Supplementary Table 5).

Gains in discovery through adding individuals with different mood disorder diagnoses

The PGC MDD analysis was meta-analysed with PGC BD and UKB MDD cohorts and with the subtypes of both bipolar disorder and major depressive disorder. The relative increase in mood-disorder associated loci obtained by adding 1000 effective cases from different definitions to the PGC MDD GWAS was assessed. Effective cases were defined as half of the effective N (2 / [[1+Cases] + [1+Controls]]) (57). The resultant increase in locus discovery per 1000 effective cases of UKB MDD, PGC BD and each subtype is described in Supplementary Table 20. With the exception of SAB (the power of which is very low), meta-analysis with PGC MDD resulted in an increased number of loci in all cases, with BD2 providing the most additional loci per 1000 effective cases (0.67). BD1 cases provided a similar amount of additional loci to rMDD (0.5 vs 0.51), and both out-performed sMDD (0.2). This suggests BD1 cases may function in a similar manner to rMDD cases in meta-analysis with PGC MDD, while BD2 cases appear to be equivalent to more extreme rMDD cases. As expected, like-for-like, rMDD cases provide more loci than sMDD cases, most likely due to increased heterogeneity of sMDD cases (potentially because single depressive episodes may be more likely to represent a reaction to a specific event). This fits with the higher heritability of recurrent major depressive disorder (45%) versus single episode major depressive disorder (34%) (58). These conclusions mirror the increase in mean-chi-square of each meta-analysis compared to PGC MDD alone (Supplementary Table 20). However, limitations remain, including the unknown effects of error (such that it is difficult to assess the meaning of differences between subtypes robustly) and the fact that the major depressive disorder subtypes are drawn from the same source

(UK Biobank), which may differ from clinically-ascertained major depressive disorder cohorts, both in heterogeneity and in severity (4, 59).

Associations of polygenic risk scores for PGC BD with UKB MDD subtypes

Polygenic risk scores derived from the PGC BD analysis (Supplementary Table 21, Supplementary Figure 41) were significantly positively associated with rMDD when compared to sMDD ($p = 3x10^{-16}$; empirical $p = 5x10^{-5}$) and when compared to subMDD ($p = 3x10^{-19}$; empirical $p = 5x10^{-5}$). In contrast, the association between the PGC BD risk score and sMDD compared to subMDD was not significant when taking into account the multiple thresholds tested ($p = 0.04$; empirical $p = 0.13$). Grouping rMDD and sMDD together as UKB MDD cases, the PGC BD risk score was significantly positively associated with UKB MDD cases compared to controls ($p = 6x10^{-40}$; empirical $p = 5x10^{-5}$). Taken together, these results suggest that rMDD has more in common genetically with PGC BD than does sMDD. This mirrors previous findings that showed BD2 was more similar genetically to PGC MDD than was BD1 (16).

Relationship of meta-analysis results (hierarchical clustering)

Hierarchical clustering of the significant loci from MOOD and combined MDD with the same loci from PGC MDD, UKB MDD, and PGC BD (and the PGC2 SCZ for comparison) (22) resulted in MOOD clustering most closely with PGC MDD. This indicates that the primary contribution to significant loci in the meta-analysis came from PGC MDD rather than PGC BD (Supplementary Figure 42). Results from UKB MDD for these loci clustered closer to PGC BD than to PGC MDD, suggesting that the component analyses cluster primarily by their contribution to the meta-analysis, rather than by trait. Despite this similarity between UKB MDD and PGC BD when

considering genome-wide significant loci, comparisons of the SNP-heritability of the component analyses (Supplementary Table 2) and of the genetic correlations between them (Supplementary Table 10) confirm that UKB MDD is more similar in general to PGC MDD than to PGC BD.

Sensitivity analysis - Equivalently-powered cohorts

Summary statistics were available from the PGC comprising the PGC MDD cohort without the inclusion of the 23andMe and the original UK Biobank cohorts. The mean chi-square of the meta-analysis between the down-sampled PGC MDD and UKB MDD was 1.35 (compared to 1.70 in combined MDD), similar to the mean chi-square of PGC BD and therefore suitable for the purpose of the sensitivity analysis (Supplementary Table 2). We therefore meta-analysed down-sampled PGC MDD, PGC BD and UKB MDD (down-sampled MOOD; cases = 95,418, controls = 192,514, non-overlapping N = 280,214).

19 loci reached genome-wide significance, of which 17 were present in MOOD and two did not reach significance in any of the main analyses (Supplementary Table 3). Hierarchical clustering of the significant loci from down-sampled MOOD with the same loci from down-sampled PGC MDD, UKB MDD, and PGC BD (and the PGC2 SCZ for comparison) (22) resulted in all three component analysis clustering together, with the meta-analysis clustering separately (Supplementary Figure 43). This suggests that the clustering of PGC MDD with MOOD in the main paper resulted from the power difference. UKB MDD again clustered more closely with PGC BD than with down-sampled PGC MDD, although the genetic correlation of UKB MDD with down-sampled PGC MDD (r_g = 0.86) was still greater than with PGC BD (r_g = 0.34).

Nine of the 44 PGC MDD loci reached genome-wide significance in the down-sampled MOOD meta-analysis (20% of all PGC MDD loci), as did both of the loci that reached genome-wide significance in down-sampled PGC MDD (Supplementary Table 3). In comparison, only two of the 19 PGC BD loci reached genome-wide significance in the meta-analysis (11%), suggesting that the addition of individuals with bipolar disorder to major depressive disorder cohorts still appears to enrich more for associations with major depressive disorder than for bipolar disorder.

Two loci reaching genome-wide significance in down-sampled MOOD did not reach genome-wide significance in MOOD, of which one reached significance in PGC BD. The other is a multi-gene locus on chromosome 3 that has reached genome-wide significance in a wide variety of traits, including depressive symptoms (60). In addition to this locus, a further seven loci reached genome-wide significance in down-sampled MOOD that did not reach significance in PGC MDD or PGC BD including locus 30, near *PCLO* (but not locus 51, near *DRD2*).

The estimate of SNP-heritability for down-sampled MOOD (11% with population prevalence 16%) was greater than that for MOOD (8.8%), but still remains more similar to PGC MDD (9%) than to PGC BD (17-23%; Supplementary Table 2) (1, 16). Similarly, the genetic correlations between down-sampled MOOD and other traits broadly recapitulated those for MOOD (Supplementary Table 5). Significantly greater correlations (compared with MOOD) were seen between down-sampled MOOD and bipolar disorder, schizophrenia, combined analyses of bipolar disorder and schizophrenia, and the cross-disorder analysis, while reduced correlations were seen with PGC MDD and anxiety (Supplementary Table 7). Interestingly, a significant negative correlation with IQ was observed (r_g = -0.13, p = $5x10^{-7}$), which was not observed in MOOD, PGC MDD nor PGC BD. Further

investigation of this genetic correlation revealed that the 23andMe depression cohort has a positive genetic correlation with IQ (r_g = 0.06, p = 0.01); including this cohort in the PGC MDD sample obscured a negative genetic correlation with IQ.

Overall, the sensitivity analyses suggest that the difference in power between combined MDD and PGC BD does contribute to the greater similarity of MOOD to PGC MDD than to PGC BD. However, the pervasive similarity to PGC MDD seen in the down-sampled analysis suggests the results seen in the main analysis are not just a consequence of the power difference.

The observed SNP-based heritability of down-sampled MOOD from HESS was 11% (compare LDSC 8%; Supplementary Tables 2 and 18). Only one region, part of locus 25, had local SNP-based heritability significantly >0 in down-sampled MOOD. One novel region on chromosome 10 had local SNP-based heritability significantly >0 in down-sampled MDD (and in the down-sampled PGC MDD) – however, no significant variants were observed in this region, so this may be spurious. Down-sampled MDD and PGC BD were significantly genetically correlated (0.33, compare 0.37 from LDSC), but no regions had local genetic covariance that significantly differed from 0 (all p > 2.94×10^{-5}; Supplementary Table 19).

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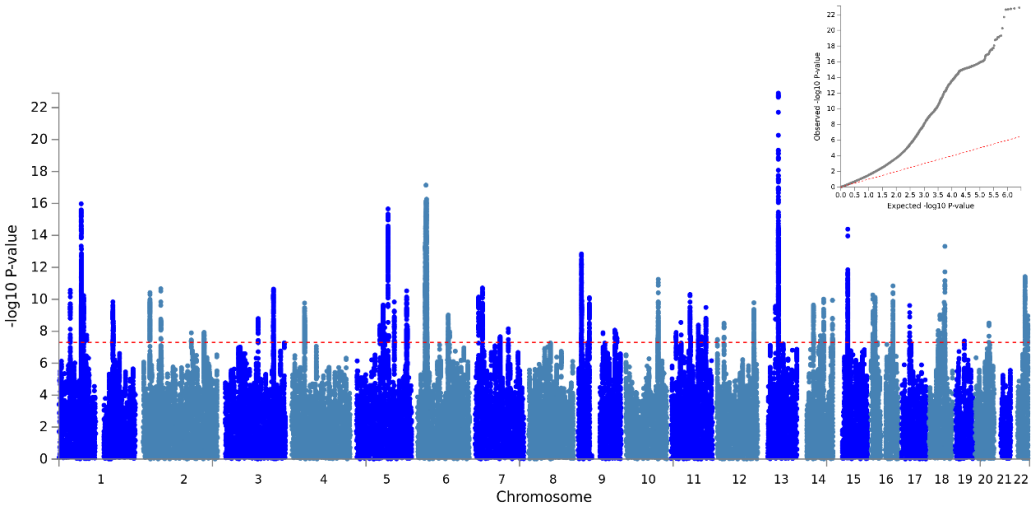
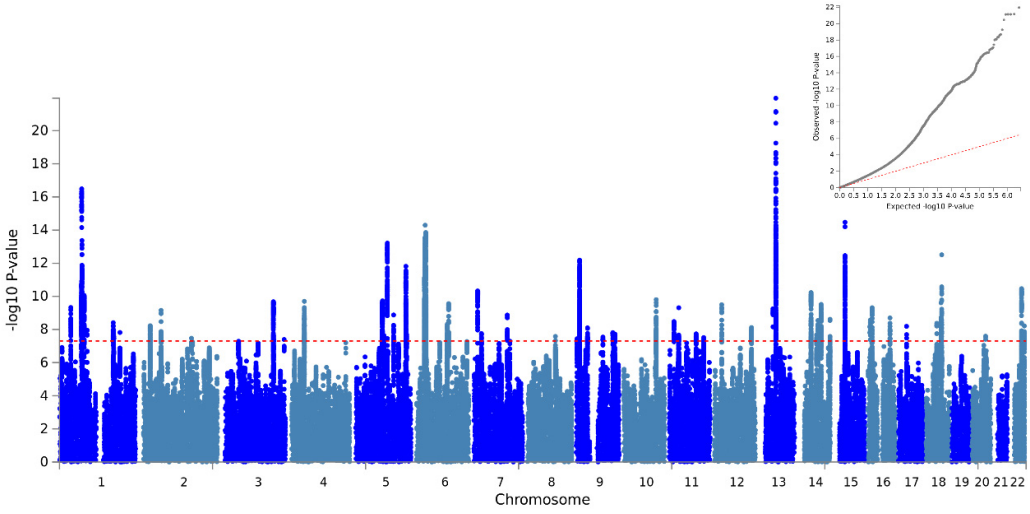
Supplementary Figures

Supplementary Figure 1



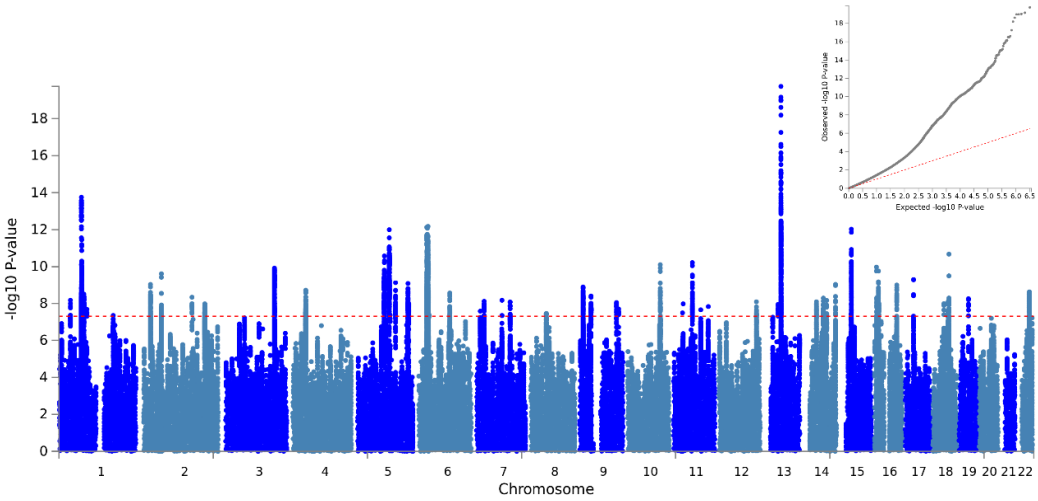
Supplementary Figure 1: Manhattan and QQ plot of results for the mood disorders (MOOD) meta-analysis. Red line is $5x10^{-8}$

Supplementary Figure 2



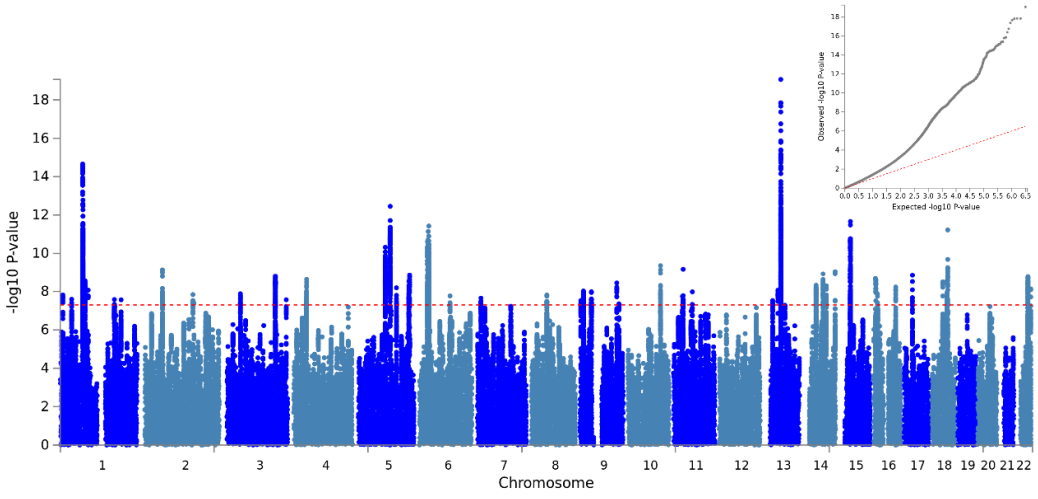
Supplementary Figure 2: Manhattan and QQ plot of results for the combined MDD meta-analysis. Red line is $5x10^{-8}$

Supplementary Figure 3



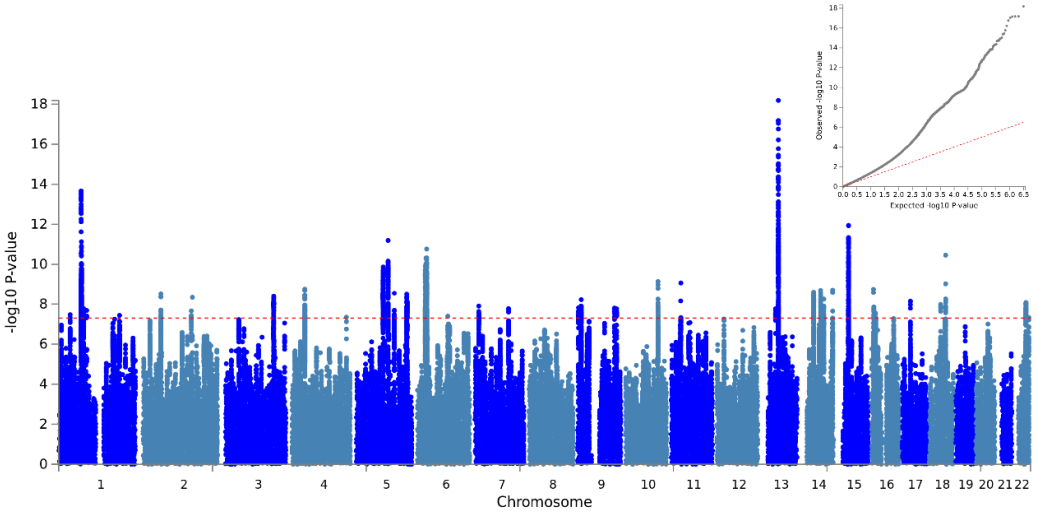
Supplementary Figure 3: Manhattan and QQ plot of results for the MDD-BD1 meta-analysis. Red line is $5x10^{-8}$

Supplementary Figure 4



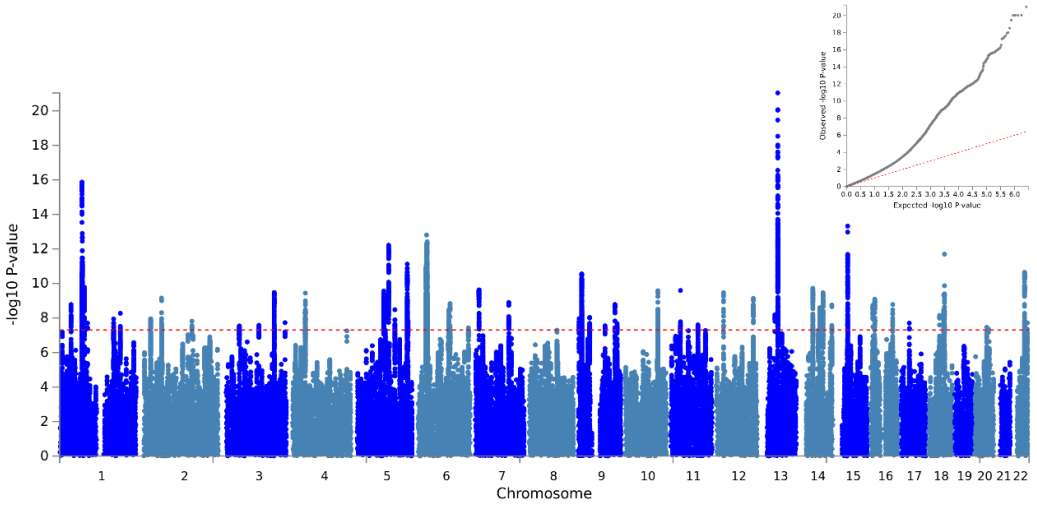
Supplementary Figure 4: Manhattan and QQ plot of results for the MDD-BD2 meta-analysis. Red line is $5x10^{-8}$

