

Immune, Developmental, and Synaptic Pathways Define Bipolar Disorder Clinical

Heterogeneity

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Key Points

Question What are the distinct genetic architectures underlying the clinical heterogeneity of bipolar disorder?

Findings In this genetic study of 23,819 bipolar disorder (BD) cases and 163,839 controls, clinical heterogeneity mapped onto four genetically-informed dimensions. A severe illness dimension was defined by a neuro-immune signature (*HLA-DMB*) shared with schizophrenia. An affective comorbidity dimension was distinguished by neurodevelopmental pathways involving axonal guidance (*DCC*). Notably, the rapid-cycling phenotype showed evidence of purifying selection, suggesting influence by rare, highly penetrant alleles.

Meaning These findings provide a data-driven biological framework for bipolar disorder, guiding future research toward patient stratification and targeted therapeutics.

Abstract

Importance The clinical heterogeneity of bipolar disorder (BD) is a major obstacle to improving diagnosis, predicting patient outcomes, and developing personalized treatments. A genetic approach is needed to deconstruct the disorder and uncover its fundamental biology. Previous genetic studies focusing on broad diagnostic categories have been limited in their ability to parse this complexity.

Objective To test the hypothesis that clinically distinct subphenotypes of BD are associated with different underlying common variant genetic architectures.

Design, Setting, and Participants This multicenter study included a primary genome-wide association study (GWAS) of up to 23,819 bipolar disorder (BD) cases and 163,839 controls. These results were integrated via multi-trait analysis of GWAS (MTAG) with external summary statistics for BD (59,287 cases; 781,022 controls) and schizophrenia (SCZ; 53,386 cases; 77,258 controls). Sample overlap was statistically accounted for.

Main Outcomes and Measures The primary outcomes were the genetic dimensions underlying BD heterogeneity, differentiated by single nucleotide polymorphism (SNP)-heritability (h^2_{SNP}), genetic correlations, genomic loci ($P \leq 5 \times 10^{-8}$), and functional, cell-type, and gene-expression pathway analyses.

Results We identified four genetically-informed dimensions of BD: Severe Illness, Core Mania, Externalizing/Impulsive Comorbidity, and Internalizing/Affective Comorbidity. The analyses yielded up to 181 subphenotype-associated loci, 53 of which are novel. The Severe Illness Dimension was characterized by a unique neuro-immune signature (a protective association with *HLA-DMB*, $P = 2.50 \times 10^{-273}$) evident only when leveraging SCZ genetic data. The Internalizing/Affective dimension was associated with neurodevelopmental genes (e.g., *DCC*). Notably, the rapid-cycling subphenotype showed a unique signature of strong negative selection, a finding not observed in other subphenotypes.

Conclusions and Relevance

The clinical heterogeneity of bipolar disorder appears to be defined by a complex and multi-layered genetic architecture. The presented findings provide an empirical framework that may advance psychiatric nosology beyond its current diagnostic boundaries. These results may also inform future research to identify targets for

personalized interventions. The delineation of these genetically-informed dimensions offers specific, biologically-grounded hypotheses for subsequent therapeutic discovery. Establishing such a framework is an essential step toward refining diagnostic criteria and developing more effective, personalized treatments. This work lays the foundation for a transition from a uniform treatment model to the paradigm of precision psychiatry.

Introduction

Bipolar disorder (BD) is a severe, chronic psychiatric illness affecting around 1% of the population. The disorder has a high heritability of over 80%, and its clinical variability complicates diagnosis, treatment, and research.¹⁻⁴ Previous work established distinct genetic overlaps between BD subtypes and other major psychiatric disorders: bipolar disorder I (BD1) shows a high genetic correlation with schizophrenia (SCZ),^{3, 5-8} while bipolar disorder II (BD2) links more strongly to major depressive disorder (MDD) and attention-deficit/hyperactivity disorder (ADHD).^{2, 6, 9} This overlap indicates that biological pathways are not constrained by diagnostic manuals, necessitating a data-driven approach to nosology. Given the genetic continuum between BD and SCZ, we hypothesized deconstructing severe BD requires comparing its genetic architecture with SCZ's to isolate disorder-specific from transdiagnostic risk signals. This heterogeneity impacts treatment, as features including psychosis or comorbidities guide distinct pharmacological strategies, and the iterative process of personalizing an effective regimen may contribute to the illness burden.¹⁰

This heterogeneity is evident across multiple clinical domains. Age of onset (AOO) is a critical factor; an earlier AOO typically signifies a greater genetic liability and a more severe disease trajectory.^{11, 12} An onset before 28 years of age increases the risk for psychotic features, rapid cycling (RC), comorbid anxiety disorders, alcohol or substance use disorders (AlcSUD), and suicide attempts (SA).¹³ RC (defined as ≥ 4 mood episodes/year),¹⁴ is linked to a family history of mood instability, high psychiatric comorbidity, and a lack of responsiveness to lithium, making it a challenging clinical presentation.^{15, 16, 17} The long-observed clinical association between thyroid dysfunction and mood instability in RC is a key aspect of this profile.^{18, 19} While preliminary studies suggest benefits from using adjunctive thyroid hormone for RC, a definitive mechanistic link remains unproven.^{17, 20}

Genetic research into clinically distinct BD subphenotypes has been hampered by inadequate statistical power. This study tested the hypothesis that the clinical heterogeneity of BD is linked to underlying genetic heterogeneity defined by specific biological pathways. We employed a two-step MTAG approach, first with additional BD cases and second by integrating large-scale SCZ GWAS data, to identify specific genetic mechanisms. Our multivariate approach aimed to reveal genetic factors that confer risk for specific psychopathologies, and those that underlie the observed genetic overlaps with other major psychiatric traits. Here, we first establish a robust genetic-clinical framework of four dimensions, and then interrogate the unique

and shared biological pathways—spanning neuro-immune, neurodevelopmental, and synaptic systems—that define them.

Methods

This study followed STREGA in a genetic analytical pipeline (Figure 1). It received formal review and approval from appropriate institutional review boards, and written informed consent was obtained from all participants. The sample comprised 23,819 BD cases and 163,839 controls of European descent across 56 cohorts, diagnosed using international criteria.^{14, 21}

Standard Genome-Wide Association Study (GWAS) procedures were conducted using the RICOPILI²² automated pipeline for quality control (QC), imputation, and association analysis. Standard QC protocols were applied. Imputation was performed against the Haplotype Reference Consortium (HRC r1.1 2016) panel,²³ with a post-imputation INFO score cutoff of 0.8. Linkage Disequilibrium Score Regression (LDSC) confirmed that confounding from population stratification was minimal (median intercept = 1.015) and was used to estimate SNP-based heritability (h^2_{SNP}).²⁴ QQ plots confirmed minimal inflation (eFigure 1). See Supplement for additional details.

To enhance statistical power, MTAG²⁵ combined our subphenotype GWAS with summary statistics from large external BD² and SCZ²⁶ GWAS (eTable 1), contingent on strong genetic correlation ($r_G > .70$). Our two-stage MTAG design dissects genetic effects: first with external BD data for BD-centric signals, then adding SCZ data to resolve psychosis-spectrum architecture. The low median maxFDR ($< .05\%$) confirmed a true synthesis of signals, not a distortion driven by the larger SCZ GWAS. Ten subphenotypes with reliable MTAG results were selected for downstream analysis, with Manhattan plots provided in eFigure 2.

To translate genetic associations into biological insights, FUMA v1.8.0²⁷ was utilized for gene-mapping and functional annotation (eTable 2), with SNP-to-gene annotations visualized in eFigure 3-4. MAGMA v1.10²⁸ performed gene set enrichment analysis against 17,023 curated gene sets.²⁹ Subphenotype cell type specificity was explored³⁰ using public human brain single-cell RNA-sequencing (scRNA-seq) datasets.³¹⁻³⁵ Conditional Transcriptome-Wide Association Studies (TWAS) using FUSION software³⁶ assessed the impact of genetic variants on gene expression in 15 brain tissues, with the understanding that such associations imply but do not prove causal relationships³⁷. LAVA³⁸ was used to identify local genetic correlations between subphenotypes. Polygenic Risk Scores (PRS) were constructed using PRS-CS-auto,³⁹ and their predictive power was assessed in logistic regression models, including the first ten principal components of ancestry as covariates.

Results

Identification of Four Genetic Dimensions

This study included 52% females, with a median age at interview of 22 (IQR, 17-30) years. Clinical characteristics are detailed in eTables 3-8. An assessment of phenotypic homogeneity confirmed consistent data across geographic regions (eTable 9; eFigure 5). A Confirmatory Factor Analysis (CFA) of the 11 BD subphenotypes empirically derived a robust four-factor clinical model, providing a framework for understanding BD heterogeneity (eFigure 6). This determination was supported by parallel analysis (eFigure 7). The model identified: (1) a Psychosis-Spectrum Factor (schizoaffective disorder, bipolar type [SZA], Psychosis); (2) a Core Bipolar Subtype Factor (BD1, BD2); (3) a Comorbidity and Mood Instability Factor (RC, panic disorder [PD], obsessive compulsive disorder [OCD], AlcSUD, SA, unipolar mania [UM]⁴⁰⁻⁴²); and (4) an Age of Onset Factor. Full details of the factor loadings and model fit are available in S1. An *a priori* (eFigure 8) and subsequent Principal Component Analysis (PCA) of MTAG loci aligned with these clinical factors (eFigure 9), underscoring a genetic basis for the observed clinical distinctions. This genetic PCA explained 81.5% of the variance and revealed four distinct dimensions, or clusters, that may represent points along a biological continuum rather than discrete entities. The statistical validity of this structure was confirmed by a one-way ANOVA, which revealed a robust difference in local genetic correlation (ρ) between the clusters, $F(3, 1038) = 203.2$, $P < 2.00 \times 10^{-16}$.

The four dimensions were interpreted as representing:

- A **Severe Illness** Dimension (Psychosis, SZA)
- A **Core Mania** Dimension (BD1)
- An **Externalizing/Impulsive Comorbidity** Dimension (SA, AlcSUD)
- An **Internalizing/Affective Comorbidity** Dimension (BD2, PD, OCD, RC, UM)

Dimension 1: Severe Illness

This dimension is defined by profound genetic overlap with SCZ, a link substantiated by our analyses (eFigure 10) and consistent with large-scale genomic dissections of the two disorders.^{43,44} The inclusion of SCZ variants in our MTAG massively amplified shared signals; for instance, the number of shared loci between Psychosis

and SZA increased by 63% (from 16 to 26) in the BD-SCZ analysis (eTable 10). Biologically, this dimension is differentiated by a unique neuro-immune signature. The TWAS analysis revealed that expression of *HLA-DMB* in the cerebellum showed a strong protective association ($P = 2.50 \times 10^{-273}$) only in the BD-SCZ MTAG context; this signal was not robust in the BD-only analysis, indicating this specific immune pathway is a primary feature linking severe BD to SCZ (eTable 11; Figure 2, eFigure 11). This synaptic link is mirrored at the cellular level, where the genetic enrichment for GABAergic and cortical neurons became more robust in the BD-SCZ context (P -adjusted for Psychosis-BD GABAergic neurons = 3.39×10.0^{-7} vs. 1.96×10^{-11} for Psychosis-BD-SCZ), underscoring a shared cellular vulnerability (eTable 12; Figure 3, eFigure 12). Furthermore, this dimension is characterized by specific synaptic biology. The novel, deleterious variant in the neuronal sodium channel gene *SCN2A* (Combined Annotation Dependent Depletion[CADD]=19.83)⁴⁵ was associated specifically with the Psychosis and BD1 subphenotypes (eTable 13), directly implicating fundamental neuronal excitability. This is mirrored in the gene-set analysis, where the significance for pathways including "GOCC_POSTSYNAPTIC_SPECIALIZATION", driven by genes involved in scaffolding proteins and glutamatergic receptor subunits, became orders of magnitude stronger for this cluster when SCZ data was added (e.g., for SZA, P (Bonferroni) = 1.35×10^{-12}), confirming that the shared biology is concentrated at the synapse (eTable 14; Figure 4, eFigure 13).

Dimension 2: Core Mania

While genetically related to the Severe Illness Dimension, the BD1 dimension is distinguished by specific loci related to neuronal function and development. The TWAS analysis identified *PACSI*, involved in neuronal protein trafficking, as uniquely associated with BD1 via its expression in the cortex (eTable 15). The association with *PACSI* suggests altered neurotrophic support may be a specific biological feature of the core manic phenotype. Furthermore, BD1 was specifically associated with a variant in *ADCY2* (rs78308718), a gene previously linked to lithium response.⁴⁶⁻⁴⁹ This suggests a distinct biological pathway related to treatment response that is characteristic of this core manic phenotype. This was complemented by findings for *CACNA1C*, a well-established risk gene for BD, which showed its strongest association within the Core Mania dimension, reinforcing the importance of calcium channel signaling in mania.³ This contrast is particularly evident when comparing BD1 and RC; while BD1 shows genetic specificity, RC displays a highly pleiotropic profile, with associated variants overlapping extensively with other subphenotypes (eFigure 14).

Dimension 3: Externalizing/Impulsive

This dimension is defined by a strong shared liability for impulsive and externalizing behaviors. This was evident in the high global genetic correlation between suicide attempt (SA) and alcohol/substance use disorder (AlcSUD) ($r_G \approx .80$, $s.e.m. = .056$, eFigure 10) and was validated by LAVA, which identified three shared local genetic loci between them (eTable 16). The three local genetic loci shared between SA and AlcSUD included a region on chromosome 16 containing genes for synaptic vesicle transport, suggesting shared mechanisms of presynaptic function. Genetically, this dimension shares a common architecture with ADHD (eTable 17). Biologically, this dimension is distinguished by a strong enrichment for midbrain dopaminergic neurons, directly implicating reward and motivation pathways in the shared genetic risk for both SA and AlcSUD (eTable 12). The enrichment for dopaminergic neurons was specific to cells from the ventral tegmental area (VTA), a key hub in the mesolimbic reward circuit, providing a direct anatomical and cellular correlate for the high rates of comorbid substance use in this cluster. The novel association of the gene *MADILI*, critical for neurodevelopment, with the AlcSUD subphenotype in the BD-SCZ MTAG provides a specific biological link for this dimension (Table 1).

Dimension 4: Internalizing/Affective

This broad dimension is underpinned by a complex web of shared genetic factors related to mood instability and anxiety. While sharing the core cellular vulnerabilities seen across all clusters (e.g., GABAergic neurons, astrocytes), its distinction comes from specific gene pathways. The most powerful evidence for this clustering comes from our LAVA analysis, which uncovered a hidden relationship between OCD and PD. Despite a moderate global correlation, these two subphenotypes shared 30 local genetic loci, explaining their clustering and demonstrating a specific, shared genetic architecture for anxiety-compulsive traits that is largely independent of the psychosis axis (eTable 16; eFigure 15). The 30 shared loci between OCD and PD were significantly enriched for genes involved in postsynaptic density scaffolding and calcium signaling, suggesting a shared vulnerability based on the molecular machinery of the synapse in corticostriatal circuits. Biologically, this dimension is linked by specific neurodevelopmental and signaling pathways. A novel association of the neurodevelopmental guidance gene *DCC* was shared across the RC, UM, PD, and OCD sub-group, suggesting altered axonal guidance as a shared vulnerability pathway (Table 1). A more specific link between rapid cycling (RC) and PD was the shared association with *SMAD3*, a gene that mediates C4-regulating TGF- β signaling, a pathway known to interact with thyroid hormones,⁵⁰ and genes such as *SMAD*⁵¹ and *DGKH*^{52, 53} have been

previously linked to panic disorder. This provides a potential biological mechanism for the long-observed, but mechanistically elusive, association between thyroid dysfunction and mood instability in RC. Finally, SBayesS analysis further differentiated this cluster by showing that BD2's genetic architecture overlaps most strongly with anxiety disorders, in contrast to BD1's primary overlap with SCZ (eTable 17; Figure 16), providing a clear genetic basis for their separation. The clinical presentation of this dimension is further explored by examining the relationship between AOO and comorbidity count (eFigure 17).

Overall Genetic Discovery and Prediction

The foundational genome-wide summary statistics for the analyzed subphenotypes are available (eTable 18)(103 loci identified, mainly BD1). MTAG enhanced discovery, identifying up to 181 subphenotype-associated loci (eTable 19), including 53 novel loci not previously linked to the subphenotype, BD, or SCZ (Table 1; eTable 13). Overlap of these loci is visualized in eFigure 18 and eFigure 19. Replication of previously identified loci was confirmed (eTable 20). PRS demonstrated effective predictive power, with variance explained on the liability scale (R^2 -liability) ranging from 5.47% for PD to 12.40% for unipolar mania (eTables 21-22); see eTable 23 for prevalences. SNP-based heritability (eTable 24) was highest for the psychosis subphenotype at .278 (s.e.m.=.017). Genetic correlations between our univariate GWAS and final MTAG results are shown in eTable 25. Additional analyses confirmed methodological consistency (eFigure 20). The statistical validity of this transdiagnostic approach was confirmed by enrichment of our primary credible gene set (eTables 26-29) for established rare-variant risk genes from the SCHEMA consortium (eTable 30; $P = 4.10 \times 10^{-4}$), indicating that the identified loci represent biological convergence rather than statistical artifact.

Discussion

Our investigation reveals that the clinical heterogeneity of BD is rooted in a multi-layered interplay of shared and subphenotype-specific genetic factors. We confirmed a core architecture affecting fundamental cellular processes, while identifying distinct genetic signatures that align with clinical subphenotypes. This evidence supports a dimensional approach to nosology, challenging a purely categorical view.^{54,43} While these dimensions may not reflect distinct etiologies, they likely represent a continuum of genetic liability where different clinical features emerge at varying thresholds of risk. However, an alternative interpretation must be considered: that these dimensions do not reflect truly distinct etiologies, but rather a single continuum of genetic liability where different clinical features, such as psychosis or comorbidity, emerge at varying thresholds of risk. This dimensional framework represents a step toward precision psychiatry, offering a new lens through which to view patients not as holders of a single diagnosis, but as individuals situated along multiple, biologically-defined continua of risk. The fact that anxiety-related subphenotypes share core synaptic enrichments with severe psychotic subphenotypes suggests a unified biological basis that can manifest in diverse ways, supported by our local correlation analyses.

Notable gene findings provide leads for understanding pathophysiology. The deleterious *SCN2A* variant as a strong BD1 marker suggests a role for ion channel dysfunction,^{2-3,5,26,55} potentially disrupting activity in brain regions critical for mood regulation and plasticity, such as the hippocampus where adult neurogenesis occurs.⁵⁶ The pleiotropic *SLC39A8* variant, a known SCZ risk factor, was novel for seven subphenotypes and points to shared mechanisms involving metal homeostasis and mitochondrial function.⁵⁷⁻⁵⁹ The novel association of the neurodevelopmental guidance gene *DCC* with the RC, UM, PD, and OCD cluster suggests a shared mechanism of altered axon guidance during brain formation.⁴⁹ The finding that altered axonal guidance underpins a cluster of internalizing and mood instability disorders is particularly compelling. Other notable findings include *FOXO6* (FOX genes implicated in personality disorders)⁶⁰⁻⁶¹ associated with most subphenotypes but not BD1, and *PBRM1*^{62,2,5,63} (linked to mood-incongruent psychosis) replicated in BD1.² Our findings add to a complex genetic landscape for bipolar disorder that includes previously established risk loci such as 3p21.1,⁶³ and pathways involving endocannabinoid signaling^{64,65} and genes including *CHDH*.⁶⁶

Biological annotations showed broadly similar enrichments in synapse biology. Notably, BD2 displayed weaker genetic association with glutamatergic pyramidal cells versus GABAergic interneurons, consistent with

depression⁶⁷ and contrasting with SCZ's increased glutamatergic signaling.⁶⁸ Such cellular pathway distinctions could underpin differential treatment responses. For example, *PACSI* (unique to BD1) links to excitatory/inhibitory imbalance.^{2,3,5} the massive amplification of the protective *HLA-DMB* signal when considering SCZ variants supports an integrated neuro-immune hypothesis where foundational neuronal vulnerabilities are compounded by aberrant immune responses. The specificity of this signal suggests the immune component of risk is most relevant at the severe, psychotic end of the mood disorder spectrum, potentially providing a biomarker to stratify patients for immunomodulatory trials. This connects to other immune-related genes, such as *ZSCAN9* and *C4A*, linked to brain structure and synaptic pruning.^{69,70} While broad analyses suggest *C4* may not be central to BD overall^{5,55}, there is emerging evidence for its importance at the subphenotype level, particularly in psychosis.⁷¹

Our genetic analyses illuminate distinct biological underpinnings for clinical subtypes. BD1 demonstrates a strong genetic overlap with schizophrenia, characterized by the deleterious *SCN2A* variant. In contrast, UM clustered within the Comorbidity and Mood Instability Factor, suggesting that while UM manifests as mania, its genetic liability draws more heavily from a general predisposition to comorbidity rather than from the core psychosis-spectrum vulnerability. This implies the manic syndrome can be an endpoint for multiple distinct biological pathways. The distinct genetic signature of UM validates its unique position in psychiatric nosology and suggests it should be considered a separate entity in clinical trial design.

A novel finding was that RC exhibited a unique genetic signature characterized by the most pronounced negative selection signatures.⁷² the clinical profile of RC—early-onset, highly comorbid, and treatment-refractory—provides a rationale for this novel observation. This evidence suggests the genetic architecture of RC may be disproportionately influenced by rarer, more highly penetrant risk alleles that are actively purged from the population due to their severe fitness consequences. While compelling, this signature could also be confounded by the severe functional impairment and social instability of the phenotype, which independently impact reproductive fitness. This aligns with the clinical severity and early onset of the phenotype, providing a compelling rationale for dedicated studies of rare and de novo variation in well-phenotyped RC cohorts. This sets RC apart from other BD presentations and indicates that future research should expand beyond common variant GWAS to fully capture its etiology. The shared genetic link to *SMAD3* in RC and PD offers the first potential mechanistic bridge for the long-observed clinical association between thyroid dysfunction and mood instability in RC, via the gene's role in thyroid-interacting TGF- β signaling.¹⁸

Limitations and Future Research

Our study's primary reliance on cohorts of European ancestry limits generalizability, underscoring the need for future multi-ancestry validation. While MTAG²⁵ enhances power, its focus on intersected variants may mask unique loci. Despite rigorous QC, cohort heterogeneity and diagnostic biases remain considerations. For instance, observed genetic distinctions could be inflated by diagnostic practices (e.g., assigning comorbidities based on a primary diagnosis of SZA vs BD with psychosis). Future research must translate these associations into precise mechanistic understandings via functional genomics. Validation in larger, independent, multi-ancestry meta-analyses is crucial. Finally, conducting de novo GWAS on the four clinical factors identified here will provide deeper insights, potentially enabling biologically informed diagnostic systems and novel, personalized therapeutics.

Conclusion

Pervasive neurodevelopmental factors, coupled with a robust neuro-immune component and core deficits in synaptic function, clarify BD's etiology. Our study offers a multi-layered understanding of BD's genetic heterogeneity. These findings move BD research towards a more biologically grounded psychiatric nosology, which is a foundational step toward enabling better patient stratification and paving the way for targeted therapeutic strategies that address specific vulnerabilities in this complex illness.

Article Information

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Author Contributions: The management group, comprising a subset of authors, was responsible for the study design, conduct, primary and final interpretation, and included M.A., R.A.O., K.S.O., N.M., A.J.F., M.G-S., H.J.E., F.J.M., O.A.A., A.D.F., and A.M. The writing group for the paper was led by A.D.F. and A.M; this group was also responsible for primary drafting and editing of the manuscript. M.T. contributed clinical assessments and analyses of the clinical data. T.V. was responsible for the main analyses presented in the paper and included modified analytical code provided by J.M.K.Y., T.B., F.S.D., and K.S.O. Numerous authors beyond the initial writing group contributed to data interpretation and provided edits, comments and suggestions to the paper. All authors reviewed the manuscript critically for important intellectual content and approved the final version of the manuscript for publication. The Chair of the PGC is P.F.S. The Bipolar Disorder Working Group of the PGC is led by O.A.A.

Conflict of Interest Disclosures: E.A.S. is an employee of Regeneron Genetics Center and owns stocks of Regeneron Pharmaceutical Co. Multiple additional authors work for pharmaceutical or biotechnology companies in a manner directly analogous to academic coauthors and collaborators. A.H.Y. has given paid lectures and served on advisory boards relating to drugs used in affective and related disorders for several companies (AstraZeneca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allergan, Bionomics and Sumitomo Dainippon Pharma), was Lead Investigator for Embolden Study (AstraZeneca), BCI Neuroplasticity study and Aripiprazole Mania Study, and is an investigator for Janssen, Lundbeck, Livanova and Compass. J.I.N. is an investigator for Janssen. P.F.S. reports the following potentially competing financial interests: Neumora Therapeutics (advisory committee and shareholder). G. Breen reports consultancy and speaker fees from Eli Lilly and Illumina and grants funding from Eli Lilly. M. Landen has received speaker fees from Lundbeck. O.A.A. has served as a speaker for Janssen, Lundbeck, and Sunovion and as a consultant for Cortechs.ai. A.M.D. is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board; he is a member of the scientific advisory board of Human Longevity and the Mohn Medical Imaging and Visualization Center (Bergen, Norway); and he has received research funding from General

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Data Sharing Statement: The genome-wide association summary statistics for all analyses presented here will be made publicly available via the Psychiatric Genomics Consortium (<https://www.med.unc.edu/pgc/download-results/>) upon publication of this article. Genotype data are available for a subset of cohorts, including dbGAP accession numbers and/or restrictions, as described in the Supplement.

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Code Availability: No custom code was developed for this study. Figures 2 and 3 were generated using publicly available code originally developed by Tabea Schoeler (GitHub: <https://github.com/TabeaSchoeler>). All software and tools used for the analyses presented are publicly available and referenced within the respective sections in the Methods of the article or supplement.

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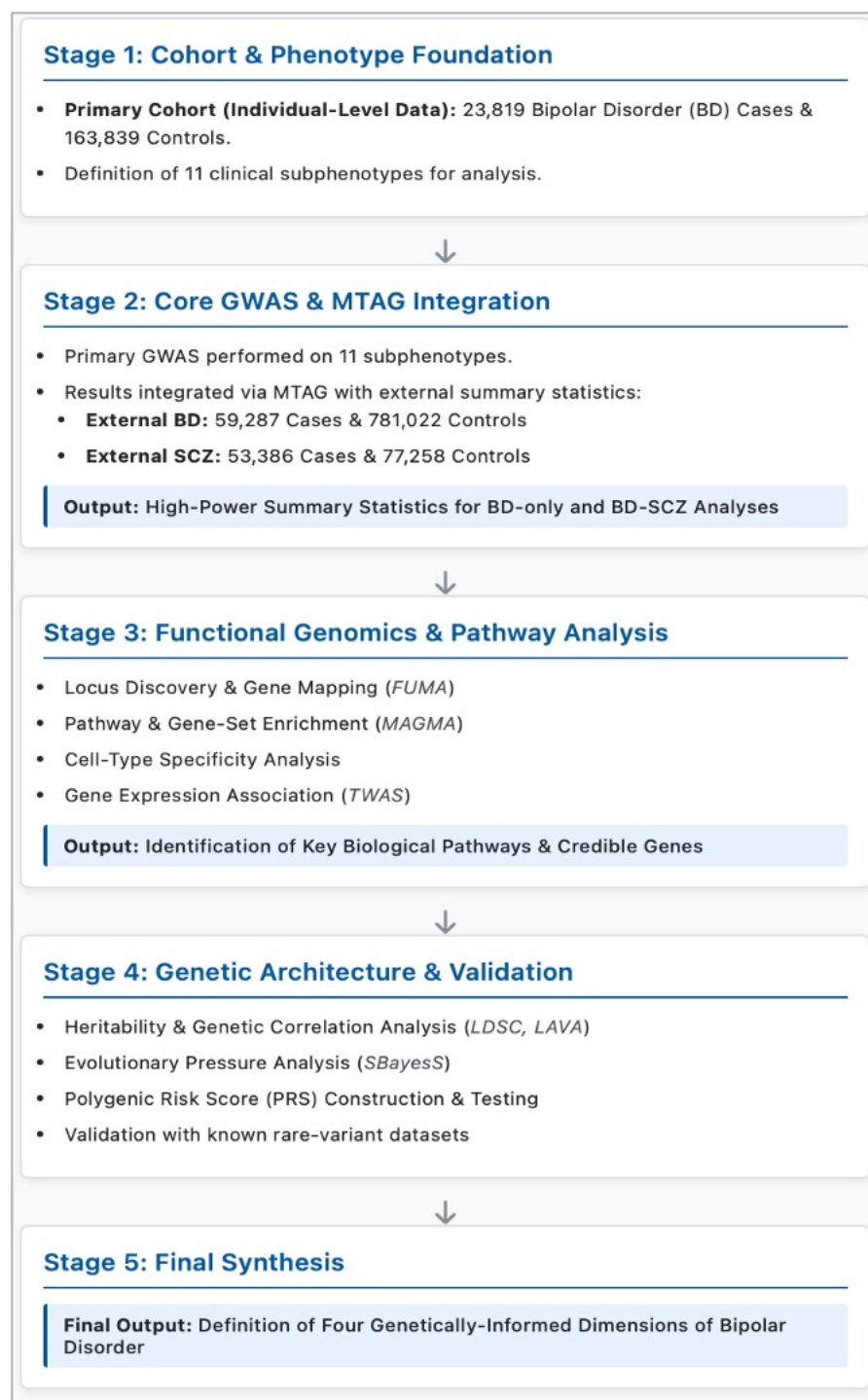


Figure 1. Overview of the Study Design and Analytical Workflow. This diagram illustrates the multi-stage analytical pipeline, beginning with cohort collection and proceeding through genome-wide association studies (GWAS), statistical enhancement with Multi-Trait Analysis of GWAS (MTAG), and concluding with downstream biological interpretation to identify key pathways and mechanisms.

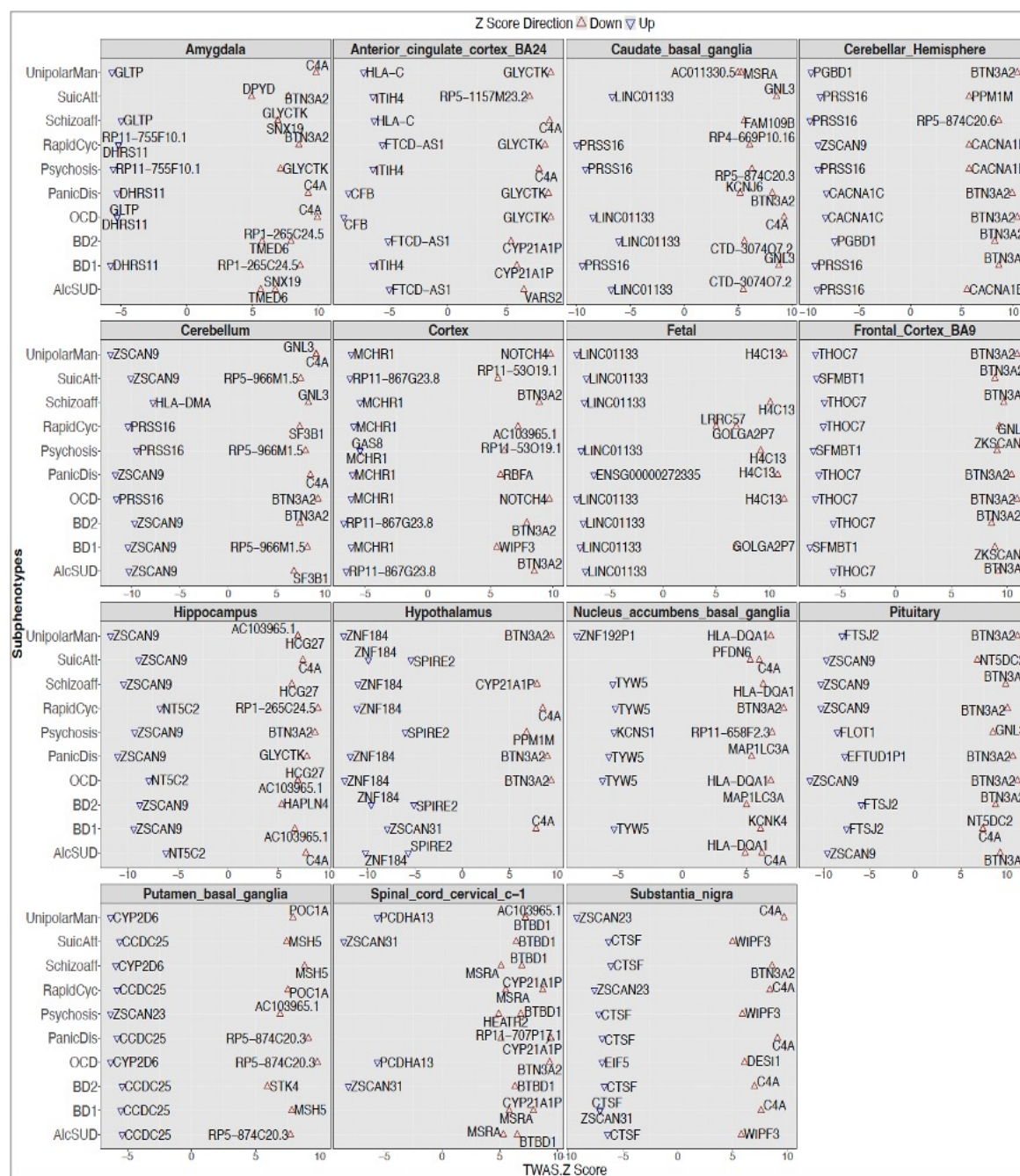


Figure 2. Top Gene Tissue Associations from the Bipolar Disorder-Schizophrenia (BD-SCZ)

Transcriptome-Wide Association Study (TWAS). The plot shows the most robust, conditionally independent gene-tissue associations for each BD subphenotype across 15 brain tissue datasets. The x-axis represents the significance of the association ($-\log_{10} P$ -value), corrected for all genes and tissues tested. The direction of effect is indicated by triangles: red for a positive Z-score (increased expression associated with risk) and blue for a negative Z-score (decreased expression associated with risk). Corresponding results from the BD-only analysis are shown in eFigure 11. The eTable 15 provides the full list of gene-tissue associations from the TWAS analysis.

Psychosis, Schizoaff, Schizoaffective disorder, BD1, bipolar disorder I, SuicAtt, suicide attempt, AlcSUD, alcohol or substance use disorder, BD2, bipolar disorder II, PanicDis, panic disorder, RapidCyc, rapid cycling, OCD, obsessive compulsive disorder, UnipolarMan, unipolar mania.

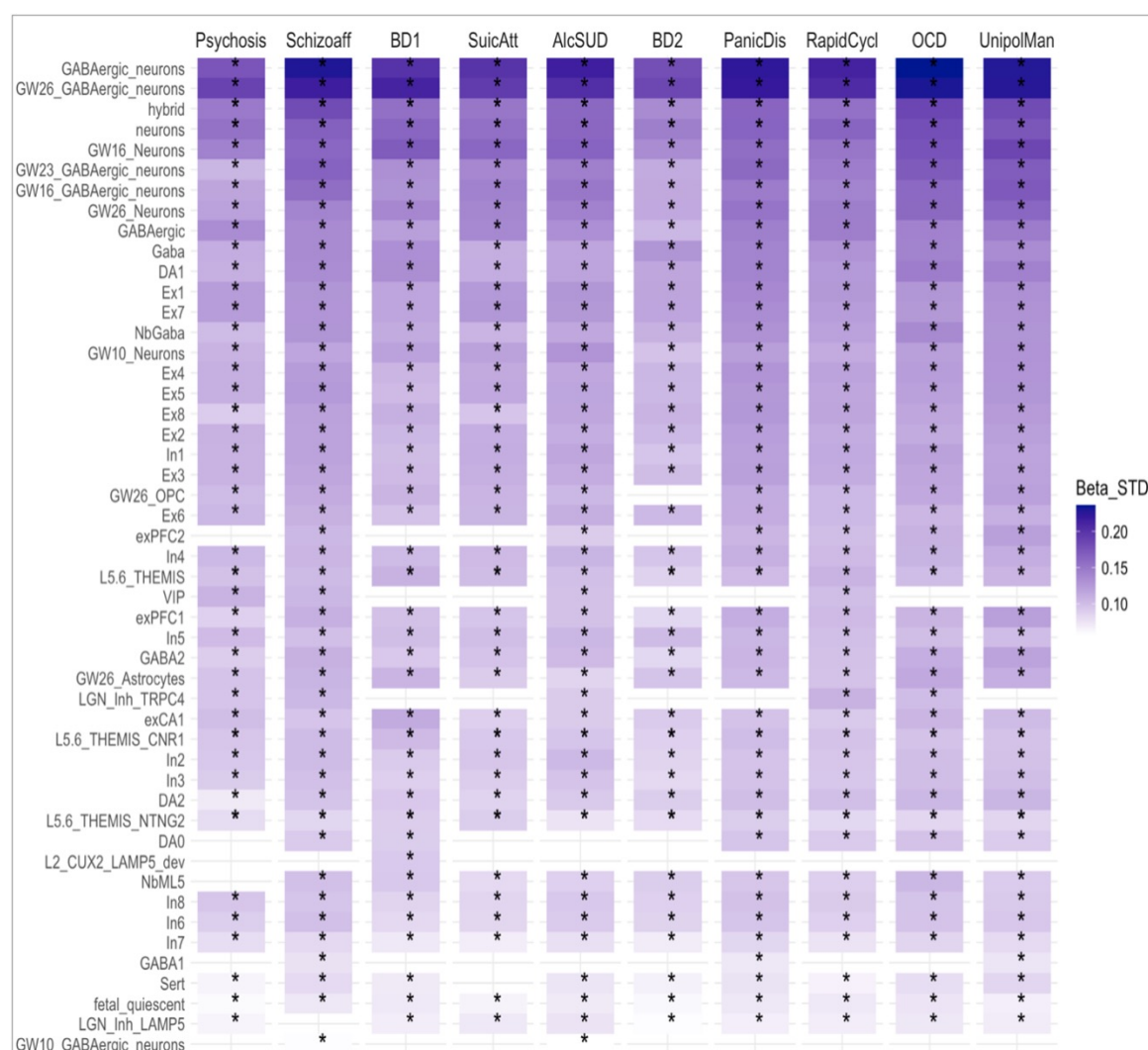


Figure 3. Cell-Type Enrichment Results from the Bipolar disorder-Schizophrenia (BD-SCZ)

Analysis. The heatmap displays standardized beta coefficients from cell-type enrichment analysis across 10 BD subphenotypes. Color intensity corresponds to the strength of the enrichment signal, with subphenotypes ordered by effect size. Absence of color indicates no association. Asterisks (*) denote associations that remained robust after Bonferroni correction for the number of cell types tested ($P < .05$). Corresponding results from the BD-only analysis are shown in eFigure 12. The eTable 12 provides the full list of gene-tissue associations from the TWAS analysis. Psychosis, Schizoaff, Schizoaffective disorder, BD1, bipolar disorder I, SuicAtt, suicide attempt, AlcSUD, alcohol or substance use disorder, BD2, bipolar disorder II, PanicDis, panic disorder, RapidCycl, rapid cycling, OCD, obsessive compulsive disorder, UnipolMan, unipolar mania.

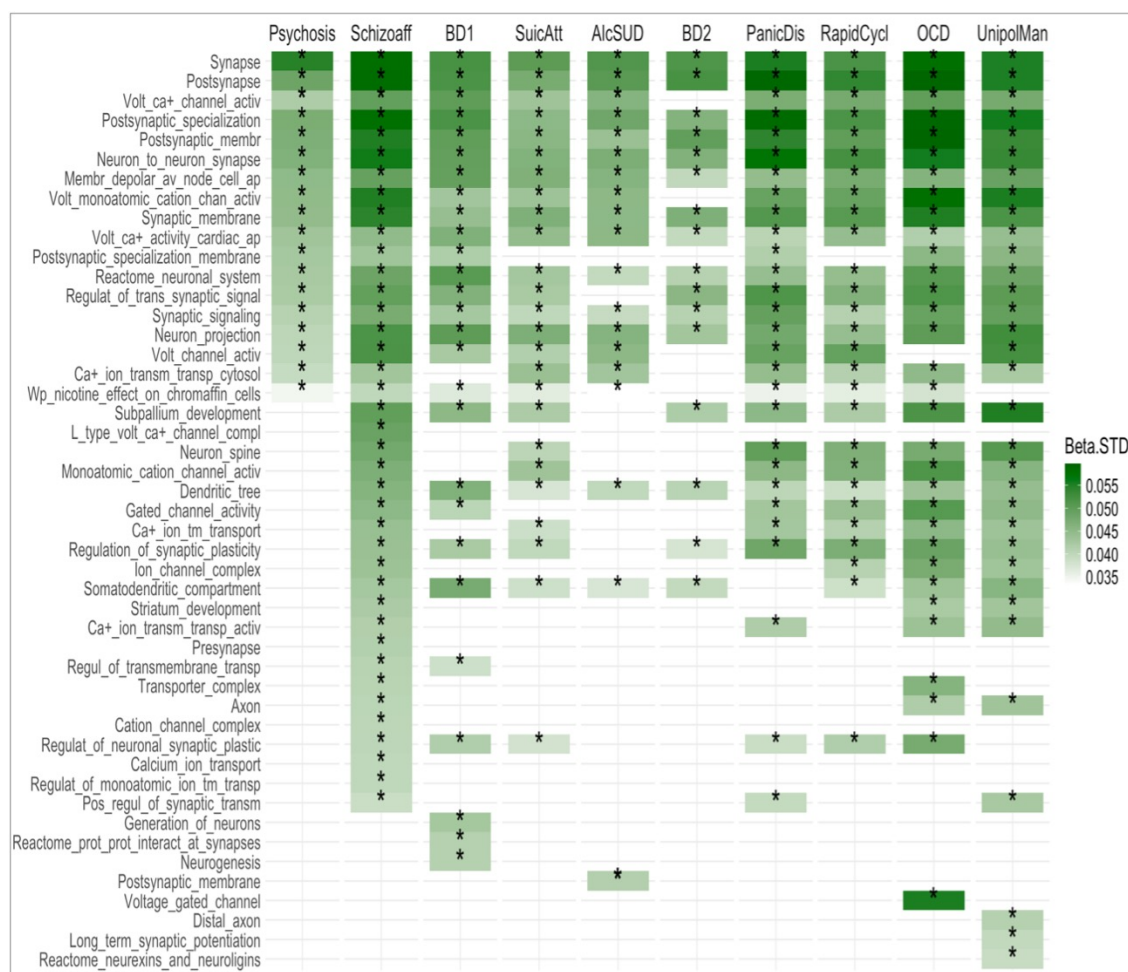


Figure 4. Gene-Set Enrichment Results from the Bipolar Disorder-Schizophrenia (BD-SCZ) Analysis. The heatmap displays standardized beta coefficients from MAGMA gene-set enrichment analysis across 10 BD subphenotypes. Color intensity corresponds to the strength of the enrichment signal, with gene sets ordered by effect size. Absence of color indicates no association. Asterisks (*) denote associations that remained robust after Bonferroni correction for the number of gene sets tested ($P < .05$). Corresponding results from the BD-only analysis are shown in eFigure 13. The eTable 14 provides the full list of gene-set associations. Psychosis, Schizoaff, Schizoaffective disorder, BD1, bipolar disorder I, SuicAtt, suicide attempt, AlcSUD, alcohol or substance use disorder, BD2, bipolar disorder II, PanicDis, panic disorder, RapidCycl, rapid cycling, OCD, obsessive compulsive disorder, UnipolMan, unipolar mania.

Table 1. Key Genetic and Biological Findings Defining the Dimensions of Bipolar Disorder

Table 1. Key Genetic and Biological Findings Defining the Dimensions of Bipolar Disorder			
Pathway	Key Finding	Primary Evidence	Analysis
Severe Illness Dimension (Psychosis, SZA)			
<i>Neuro-Immune</i>	<i>HLA-DMB</i>	Protective; $P = 2.50 \times 10^{-273}$	TWAS (BD-SCZ MTAG)
<i>Synaptic Function</i>	<i>SCN2A</i>	Deleterious; CADD = 19.83	Variant Annotation
<i>Synaptic Function</i>	Postsynaptic Specialization	P (Bonferroni) $< 1.35 \times 10^{-12}$	Gene-Set Enrichment
<i>Cellular</i>	VIP-expressing interneurons	Top enriched cell type	Cell-Type Enrichment
<i>Neurodevelopment</i>	Hippocampal Excitatory Neurons (exDG)	Enrichment in BD-SCZ analysis	Cell-Type Enrichment
Core Mania Dimension (BD1)			
<i>Synaptic Function</i>	<i>PACS1</i>	$P = 2.00 \times 10^{-19}$	TWAS (BD-only)
Externalizing Dimension (SA, AlcSUD)			
<i>Cellular</i>	Midbrain Dopaminergic Neurons	Risk enrichment	Cell-Type Enrichment
<i>Neurodevelopment</i>	<i>MAD1L1</i>	Novel Locus; $P = 1.15 \times 10^{-15}$	GWAS (BD-SCZ MTAG)
Internalizing Dimension			
<i>Neurodevelopment</i>	<i>DCC</i> (RC, UM, PD, OCD)	Shared Locus; $P < 1.37 \times 10^{-6}$	LAVA
<i>Neuro-Immune</i>	<i>SMAD3</i> (RC, PD)	PD/RC Specific Locus; $P = 3.14 \times 10^{-8}$	GWAS (BD-SCZ MTAG)

Table 1. Key Genetic and Biological Findings Defining the Dimensions of Bipolar Disorder

Pathway	Key Finding	Primary Evidence	Analysis
<i>Cellular (Gut-Brain)</i>	GLP2R enrichment (PD)	Specific cell-type enrichment	Cell-Type Enrichment
<i>Cellular</i>	Glutamatergic vs. GABAergic signaling (BD2)	Weaker glutamatergic assoc.	Cell-Type Enrichment
<i>Evolutionary</i>	Rapid cycling (RC)	Negative Selection (S) = -1.75	SBayesS
Shared / Foundational (Across Dimensions)			
<i>Foundational</i>	Chromatin Org. & DNA Repair	Top enriched pathway	Gene-Set Enrichment
<i>Systemic (Stress)</i>	Nicotine/Chromaffin Cell Pathway	Enriched in BD-SCZ analysis	Gene-Set Enrichment
<i>Systemic (Metabolic)</i>	SLC39A8, FADS1	CADD=23.1; $P = 2.11 \times 10^{-32}$	Variant Annotation, TWAS
<i>Synaptic (Endocannabinoid)</i>	CNR1 enrichment	Shared vulnerability	Cell-Type Enrichment
<i>Synaptic (Metabolic)</i>	GLYCTK	Protective; $P = 5.20 \times 10^{-110}$	TWAS (Amygdala)

Abbreviations: AlcSUD, alcohol/substance use disorder; BD1, bipolar disorder I; BD2, bipolar disorder II; CADD, Combined Annotation Dependent Depletion; GWAS, Genome-Wide Association Study; LAVA, Local Analysis of [co]Variant Annotation; MTAG, Multi-Trait Analysis of GWAS; OCD, obsessive-compulsive disorder; PD, panic disorder; RC, rapid cycling; SA, suicide attempt; SZA, schizoaffective disorder, bipolar type; TWAS, Transcriptome-Wide Association Study; UM, unipolar mania.

Supplement to:

Immune, developmental, and synaptic pathways define bipolar disorder clinical heterogeneity.

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S1. Subphenotype Definitions and Factor Analysis

This study analyzed data from 56 cohorts, comprising a final sample of 23,819 bipolar disorder (BD) cases and 163,839 controls. Several BD subphenotypes were extracted from our clinical data, which included participants with bipolar disorder I (BD1), bipolar disorder II (BD2), or schizoaffective disorder, bipolar type (SZA). Clinical characteristics are detailed in eTables 3-8. We assessed the power to detect common variants contributing to physiological distinctions in a group of variables with sufficient sample sizes: BD1, BD2, SZA, psychotic features, rapid cycling (RC), obsessive-compulsive disorder (OCD), panic disorder (PD), attempted suicide (SA), unipolar mania (UM), age at onset (AOO), and alcohol or substance abuse disorder. These variables are considered BD subphenotypes as they cluster within families,¹⁻³ suggesting more genetically homogeneous subgroups. The BD subtypes represent distinct genetic variations in the overall BD phenotype and so are also considered here as subphenotypes. Analysis of these subphenotypes has already been effective in identifying genetic associations in schizophrenia and bipolar disorder patients using global aggregates of common variants in polygenic risk scores (PRS).⁴ However, to date, most of the heritability of subphenotypes remains unaccounted for.^{5,6}

Principal component analysis (PCA) was conducted as an exploratory technique to reduce the 11 BD subphenotypes to visualize the main components of variance. Factor analysis (FA) was then applied for comparison and to identify potential subclusters of subphenotypes. Although PCA provides an initial overview of dimensionality, FA by comparison goes further to model the underlying substructure in the data to distinguish subclusters among the subphenotypes. The included subphenotypes were BD1 and BD2; SZA; psychosis; alcSUD (alcohol or substance use disorder); SA (suicide attempt); panic (comorbid panic disorder);⁷⁻⁹ comorbid OCD; RC (rapid cycling); UnipolMan (unipolar mania); AO_Man (age of onset of mania/mixed episodes); AO_depr (age of onset of depression); and AOO (age of onset of BD).

The analysis utilized Factor Analysis of Mixed Data (FAMD) in FactoMineR v2.11¹⁰ in R v4.2.2¹¹ to reduce the dimensionality of clinical data concerning 11 BD subphenotypes, facilitating the visualization of significant components. The first two components accounted for 43.4% of the variance in the dataset, highlighting the relationship between various attributes. A total of 18,800 BD cases were analysed. The FAMD approach integrates PCA for continuous data and multiple correspondence analysis (MCA) for categorical data. The resulting visualization revealed two distinct clusters of geometric points: a larger cluster near BD1 and a smaller cluster near BD2. Notably, psychosis and BD1 contributed most to the second dimension ('Dim 2'), suggesting this axis captures the variance in the severity of psychosis. Conversely, rapid cycling emerged as the primary contributor to the first dimension ('Dim 1'), which encompassed comorbid conditions. An assessment of phenotypic homogeneity confirmed consistent data across geographic regions (eTable 9; eFigure 5). A one-way ANOVA revealed a significant difference in local genetic correlation (ρ) between PCA clusters (derived from the first two principal components), $F(3,1038) = 203.2$, $P < 2.00 \times 10^{-16}$, suggesting internal reliability in our findings.

A Confirmatory Factor Analysis (CFA) of the 11 BD subphenotypes empirically derived a robust four-factor clinical model, providing a framework for understanding BD heterogeneity (eFigure 6). The analysis, conducted with the Lavaan¹² package in R, indicated acceptable fit indices ($\chi^2=588.91$, $P = 2.188 \times 10^{-87}$; SRMR .084; CFI .936). This model was selected over more parsimonious one-, two-, and three-factor models which demonstrated poorer fit indices. This determination was supported by parallel analysis (eFigure 7). The Kaiser-Meyer-Olkin Criterion (KMO)¹³ measure of sampling adequacy was .895, and Bartlett's test of sphericity was significant ($P < .001$), implying the data was adequate for EFA. An *a priori* (eFigure 8) and subsequent PCA of MTAG loci aligned with these clinical factors (eFigure 9), underscoring a genetic basis for the observed clinical distinctions. Furthermore, *SMAD3* was identified as specific to PD/RC in our BD-SCZ MTAG analyses. This gene mediates TGF- β signaling, a pathway known to interact with thyroid hormones,¹⁴ providing a potential biological mechanism for the observed association between thyroid dysfunction and mood instability in RC.