Supplementary Figure 5



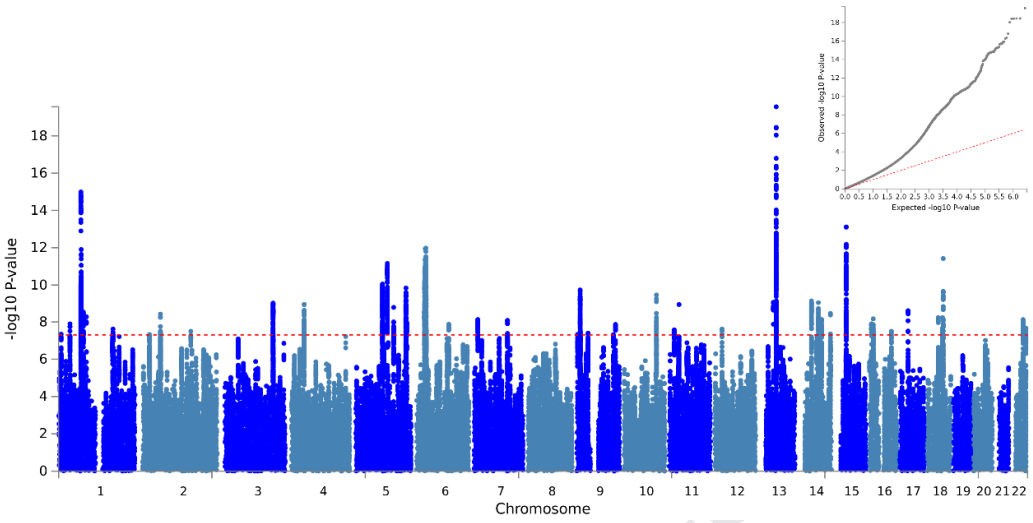
Supplementary Figure 5: Manhattan and QQ plot of results for the MDD-SAB meta-analysis. Red line is $5x10^{-8}$

Supplementary Figure 6



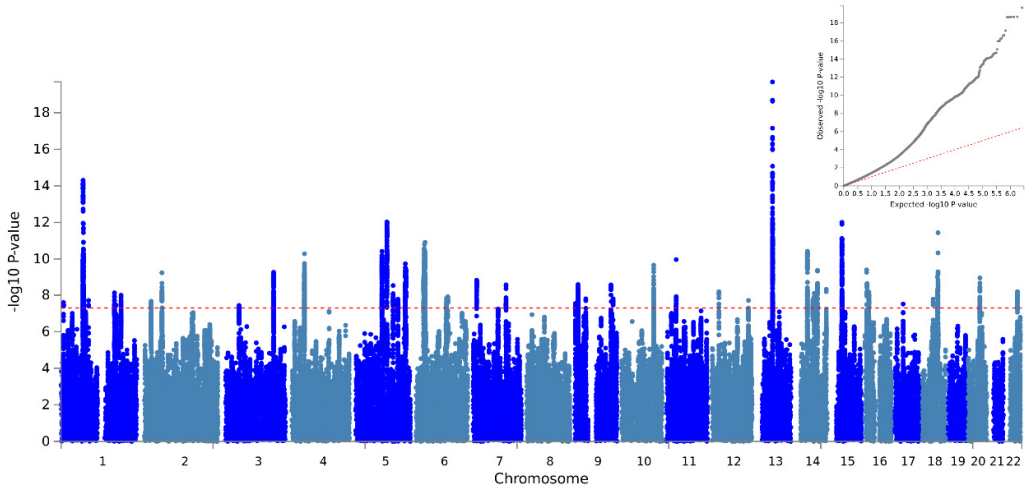
Supplementary Figure 6: Manhattan and QQ plot of results for the MDD-rMDD meta-analysis. Red line is $5x10^{-8}$

Supplementary Figure 7



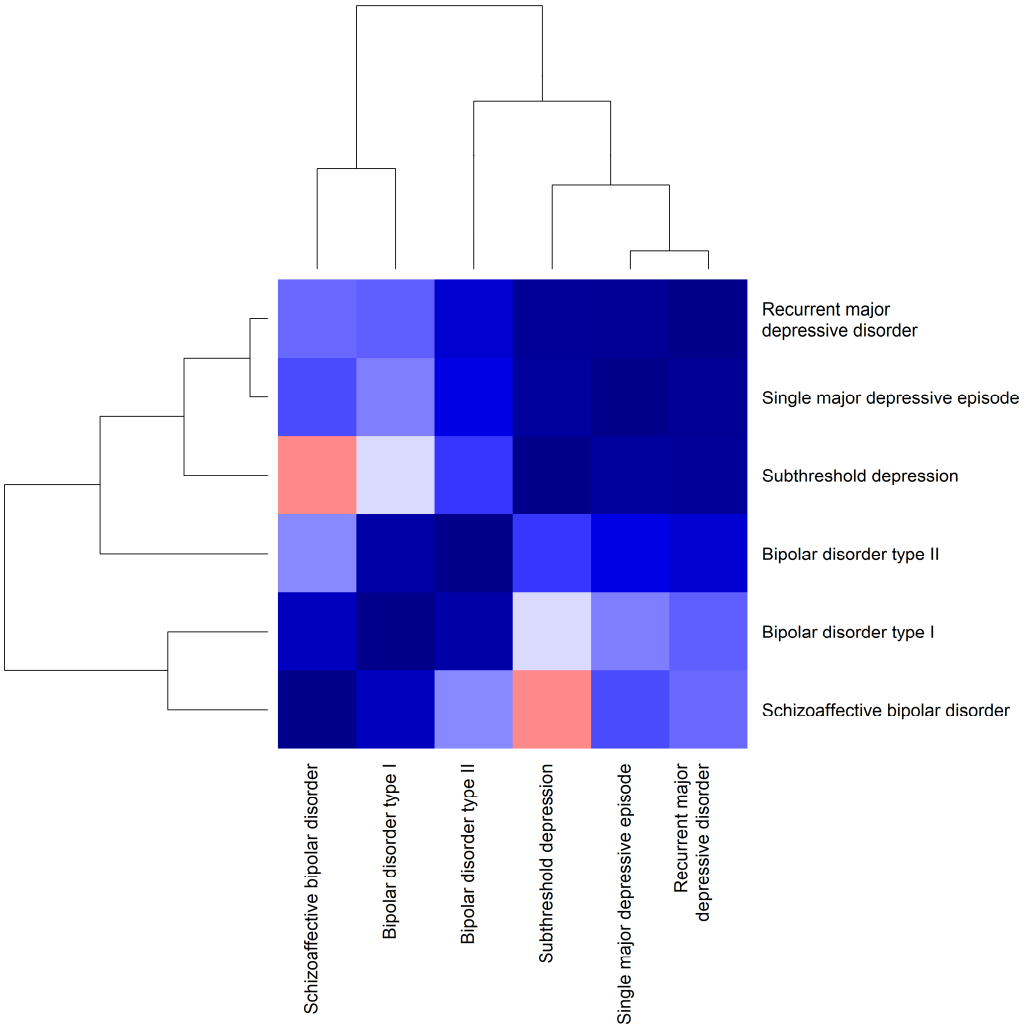
Supplementary Figure 7: Manhattan and QQ plot of results for the MDD-sMDD meta-analysis. Red line is $5x10^{-8}$

Supplementary Figure 8



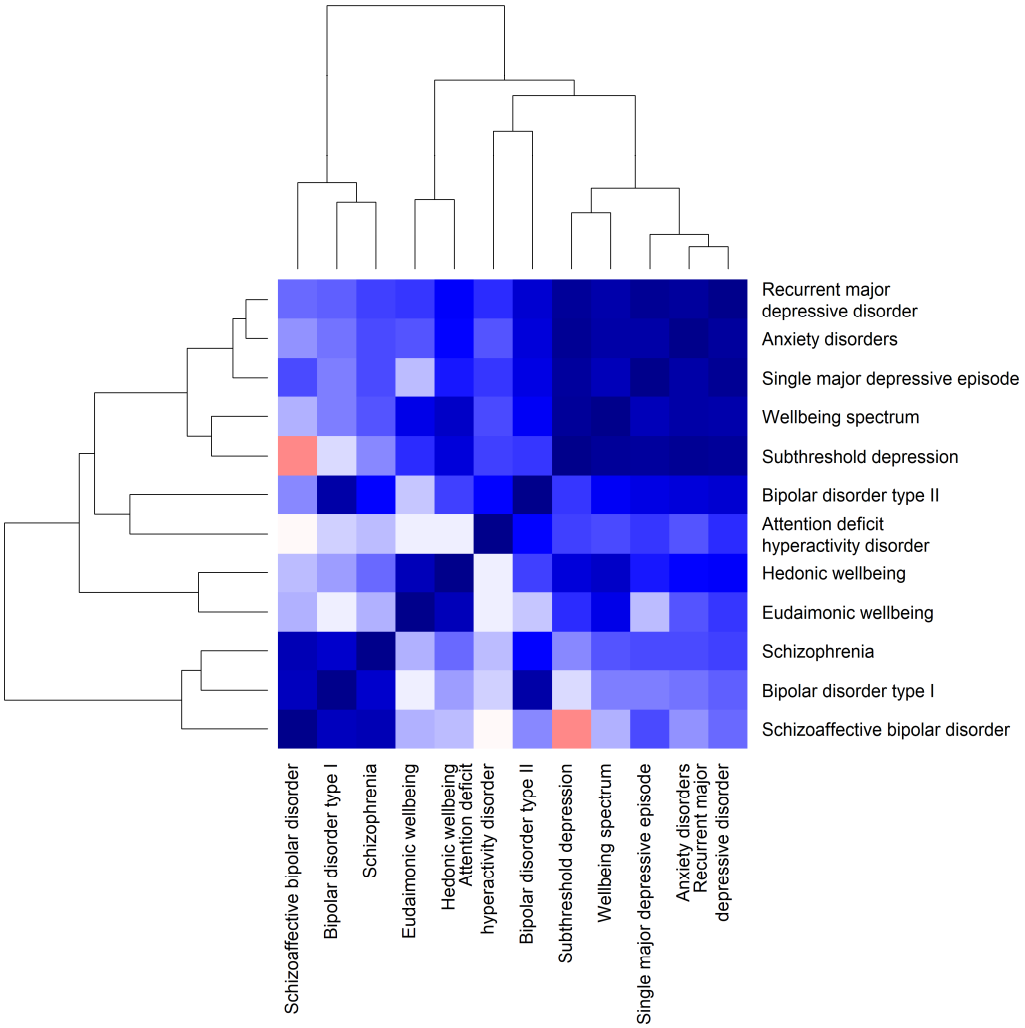
Supplementary Figure 8: Manhattan and QQ plot of results for the MDD-subMDD meta-analysis. Red line is $5x10^{-8}$

Supplementary Figure 9



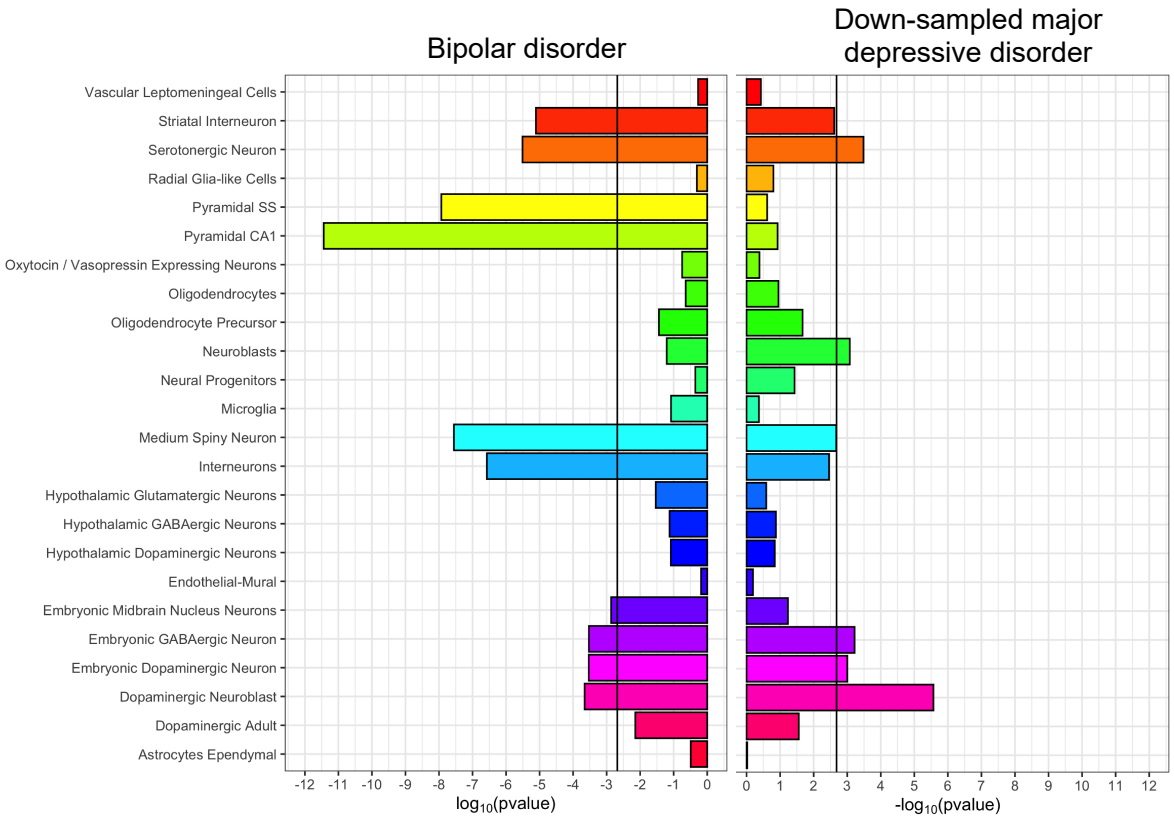
Supplementary Figure 9: Hierarchical clustering of the genetic correlations between major depression subtypes from UK Biobank (rMDD, sMDD, subMDD) and bipolar disorder subtypes (BD1, BD2, SAB). Blue = positive genetic correlation. Red = negative genetic correlation. Full genetic correlation results are provided in Supplementary Table 4.

Supplementary Figure 10



Supplementary Figure 10: Hierarchical clustering of the genetic correlations between major depression subtypes from UK Biobank (rMDD, sMDD, subMDD) and bipolar disorder subtypes (BD1, BD2, SAB), in the context of genetic correlations with external traits (schizophrenia, anxiety disorders, attention deficit hyperactivity disorder, the wellbeing spectrum, hedonic wellbeing and eudaimonic wellbeing). Genetic correlations with the wellbeing spectrum are reversed, such that they are correlations with low wellbeing. Blue = positive genetic correlation. Red = negative genetic correlation. Full genetic correlation results are provided in Supplementary Table 4 and Supplementary Table 7 (for external traits).

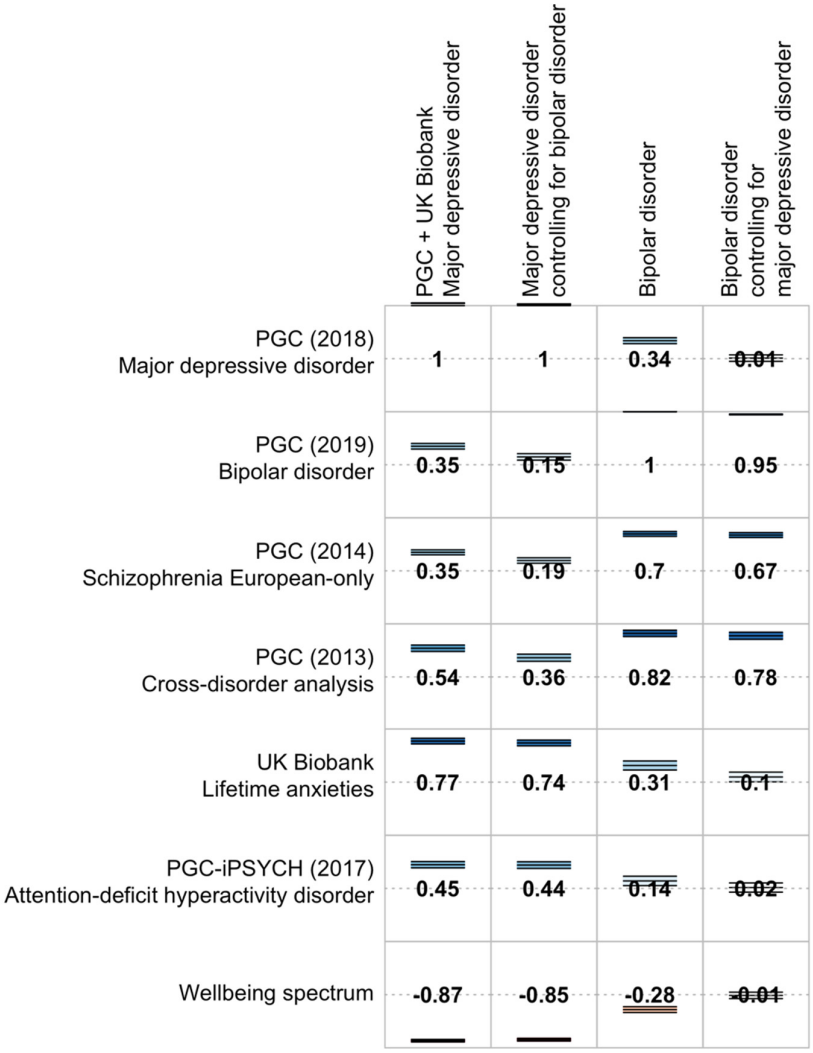
Supplementary Figure 11



Supplementary Figure 11: Cell-type expression specificity of genes associated with bipolar disorder (PGC BD, left) and the down-sampled major depressive disorder GWAS (down-sampled MDD, right). Black vertical lines = significant enrichment ($p < 2x10\text{-}3$, Bonferroni correction for 24 cell types). See Supplementary Table 15 for full results.

Supplementary Figure 12

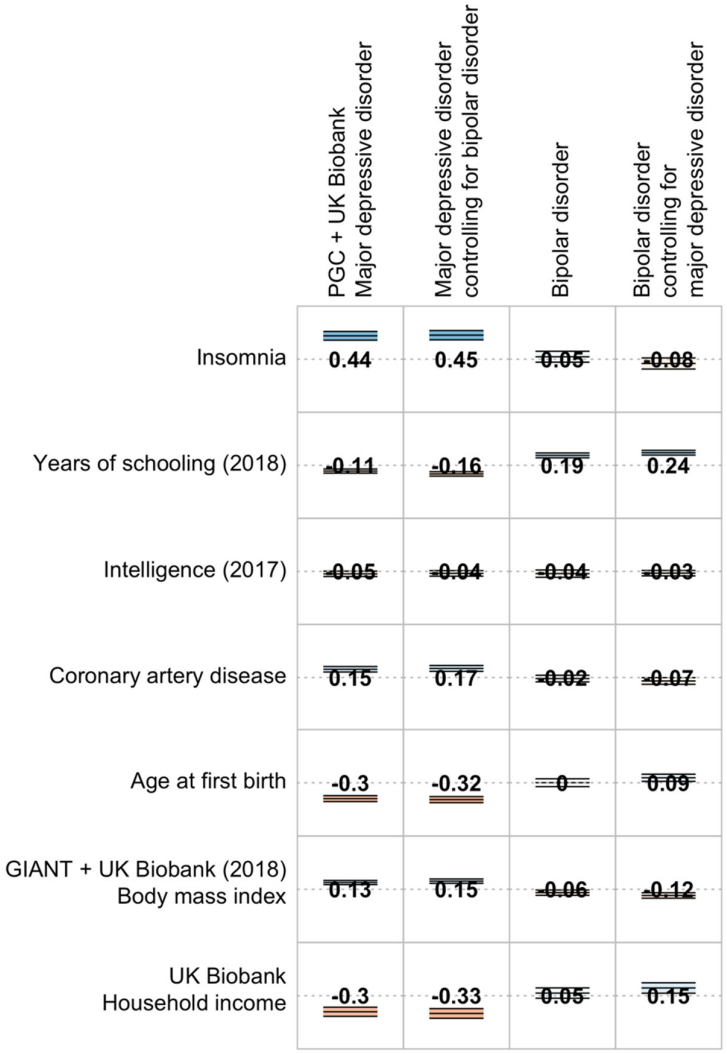
a)



Supplementary Figure 12a: Selected genetic correlations of psychiatric traits with the main and conditional analyses of MDD (combined MDD, MDDcBD), and bipolar disorder (PGC BD and BDcMDD). Full genetic correlation results are provided in Supplementary Table 5.

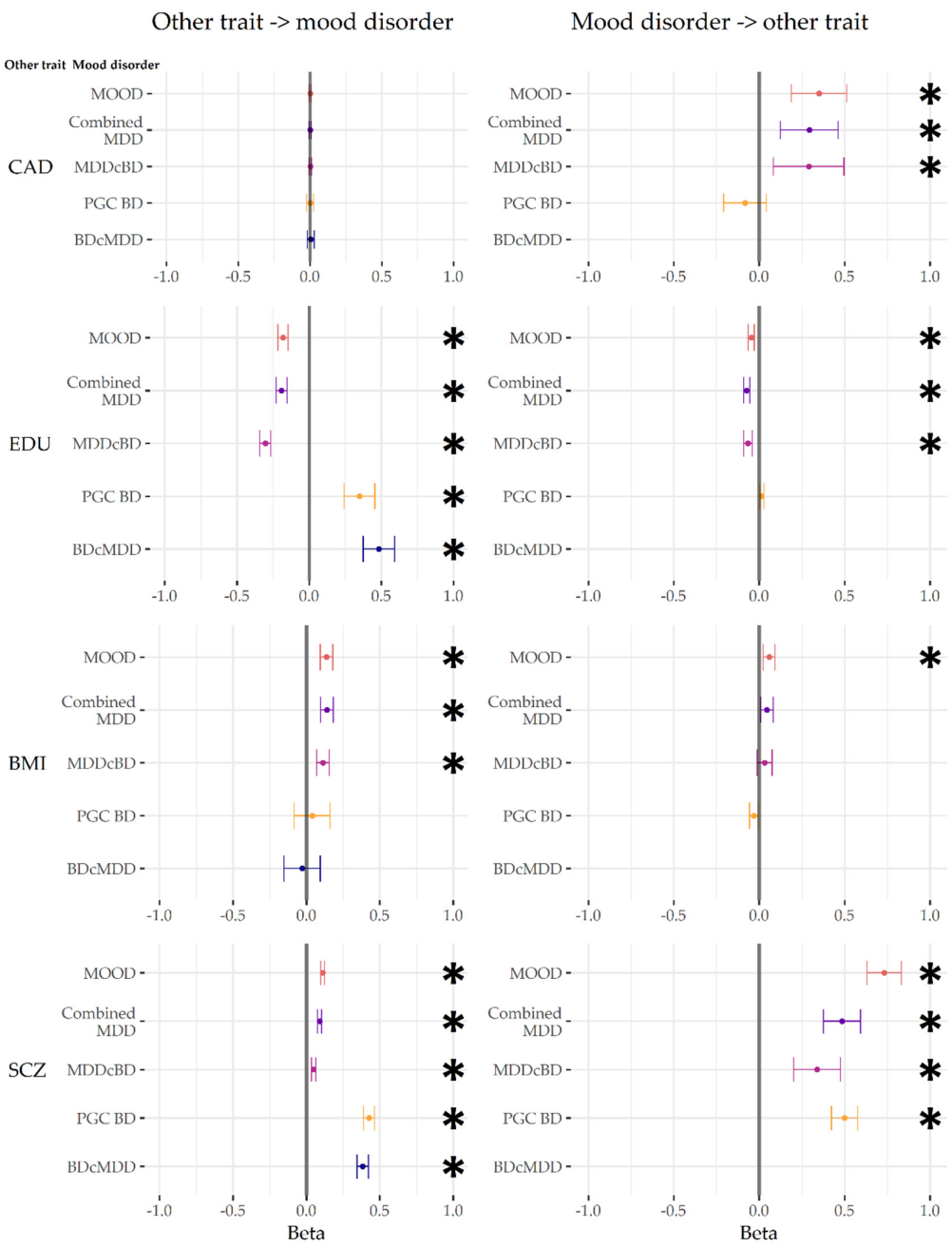
Supplementary Figure 12 (continued)

b)



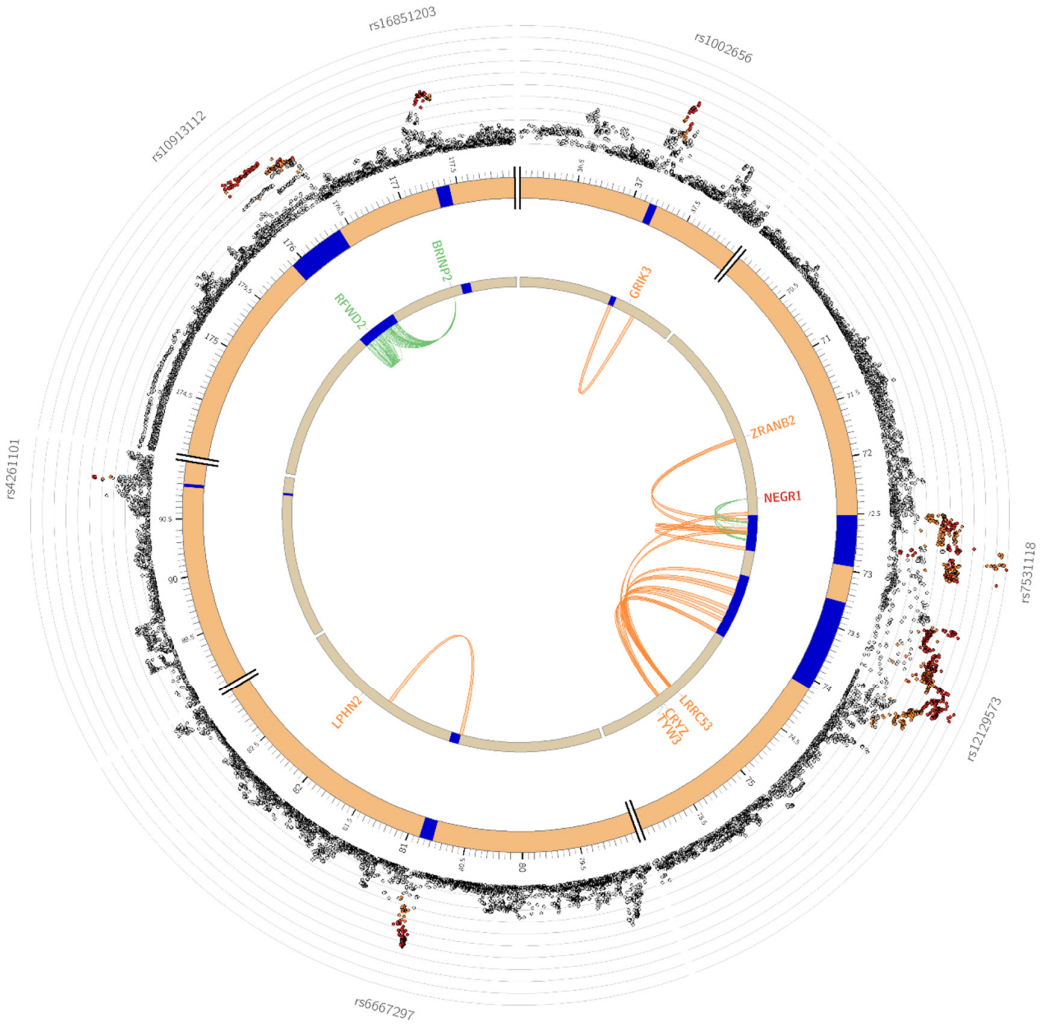
Supplementary Figure 12b: Selected genetic correlations of other traits with the main and conditional analyses of MDD (combined MDD, MDDcBD), and bipolar disorder (PGC BD and BDcMDD). Full genetic correlation results are provided in Supplementary Table 5.

Supplementary Figure 13



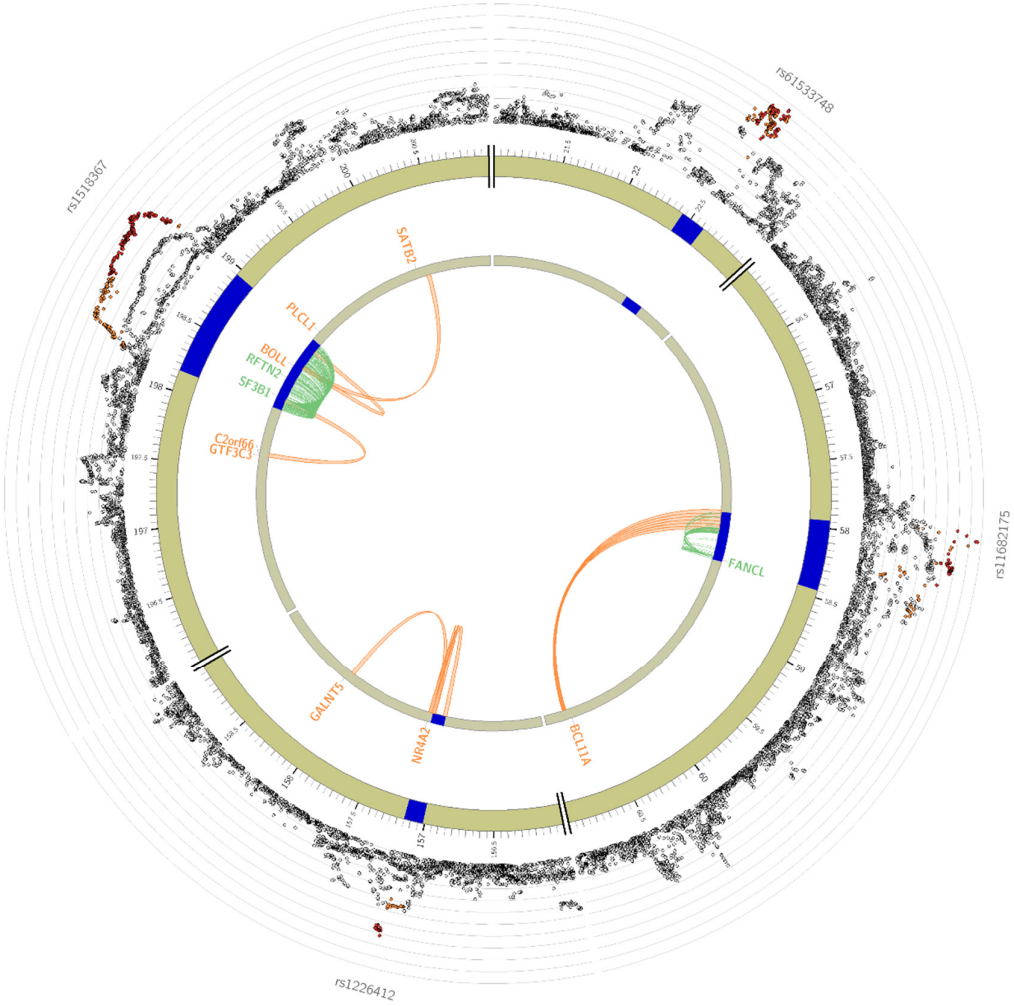
Supplementary Figure 13: GSMR results from analyses with the main meta-analysis (MOOD), the main and conditional MDD (combined MDD, MDDcBD) and bipolar disorder (PGC BD, BDcMDD) analyses. External traits are coronary artery disease (CAD), educational attainment (EDU), body mass index (BMI), and schizophrenia (SCZ). * p < 0.004 (Bonferroni correction for two-way comparisons with six external traits). For figure data, including the number of non-pleiotropic SNPs included in each instrument, see Supplementary Table 12.

Supplementary Figure 14



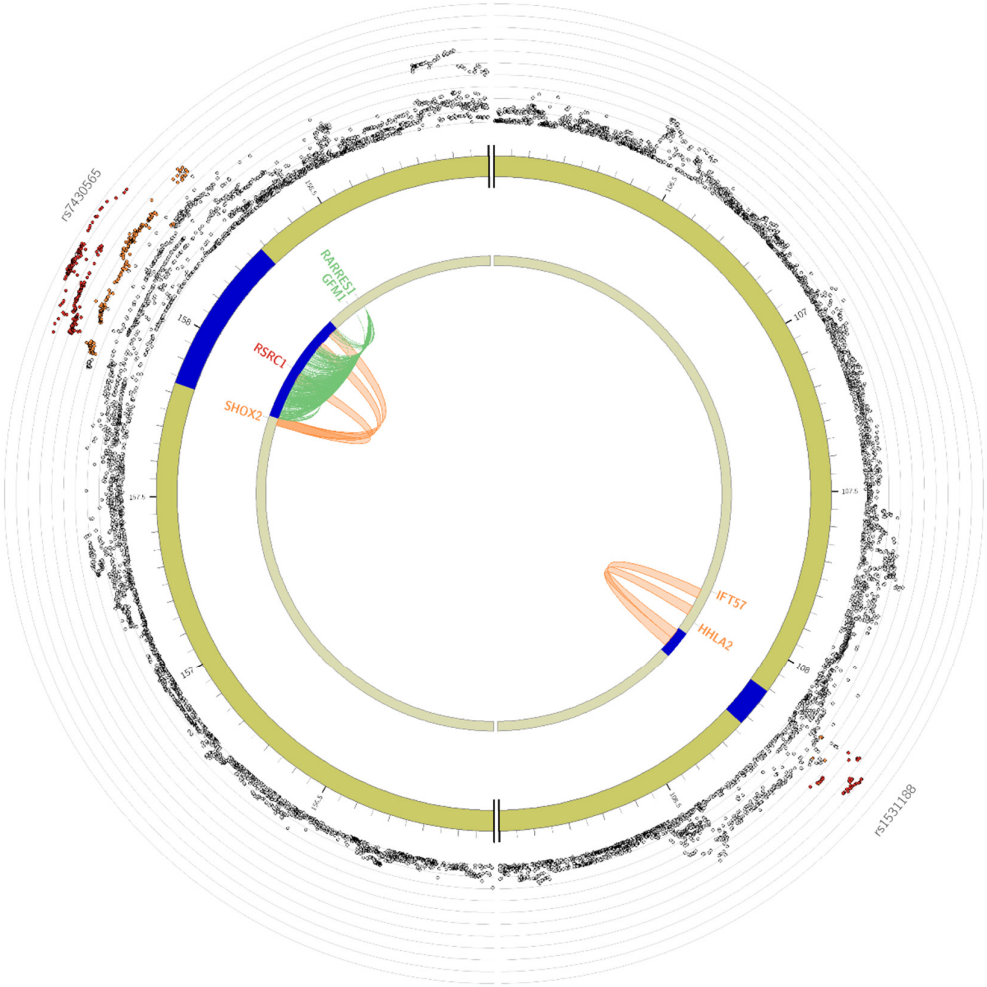
Supplementary Figure 14: Circos plot of significant loci from mood disorders (MOOD) on chromosome 1. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 15