S2. Comprehensive Genetic Methods

This study used a genetic analytical pipeline (Figure 1).

Subphenotype-GWAS Quality control: Preimputation quality control (QC) removed variants with a call-rate $< .95$, post-sample pruning call-rate $< .98$, missing difference $> .02$, invariant positions, minor allele frequency (MAF) $> .01$, Hardy-Weinberg equilibrium (HWE) $P < 1 \times 10^{-6}$ in controls, and HWE $P < 1 \times 10^{-10}$ in cases, and samples with call-rate $< .98$ or FRET outside $\pm .20$. Principal components (PCs) were generated using EIGENSTRAT v6.1.4.¹⁵ Variants were imputed using the Haplotype Reference Consortium (HRC) reference panel¹⁶ with Eagle v2.3.5¹⁷ and Minimac3 v2.0.1.¹⁸ Genome-wide association studies (GWAS) were conducted in PLINK v1.90,^{19,20} co-varying for five PCs. Meta-analyses were conducted in METAL.²¹ Only SNPs present in $> 75\%$ of the effective sample and not removed by DENTIST²² were included. QQ plots confirmed minimal inflation (eFigure 1). For the 10 subphenotypes included in the MTAG analyses, the attenuation ratio (an estimate of the proportion of the GWAS signal due to confounding biases) had a median of .183. These values are in line with those reported for similar large-scale multivariate psychiatric analyses.²³ The foundational genome-wide summary statistics for the analyzed subphenotypes are available which identified 103 loci, mainly BD1 (eTable 18).

Subphenotype-MTAG: To enhance statistical power, Multi-Trait Analysis of GWAS (MTAG)²⁴ combined our subphenotype GWAS with summary statistics from large external BD²⁵ and SCZ²⁶ GWAS (eTable 1), contingent on strong genetic correlation ($r_G > .70$). The MTAG analyses showed high reliability, with median maximum False Discovery Rate (maxFDR) values (BD-only: .0004; BD+SCZ: .0003) comparable to those reported in other large-scale psychiatric genetic studies.²⁷⁻²⁸ This indicates a maximum false discovery rate of less than .05%, affirming the high reliability of the identified associations. Ten subphenotypes with reliable MTAG results were selected for downstream analysis, with Manhattan plots provided in eFigure 2. The suicide ideation (SI) and the three age of onset (AOO, AO_Dep, AO_Man/Mix) phenotypes were excluded from this and subsequent analyses because they exhibited high maximum False Discovery Rates (maxFDR), which affects the reliability of the results. Genetic correlations between our univariate GWAS and final MTAG results are shown in eTable 25. MTAG enhanced discovery, identifying up to 181 subphenotype-associated loci (eTable 19), including 53 novel loci (Table 1; eTable 13; eFigure 19). Replication of previously identified loci was confirmed (eTable 20), including an association in the *TRANK1* gene for suicide attempt.²⁹ The inclusion of SCZ variants in our MTAG massively amplified shared signals; for instance, the number of shared loci between psychosis and SZA increased by 63% (from 16 to 26) in the BD-SCZ analysis (eTable 10). Overlap of these loci is visualized using UpSet plots³⁰ in eFigure 18 and eFigure 19. This contrast is particularly evident when comparing BD1 and RC; while BD1 shows genetic specificity with numerous unique loci, RC displays a highly pleiotropic profile, with its associated variants overlapping extensively with other subphenotypes (eFigure 14).

Biological annotation and functional analyses: To translate genetic associations into biological insights, Functional Mapping and Annotation of genetic associations (FUMA) v1.8.0³¹ was utilized for gene-mapping and functional annotation (eTable 2), with SNP-to-gene annotations visualized in eFigure 3 and eFigure 4. The SNP2GENE function was employed to identify independent genomic loci and annotate putative causal genes (Bonferroni correction applied across 19,139 annotated genes, $P < 2.612 \times 10^{-6}$). For functional annotation, we applied standard clumping in FUMA ($r^2 = .1$, 250 kb merge window), utilizing the 1000 Genomes Project Consortium European-ancestry reference panel.³² This generated Combined Annotation Dependent Depletion (CADD) scores predicting potentially deleterious SNP effects.³³ Independent Significant SNPs (Ind. sig. SNPs) were defined as variants achieving a user-specified genome-wide significance threshold (e.g., $P \leq 5 \times 10^{-8}$) and pruned for linkage disequilibrium (LD) to ensure remaining signals were independent (e.g., at $r^2 < .6$). Lead SNPs were identified as a subset of Ind. sig. SNPs that met a more stringent LD independence criterion (e.g., $r^2 < .1$). Genomic Risk Loci were subsequently defined by grouping Ind. sig. SNPs that were either in LD ($r^2 \geq .1$) or physically proximal (e.g., within 250 kb), with each locus represented by its most significant Lead SNP. Candidate SNPs for downstream analysis were identified as all variants in LD (e.g., $r^2 \geq .6$) with any Ind. sig. SNP. We classified novel loci as those situated more than 500 kb from loci previously reported in earlier BD or SCZ GWAS studies or which had not been significantly associated within the GWAS Catalogue.³⁴ The novel, deleterious variant in the neuronal sodium channel gene *SCN2A* (CADD=19.83) was associated specifically with the psychosis and BD1 subphenotypes (eTable 13), directly implicating fundamental neuronal excitability. The MAGMA (v1.10)³⁵ gene-set analysis implemented in FUMA, with a window of 35 kb upstream and 10 kb downstream and incorporating 17,023 gene sets from MsigDB v2023.1Hs (Bonferroni-correction applied was $P < 2.937 \times 10^{-6}$), was utilized to explore which sets of biologically related genes exhibited the strongest evidence of association. This is mirrored in the gene-set analysis, where the significance for pathways including

"GOCC_POSTSYNAPTIC_SPECIALIZATION" became orders of magnitude stronger, confirming that the shared biology is concentrated at the synapse (eTable 14; Figure 4; eFigure 13).

Cell Type Specificity: To investigate which cell types were specific to subphenotypes, we used the FUMA Cell Type pipeline. This analysis utilized a 3-step workflow consisting of per-dataset analysis, within-dataset conditional analysis, and cross-dataset conditional analysis. We estimated cell type enrichment using curated single-cell RNA sequencing datasets integrated within the FUMA platform. A Bonferroni-threshold ($P \leq 2.201 \times 10^{-5}$) was applied across all tested cell types. This synaptic link is mirrored at the cellular level, where the genetic enrichment for GABAergic and cortical neurons became more robust in the BD-SCZ context, underscoring a shared cellular vulnerability (eTable 12; Figure 3; eFigure 12).

Transcriptome-wide association (TWAS): We conducted a series of transcriptome-wide association studies (TWAS)³⁶ using FUSION,³⁷ implemented in GenomicSEM,³⁸ utilizing precomputed functional weights for 15 brain tissue types and the European 1000 genomes project LD panel.³² The analyses were restricted to genes with significant evidence of cis-heritable expression ($P < .01$). A Bonferroni threshold ($P \leq 5.544 \times 10^{-7}$) established transcriptome-wide significance. The TWAS analysis revealed that expression of *HLA-DMB* in the cerebellum showed a strong protective association ($P = 2.50 \times 10^{-273}$) only in the BD-SCZ MTAG context, indicating this specific immune pathway is a primary feature linking severe BD to SCZ (eTable 10; Figure 2; eFigure 11). The TWAS analysis identified *PACSI*, involved in neuronal protein trafficking, as uniquely associated with BD1 via its expression in the cortex (eTable 15).

Convergence with Rare-Variant Evidence: To prioritize a high-confidence set of risk genes, we integrated evidence from FUMA and TWAS. A gene was defined as "credible" if it met two criteria: 1) Its genetically predicted expression was significantly associated with a subphenotype in conditional TWAS analysis, and 2) the gene was also implicated by at least one of three mapping strategies in FUMA (positional, eQTL, or chromatin interaction). The primary BD-SCZ analysis identified a large set of 85 credible genes (eTables 26-29). Genes such as *GLYCTK*, *GNL3*, and *HLA-DMB* were associated with all 10 subphenotypes, confirming their status as core, transdiagnostic risk factors. Others displayed more specific patterns; for instance, *DRD2* and *GRIN2A* were credibly associated almost exclusively with the psychosis-spectrum subphenotypes. Comparing these with the smaller BD-Only credible sets (27 genes, eTables 26-29) was highly informative. The stark contrast—for example, the reduction of 17 MHC-region genes in the BD-SCZ analysis to just two in the BD-Only analysis—suggests the strong neuro-immune component is a key feature of the shared genetic architecture between BD and SCZ.

The statistical validity of this transdiagnostic approach was confirmed by enrichment of our primary credible gene set (eTables 26-29) for established rare-variant risk genes from the SCHEMA³⁹ and BipEx⁴⁰ consortia using a one-sided Fisher's exact test. Statistical significance was defined as $P < .0125$ (Bonferroni correction for four tests). Our analysis revealed a significant convergence between common- and rare-variant evidence. The enrichment for our primary BD-SCZ credible sets with SCHEMA rare-variant genes was highly significant (e.g., for BD-SCZ_noMHC set, $P = 4.1 \times 10^{-4}$), driven by overlapping genes *TCF4*, *PBRM1*, and *ZEB2*. The secondary BD-Only sets showed only a nominal enrichment that did not survive correction (eTable 30). This pattern suggests the convergence is most robust for transdiagnostic factors shared between BD and SCZ. While exploratory analyses of the BD-Only sets yielded suggestive trends for *PBRM1* and *TRANK1*, the overall results allow us to begin genetically dissecting the core components of BD from the broader, transdiagnostic risk factors it shares with SCZ.

S3. BD Subphenotype Genetic Architecture

SNP-based Heritability and Global Genetic Correlations: See eTable 24, SNP-based heritability was highest for the psychosis subphenotype at .278 (s.e.m.=.017). Genetic correlations (rG) were calculated using LD Score regression (LDSC). Heritability was transformed to the liability scale and rG were standardised in the GenomicSEM package.³⁸ We acquired summary statistics from large-scale GWAS for 10 other psychiatric and 7 cognitive cross-traits. The psychiatric disorders included schizophrenia (SCZ)²⁶, major depressive disorder (MDD)⁴¹, attention deficit and hyperactivity disorder (ADHD)⁴², anxiety (ANX)⁴³, autism spectrum disorder (ASD)⁴⁴, mood swings (MOOD)⁴⁵, post-traumatic stress disorder (PTSD)⁴⁶, and borderline personality disorder (BPD)⁴⁷. The cognitive traits included intelligence (INTEL)⁴⁸, insomnia (INS)^{49,50}, and seven tests of general

cognitive function (Matrix Pattern Completion, Memory–Pairs Matching, Trail Making Test–B, Tower Rearranging, Symbol Digit Substitution, Verbal Numerical Reasoning, and Reaction Time).⁵¹ Bivariate genetic correlations were calculated for our 11 subphenotype-BD MTAG results against these traits (eFigure 10, eTable 24), with *P*-values Bonferroni-corrected ($P < 1.84 \times 10^{-4}$). To align phenotypes, only GWAS summary statistics without 23andMe self-report data were included. The analyses used the 1000 Genomes Project Consortium³² and HapMap3 LD reference panel.⁵²

SbayesS⁵³ Genetic Architecture analysis: Analyses were conducted to compare the genetic architecture of a subset of the subphenotypes. SBayesS is a summary-level method which uses a Bayesian mixed linear model to estimate h^2 SNP, polygenicity, and a measure of negative selection (*S*). Shrunk LD matrix was obtained from GCTA.⁵⁴ Heritability (h^2 SNP) was transformed to the liability scale.⁵⁵ Finally, SBayesS analysis further differentiated this cluster by showing that BD2’s genetic architecture overlaps most strongly with anxiety disorders, in contrast to BD1’s primary overlap with SCZ (eTable 17; eFigure 16), providing a clear genetic basis for their separation.

Local genetic correlations: Shared genetic architecture of traits was estimated using Local Analysis of [Co]variant Association (LAVA).⁵⁶ This was evident in the high global genetic correlation between Suicide Attempt (SA) and AlcSUD, and was validated by LAVA, which identified three shared local genetic loci between them (eTable 16). Furthermore, these two subphenotypes shared 30 local genetic loci, powerfully explaining their clustering and demonstrating a specific, shared genetic architecture for anxiety-compulsive traits that is largely independent of the psychosis axis (eTable 17; eFigure 16).

S4. Subphenotype-specific polygenic risk scores (MTAG-BD-PRS)

Methods

The study evaluated the predictive performance of PRS for BD and its subphenotypes. The core methodology involved developing subphenotype-specific PRS using MTAG. These MTAG-derived effect sizes were then used for PRS construction in target cohorts via PRS-CS-auto,⁵⁷ employing a leave-one-cohort-out approach. Within each target cohort, PRS were standardized and their association with phenotype status was assessed using logistic regression, adjusted for the first five PCs. Nagelkerke’s *R*² was converted to *R*² on the liability scale (*R*²-liability) using the method by Lee et al. (2012).⁵⁸ A formal random-effects (RE) meta-analysis of the per-cohort *R*²-liability values was conducted. Sensitivity analyses using methods including Slope-Hunter⁵⁹ to adjust for potential index event bias were explored but deemed unreliable as this inflated the test statistics.

Results

The primary results presented here focus on analyses using an assumed population prevalence (*K*) of 2%. *PRS Performance and Risk Stratification (Weighted Averages at K=2%)* eTable 22 provides a descriptive summary of PRS performance using overall weighted averages of per-cohort estimates, assuming *K*=2%. The overall weighted average *R*²-liability ranged from 4.38% for panic disorder to a notable 10.61% for unipolar mania. For the broader bipolar disorder categories, BD1 yielded an *R*²-liability of 8.76%, and BD2 showed 8.18%. These *R*²-liability values generally surpass the ~4.57% reported for overall BD by Mullins et al. (2021)⁶⁰ (Psychiatric Genomics Consortium [PGC]3, *K*=2%) and are competitive with, or in some instances exceed, the 8.4%-9.0% *R*²-liability reported by O’Connell et al. (2025)²⁵ for their best-performing multi-ancestry PRS in European samples (also at *K*=2%). The PRS demonstrated notable risk stratification capacity. The absolute risk for individuals in the top 1% of the PRS distribution for BD1 was estimated at 9.27% (eTable 22). This aligns with strong risk stratification reported in PGC studies, such as the odds ratio (OR) of 3.5 for the top PRS decile reported by Mullins et al. (2021)⁶⁰ and an OR of 7.06 for the top PRS quintile by O’Connell et al. (2025)²⁵; direct OR comparisons require caution due to differing metrics and reference groups. Our findings show a marked increase in absolute risk for higher PRS strata across phenotypes (e.g., for BD1, top quintile absolute risk of 4.204% vs. bottom quintile of .58%).

Meta-Analysis of R²-liability (Random-Effects Model at K=2%) Given the substantial between-cohort heterogeneity observed across all analyses (all *I*²>80%, see Heterogeneity Assessment and Table 21), the RE model was deemed more appropriate for formal meta-analysis of PRS performance. Table 21 presents these RE

meta-analysis results for R2-liability (K=2%). The summary R2-liability (RE, K=2%) for BD1 was 9.838% (95% CI: 7.047% - 12.980%) and for BD2 was 7.280% (95% CI: 5.804% - 8.896%). These formally meta-analyzed values are also consistent with or exceed the performance metrics from both Mullins et al. (2021)⁶⁰ (~4.57% R2-liability at K=2%) and the European-specific PRS from O'Connell et al. (2025)²⁵ (8.4%-9.0% R2-liability at K=2%). Critically, several subphenotypes demonstrated strong PRS performance, potentially outperforming broader BD classifications, even if their contributing sample sizes were smaller. unipolar mania (UM) exhibited the highest summary R2-liability at 12.402% (95% CI: 7.572% - 18.036%), followed by alcohol or substance use disorder (AlcSUD) at 11.807% (95% CI: 9.168% - 14.684%). Other subphenotypes, including psychosis (9.340%) and rapid cycling (9.039%), also showed R2-liability values comparable to or exceeding that of BD2 and the higher end of O'Connell et al.'s estimates. This suggests the subphenotypic MTAG approach can effectively leverage specific genetic signals to achieve substantial explanatory power. Panic disorder showed the lowest R2-liability at 5.469%. PRS demonstrated effective predictive power, with variance explained on the liability scale (R²-Liability) ranging from 5.47% for PD to 12.40% for unipolar mania (eTables 21-22); see eTable 23 for prevalences. Additional analyses confirmed methodological consistency (eFigure 20).

Heterogeneity Assessment: Substantial and statistically significant heterogeneity was observed across cohorts for all phenotypes (I² values ranging from 83.6% for rapid cycling to 96.4% for BD1; all Q-statistic *P*-values < .0001). This high level of heterogeneity, a common finding in large psychiatric genetic studies including those by Mullins et al. (2021)⁶⁰ and O'Connell et al. (2025)²⁵, underscores the appropriateness of the random-effects model for pooling estimates. Rapid cycling (I²=83.6%) exhibited lower heterogeneity than BD1 (I²=96.4%) and was comparable to BD2 (I²=85.0%), while most other subphenotypes also displayed high I² values.

Conclusions

This study demonstrates that Polygenic Risk Scores derived using an MTAG approach effectively stratify risk for bipolar disorder constituent subphenotypes. Based on a 2% population prevalence, the variance explained on the liability scale (R2-liability) from random-effects meta-analyses varied across phenotypes, ranging from approximately 5.469% for panic disorder to a significant 12.402% for unipolar mania (eTable 23). These figures are competitive with, and for several phenotypes including BD1 and certain subphenotypes (e.g., unipolar mania, alcohol/substance use disorder), exceed the R2-liability reported in recent large-scale PGC studies (Mullins et al., 2021; O'Connell et al., 2025)^{60,25} for broadly defined BD. This suggests that the subphenotypic MTAG approach can enhance predictive power by leveraging more specific genetic signals, even when individual cohort sample sizes for subphenotypes might be smaller. The high levels of heterogeneity (I²>80% for all analyzed phenotypes at K=2%) affirmed the random-effects model as the most appropriate for summarizing PRS performance, providing more conservative and realistic estimates by accounting for between-cohort variance. While only rapid cycling demonstrated consistently lower heterogeneity in R2-liability compared to BD1, the varying levels of predictive power and distinct risk profiles observed across different subphenotypes (highlighted by both R2-liability in eTable 21 and absolute risk estimates in eTable 22) underscore the potential clinical and research utility of this stratified approach for understanding the multifaceted genetic architecture of bipolar disorders.

Limitations

Several limitations should be considered when interpreting these findings. First, while statistically significant, the explanatory power of current PRS for complex psychiatric disorders, including BD remains modest, accounting for a limited portion of the total variance in liability. Therefore, absolute risk estimates derived from PRS reflect group averages and are not sufficiently predictive for standalone individual clinical decision-making, a caveat also highlighted in large PGC studies. Second, the conversion of observed-scale R2 to R2-liability and subsequent absolute risk estimations are critically dependent on the assumed population prevalence (K=2% for the primary results presented). Misspecification of K could bias these estimates. Third, some strata or cohorts, particularly those with smaller sample sizes, may yield incalculable or unstable estimates for certain metrics. The "Overall Weighted Average" metrics (eTable 22), while informative, are simple averages weighted by effective sample size and can be heavily influenced by larger cohorts; they do not formally account for heterogeneity in the same way as the random-effects meta-analysis (Table 21) and may not uniformly represent all contributing cohorts. Finally, the current findings are based on data from individuals of European ancestry. Due to differences in genetic architecture, linkage disequilibrium patterns, allele frequencies, and potential gene-environment interactions, these results may not be generalizable to populations of other ancestries, a common limitation in current PRS research.

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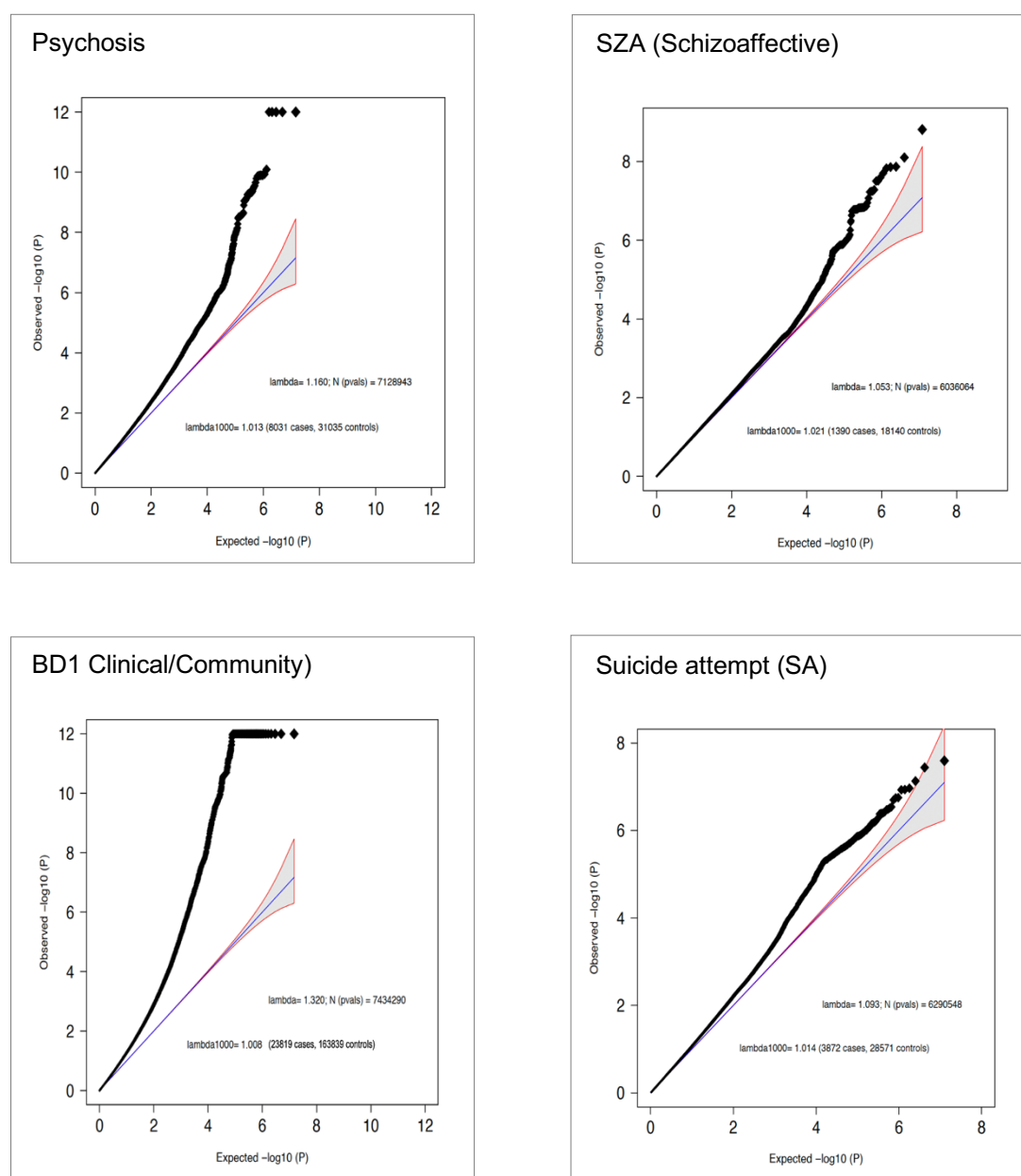
eTable 29. Additional Credible Genes from the MHC Region (BD-Only MTAG) ($N=2$).