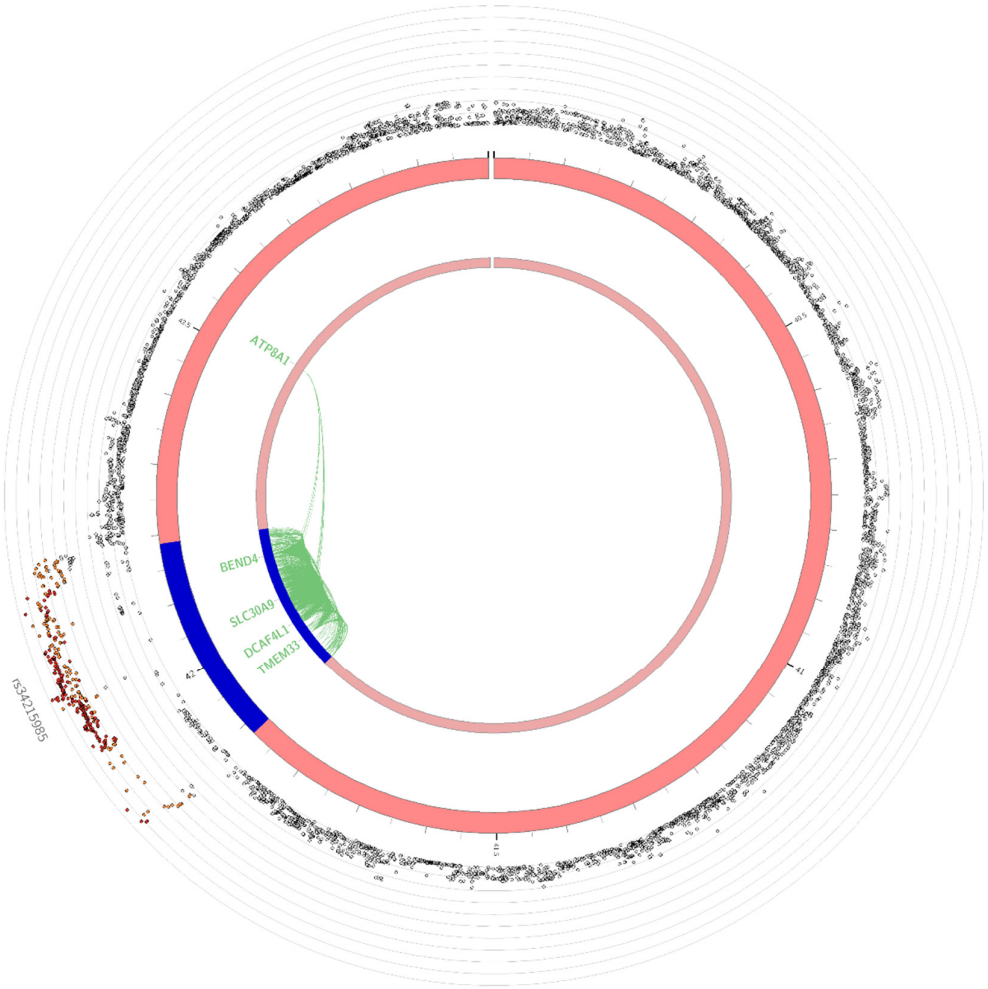
Supplementary Figure 15: Circos plot of significant loci from mood disorders (MOOD) on chromosome 2. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 16



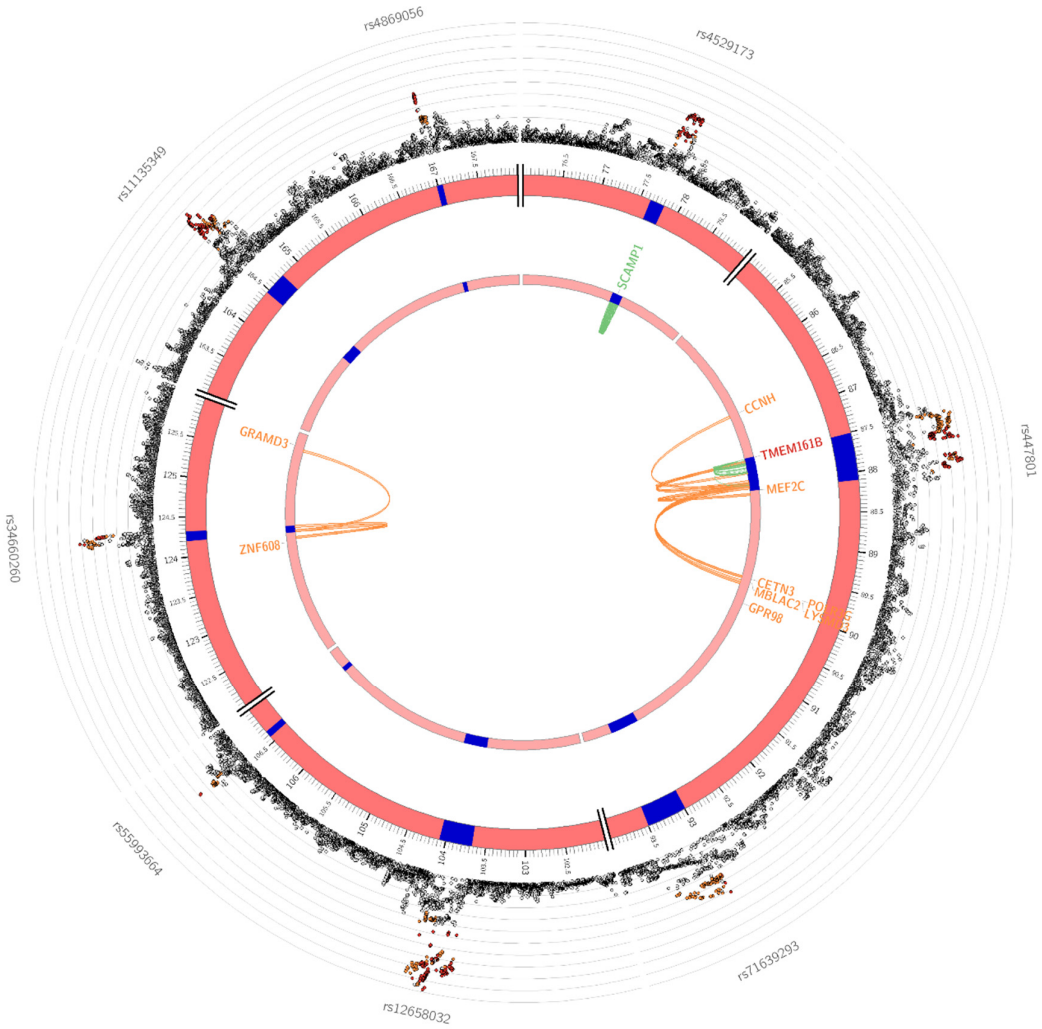
Supplementary Figure 16: Circos plot of significant loci from mood disorders (MOOD) on chromosome 3. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 17



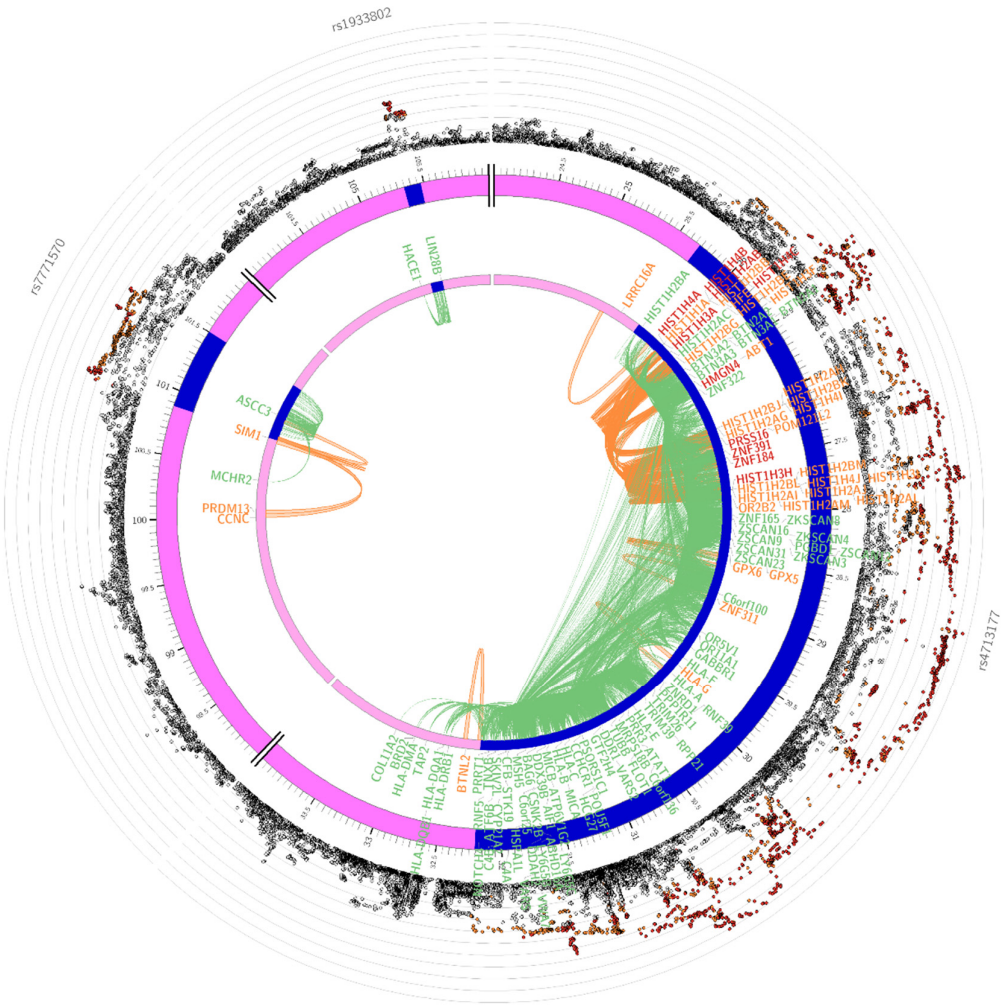
Supplementary Figure 17: Circos plot of significant loci from mood disorders (MOOD) on chromosome 4. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 18



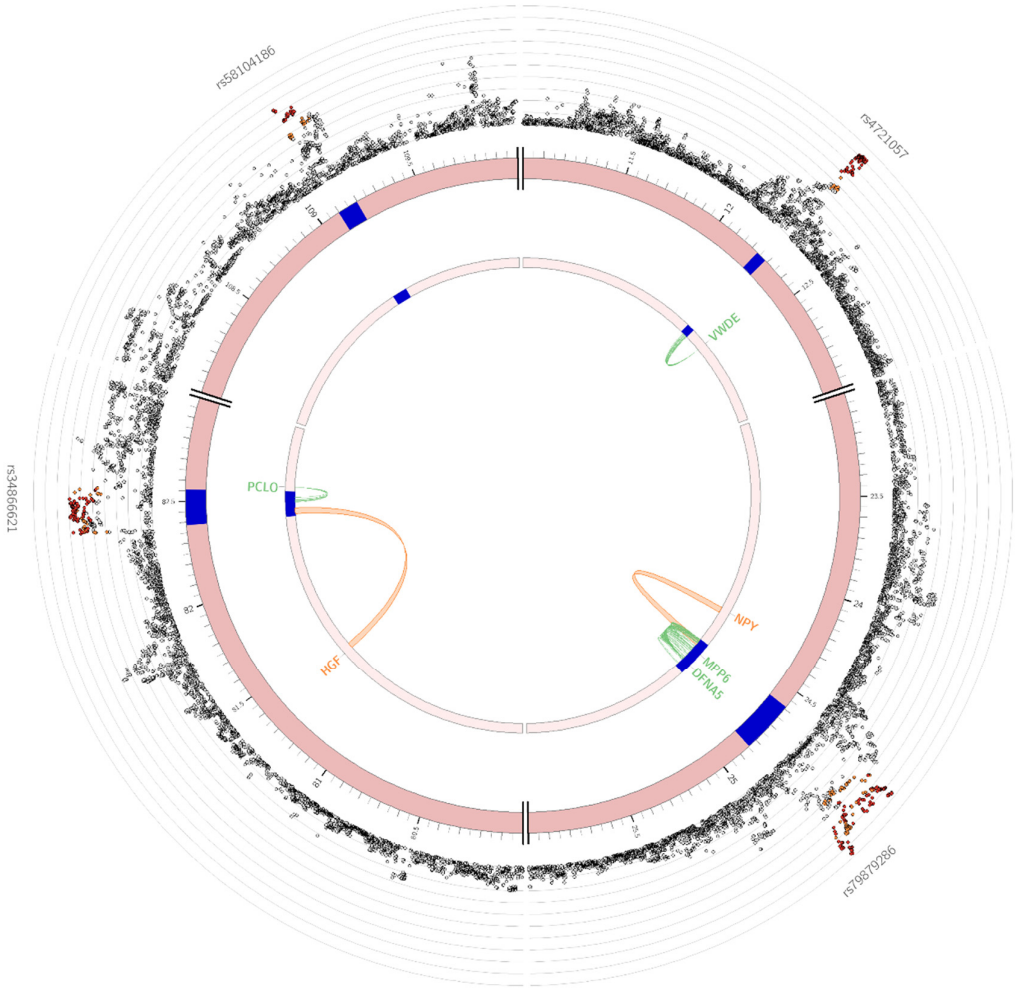
Supplementary Figure 18: Circos plot of significant loci from mood disorders (MOOD) on chromosome 5. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 19



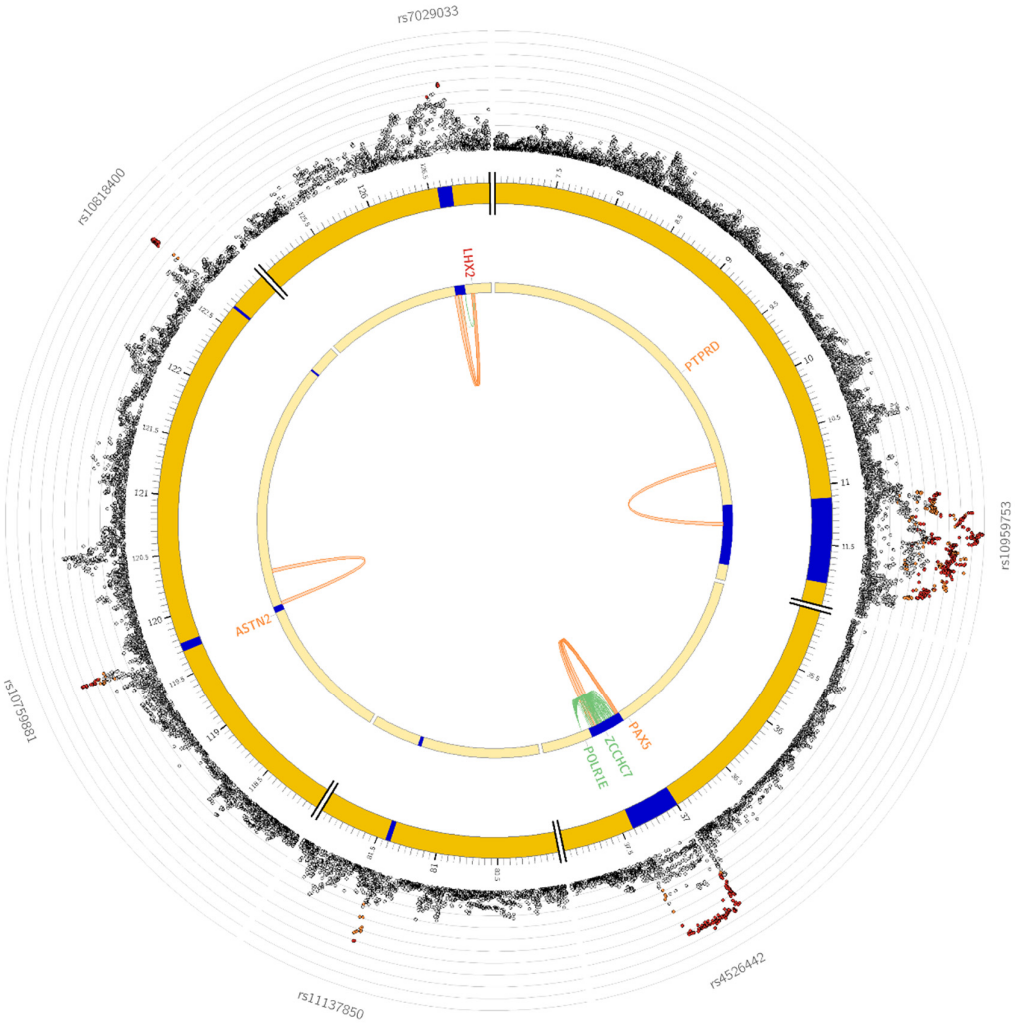
Supplementary Figure 19: Circos plot of significant loci from mood disorders (MOOD) on chromosome 6. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 20



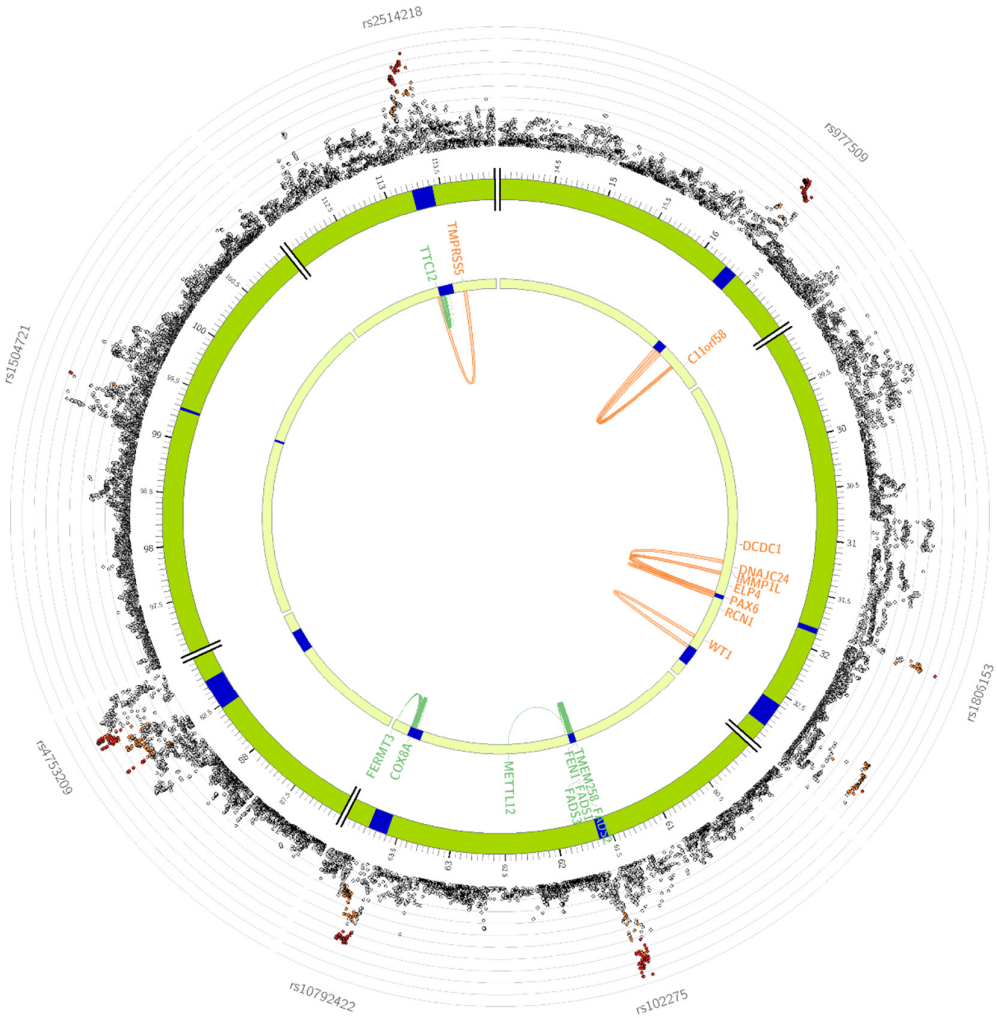
Supplementary Figure 20: Circos plot of significant loci from mood disorders (MOOD) on chromosome 7. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 21



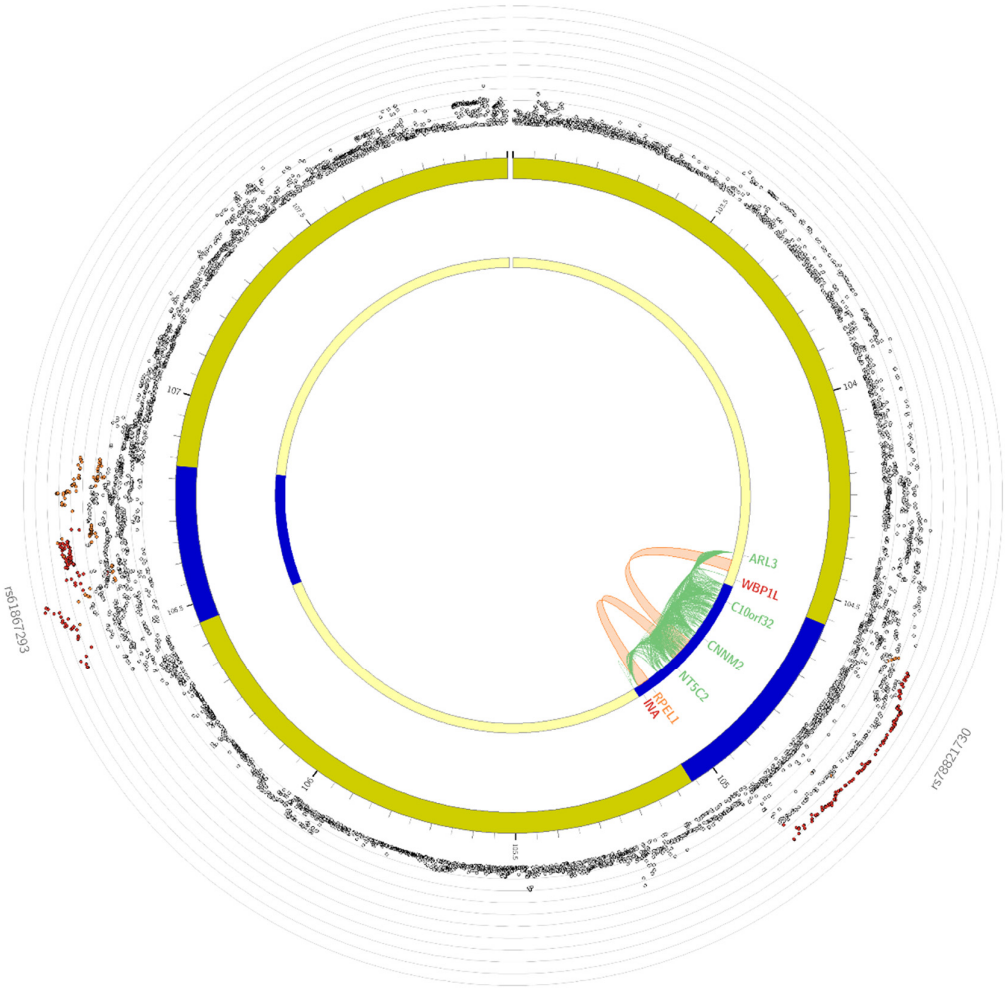
Supplementary Figure 21: Circos plot of significant loci from mood disorders (MOOD) on chromosome 9 (Note – there are no significant loci present on chromosome 8, so no circos plot is required). Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 22



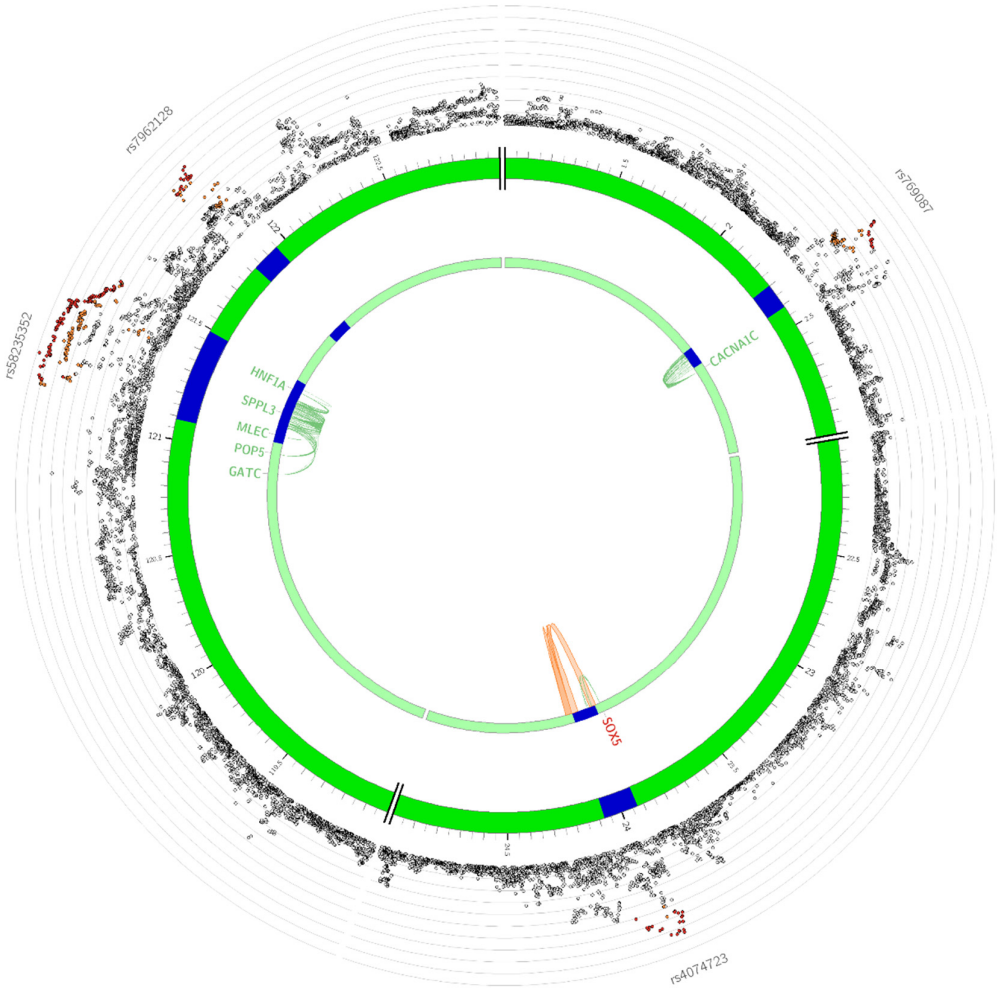
Supplementary Figure 22: Circos plot of significant loci from mood disorders (MOOD) on chromosome 10. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 23



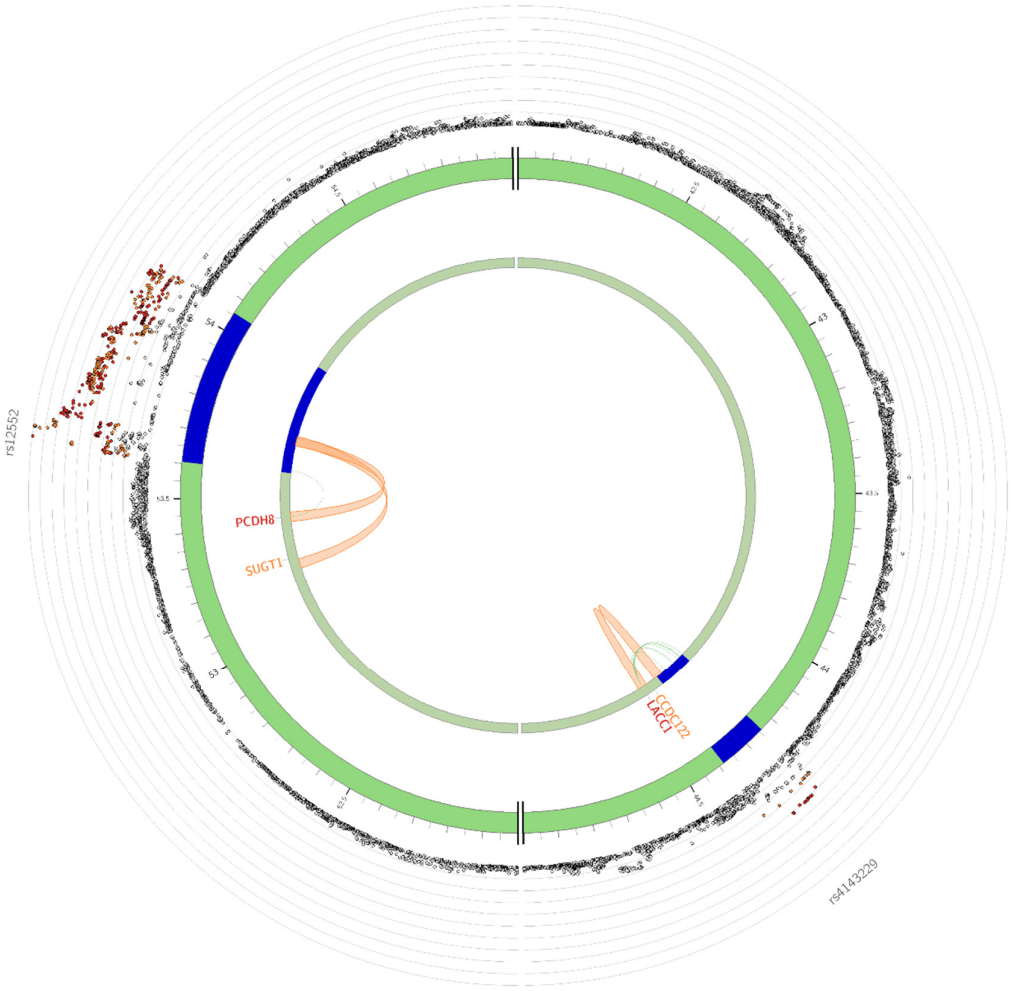
Supplementary Figure 23: Circos plot of significant loci from mood disorders (MOOD) on chromosome 11. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 24



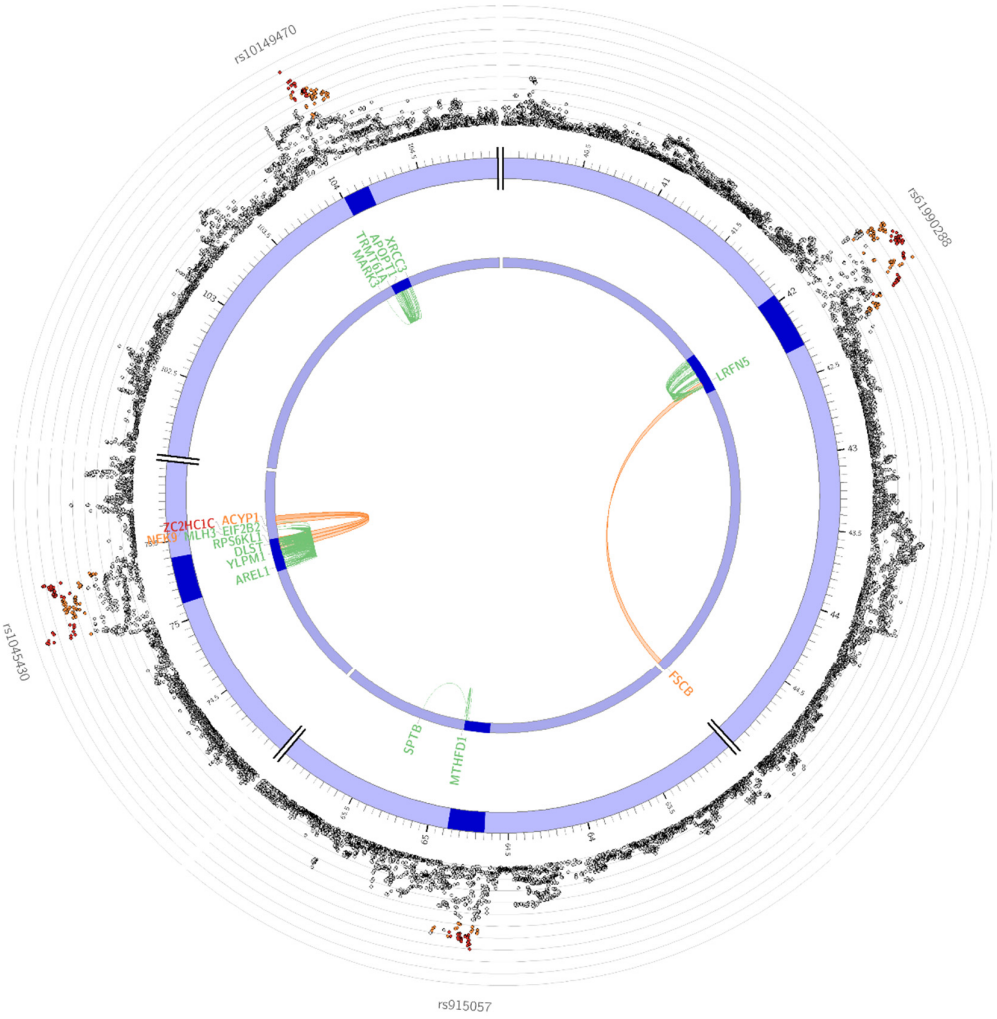
Supplementary Figure 24: Circos plot of significant loci from mood disorders (MOOD) on chromosome 12. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 25



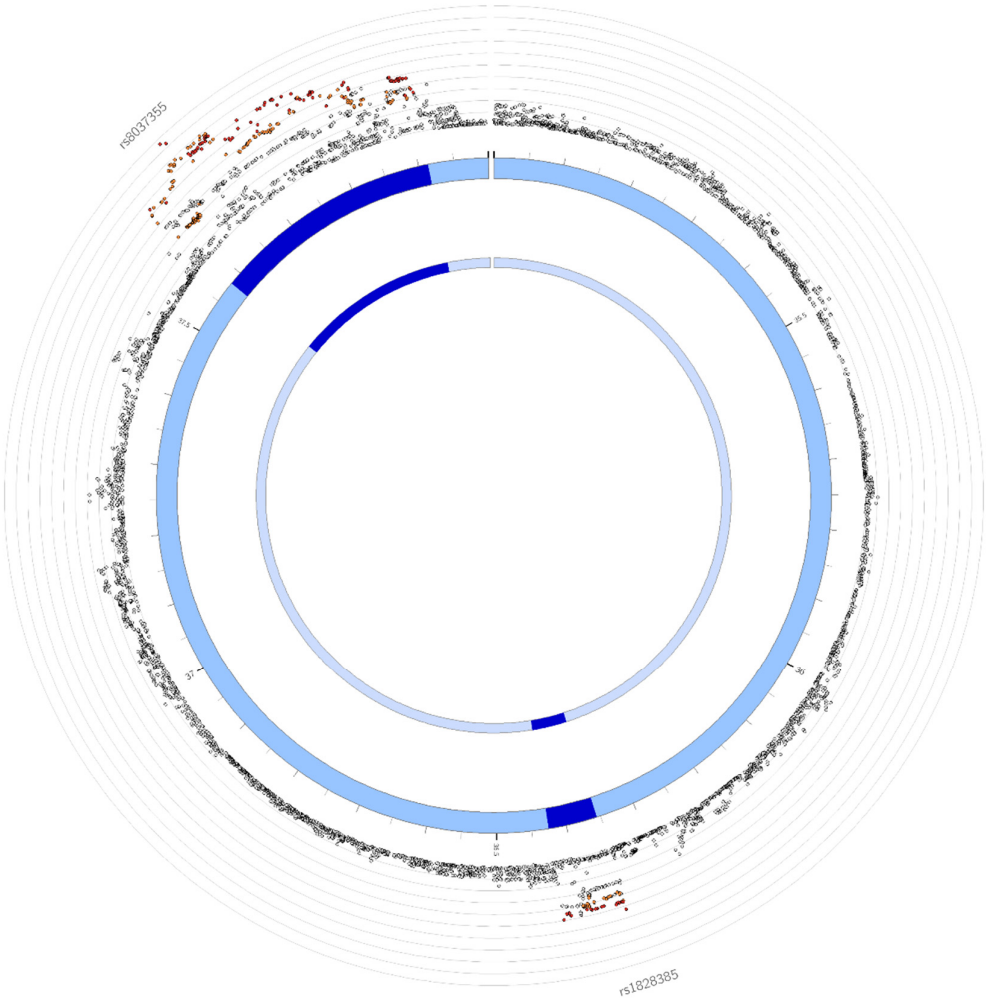
Supplementary Figure 25: Circos plot of significant loci from mood disorders (MOOD) on chromosome 13. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 26