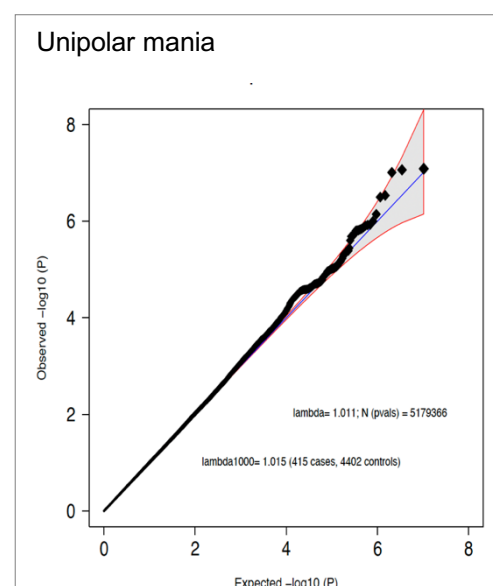
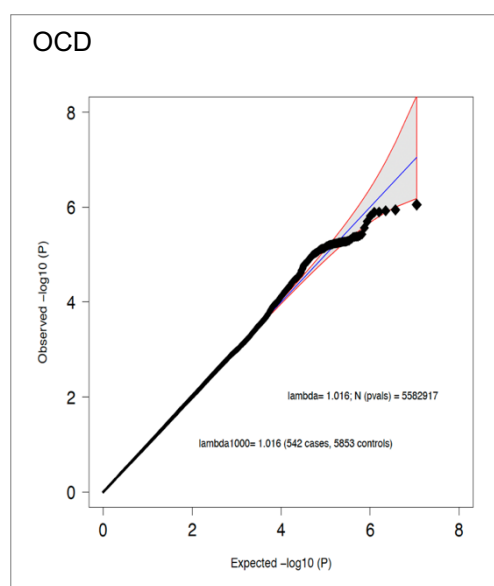
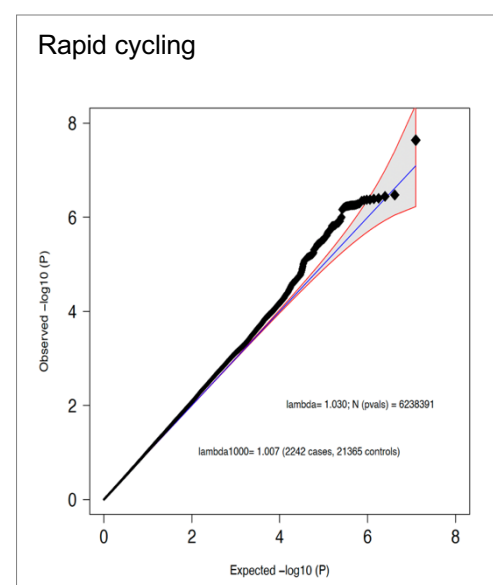
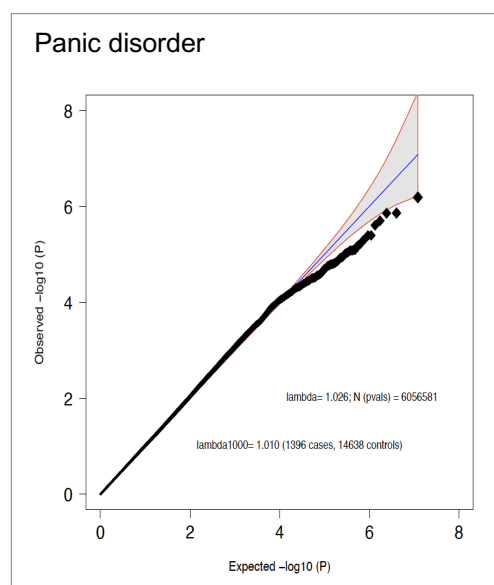
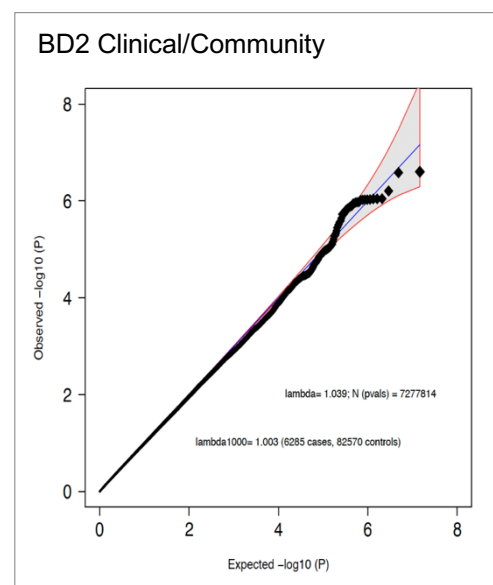
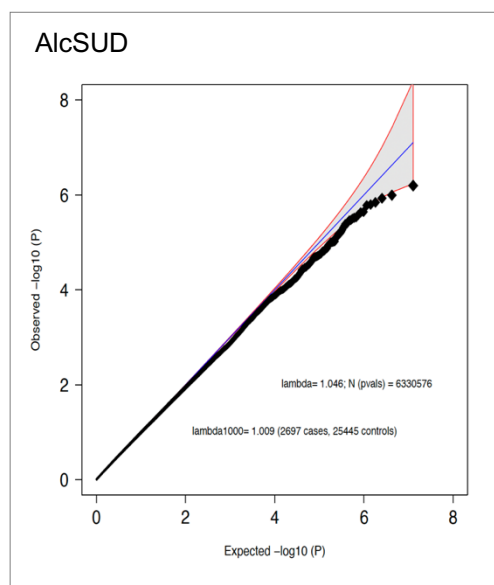
eTable 30. Enrichment of Credible Gene Sets with SCHEMA Rare-Variant Genes ($N=33$).

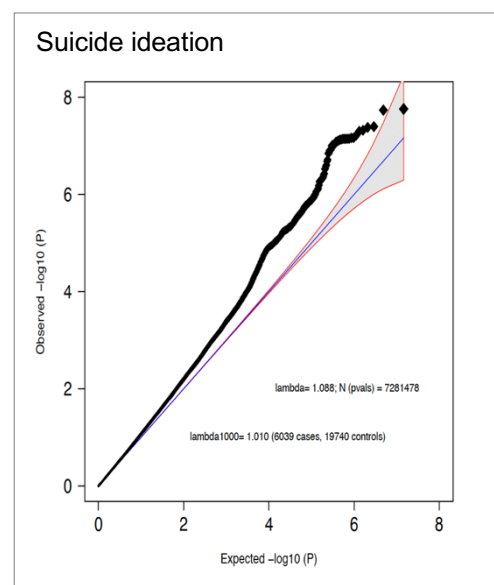
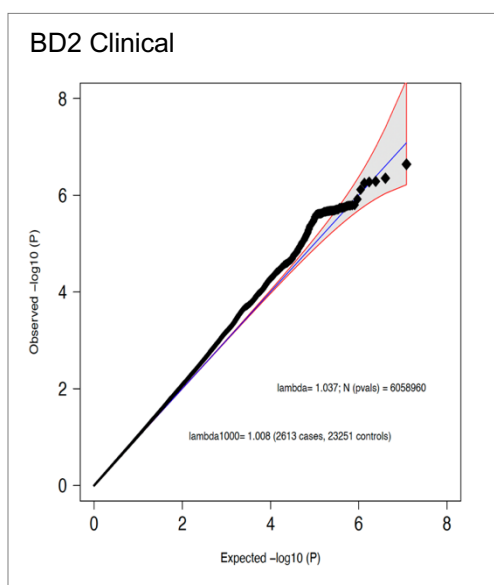
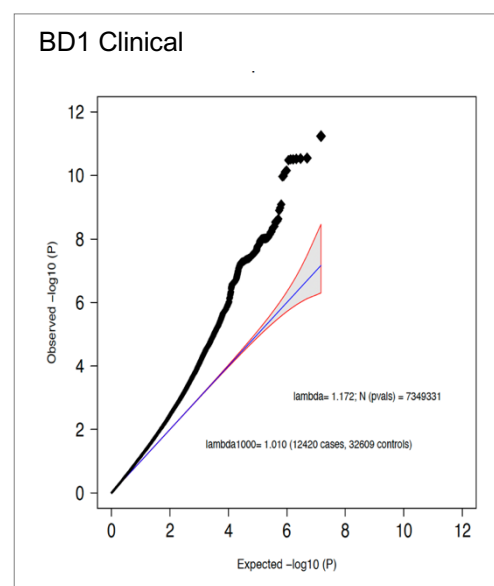
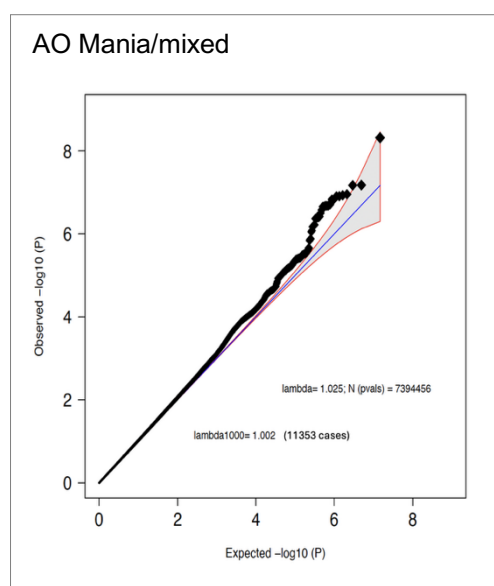
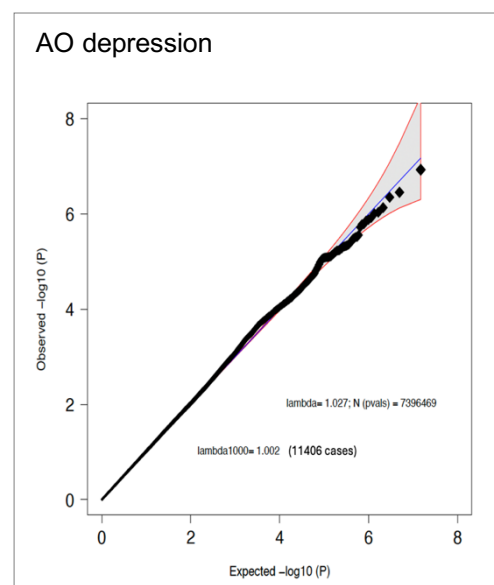
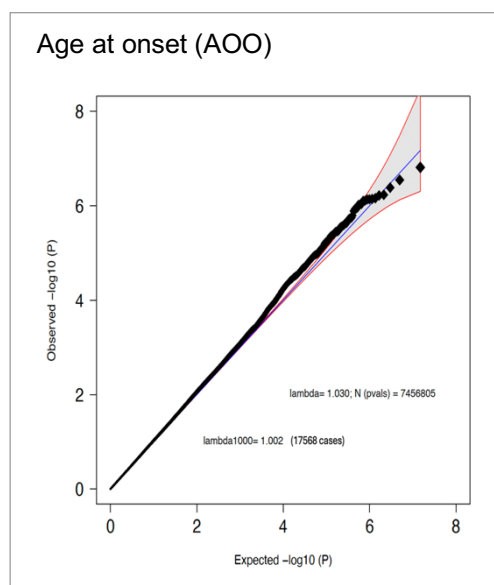
S7. Supplementary Figures

eFigure 1. QQ plots for each of the 11 core subphenotype-GWAS.

Each plot shows the observed $-\log_{10}(P\text{-values})$ against the expected $-\log_{10}(P\text{-values})$ under the null hypothesis of no association. Genomic inflation factors (λ_{GC}) are indicated within each plot. These plots indicate minimal confounding from uncorrected population stratification or cryptic relatedness, supporting the validity of the genetic associations. The eTable 18 presents the results from 16 distinct genome-wide association studies (GWAS) conducted on 11 subphenotypes. These analyses include three different definitions of age of onset and a specific analysis of suicide ideation.



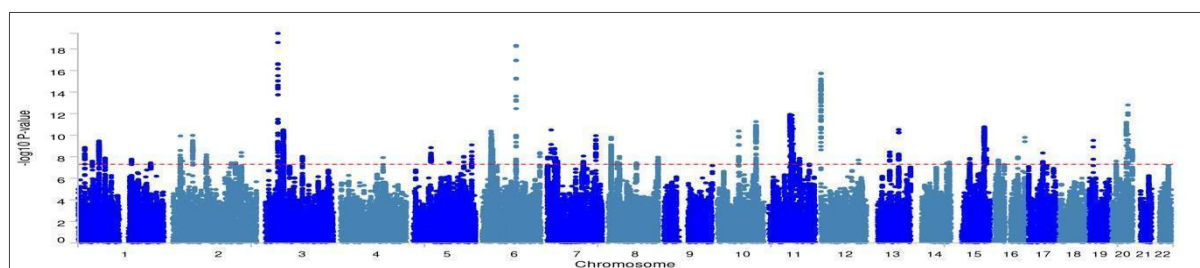




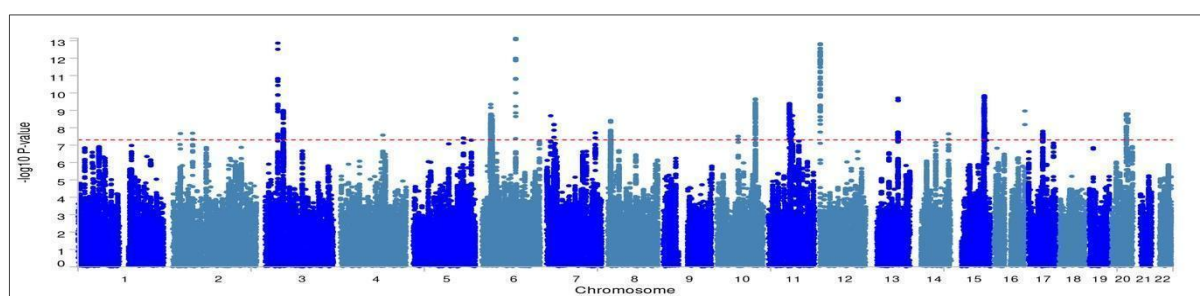
eFigure 2. Manhattan plots for each of the 10 subphenotype-BD MTAG analyses.

Each plot displays the $-\log_{10}(P\text{-values})$ of all SNPs across the genome. The red line indicates the genome-wide significance threshold ($P < 5 \times 10^{-8}$). These plots visually represent the increased statistical power and identified loci from the BD-only MTAGs. eTable 13 presents the results from the 10 subphenotype-BD-only and the 10 subphenotype-BD-SCZ MTAGs.

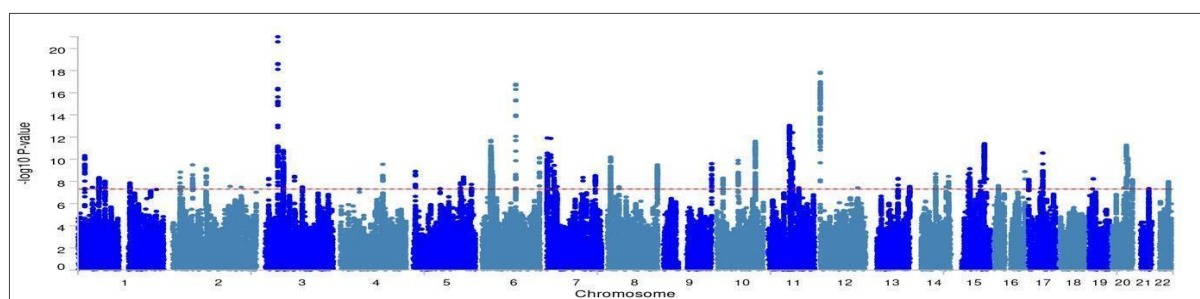
Psychosis



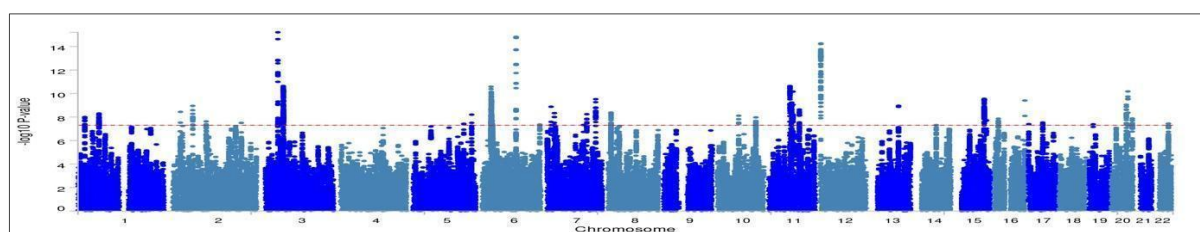
SZA (Schizoaffective)



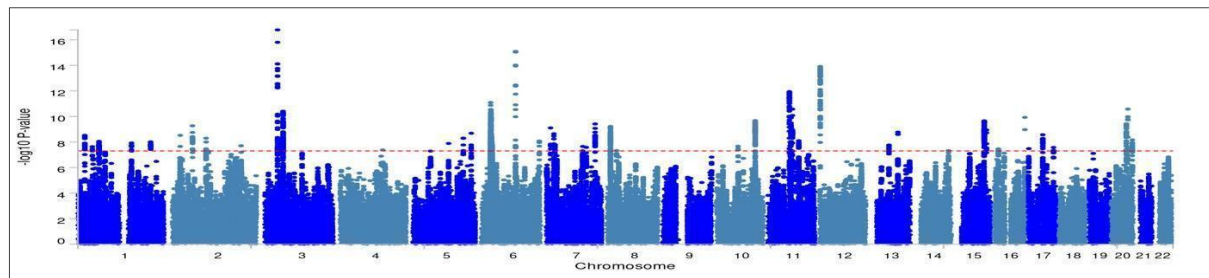
BD1 clinical/community



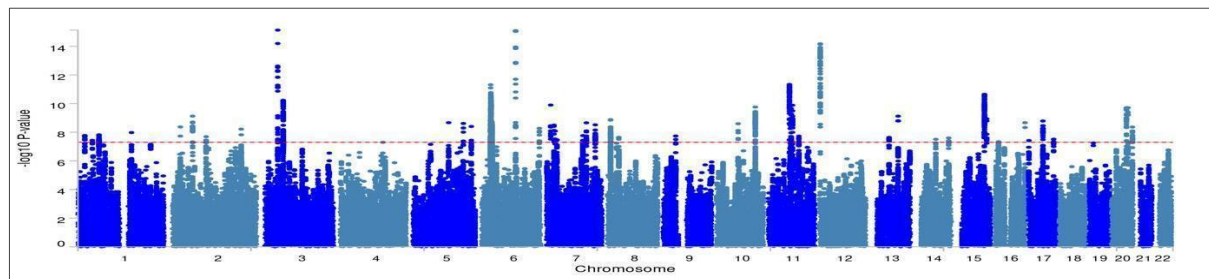
Suicide attempt



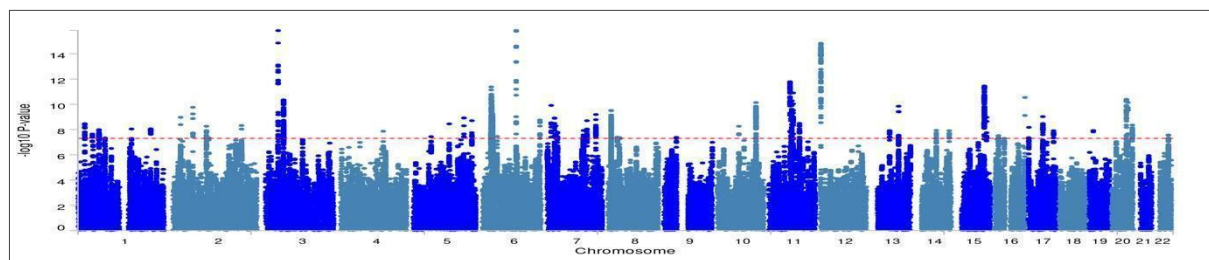
AlcSUD



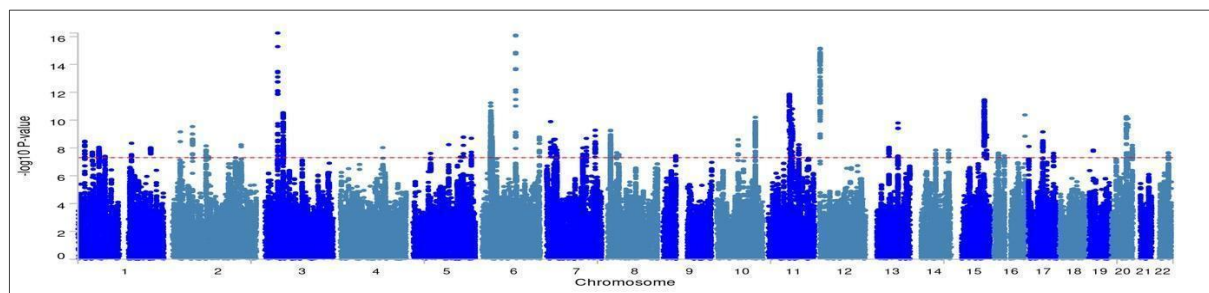
BD2 clinical/community



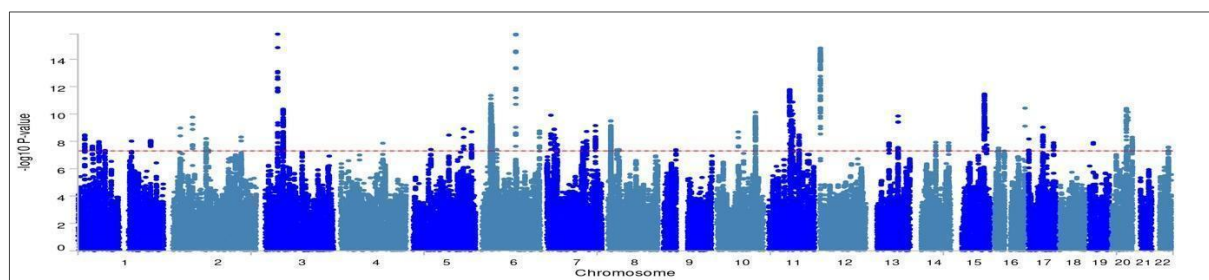
Panic disorder



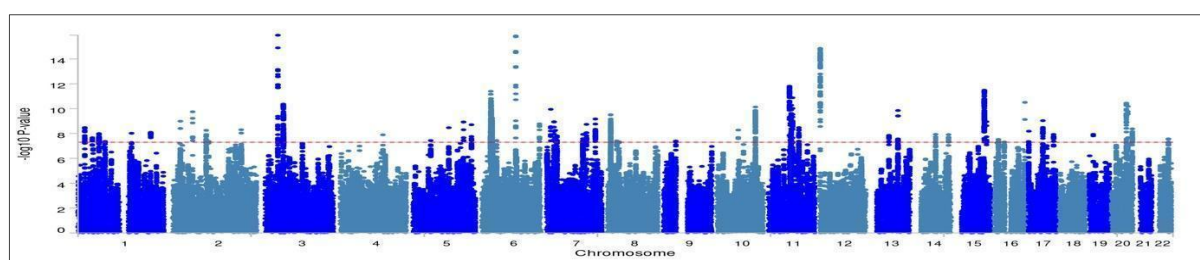
Rapid-cycling



OCD

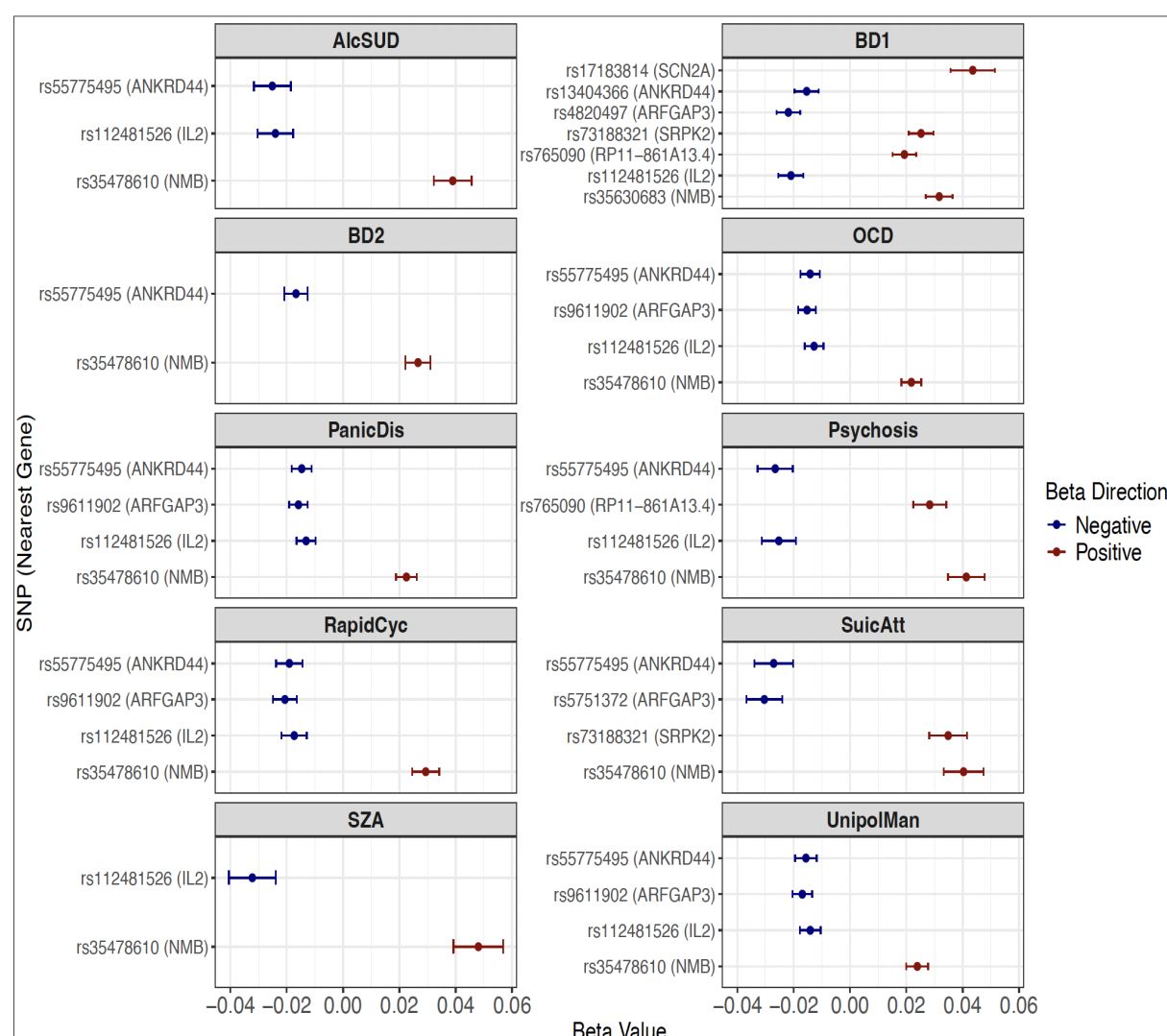


Unipolar mania



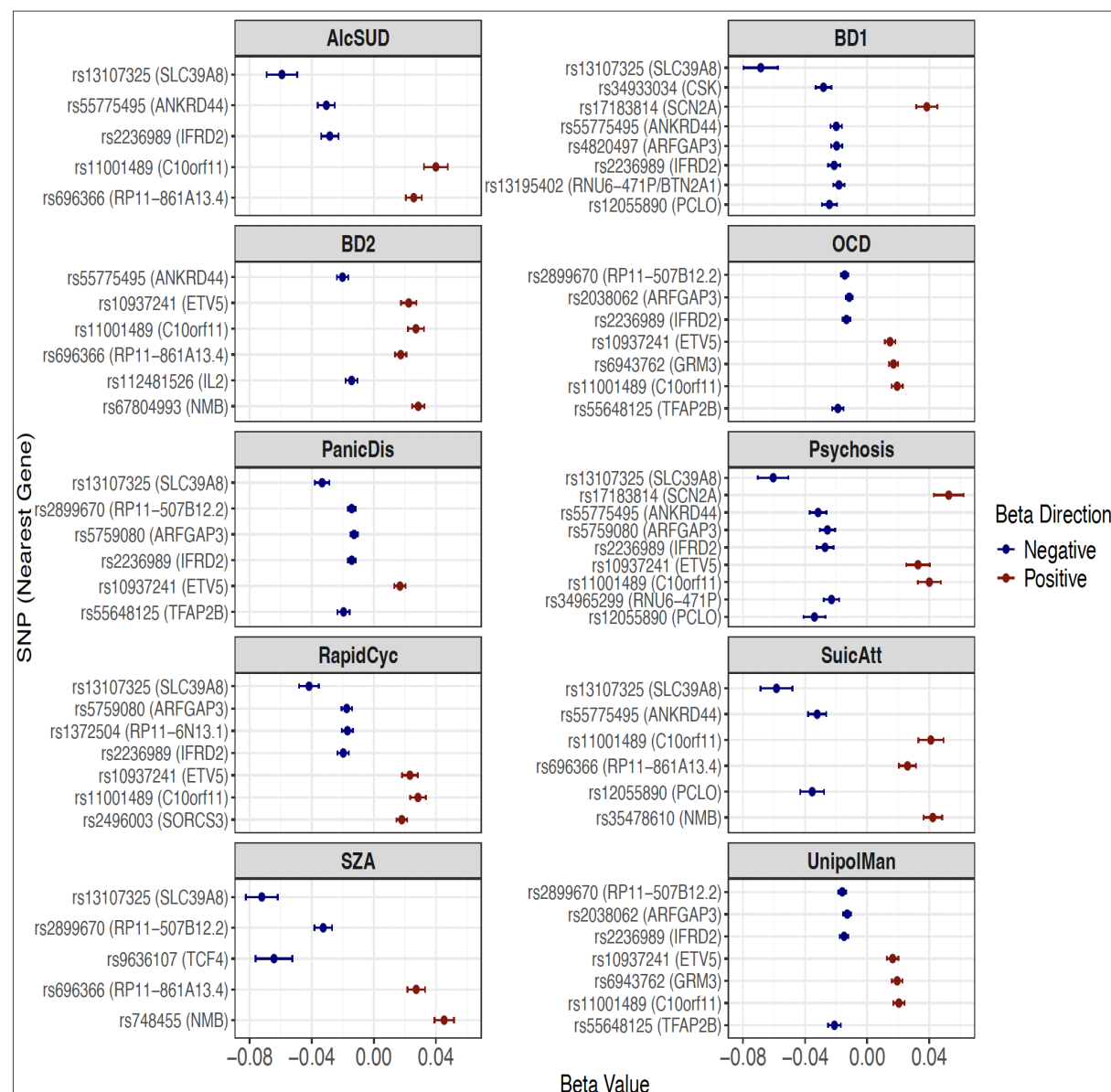
eFigure 3: MTAG SNP to gene annotations for 10 Subphenotype-BD results.