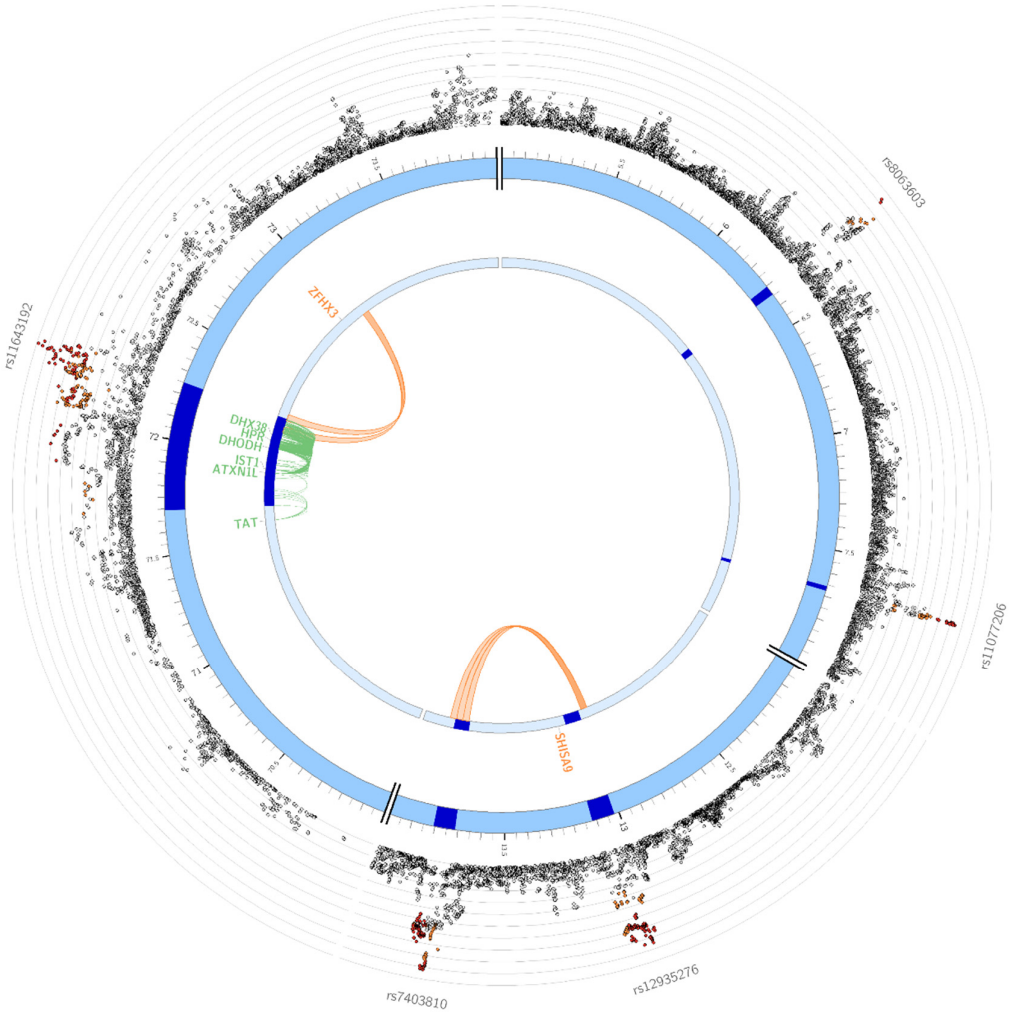
Supplementary Figure 26: Circos plot of significant loci from mood disorders (MOOD) on chromosome 14. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 27



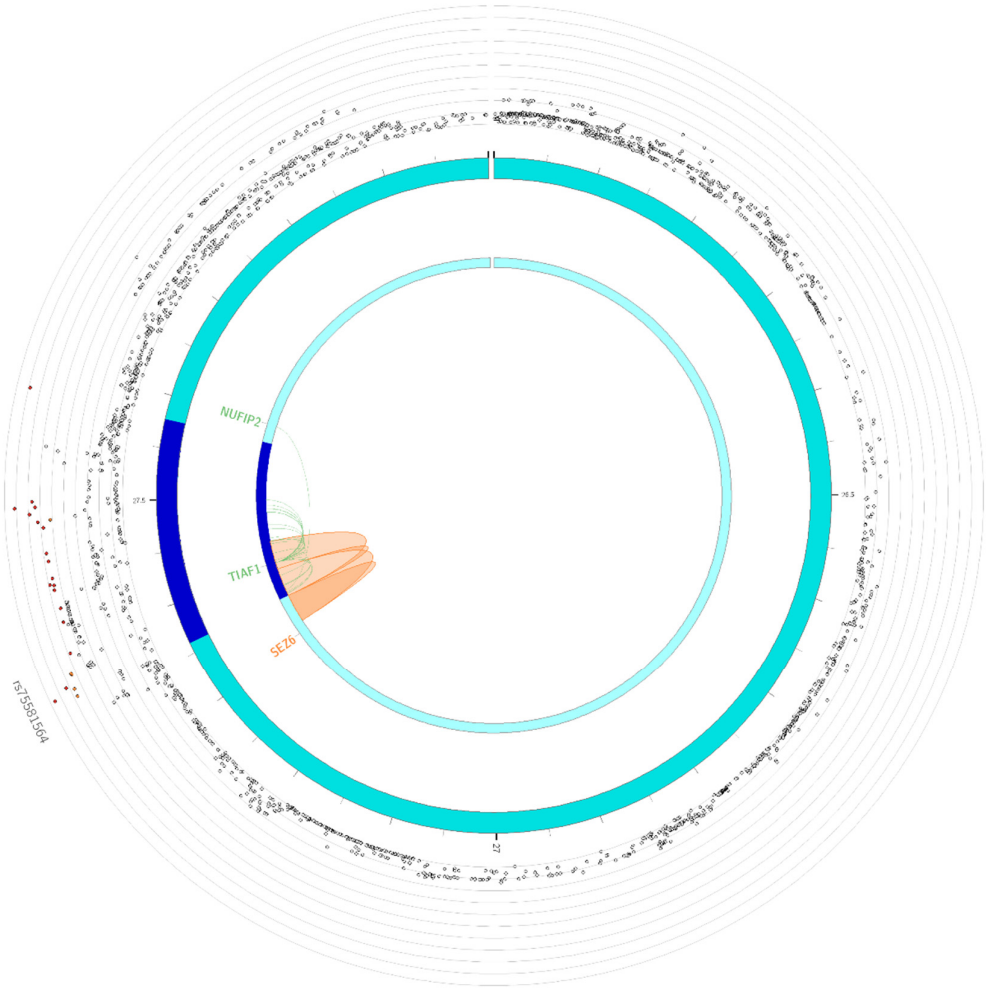
Supplementary Figure 27: Circos plot of significant loci from mood disorders (MOOD) on chromosome 15. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 28



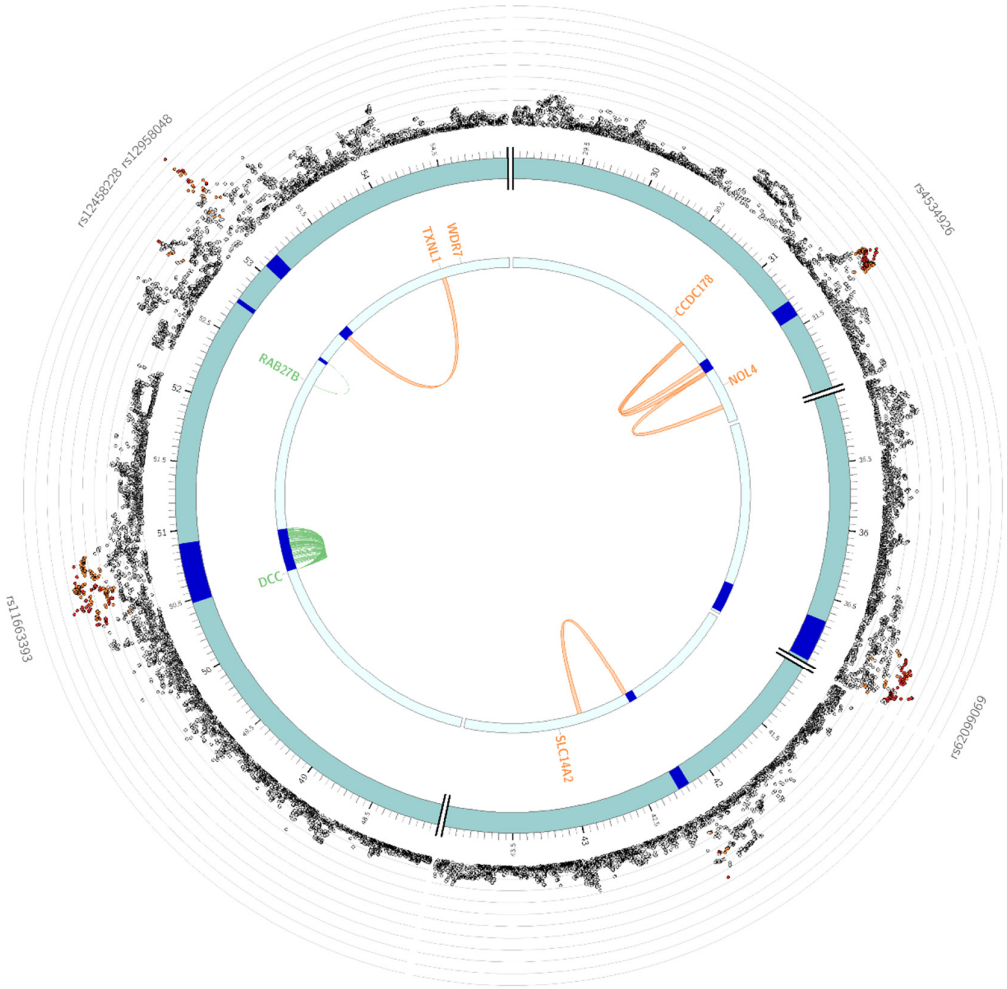
Supplementary Figure 28: Circos plot of significant loci from mood disorders (MOOD) on chromosome 16. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 29



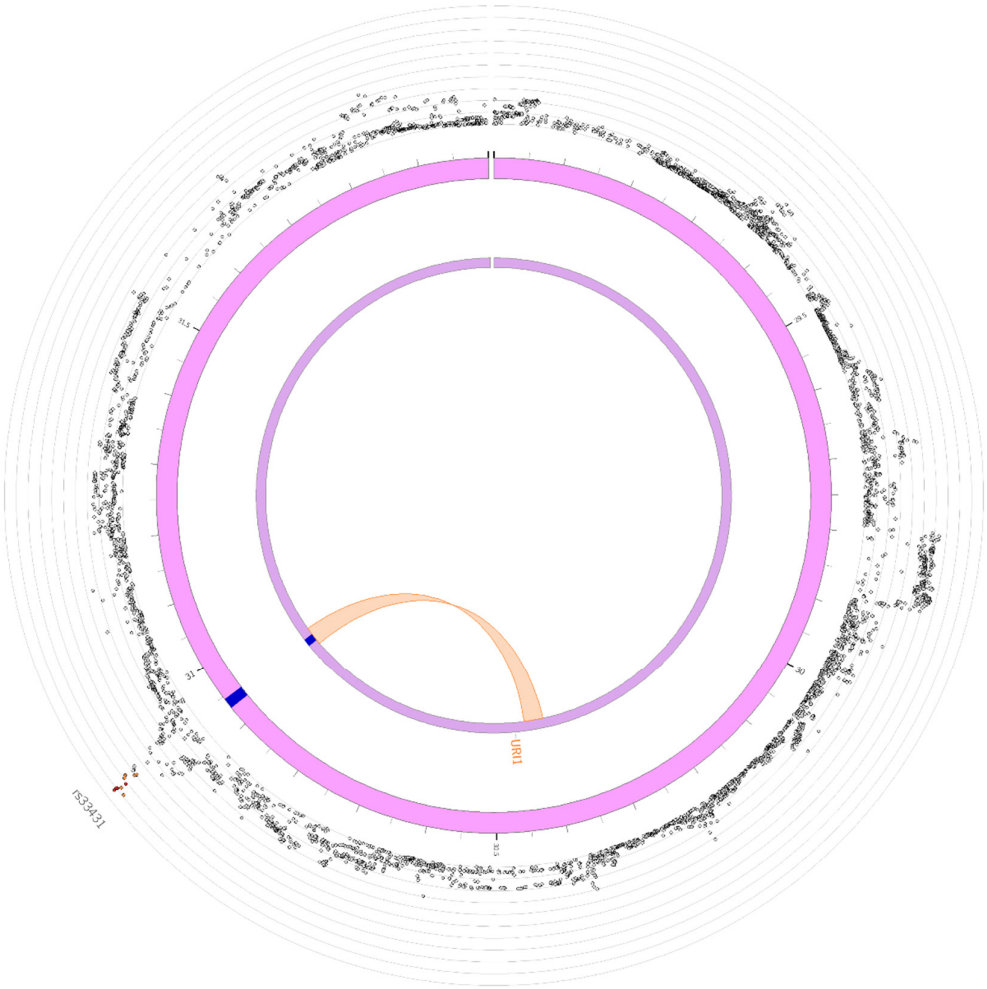
Supplementary Figure 29: Circos plot of significant loci from mood disorders (MOOD) on chromosome 17. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 30



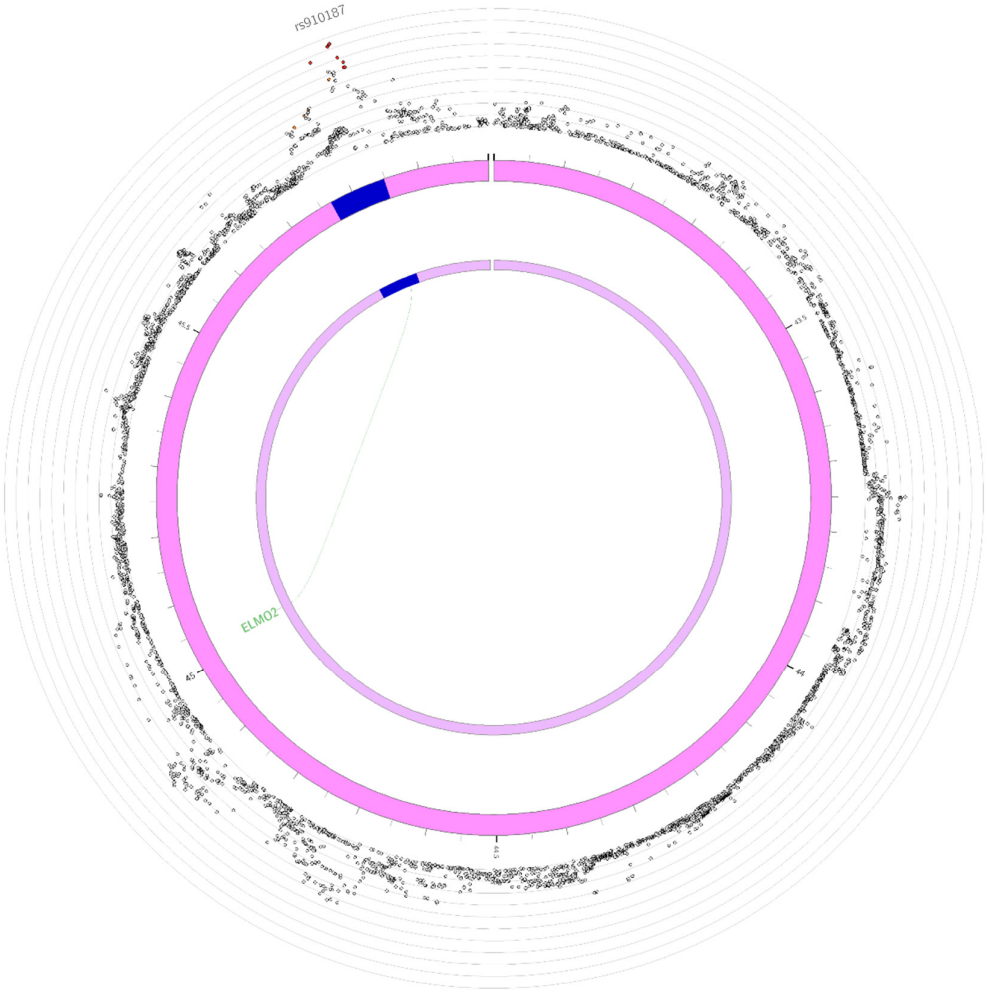
Supplementary Figure 30: Circos plot of significant loci from mood disorders (MOOD) on chromosome 18. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 31