MTAG SNP to gene annotations for 10 Subphenotype-BD results. Plot of MTAG SNP to gene annotations (y-axis) for 10 Subphenotype-BD results ordered by the highest CADD values (CADD > 12.37), i.e. most deleterious SNP (gene) first. Standardised (significant $P < 5.0 \times 10^{-8}$) beta coefficients (β_{std}) and their standard errors plotted on x-axis for comparison across the 10 subphenotypes. Direction of coefficients are indicated in blue (positive) and red (negative). The eTable 2 presents the results from the gene-based tests.



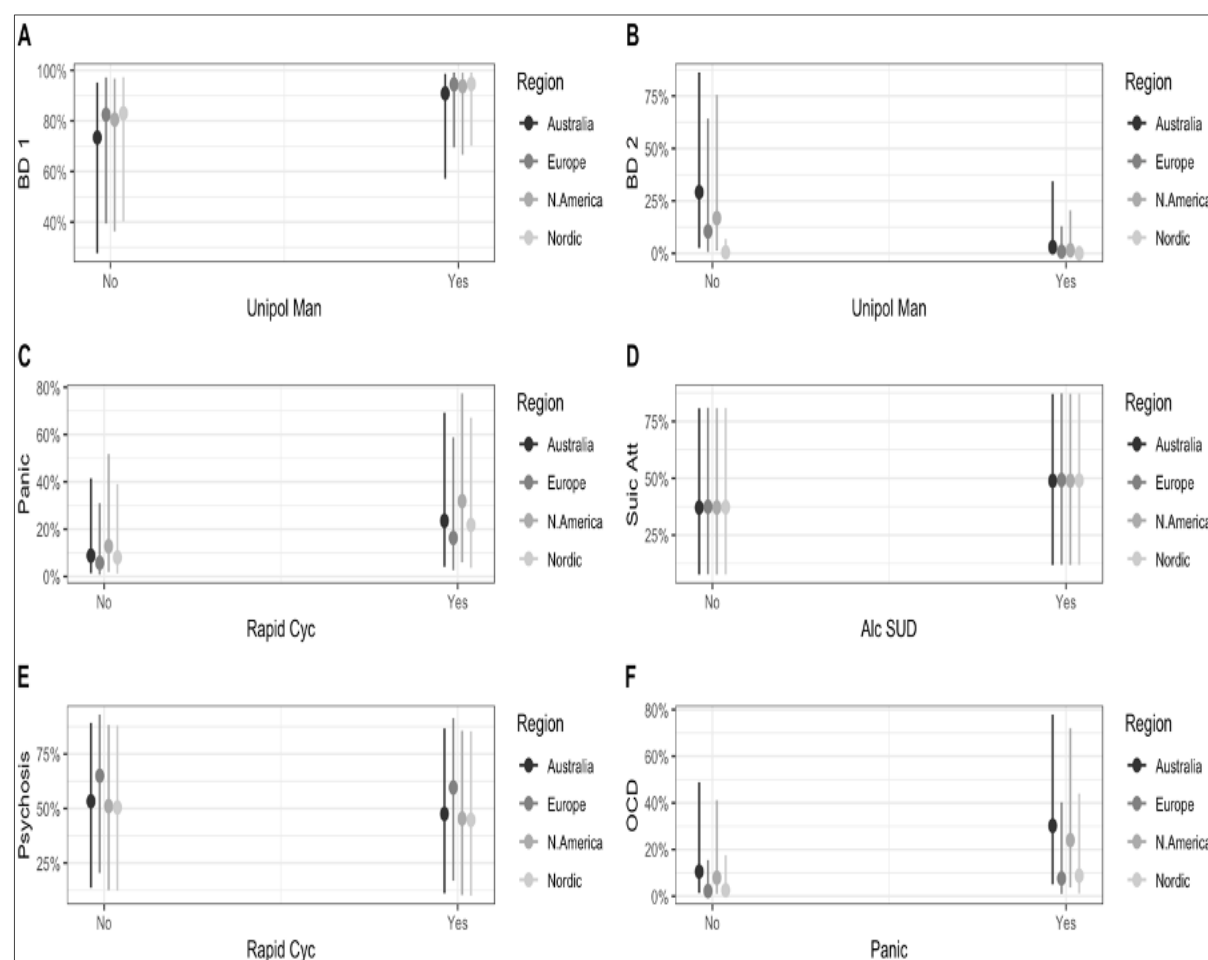
eFigure 4: MTAG SNP to gene annotations for 10 Subphenotype-BD-SCZ results.

MTAG SNP to gene annotations for 10 Subphenotype-BD-SCZ results. Plot of MTAG SNP to gene annotations (y-axis) for 10 Subphenotype-BD-SCZ results ordered by the highest CADD values (CADD > 12.37), i.e. most deleterious SNP (gene) first. Standardised (significant $P < 5.0 \times 10^{-8}$) beta coefficients (β_{std}) and their standard errors plotted on x-axis for comparison across the 10 subphenotypes. Direction of coefficients are indicated in blue (positive) and red (negative). The eTable 2 presents the results from the gene-based tests.



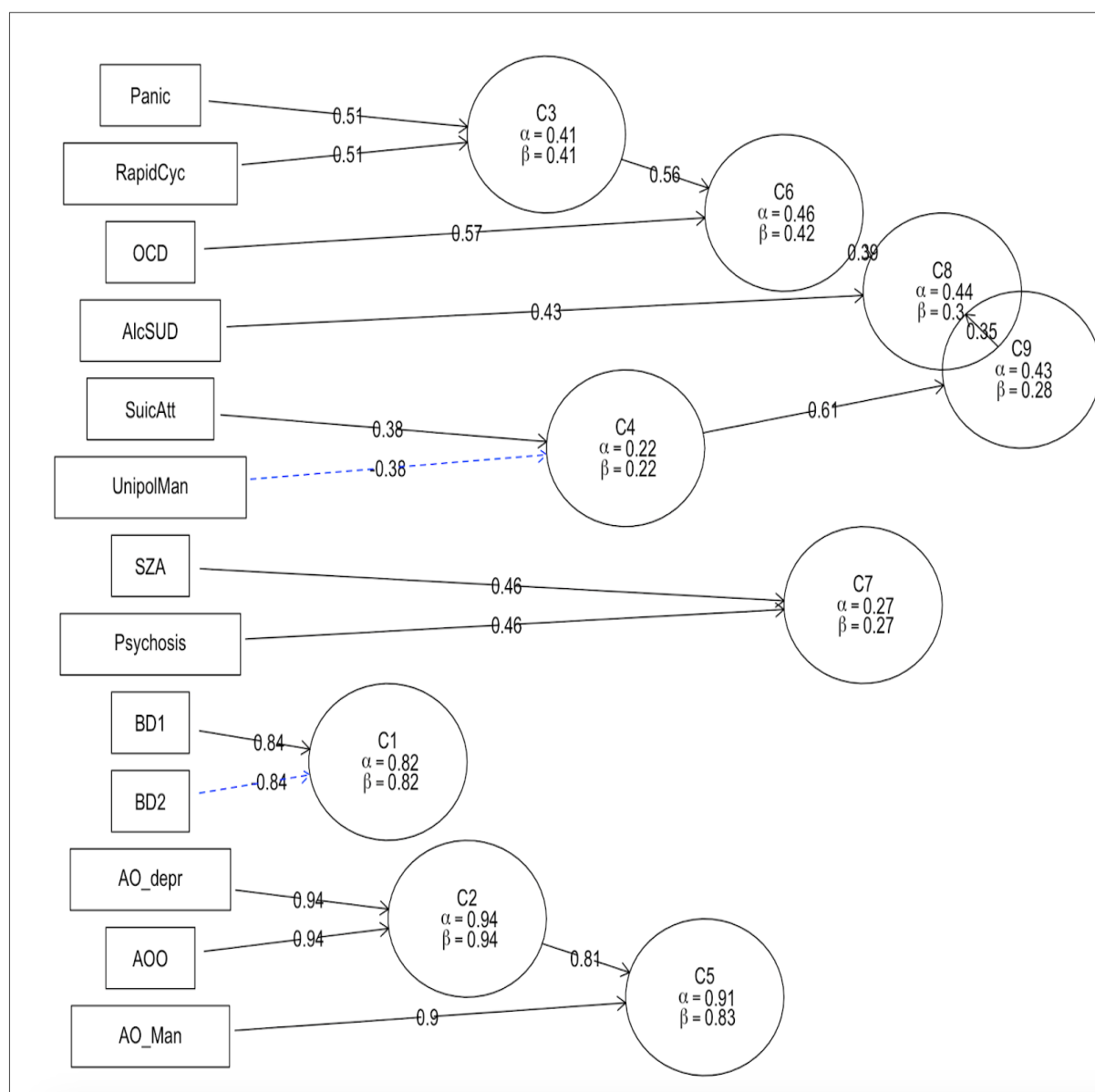
eFigure 5: Mixed regression models of homogeneity in phenotype regions.

Generalized linear mixed effects (GLMER) models were constructed using pairwise analyses of BD subphenotypes to assess phenotype heterogeneity across geographical sites, termed ‘Region’ which was used as the random effect, $N = 18,800$ BD cases. ‘Region’ included symptom-level data from cohorts across Australia, Europe, North American or Nordic countries. Confidence intervals (95% CI) of predicted probabilities (y-axis) overlapped indicating homogeneous responses to target phenotypes(x-axis) which met international consensus measures (DSM-IV, DSM-V, ICD-9, or ICD-10). See eTable 9.



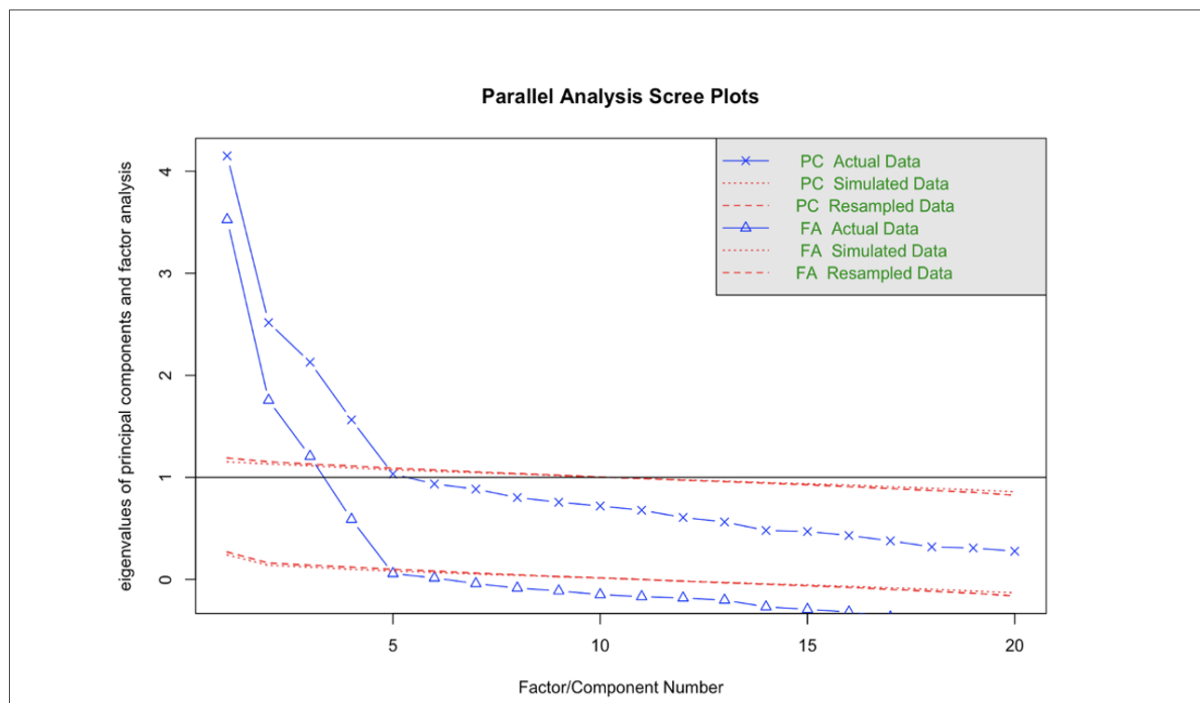
eFigure 6: Confirmatory Factor Analysis (CFA) model for BD heterogeneity.

Factor analysis was performed using the psych package (v2.3.6) in the R environment (R Core Team (2022) (v4.2.2))¹¹ to produce a visualisation of the homogeneous subgroups (subphenotypes) and their interrelatedness. The 'iclust' algorithm in the psych package was utilized to investigate hierarchical clusters that formed composite scales. Subphenotypes were merged when the coefficients alpha and beta, derived from the polychoric correlation function, increased in the new cluster. The analysis included $N = 18,800$ BD cases. The factor analysis robustly supported four primary clinical factors for BD heterogeneity: (F1) SZA and Psychosis; (F2) BD1 and BD2; (F3) a cluster of RC, PD, OCD, AlcSUD, SA, and UM; and (F4) AOO, AO-depression, and AO-mania/mixed. Notably, unipolar mania had a negative loading on C4 with suicide attempts, and BD2 negatively loaded to C1 along with BD1. See eTable 4 for per-cohort sample sizes for each subphenotype analysis. A Confirmatory Factor Analysis (CFA) of the 11 BD subphenotypes empirically derived a robust four-factor clinical model, providing a framework for understanding BD heterogeneity. The analysis, conducted with the Lavaan¹² package in R, indicated acceptable fit indices ($\chi^2=588.91$, $P = 2.188 \times 10^{-87}$; SRMR .084; CFI .936). This model was selected over more parsimonious one-, two-, and three-factor models which demonstrated poorer fit indices. This determination was supported by parallel analysis (eFigure 7). The Kaiser-Meyer-Olkin Criterion (KMO)¹³ measure of sampling adequacy was .895, and Bartlett's test of sphericity was significant ($P < .001$), implying the data was adequate for EFA.



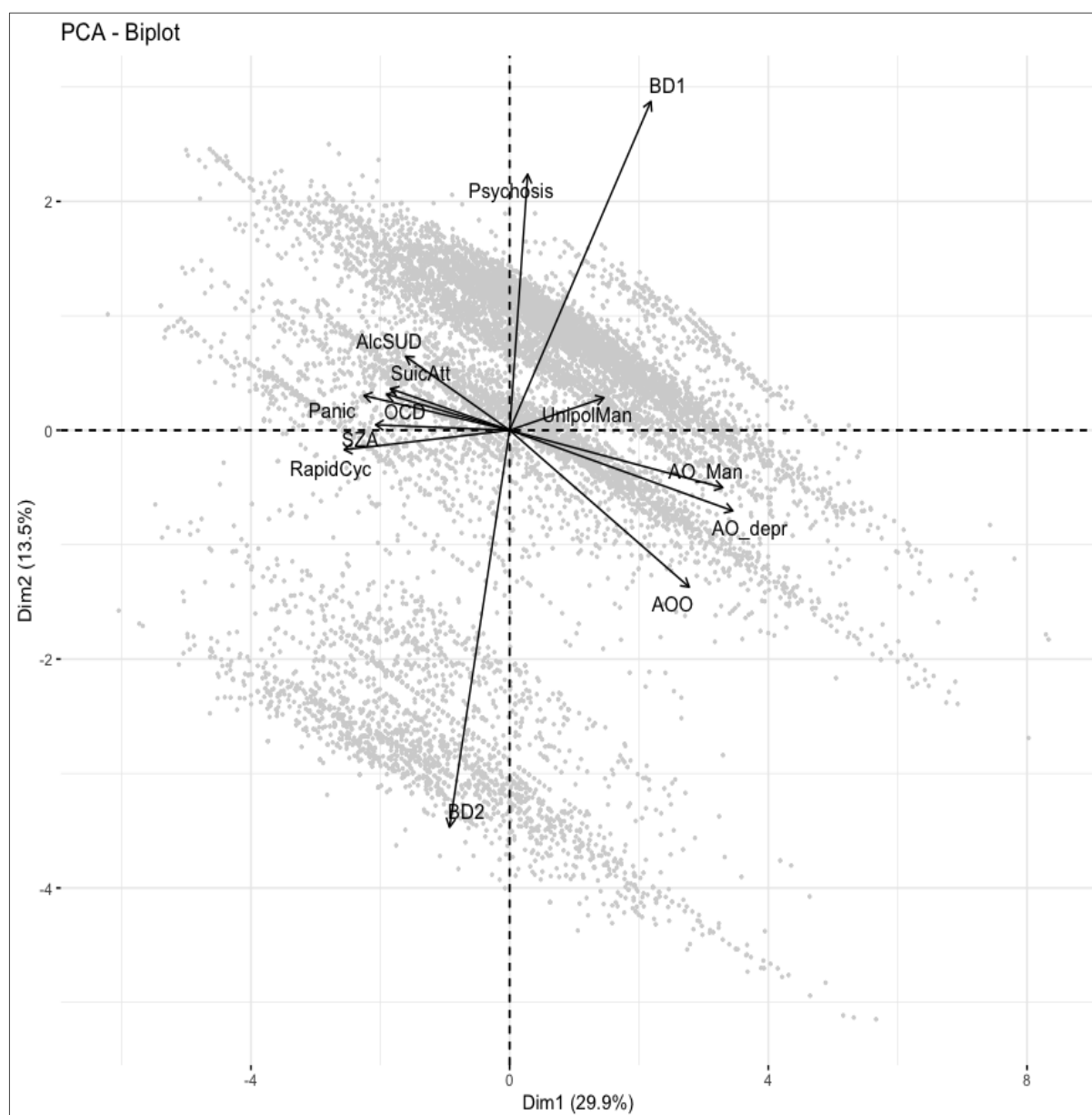
eFigure 7: Parallel analysis plot for factor determination.

Parallel analysis determined the number of lower dimensions in the dataset to be four. Eigenvalues for principal components (PC) and factor analysis (FA) converged on four eigenvalues (factors), which are above the PC (upper red line) and FA (lower red line) cutoff. See eFigure 6 and S1 for fit indices.



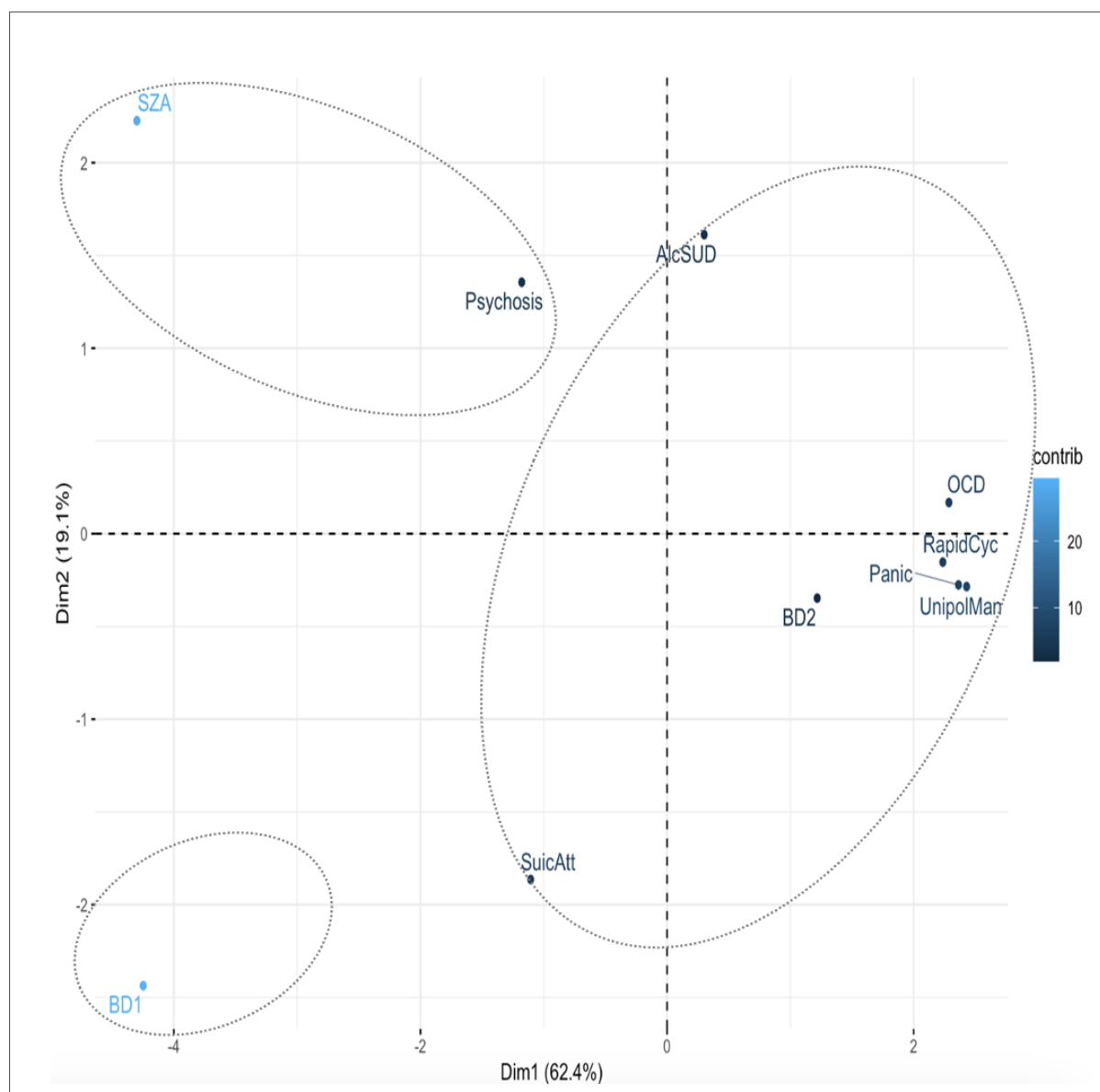
eFigure 8: PCA visualization of 11 BD subphenotypes.

PCA visualization of 11 BD subphenotypes, showing clustering. This figure visualizes how components account for variance in the dataset. See eTable 4 for per-cohort sample sizes for each subphenotype analysis.



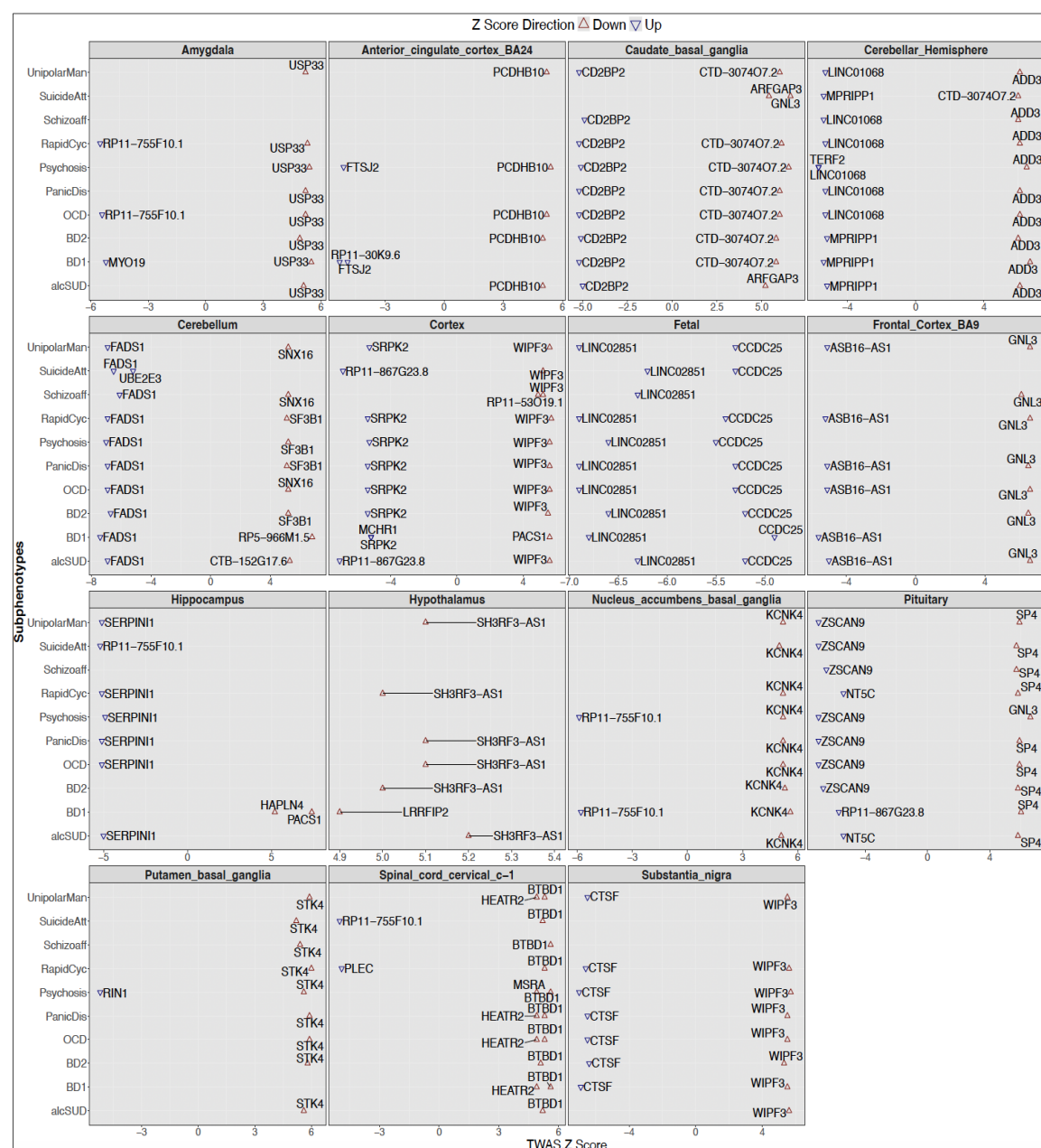
eFigure 9: PCA biplot of genomic loci in 10 subphenotype-BD-MTAGs.

Principal component analysis (PCA) biplot of genomic loci from 10 subphenotype-BD MTAG results. The first two dimensions account for 81.5% of the variance. Subphenotypes with similar genetic architectures are closer on the biplot. Lighter colors indicate higher contribution (factor loading) to dimensional variance. Psychosis, SZA and BD1 contributed most to Dim2 and RC to Dim1. The biological BD model differentiates subphenotypes similar to the clinical four-factor model. Psychosis distance to BD1 is greater than to SZA. RC clusters with comorbid diagnoses (F3) as in the a priori clinical model. A one-way ANOVA revealed a significant difference in local genetic correlation (ρ) between PCA clusters, $F(3, 1038) = 203.2$, $P < 2.00 \times 10^{-16}$, suggesting internal reliability. The eTable 13 presents the results from the 10 subphenotype-BD-only and the 10 subphenotype-BD-SCZ MTAGs.



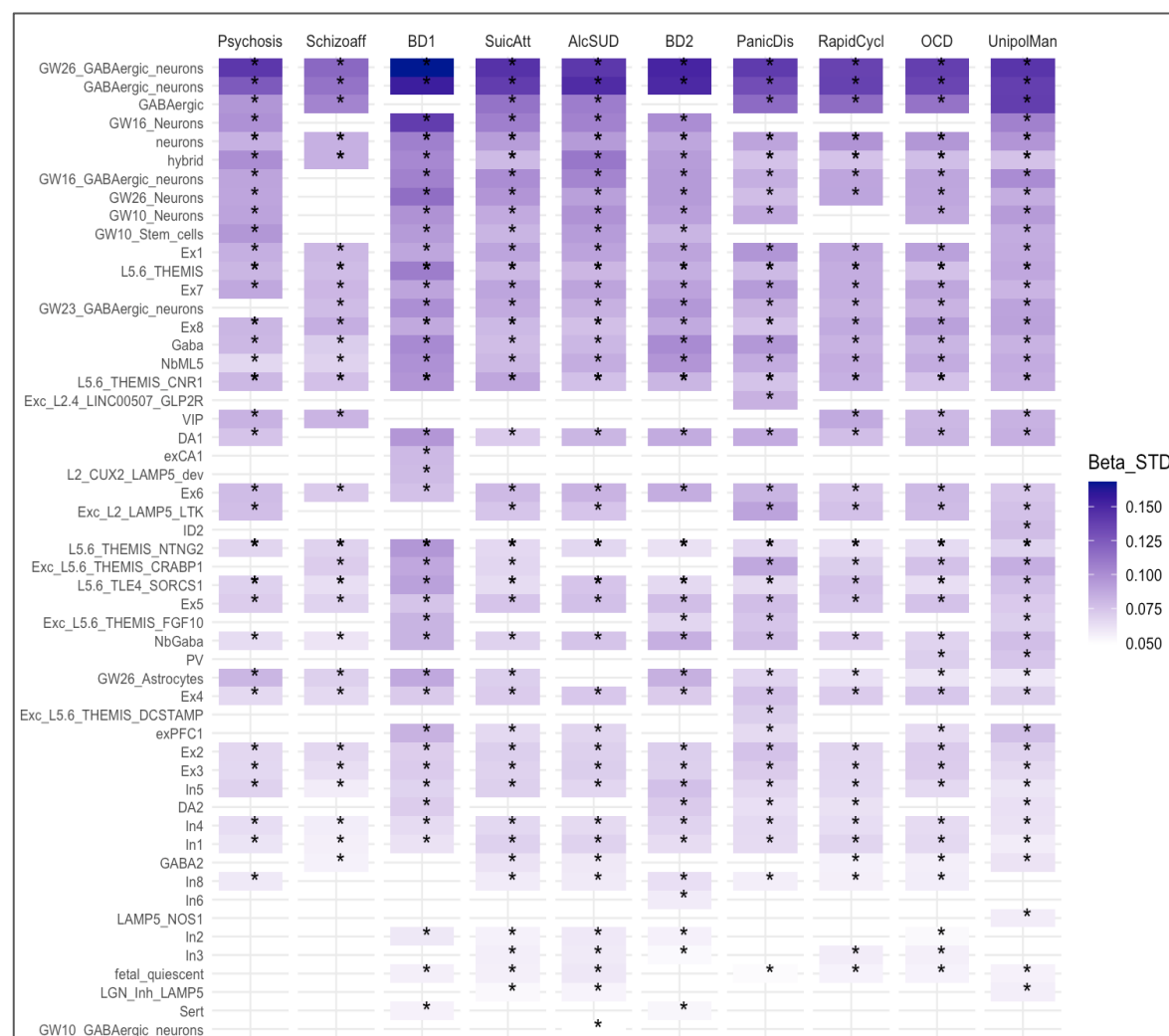
eFigure 11: Heatmap of TWAS joint tissue associations (BD-only MTAGs).

Heatmap illustrating TWAS joint tissue associations in 10 subphenotype-BD MTAGs. Effect sizes, categorized by tissue, represent findings across 15 adult and fetal brain tissues, including MHC. Red (positive) and blue (negative) triangles represent the direction of effect of the TWAS Z-statistic score. Conditional analysis was employed to identify statistically independent signals. For genes expressed across multiple tissues, only the tissue association with the strongest standardized beta was reported. On the x-axis, Bonferroni-corrected $-\log_{10}(P)$ values correspond to the TWAS Z-statistic effects; positive values indicate a positive association, while negative values reflect an inverse relationship. See Figure 2, a heatmap of the 10 subphenotype-BD-SCZ MTAG analyses. The eTable 15 presents the cell type enrichment analysis. Psychosis, Schizoaffect, Schizoaffective disorder, BD1, bipolar disorder I, SuicAtt, suicide attempt, AlcSUD, alcohol or substance use disorder, BD2, bipolar disorder II, PanicDis, panic disorder, RapidCyc, rapid cycling, OCD, obsessive compulsive disorder, UnipolarMan, unipolar mania.



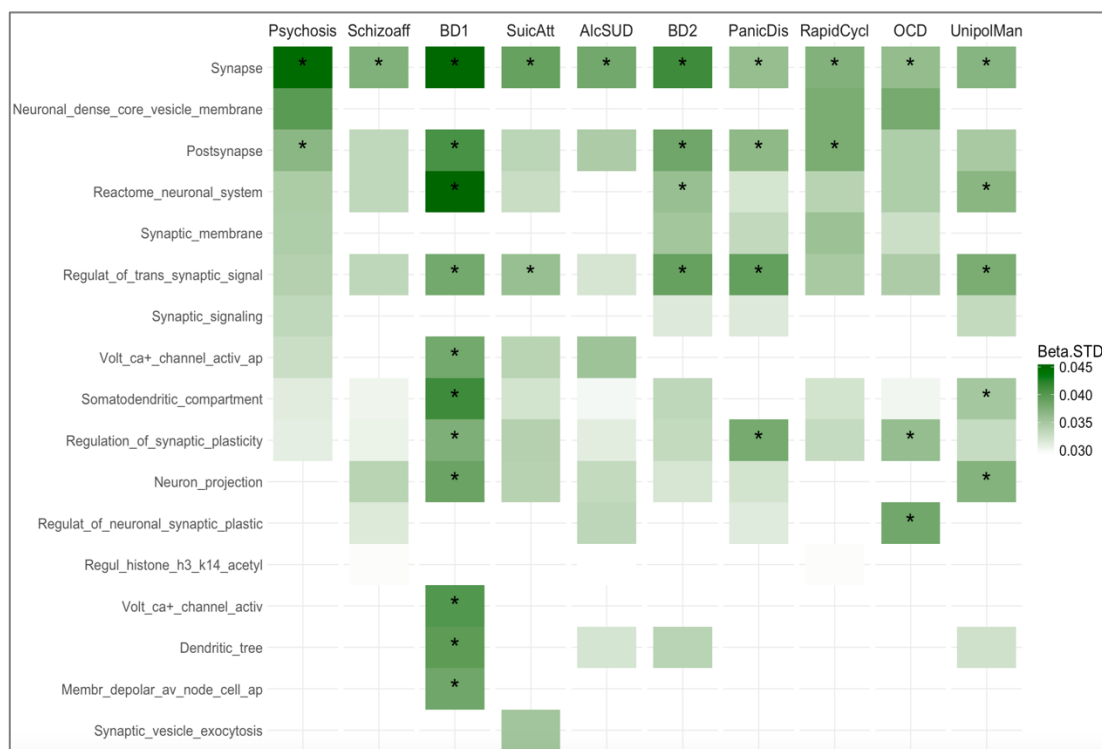
eFigure 12: Heatmap illustrating differential cell type enrichment (BD-only MTAGs).

The heatmap illustrates differential cell type enrichment across 10 subphenotype-BD MTAG analyses. Cell types are arranged according to their effect sizes. Color intensity corresponds to the strength of the standardized beta, signifying a more enriched signal for the corresponding cell type. An asterisk (*) marks cell-type associations that survive correction (P (Bonferroni) $< .05$). The absence of color indicates no association. See Figure 3, a heatmap of the 10 subphenotype-BD-SCZ MTAG analyses. eTable 12 presents the cell type enrichment analysis. Psychosis, Schizoaff, Schizoaffective disorder, BD1, bipolar disorder I, SuicAtt, suicide attempt, AlcSUD, alcohol or substance use disorder, BD2, bipolar disorder II, PanicDis, panic disorder, RapidCycl, rapid cycling, OCD, obsessive compulsive disorder, UnipolMan, unipolar mania.



eFigure 13: Heatmap illustrating differential gene set enrichment (BD-only MTAGs).

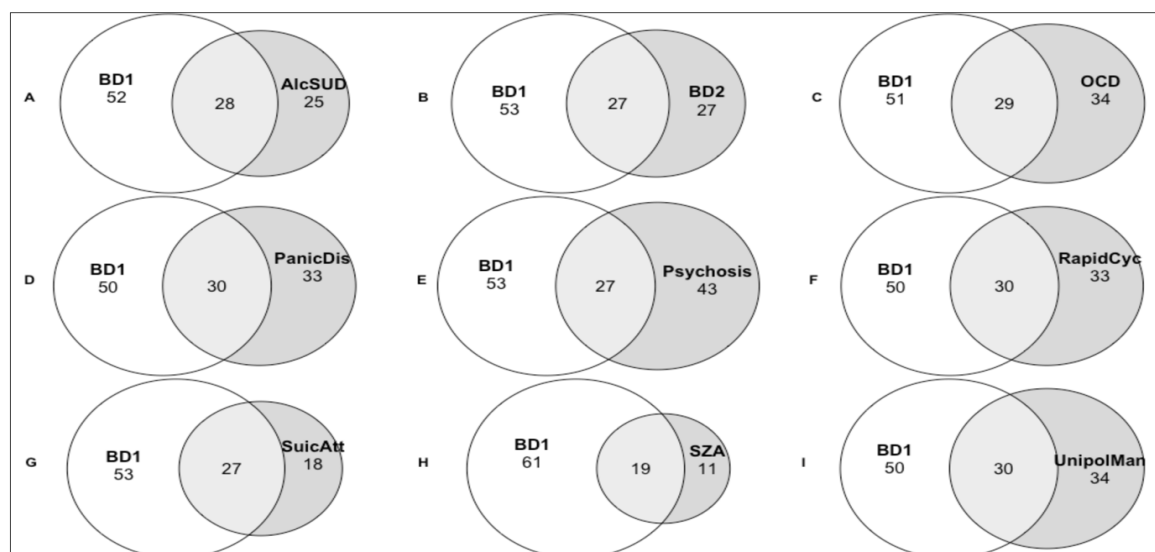
The heatmap illustrates differential gene set enrichment across 10 subphenotype-BD MTAG analyses. Gene sets are arranged according to their effect sizes. Color intensity corresponds to the strength of the standardized beta, representing stronger enriched signals for the associated gene sets. An asterisk (*) marks gene sets that survive Bonferroni correction (P (Bonferroni) $< .05$). The absence of color indicates no association. See Figure 4, a heatmap of the 10 subphenotype-BD-SCZ MTAG analyses. eTable 14 presents the cell type enrichment analysis. Psychosis, Schizoaffect, Schizoaffective disorder, BD1, bipolar disorder I, SuicAtt, suicide attempt, AlcSUD, alcohol or substance use disorder, BD2, bipolar disorder II, PanicDis, panic disorder, RapidCycl, rapid cycling, OCD, obsessive compulsive disorder, UnipolMan, unipolar mania.



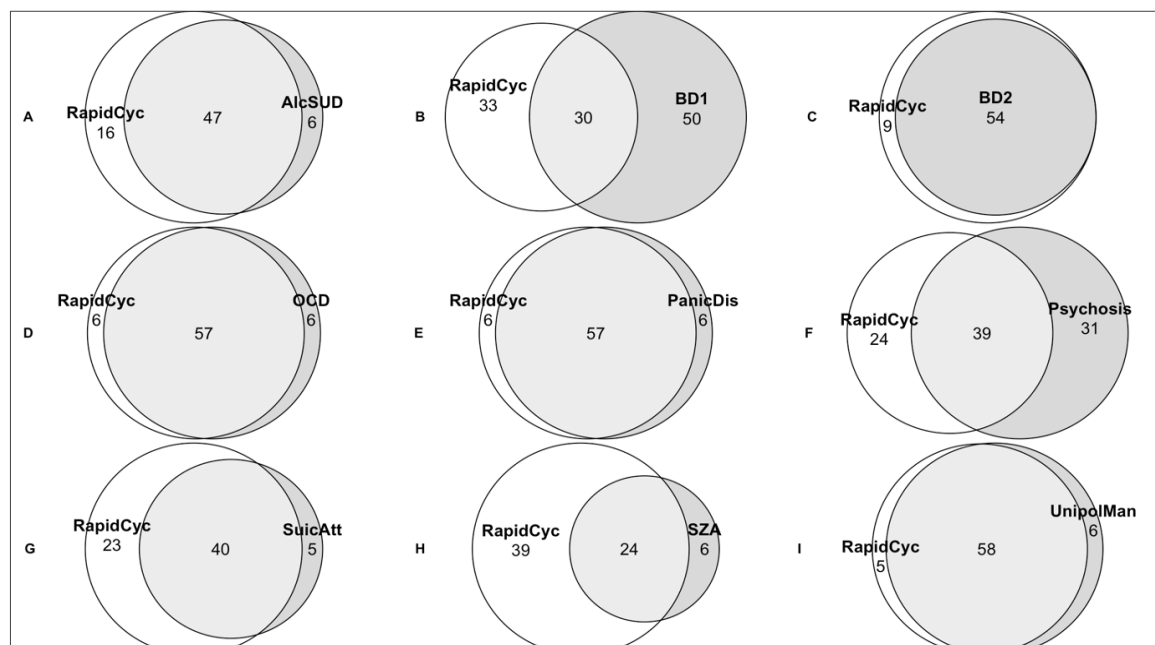
eFigure 14: Overlap visualizations of lead SNPs across subphenotypes.

Visualization of shared and unique lead SNPs for bipolar disorder I (BD1) and rapid cycling (RC) from the subphenotype-BD-only MTAG analyses. The plots demonstrate that BD1 (A) is defined by a high degree of genetic specificity, characterized by many loci not shared with other subphenotypes. Conversely, rapid cycling (B) exhibits extensive genetic overlap, where its risk variants are broadly shared across other subphenotypes, indicating a more pleiotropic architecture. The size of the circles corresponds to the number of SNPs in each intersection. See eTable 19 for loci identified in subphenotype-BD-only and subphenotype-BD-SCZ MTAG analysis.

(A)

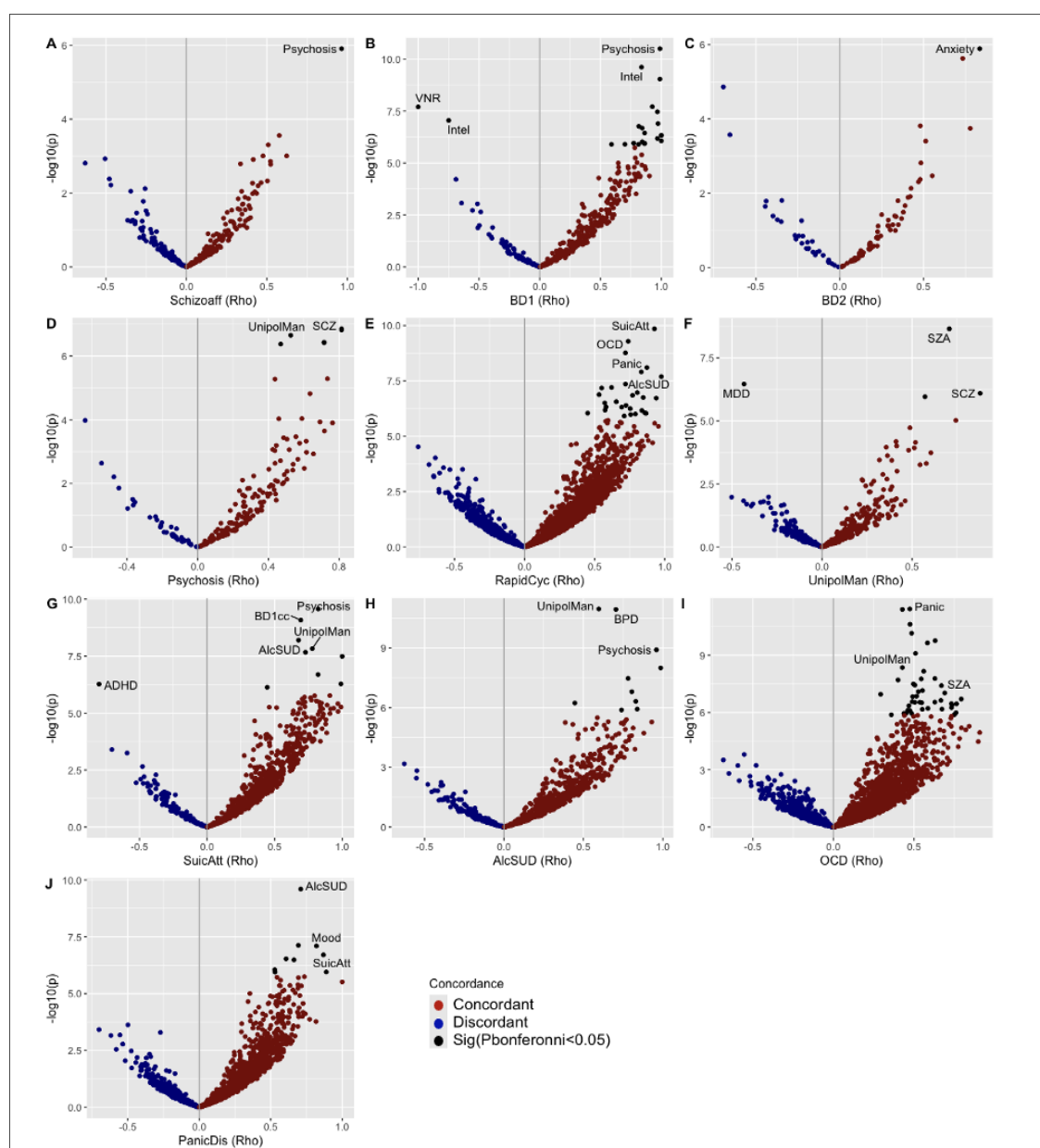


(B)



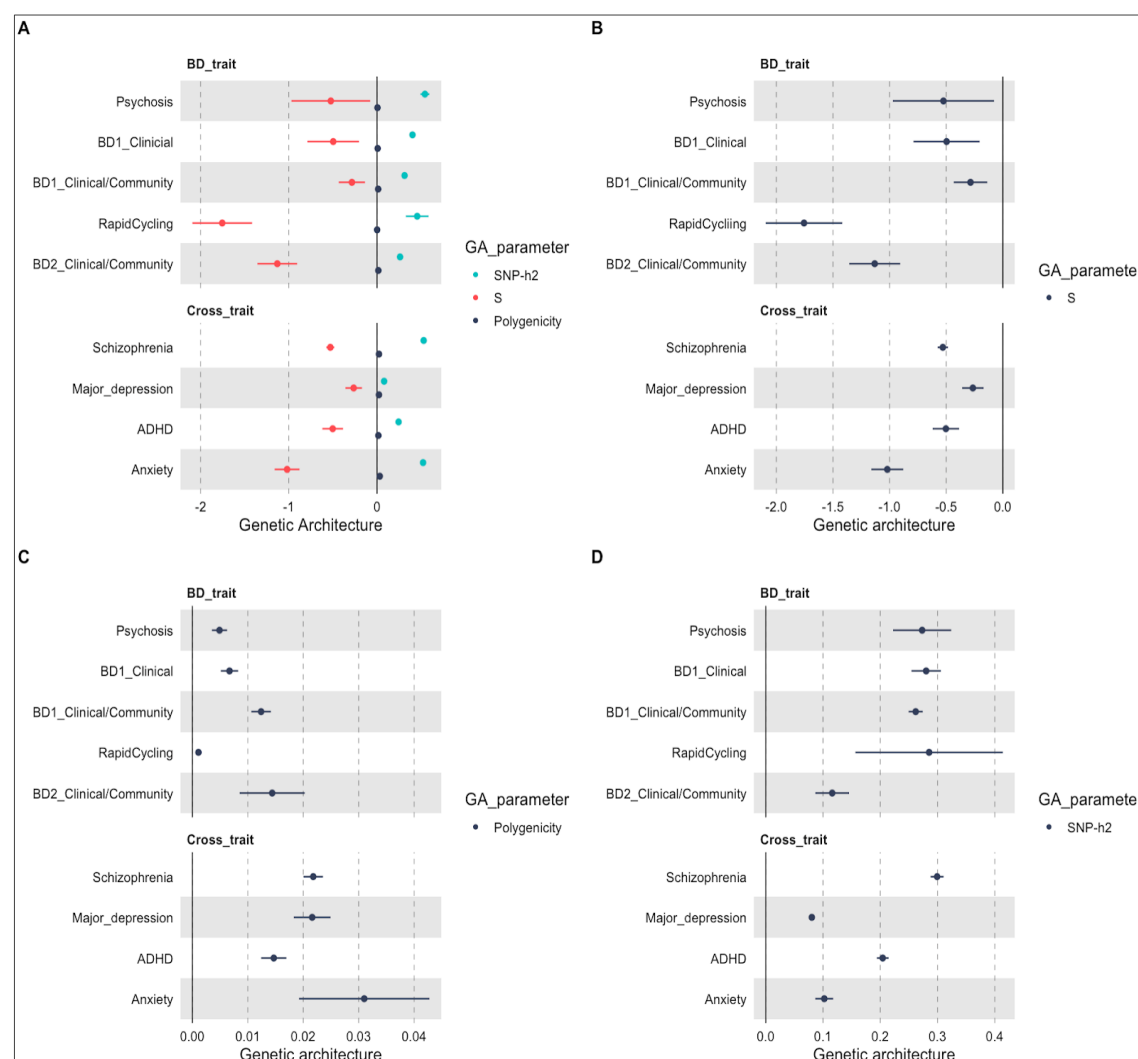
eFigure 15: Scatter plots of local genetic correlations.