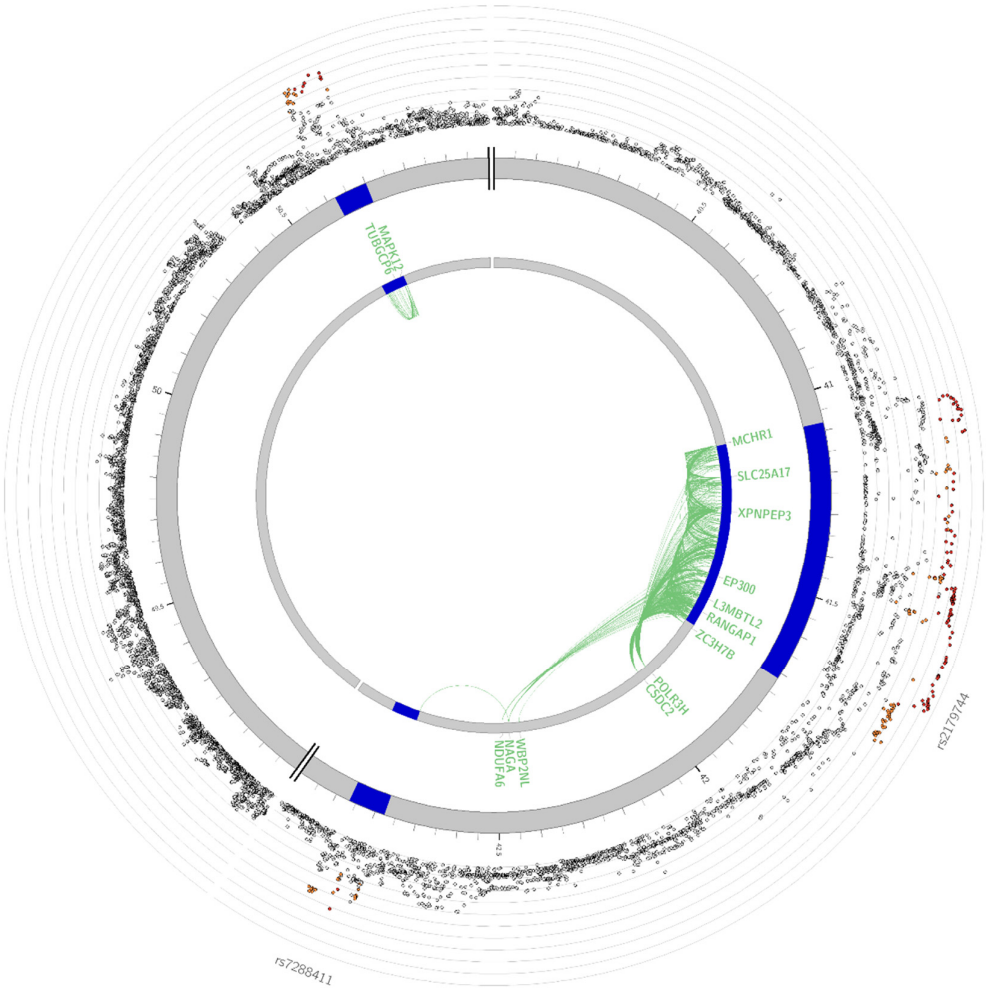
Supplementary Figure 31: Circos plot of significant loci from mood disorders (MOOD) on chromosome 19. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 32



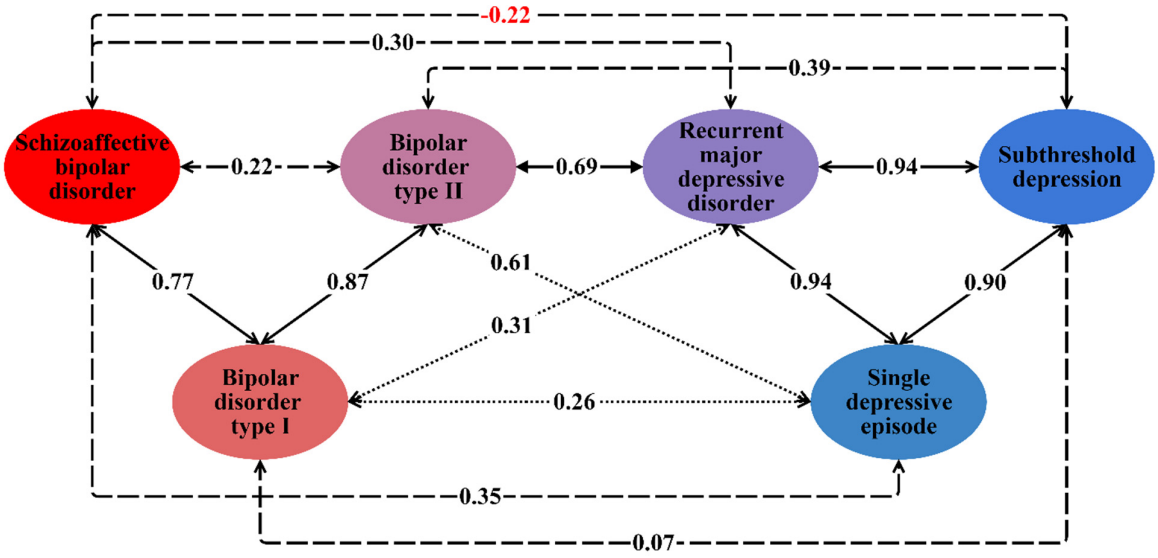
Supplementary Figure 32: Circos plot of significant loci from mood disorders (MOOD) on chromosome 20. Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 33



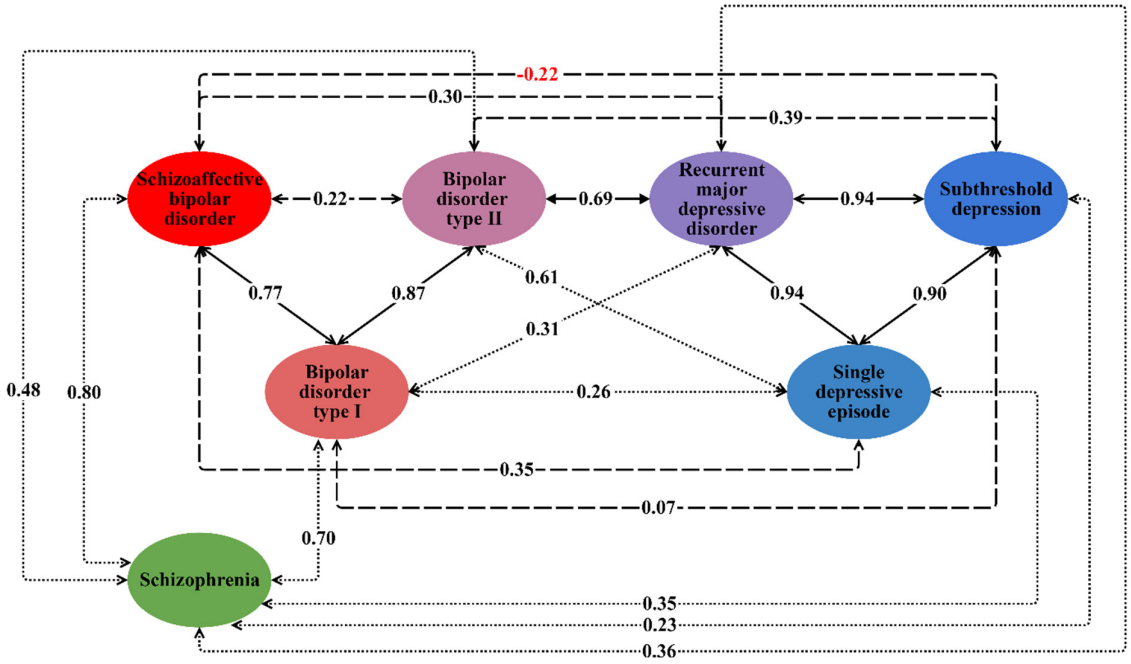
Supplementary Figure 33: Circos plot of significant loci from mood disorders (MOOD) on chromosome 22 (Note – there are no significant loci present on chromosome 21, so no circos plot is required). Outer circle: Plot of individual variants in each locus, coloured by LD to labelled index variant (r2 0.8 -> 1, orange -> red). Middle ring: position of locus on chromosome, loci shown in blue. Inner ring: Links between loci and nearby genes, by eQTLs (green), chromatin contacts (orange) or both (red)

Supplementary Figure 34



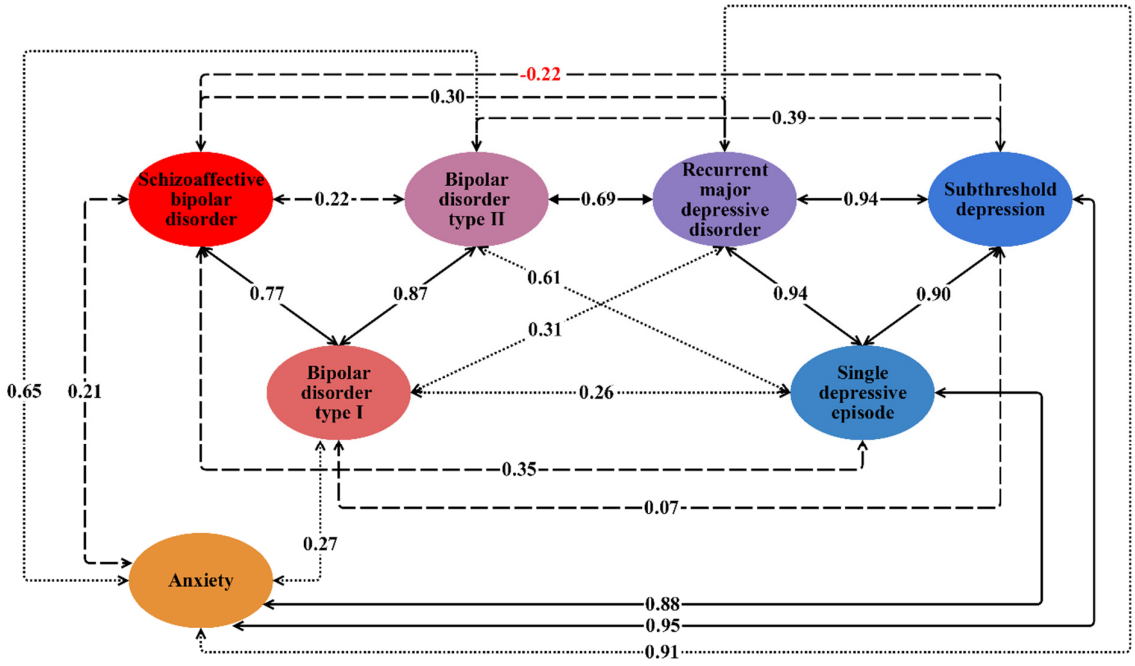
Supplementary Figure 34: Genetic correlations across the mood disorder spectrum, with all paths. Arrows labels show genetic correlations. Solid arrows represent genetic correlations significantly different from 0 and not significantly different from 1.
Dotted arrows represent genetic correlations significantly different from 0 and from 1.
Dashed arrows represent genetic correlations not significantly different from 0.
Significance in both cases means $p < 0.00333$ (Bonferroni correction for 15 tests).

Supplementary Figure 35



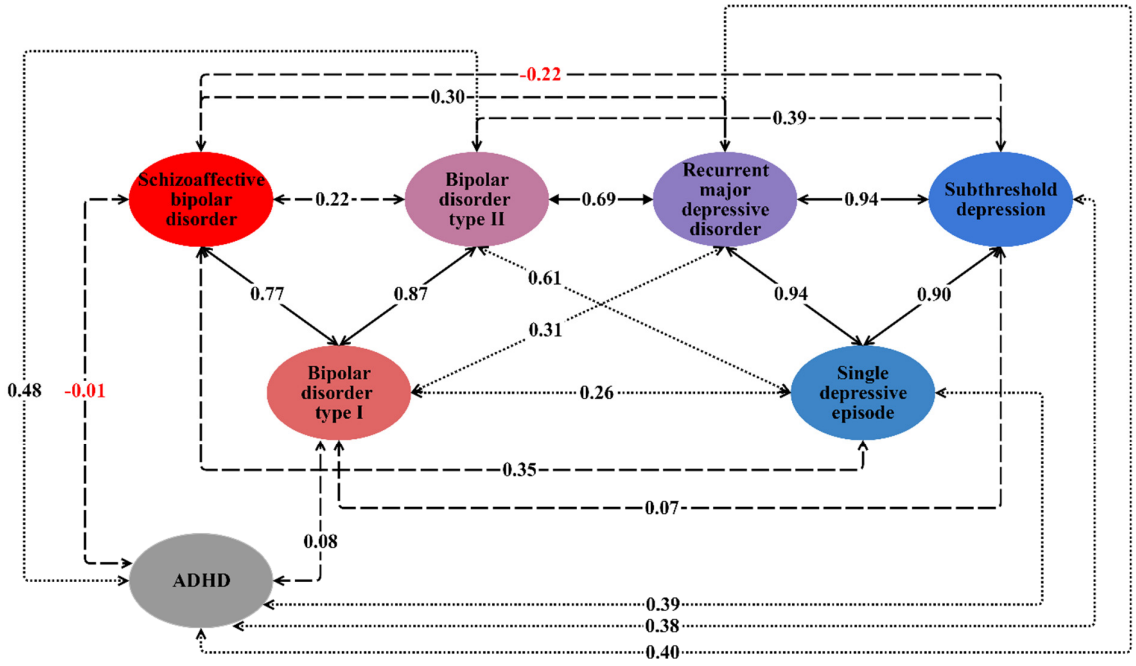
Supplementary Figure 35: Genetic correlations across the mood disorder spectrum with all paths (as Supplementary Figure 34), in the context of genetic correlations with schizophrenia. Arrows labels show genetic correlations. Solid arrows represent genetic correlations significantly different from 0 and not significantly different from 1. Dotted arrows represent genetic correlations significantly different from 0 and from 1. Dashed arrows represent genetic correlations not significantly different from 0. For consistency with Supplementary Figure 31, significance in both cases means $p < 0.00333$ (Bonferroni correction for 15 tests).

Supplementary Figure 36



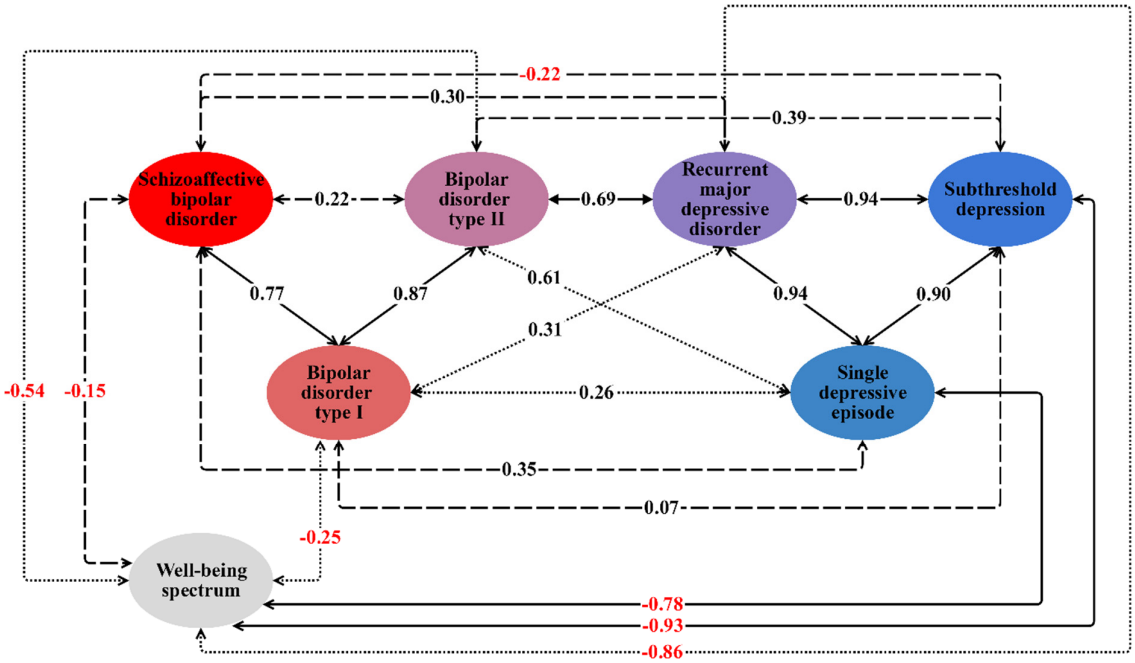
Supplementary Figure 36: Genetic correlations across the mood disorder spectrum with all paths (as Supplementary Figure 34), in the context of genetic correlations with anxiety. Arrows labels show genetic correlations. Solid arrows represent genetic correlations significantly different from 0 and not significantly different from 1.
Dotted arrows represent genetic correlations significantly different from 0 and from 1.
Dashed arrows represent genetic correlations not significantly different from 0.
For consistency with Supplementary Figure 31, significance in both cases means $p < 0.00333$ (Bonferroni correction for 15 tests).

Supplementary Figure 37



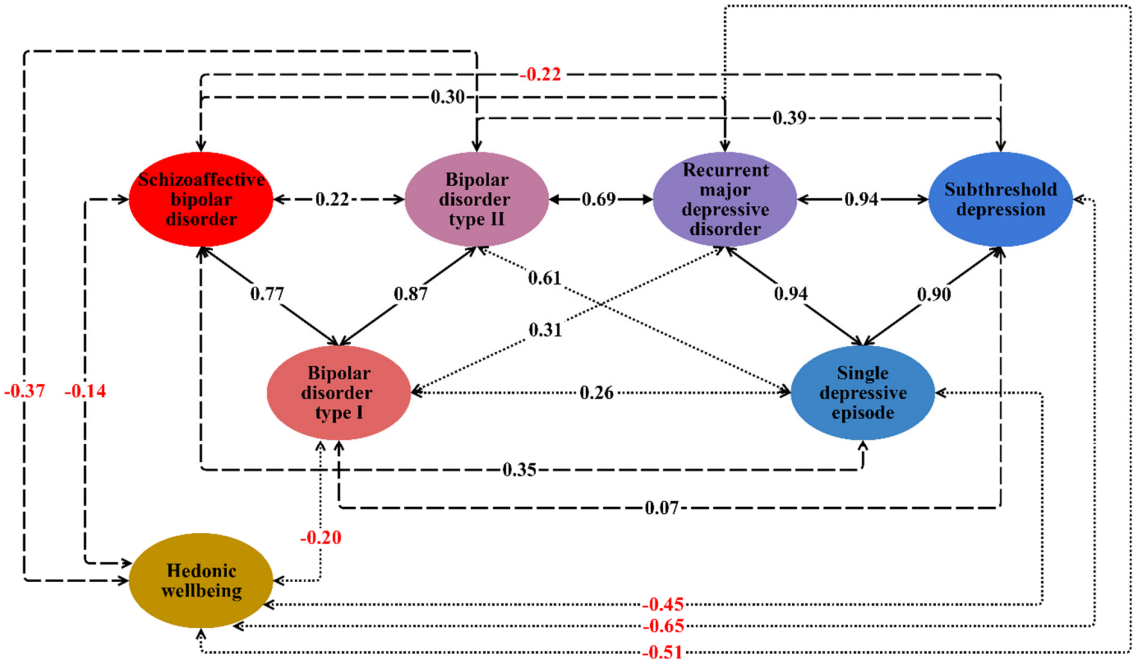
Supplementary Figure 37: Genetic correlations across the mood disorder spectrum with all paths (as Supplementary Figure 34), in the context of genetic correlations with ADHD. Arrows labels show genetic correlations. Solid arrows represent genetic correlations significantly different from 0 and not significantly different from 1. Dotted arrows represent genetic correlations significantly different from 0 and from 1. Dashed arrows represent genetic correlations not significantly different from 0. For consistency with Supplementary Figure 31, significance in both cases means $p < 0.00333$ (Bonferroni correction for 15 tests).

Supplementary Figure 38



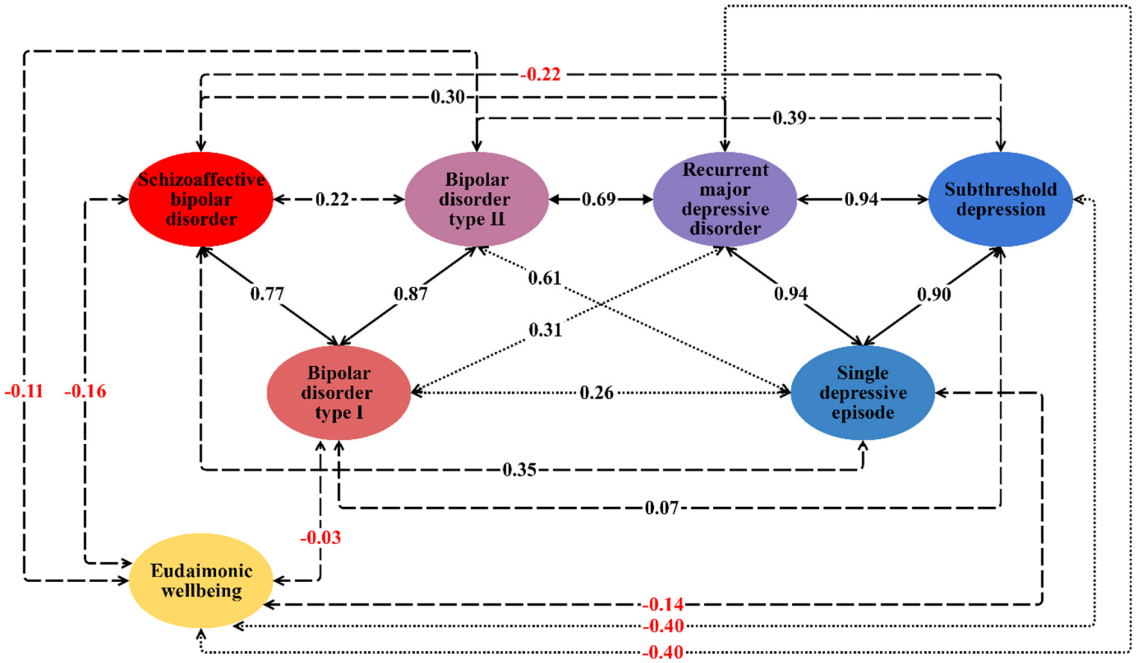
Supplementary Figure 38: Genetic correlations across the mood disorder spectrum with all paths (as Supplementary Figure 34), in the context of genetic correlations with the well-being spectrum. Arrows labels show genetic correlations. Solid arrows represent genetic correlations significantly different from 0 and not significantly different from 1. Dotted arrows represent genetic correlations significantly different from 0 and from 1. Dashed arrows represent genetic correlations not significantly different from 0. For consistency with Supplementary Figure 31, significance in both cases means $p < 0.00333$ (Bonferroni correction for 15 tests).

Supplementary Figure 39



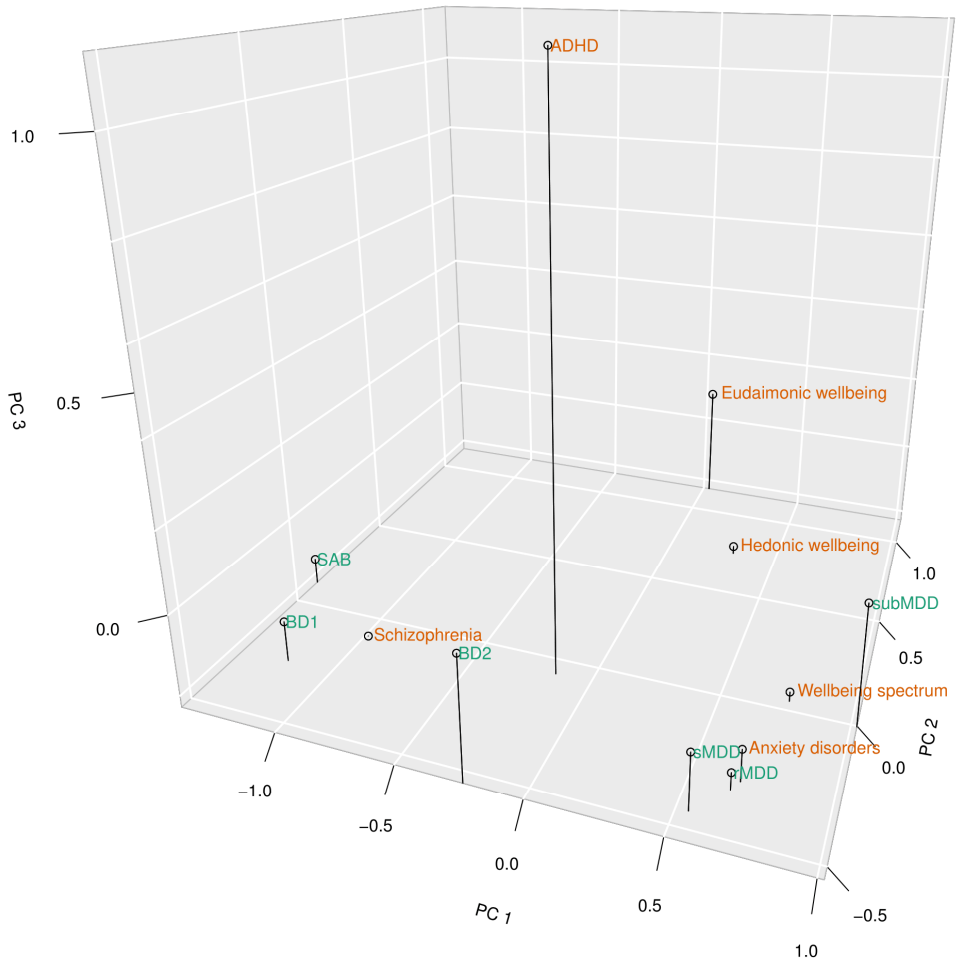
Supplementary Figure 39: Genetic correlations across the mood disorder spectrum with all paths (as Supplementary Figure 34), in the context of genetic correlations with hedonic well-being. Arrows labels show genetic correlations. Solid arrows represent genetic correlations significantly different from 0 and not significantly different from 1.
Dotted arrows represent genetic correlations significantly different from 0 and from 1.
Dashed arrows represent genetic correlations not significantly different from 0.
For consistency with Supplementary Figure 31, significance in both cases means $p < 0.00333$ (Bonferroni correction for 15 tests).

Supplementary Figure 40



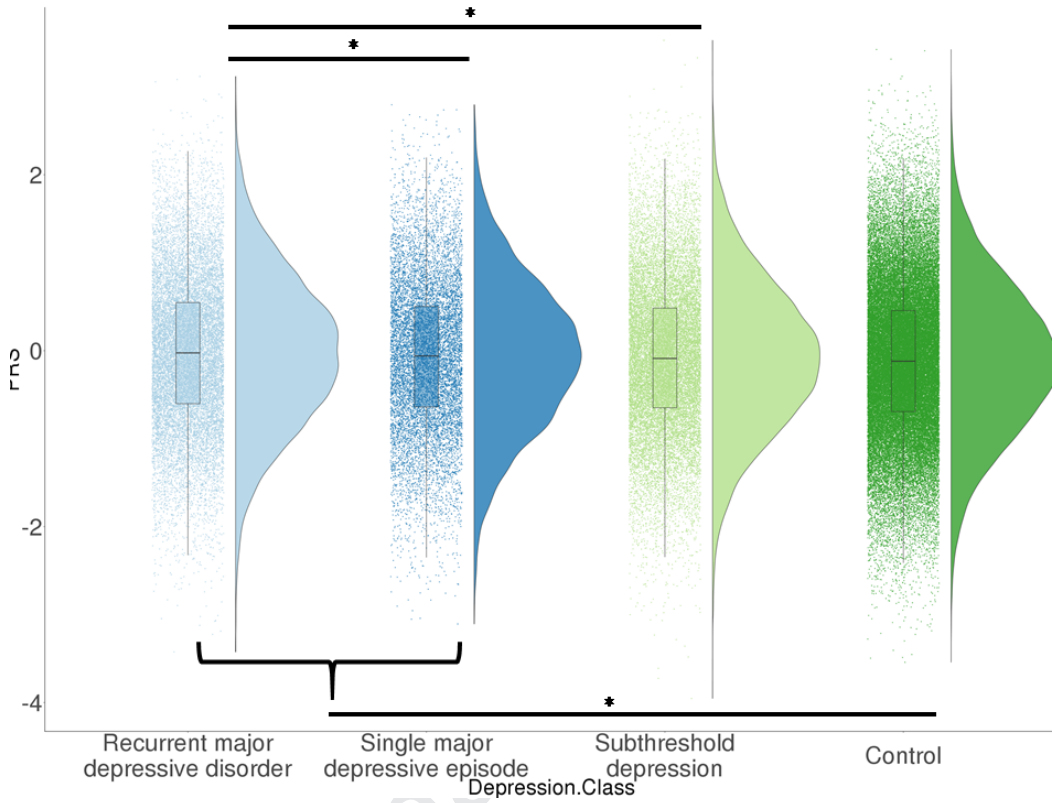
Supplementary Figure 40: Genetic correlations across the mood disorder spectrum with all paths (as Supplementary Figure 34), in the context of genetic correlations with eudaimonic well-being. Arrows labels show genetic correlations. Solid arrows represent genetic correlations significantly different from 0 and not significantly different from 1. Dotted arrows represent genetic correlations significantly different from 0 and from 1. Dashed arrows represent genetic correlations not significantly different from 0. For consistency with Supplementary Figure 31, significance in both cases means $p < 0.00333$ (Bonferroni correction for 15 tests).

Supplementary Figure 41



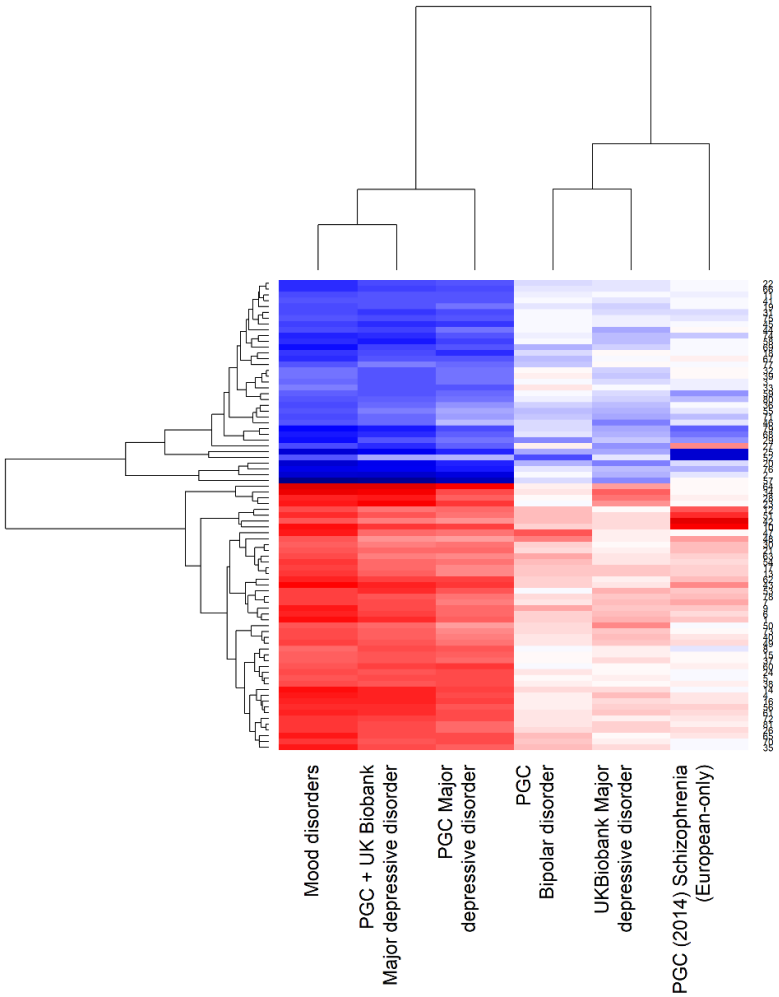
Supplementary Figure 41: Three-dimensional scatterplot of the first three principal components of the genetic correlation matrix of the mood disorder subtypes (green labels) with six external GWAS (orange labels). Principal component (PC) 1 separates BD1, SAB and schizophrenia from the depressive disorders, with BD2 and ADHD intermediate. PC2 separates eudaimonic and hedonic wellbeing from the other phenotypes. PC3 separates ADHD from the other phenotypes.

Supplementary Figure 42



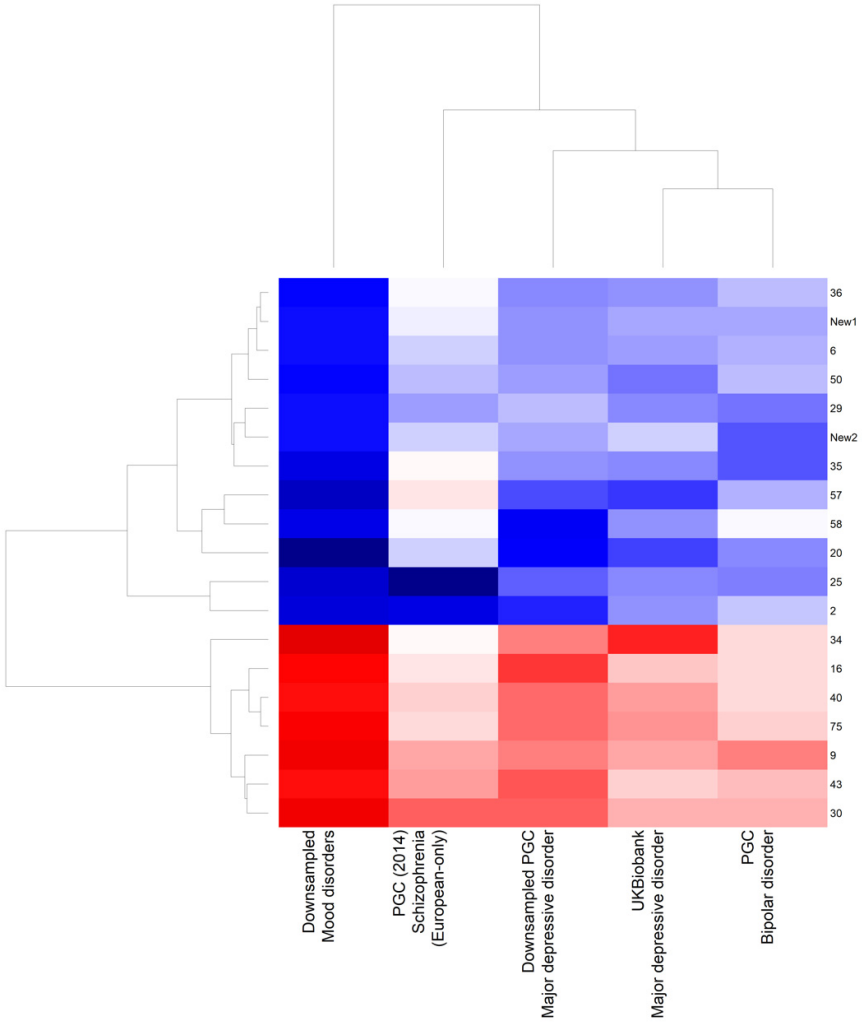
Supplementary Figure 42: Distribution of polygenic risk scores derived from PGC BD (pThresh = 0.2) in individuals with recurrent major depressive disorder (rMDD cases), single episode major depressive disorder (sMDD cases), subthreshold depression (subMDD pseudo-cases) and controls. Black bars - significant differences in means (empirical $p < 0.05$)

Supplementary Figure 43



Supplementary Figure 43: Hierarchical clustering of the significant loci from the mood disorders meta-analysis (MOOD) with the same loci from PGC MDD, UKB MDD, PGC BD, and SCZ. Blue = positive direction of effect. Red = negative direction of effect.

Supplementary Figure 44



Supplementary Figure 44: Hierarchical clustering of the significant loci from the down-sampled mood disorders meta-analysis (down-sampled MOOD) with the same loci from down-sampled PGC MDD, UKB MDD, PGC BD, and SCZ. Blue = positive direction of effect. Red = negative direction of effect.