The (ρ) negative or positive correlation (x-axis) and log₁₀-*p* values (y-axis) for each pairwise BD subphenotype analysis per locus. Black dots represent the correlated loci after Bonferroni correction. The top pairwise traits with the smallest *P*-values are labelled. Subphenotypes included were (A) Schizoaffect, schizoaffective BD type, (B) BD1, BD1 clinical and community ascertained, (C) BD2, BD2 clinical and community ascertained, (D) Psychosis, (E) RapidCyc, rapid cycling, (F) UnipolMan, unipolar mania, (G) SuicAtt, suicide attempt, (H) AlcSUD, alcohol and substance use disorder, (I) OCD, obsessive-compulsive disorder, and (J) PanicDis, panic disorder. Subphenotype loci show concordance with those of other psychiatric disorders. See eTable 16, local genetic correlation (LAVA) results.



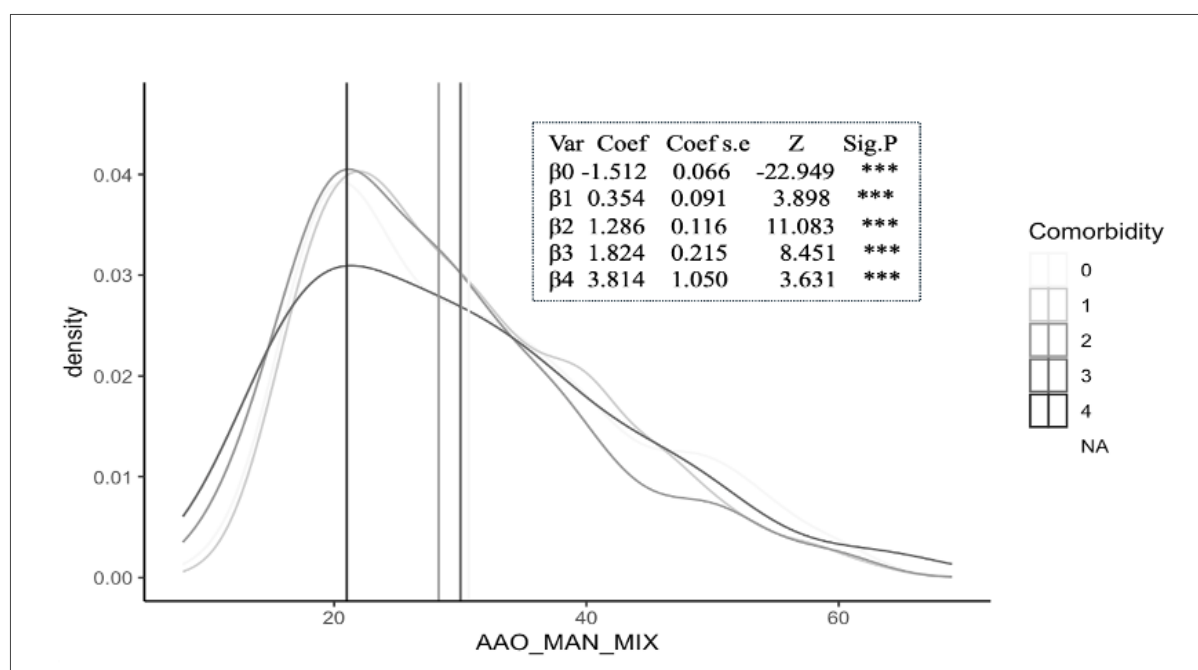
eFigure 16: SBayesS plots showing genetic architecture parameters.

SbayesS⁵³ is a summary-level method which uses a Bayesian mixed linear model method, to estimate SNP-based heritability (h^2_{SNP}) polygenicity (proportion of SNPs with nonzero effects) and a measure of negative selection (S) from the relationship of allele frequency to SNP effects. Estimates for (a) three Genetic Architecture (GA) parameters in BD subphenotypes, relative to other traits; (b) selection (S) parameters and (c) polygenicity (π), π represents the proportion of (HapMap3) SNPs estimated to be causal, and S describes the effect size-MAF relationship, S is a signature of negative selection, (d) indicates SNP heritability (h^2_{SNP}). All three parameters had good convergence measured by Gelman and Rubin, $\hat{R} < 1.2$.⁵³ BD subphenotypes included psychosis, BD1 Clinically ascertained, BD1 Clinical/Community, rapid cycling, BD2 Clinical and BD2 Clinical/Community ascertained, which were compared to cross-traits (SCZ, MDD, ADHD and anxiety disorders). Confidence intervals for both psychosis and BD1 overlapped with SCZ, and BD2 with anxiety. Rapid cycling (RC) was most negatively skewed indicating a pervasive negative selection. See eTable 17 which presents the genetic architecture parameter results.



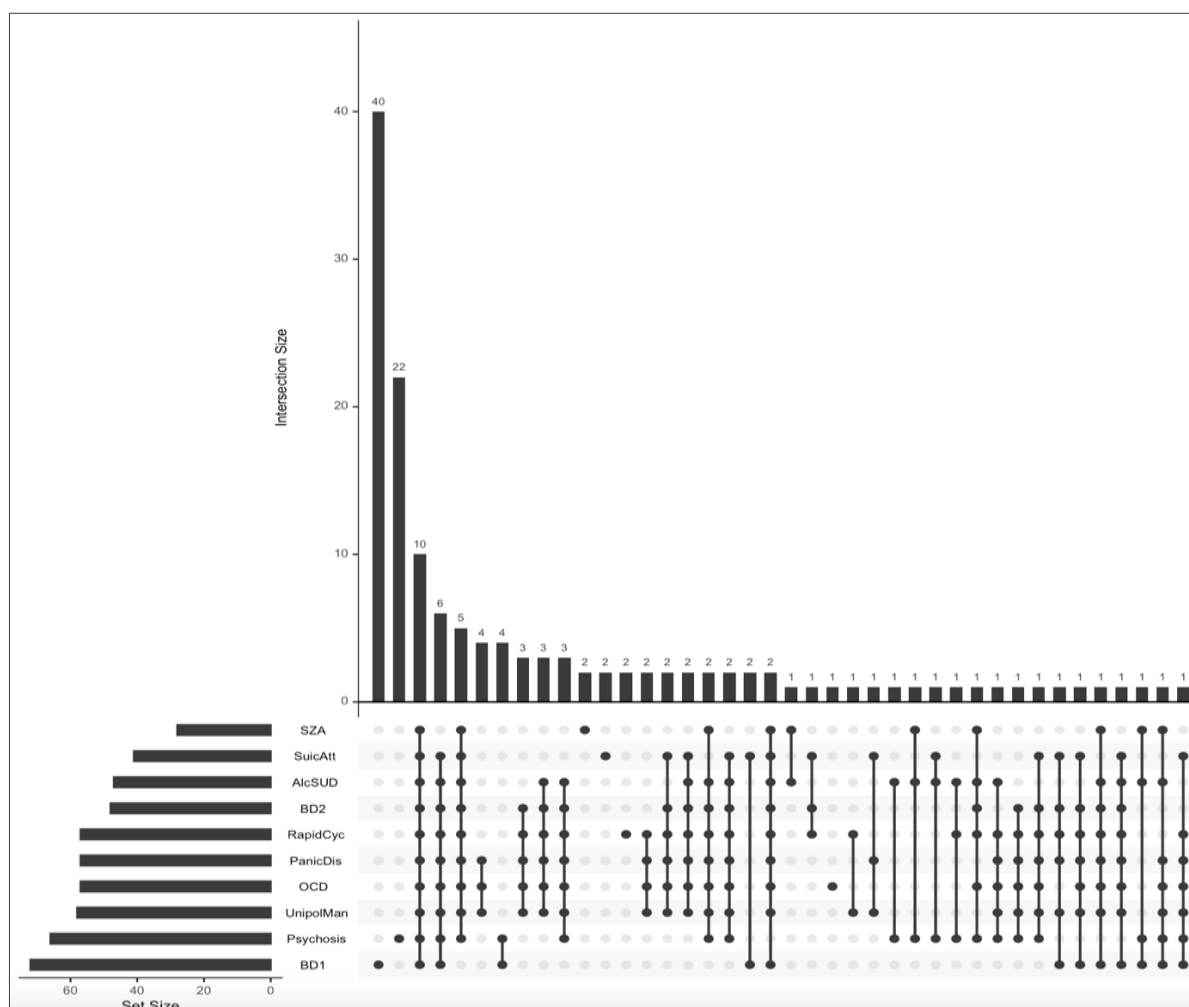
eFigure 17: Density plot of Age of onset of mania/mixed episode (AAO_MAN_MIX) vs. comorbidity count.

Density plot of Age of onset of mania/mixed episode (AAO_MAN_MIX) reveals higher risk for comorbidities (0, no comorbidities, 1 – 4, comorbid suicide attempt, AlcSUD, panic disorder and/or OCD). See the insert box for the coefficients showing association with rapid cycling (BD-RC) increasing as the number of comorbidities (0 – 4) accumulates. This visualizes that RC is a marker of severe, complex illness, which helps explain its unique genetic signature (eFigure 14) and reinforces the validity of the “Comorbidity and Mood Instability” dimension identified in this study (S1).



eFigure 18: UpSet plot of genomic loci overlap (BD-only MTAGs).

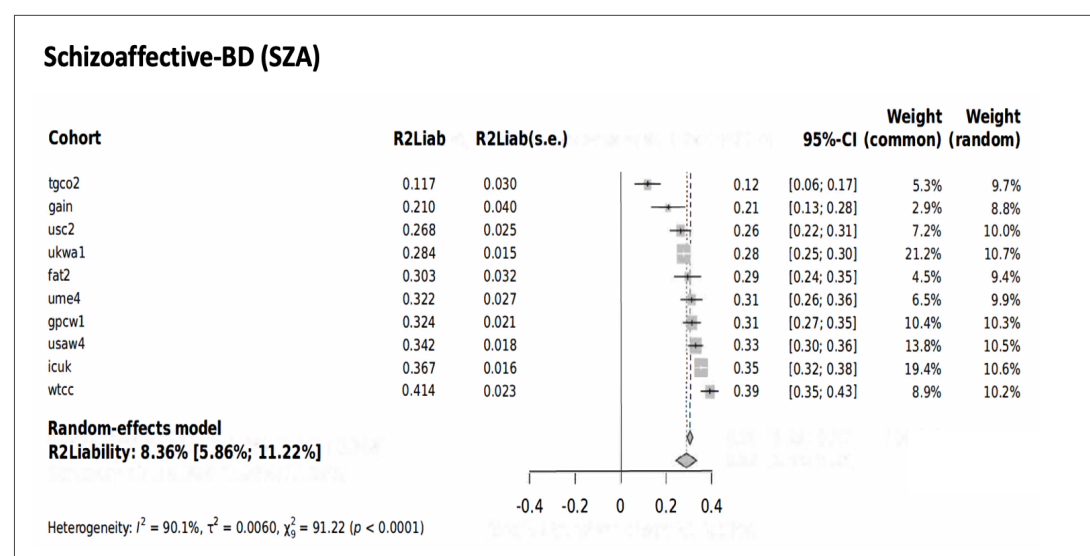
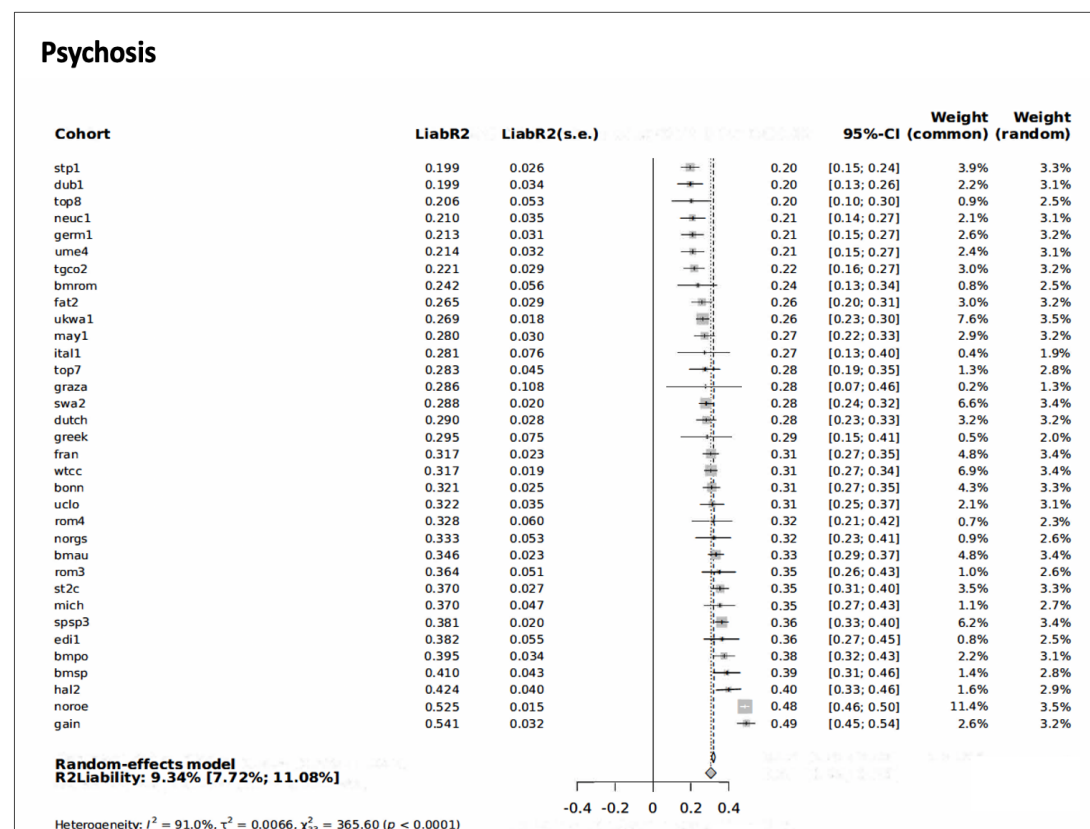
Overlap of genomic loci in 10 subphenotype-BD MTAG analyses. UpSet plot representing the overlap in genomic loci across the 10 MTAG subphenotype-BD results. The plot visualizes the number of shared and unique genomic risk loci across the 10 subphenotype analyses, indicating the size of each intersection. The table visualizes the counts of shared and unique loci. See eTable 13 for genomic loci in 10 subphenotype-BD and 10 subphenotype-BD-SCZ MTAG analyses.



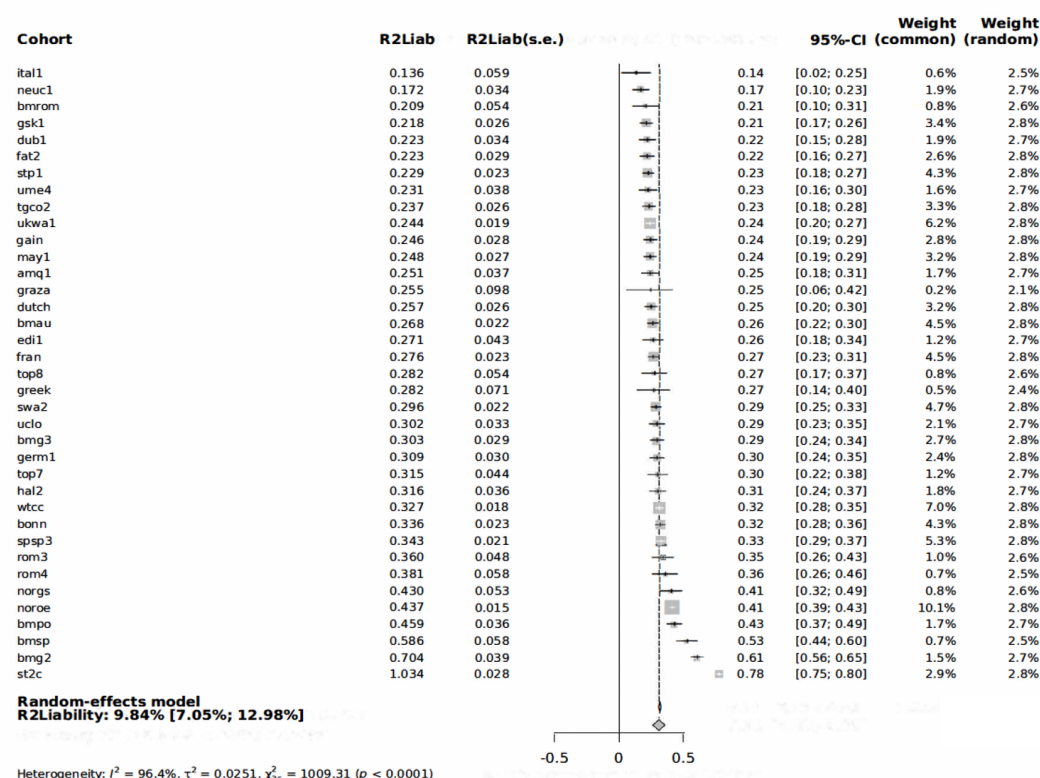
	Psy- chosis	SZA	BD1 cc	SA	Alc SUD	BD2 cc	PD	RC	OCD	UM
Psy- chosis	71	16	62	28	32	26	28	35	30	9
SZA	18.0%	68	52	24	26	25	27	31	29	8
BD1cc	69.7%	51.5%	70	25	29	24	26	32	27	7
SA	28.3%	23.3%	25.5%	49	25	22	24	28	25	7
Alc SUD	33.0%	26.5%	31.5%	29.8%	38	18	21	26	23	5
BD2 cc	27.1%	25.5%	25.3%	25.3%	21.2%	35	20	25	22	6
PD	27.7%	26.7%	26.5%	26.4%	24.1%	23.0%	43	29	30	8
RC	34.0%	3.1%	32.7%	31.8%	29.5%	28.7%	31.5%	44	29	6
OCD	29.1%	28.2%	27.8%	28.1%	26.1%	25.6%	32.3%	31.5%	33	8
UM	9.7%	8.6%	7.9%	8.8%	6.3%	7.8%	9.9%	7.5%	9.8%	20

eFigure 20: Forest plot from the meta-analysis of Polygenic Risk Score (PRS).

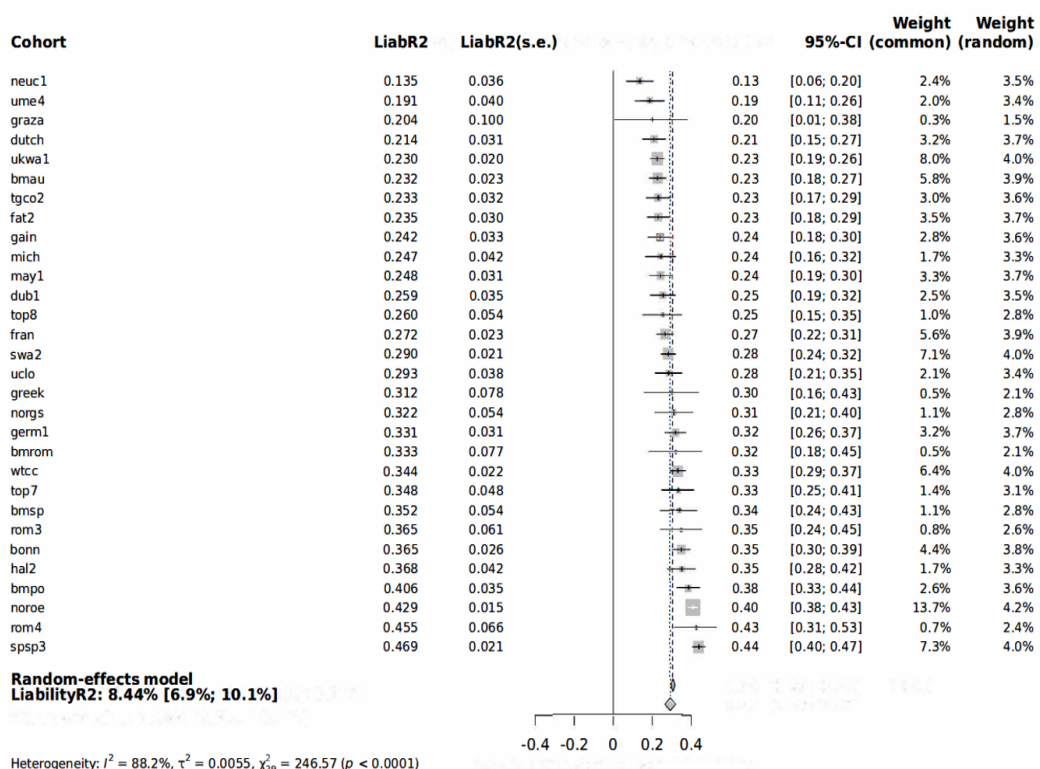
Forest plot from the meta-analysis of Polygenic Risk Score (PRS) for Subphenotype-specific-BD MTAG (includes additional BD cases lacking subphenotype information). The analysis summarized the per-cohort R² values on the liability scale, assuming a population prevalence of 2%. Each cohort is represented by a square, where the center indicates the point estimate of the R²-liability, and the square's size is proportional to the cohort's weight in the meta-analysis. Horizontal lines extending from each square denote the 95% confidence interval (CI) for that cohort's estimate. A diamond at the bottom of the plot depicts the pooled summary Z-score and its 95% CI, derived from a random-effects meta-analysis. Key heterogeneity statistics, including I², τ^2 (Tau-squared), and Cochran's Q-statistic with its *P*-value, are displayed to assess the consistency of effects across cohorts. See eTable 21 and section S4, additional PRS results are presented in eTable 22 and eTable 23.



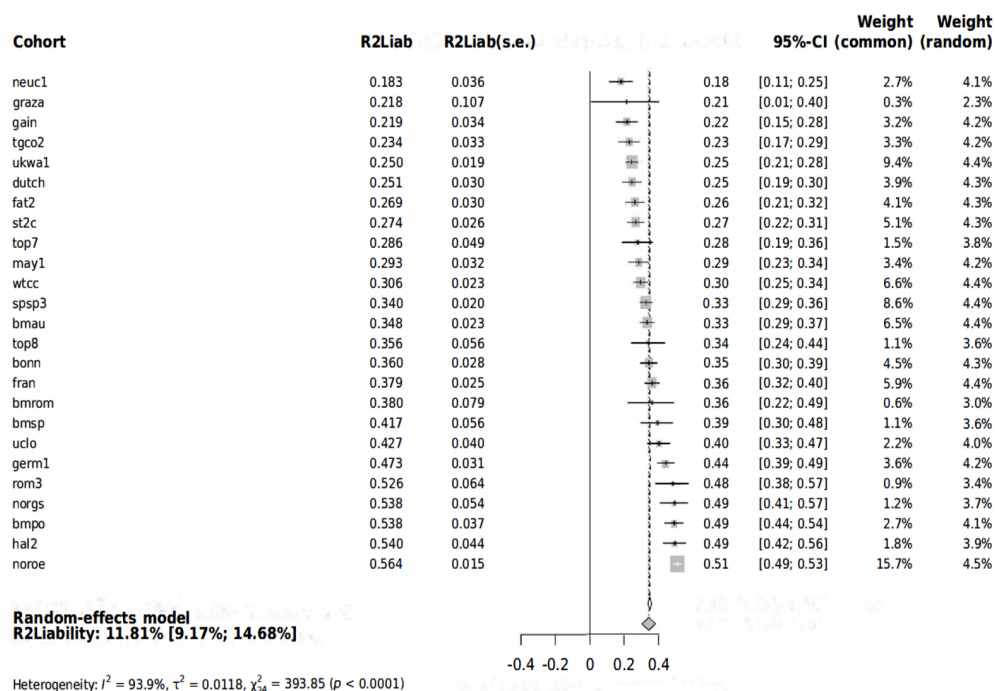
BD1



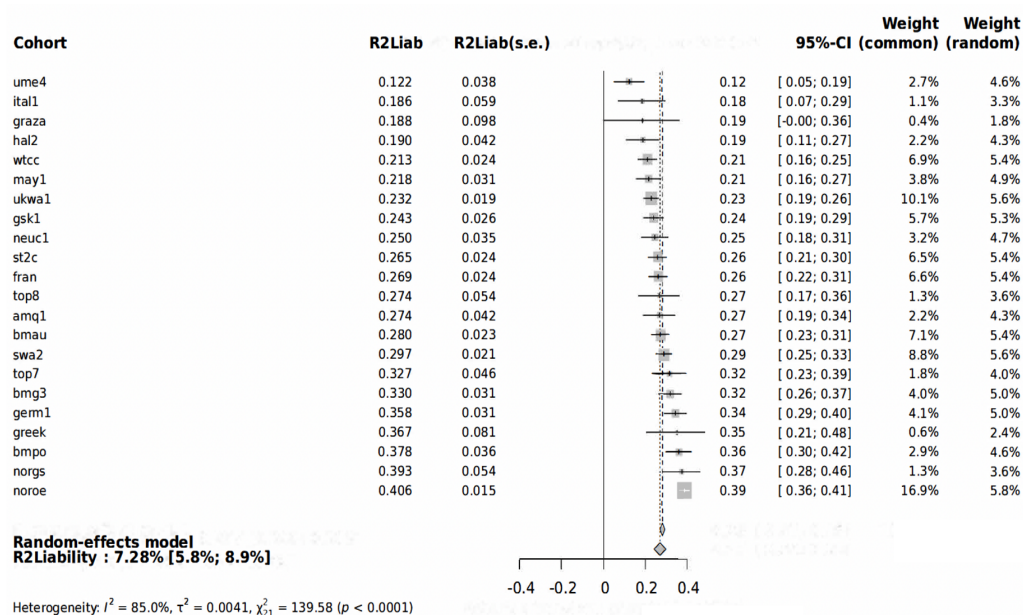
Suicide attempt (SA)



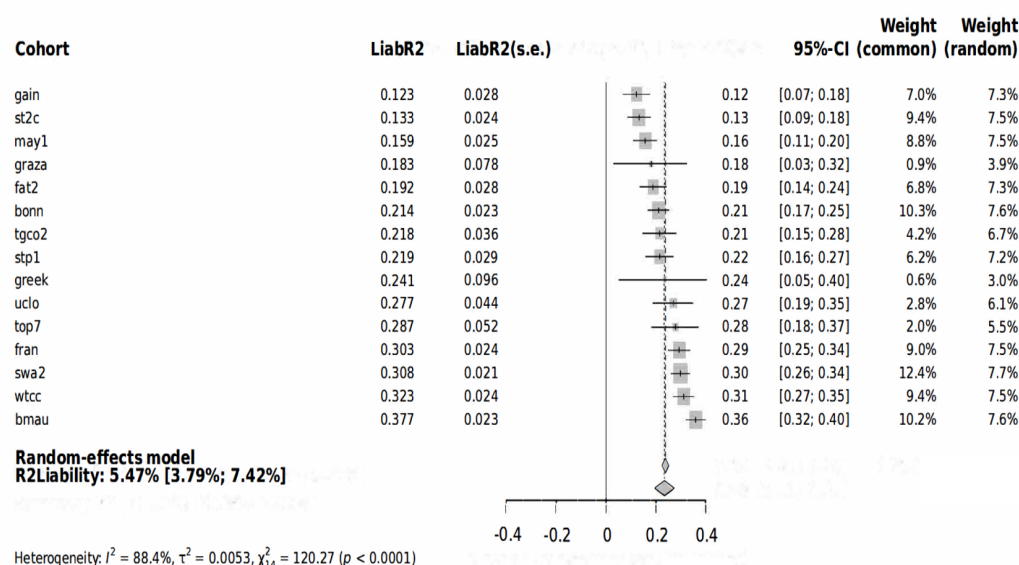
Comorbid AlcsUD



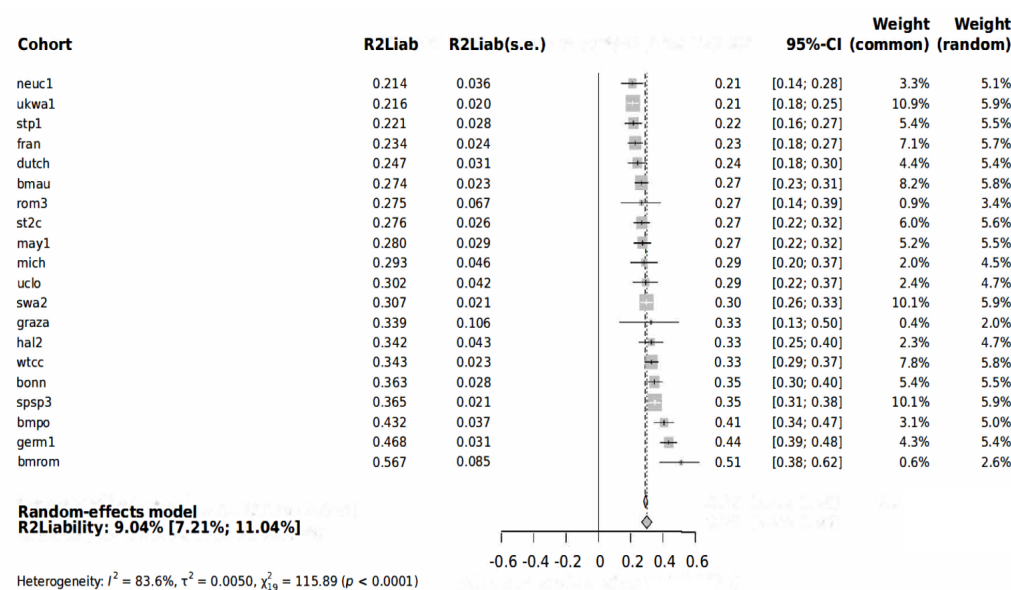
BD2



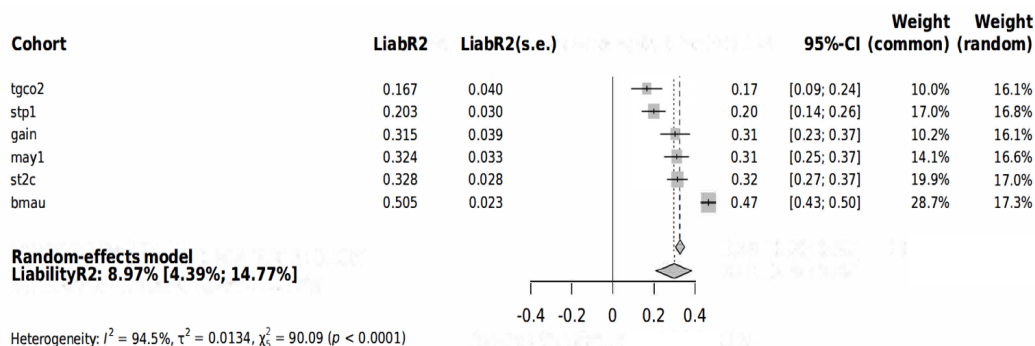
Comorbid Panic disorder (PD)



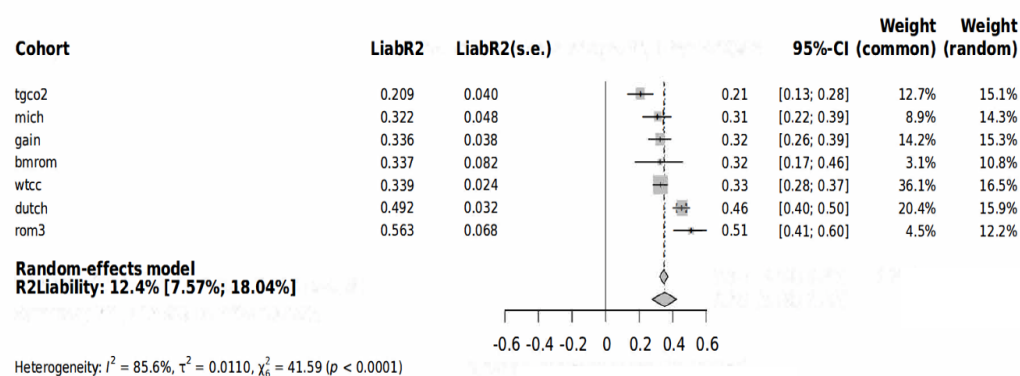
Rapid Cycling (RC)



Comorbid OCD



Unipolar Mania (UM)



S8. Supplementary Figures

eTable 1: Details of External GWAS Summary Statistics Used in Cross-Trait Analyses.

To align phenotypes, only GWAS summary statistics without 23andMe self-report data were included. Matrix = Matrix Pattern Completion task; Memory = Memory – Pairs Matching Test; RT = Reaction Time; Symbol Digit = Symbol Digit Substitution Task; Trails-B = Trail Making Test – B; Tower = Tower Rearranging Task; VNR = Verbal Numerical Reasoning Test. Phenotype data was scaled before analyses and higher scores aligned to indicate better cognitive performance. See eFigure 10, a presentation of the global genetic correlations presented in eTable 24.

Summary Statistics (abbrev.)	Study	N
Bipolar disorder	O'Connell et al., 2025 ²⁵	840,309
Schizophrenia (SCZ)	Trubetskoy et al., 2022 ²⁶	130,644
Major depressive disorder (MDD)	Howard et al., 2019 ⁴¹	500,199
Attention deficit and hyperactivity disorder (ADHD)	Demontis et al., 2023 ⁴²	225,534
Anxiety (ANX)	Purves et al., 2020 ²⁰	114,091
Autism spectrum disorder (ASD)	Grove et al., 2019 ⁴⁴	46,350
Mood swings (MOOD)	Neale Lab UKBB, 2018 ⁴⁵	604,063
Intelligence (INTEL)	Savage et al., 2019 ⁴⁸	269,867
Insomnia (INS)	Watanabe et al., 2022 ⁵⁰	386,888
Post traumatic stress disorder (PTSD)	Nievergelt et al., 2019 ⁴⁶	174,659
Borderline personality disorder (BPD)	Witt et al., 2017 ⁴⁷	2,543
Matrix	de la Fuente et al., 2020 ⁵¹	11,356
Memory	de la Fuente et al., 2020	331,679
Trail Making Test B (TMTB)	de la Fuente et al., 2020	78,547
Tower	de la Fuente et al., 2020	11,263
Symbol and digit (SymDig)	de la Fuente et al., 2020	87,741
VNR	de la Fuente et al., 2020	171,304
Reaction time (RT)	de la Fuente et al., 2020	330,024

eTable 2. Gene-based Tests Using Gene Annotations of MTAG Results. [This table is provided as a separate file.]

eTable 3. Characteristics of Participating Cohorts. [This table is provided as a separate file.]

eTable 4. Per-Cohort Sample Sizes for each Subphenotype Analysis. [This table is provided as a separate file.]

eTable 5. Summary Statistics for Subphenotype GWAS and Post-QC Variant Counts. [This table is provided as a separate file.]

eTable 6. Clinical Characteristics Stratified by BD Subphenotype.

See eTables 3-4 for cohort and per-cohort subphenotype sample sizes , and S9 for detailed cohort information.

Clinical characteristics bipolar disorder		
Characteristic	BD, N = 18,800 Controls, N = 44,113 ¹	Abbreviation
Psychosis	8476 (62%)	Psy
UnipolarMania	649 (7.8%)	UnipolMan, UM
RapidCycling	2373 (30%)	RapidCyc, RC
Suicide attempt	3915 (40%)	SuicAtt, SA
Alcohol or substance use disorder	3216 (27%)	AlcSUD, Alc
Panic disorder	1510 (16%)	Panic, Pan
Obsessive compulsive disorder	676 (7.8%)	OCD
Subtypes:		
Not Otherwise Specified	405 (2.6%)	NOS
Bipolar disorder subtype 2	2401 (15%)	BD2
Bipolar disorder subtype 1	11,553 (73%)	BD1
Schizoaffective disorder bipolar type	1449 (9.2%)	SZA
Age onset BD	15,504; 22 (17, 30)	AOO
Age onset mania/mixed	7938; 25 (19, 35)	AO_man
Age onset depression	8155; 22 (16, 31)	AO_depr
N (%); Median (IQR)		
¹ Control samples were mostly screened for the absence of lifetime psychiatric disorders; however, some cohorts used controls that were not screened for BD.		

eTable 7. Clinical Characteristics Stratified by BD Subtype.

See eTables 3-4 for cohort and per-cohort subphenotype sample sizes , and S9 for detailed cohort information.

Clinical characteristics bipolar disorder				
	Subtype			
Characteristic	NOS, N = 405 ¹	BD2, N = 2401 ¹	BD1, N = 11 553 ¹	SZA, N = 1449 ¹
Psychosis	86 (56%)	476 (25%)	6473 (68%)	593 (96%)
RapidCycling	27 (31%)	586 (45%)	1505 (29%)	58 (39%)
UnipolarMania	5 (19%)	6 (.7%)	512 (8.5%)	21 (6.0%)
Suicide attempt	20 (57%)	464 (39%)	2852 (41%)	139 (49%)
Alcohol/substance use disorder (AlcSUD)	38 (25%)	449 (26%)	2339 (27%)	122 (35%)
Panic disorder	2 (4.9%)	269 (19%)	1121 (17%)	50 (35%)
OCD	1 (2.9%)	123 (9.0%)	523 (8.1%)	12 (9.2%)
Age onset BD	23 (18, 33)	22 (16, 31)	22 (16, 29)	21 (17, 27)
Age onset mania/mixed	22 (20, 24)	21 (16, 32)	26 (20, 35)	25 (20, 32)
Age onset depression	23 (17, 33)	20 (15, 30)	22 (17, 32)	22 (16, 29)
¹ n (%); Median (IQR)				

eTable 8. Clinical Characteristics Stratified by Homogenous Groups.

See eTables 3-4 for cohort and per-cohort subphenotype sample sizes, and S9 for detailed cohort information.

Clinical characteristics bipolar disorder						
Characteristic	Psychosis		Rapid Cycling		Unipolar Mania	
	No, N= 5186 ¹	Yes, N= 8476 ¹	No, N = 5617 ¹	Yes, N = 2373 ¹	No, N = 7648 ¹	Yes, N = 649 ¹
Suicide attempt	1292 (40%)	2218 (41%)	1533 (37%)	703 (47%)	2233 (41%)	111 (20%)
Alcohol/substance use (AlcSUD)	1105 (25%)	1892 (29%)	1139 (22%)	635 (33%)	2059 (32%)	155 (28%)
Panic disorder	614 (17%)	777 (15%)	312 (7.9%)	438 (27%)	889 (17%)	60 (12%)
OCD	263 (7.9%)	362 (7.8%)	129 (3.5%)	210 (14%)	422 (8.5%)	24 (5.1%)
Subtype						
NOS	68 (1.5%)	86 (1.1%)	60 (1.3%)	27 (1.2%)	22 (.3%)	5 (.9%)
BD2	1445 (32%)	476 (6.2%)	704 (15%)	586 (27%)	902 (13%)	6 (1.1%)
BD1	2995 (66%)	6473 (85%)	3741 (81%)	1505 (69%)	5512 (81%)	512 (94%)
SZA	27 (.6%)	593 (7.8%)	91 (2.0%)	58 (2.7%)	329 (4.9%)	21 (3.9%)
Age onset BD	23 (16,31)	22 (17,29)	24 (19,32)	20 (15,29)	20 (16,29)	24 (18,32)
Age onset mania/mixed	26 (19,38)	25 (20,34)	27 (21,37)	22 (16,30)	25 (19,35)	25 (20,34)
Age onset depression	22 (16,33)	22 (17,30)	24 (18,33)	18 (14,26)	22 (16,31)	25 (18,40)
¹ n (%); Median (IQR)						

eTable 9. Assessment of Phenotypic Homogeneity Across Geographic Regions Using Mixed Regression Models.

To assess for phenotypic heterogeneity, generalized linear mixed-effects models (GLMMs) were performed with geographic region as a random effect. The random effect was consistently non-significant across all models, confirming a high degree of phenotypic homogeneity across recruitment site regions (visualized in eFigure 5) and supporting the validity of pooling data for meta-analyses. ALC, alcohol/substance use disorder (alcSUD); BD1, bipolar disorder I; BD2, bipolar disorder II; OCD, obsessive-compulsive disorder; PD, panic disorder; RC, rapid cycling; SA, suicide attempt; SZA, schizoaffective disorder, bipolar type; UM, unipolar mania; AOO, age at onset of bipolar disorder, AO_depr, age at onset of depression, AO_man/mix, age at onset of mania or mixed episodes. Values represent the regression coefficients (standard error) for the association between the two subphenotypes.

BD	BD1	BD2	SZA	PSY	RC	UM	SA	ALC	PD	OCD
PSY	1.09 (.04) ***	-1.95 (.06) ***	2.58 (.20) ***	-	-.25 (.05) ***	.43 (.10) ***	.04 (.05)	.24 (.04) ***	-.12 (.06) *	.02 (.08)
RC	-.57 (.06) ***	.51 (.06) ***	.74 (.17) ***	-.26 (.05) ***	-	-1.92 (.29) ***	.60 (.06) ***	.42 (.06) ***	1.19 (.08) ***	1.09 (.12) ***
UM	1.29 (.18) ***	-2.63 (.41) ***	-.25 (.23)	.41 (.10) ***	-1.92 (.29) ***	-	-1.07 (.11) ***	-.17 (.10)	-.31 (.14) **	-.47 (.22) *
SA	-.01 (.06)	-.11 (.06)	.35 (.12) **	.03 (.05)	.58 (.06) ***	-1.07 (.11) ***	-	.49 (.05) ***	.51 (.07) ***	.36 (.10) ***
ALC	.007 (.05)	-.12 (.06)	.45 (.11) ***	.23 (.04) ***	.41 (.06) ***	-.18 (.10)	.49 (.05) ***	-	.50 (.06) ***	.25 (.08) **
PD	-.22 (.07) **	.15 (.08) *	.72 (.18) ***	-.13 (.06) **	1.19 (.08) ***	-.34 (.14) *	.49 (.07) ***	.50 (.06) ***	-	1.33 (.08) ***
OCD	-.08 (.10)	.12 (.10)	-.21 (.31)	.01 (.08)	1.08 (.12) ***	-.49 (.22) *	.34 (.10) ***	.25 (.08) **	1.33 (.08) ***	-
AOO	-.002 (.00) **	.008 (.00) ***	-.024 (.01) ***	-.017 (.00) ***	-.027 (.00) ***	.023 (.00) ***	-.030 (.00) ***	-.027 (.00) ***	-.024 (.00) ***	-.017 (.00) ***
AO-depr	.009 (.00) **	-.006 (.00) ***	-.029 (.01)	-.013 (.00) ***	-.045 (.00) ***	.023 (.01)	-.027 (.00) ***	-.023 (.00) ***	-.046 (.00) ***	-.027 (.01) ***
AO-man/mix	.021 (.00) ***	-.019 (.00) ***	-.021 (.01)	-.017 (.00) ***	-.034 (.00) ***	-.008 (.01)	-.014 (.00) ***	-.021 (.00) ***	-.022 (.00) ***	-.022 (.01) **

eTable 10. Pairwise Overlap of Loci Among Subphenotype-BD-SCZ MTAGs.

[This table is provided as a separate file.]

eTable 11. TWAS Results (BD-SCZ MTAG, with MHC). [This table is provided as a separate file.]

eTable 12. Cell Type Enrichment Results (BD-SCZ MTAG). [This table is provided as a separate file.]

eTable 13. Novel Loci Identified in MTAG Analyses. [This table is provided as a separate file.]

eTable 14. Gene-Set Enrichment Results (BD-SCZ MTAG). [This table is provided as a separate file.]

eTable 15. Transcriptome-wide associations (BD-only and BD-SCZ MTAG, with and without MHC). [This table is provided as a separate file.]

eTable 16. Local Genetic Correlation (LAVA) Results. [This table is provided as a separate file.]

eTable 17. SBayesS Genetic Architecture Results.

This table presents the genetic architecture parameters for bipolar disorder (BD) subphenotypes and related cross-traits, as estimated by the SBayesS model (See eFigure 16). SBayesS: A statistical method that uses genome-wide association study (GWAS) summary statistics to estimate the genetic architecture of complex traits. SNP-based heritability (h^2_{SNP}): The proportion of phenotypic variance that can be explained by all analyzed single nucleotide polymorphisms (SNPs). Polygenicity: The estimated proportion of SNPs with non-zero effects on a given trait. A higher value suggests a larger number of genetic variants contribute to the trait's heritability. Negative Selection (S): A parameter that quantifies the strength of purifying (negative) selection. More negative values indicate stronger selection against the genetic variants associated with the trait, suggesting they have a greater impact on fitness. SE: Standard Error of the estimate. Group: Indicates whether the analysis is for a bipolar disorder subphenotype from the current study (BD_trait) or a related psychiatric disorder from external GWAS summary statistics (Cross_trait). For a clear definition of Clinical and Community ascertainment, see O'Connell et al, 2025.²⁵

Trait	SNP-based Heritability (h^2_{SNP})	SE	Polygenicity	SE	Negative Selection (S)	SE	Group
Schizophrenia	.299	.006	.022	.001	-.530	.023	Cross_trait
Psychosis	.273	.026	.005	.001	-.524	.228	BD_trait
BD1_Clinical	.280	.013	.007	.001	-.497	.149	BD_trait
BD1_Clinical/Community	.262	.006	.012	.001	-.285	.076	BD_trait
Rapid Cycling	.285	.056	.001	.000	-1.75	.173	BD_trait
BD2_Clinical/Community	.116	.015	.014	.003	-1.13	.115	BD_trait
Major_depression	.080	.001	.022	.002	-.265	.048	Cross_trait
ADHD	.204	.005	.015	.001	-.503	.060	Cross_trait
Anxiety	.102	.008	.031	.006	-1.020	.072	Cross_trait

eTable 18. GWAS Summary Statistics for 16 BD Subphenotypes. [This table is provided as a separate file.]

eTable 19: Loci Identified in MTAG Analyses of Bipolar Disorder Subphenotypes. [This table is provided as a separate file.]

eTable 20: Replication of Loci Identified in Subphenotype MTAG Analyses. [This table is provided as a separate file.]

eTable 21. PRS Performance (Random-Effects Meta-Analysis).

See section S4 for an overview of the subphenotype-specific PRS methods, results (and eTable 23), conclusions and limitations.

Phenotype	Cohorts (k)	Summary R ² -liability (RE) (%)	95% CI for R ² -liability (%)	I ² (%)	95% CI for I ² (%)	τ ²	P-value (Q)
BD1	37	9.838	7.047 - 12.980	96.4	95.7 - 97.0	.025	< .0001
BD2	22	7.280	5.804 - 8.896	85.0	78.4 - 89.5	.004	< .0001
Psychosis	34	9.340	7.720 - 11.080	91.0	88.4 - 93.0	.006	< .0001
Panic Disorder (PD)	15	5.469	3.789 - 7.416	88.4	82.5 - 92.3	.005	< .0001
Rapid Cycling (RC)	20	9.039	7.205 - 11.035	83.6	75.8 - 88.9	.005	< .0001
Schizoaffective-BD (SZA)	10	8.363	5.860 - 11.218	9.1	84.0 - 93.9	.006	< .0001
Unipolar Mania (UM)	7	12.402	7.572 - 18.036	85.6	72.3 - 92.5	.011	< .0001
Suicide Attempt (SA)	30	8.435	6.897 - 1.098	88.2	84.3 - 91.2	.005	< .0001
Alc. or Subst. Use (AlcSUD)	25	11.807	9.168 - 14.684	93.9	92.1 - 95.3	.012	< .0001

eTable 22. Overall Weighted Average PRS Performance.

See section S4 for an overview of the subphenotype-specific PRS methods, results (and eTable 23), conclusions and limitations.

Phenotype	Overall Weighted Average R ² -liability (%)	Abs. Risk Top 1% PRS (%)	Abs. Risk Top 10% PRS (%)	Abs. Risk Top Quintile PRS (%)	Abs. Risk Bottom Quintile PRS (%)
BD1	8.76	9.27	5.30	4.20	.58
BD2	8.18	9.37	5.86	4.78	.80
Psychosis	9.59	9.62	5.58	4.41	.53
Panic Disorder (PD)	4.38	6.24	4.15	3.52	.89
Rapid Cycling (RC)	8.07	8.70	5.25	4.23	.59
Schizoaffective-BD (SZA)	9.07	9.47	5.38	4.25	.53
Unipolar Mania (UM)	11.61	11.17	5.67	4.46	.47
Suicide Attempt (SA)	8.58	9.06	5.39	4.29	.57
Alc. or Subst. Use (AlcSUD)	9.67	9.61	5.61	4.40	.54

eTable 23. Subphenotype-Specific Bipolar Disorder Polygenic Risk Scores. [This table is provided as a separate file.]

eTable 24. Genetic Architecture and Cross-trait correlations. [This table is provided as a separate file.]

eTable 25: Genetic Correlation Between Univariate Subphenotype GWAS and Final MTAG Results.

Bivariate genetic correlations (r_G), calculated using LDSC, are presented for 11 BD subphenotypes against 10 psychiatric disorders and 7 cognitive traits (see eTable 24). Global r_G was stronger among BD subphenotypes than with other traits, with SCZ showing the highest median r_G . High r_G values (median = .89 [.76-.91] for BD-only MTAGs; .85 [.76-.90] for BD-SCZ MTAGs) between subphenotype-GWAS and their respective MTAG results affirmed substantial shared genetic underpinnings and MTAG's fidelity. The table compares r_G of initial univariate subphenotype GWAS (Trait 1) with BD-only MTAG (Trait 2) and BD-SCZ MTAG (Trait 3) results. MTAGs were pairwise meta-analyses of univariate subphenotype GWAS with BD (PGC4, O'Connell et al., 2025, European only, $N=840,309$)²⁵ and, for BD-SCZ MTAG, also with SCZ (SCZ3, Trubetskoy et al., 2022, European only, $N=130,644$)²⁶. All included GWAS summary statistics were European-only and excluded 23andMe self-report data.

Trait 1	Trait 2	STD r_G	SE	P -value	P (Bonferonni) (.05/30 traits, $P < .001$)
AlcSUD	AlcSUD-BD	.906	.048	3.49×10^{-79}	True
BD1_Clinical_Com	BD1-BD	.952	.029	1.29×10^{-232}	True
BD2_Clinical_Com	BD2-BD	.755	.087	3.49×10^{-18}	True
OCD	OCD-BD	.729	.223	1.06×10^{-4}	True
Panic_dis	Panic_dis-BD	.744	.107	3.05×10^{-12}	True
Psychosis	Psychosis-BD	.953	.021	5.00×10^{-300}	True
RapidCyc	RapidCyc-BD	.879	.063	9.48×10^{-45}	True
Suic_att	Suic_att-BD	.890	.037	1.81×10^{-125}	True
SZA	SZA-BD	.909	.037	4.64×10^{-34}	True
UnipolMan	UnipolMan-BD	.763	.219	4.93×10^{-4}	True
Median		.885			
Trait 1	Trait 3				
AlcSUD	AlcSUD-BD-SCZ	.870	.048	2.43×10^{-72}	True
BD1_Clinical_Com	BD1-BD-SCZ	.908	.033	2.31×10^{-165}	True
BD2_Clinical_Com	BD2-BD-SCZ	.714	.079	1.07×10^{-19}	True
OCD	OCD-BD-SCZ	.713	.217	1.04×10^{-4}	True
Panic_dis	Panic_dis-BD-SCZ	.747	.107	3.28×10^{-12}	True
Psychosis	Psychosis-BD-SCZ	.914	.021	5.00×10^{-300}	True
RapidCyc	RapidCyc-BD-SCZ	.838	.059	2.92×10^{-46}	True
Suic_att	Suic_att-BD-SCZ	.855	.038	5.31×10^{-111}	True
SZA	SZA-BD-SCZ	.977	.031	1.98×10^{-45}	True
UnipolMan	UnipolMan-BD-SCZ	.792	.227	4.82×10^{-4}	True
Median		.847			

eTable 26. Credible Gene Set from BD-SCZ MTAG Analysis (no MHC) (N=68).

See section S2 for a description of the methods and results of the credible gene set analyses.

Gene	Most Significant TWAS P-value (JOINT.P)	Associated Tissue	Associated Subphenotypes (MTAG)	Top TWAS Z-score (Direction)	FUMA Evidence
<i>GLYCTK</i>	5.20×10^{-110}	Amygdala	All 10	-22.3 (Protective)	Positional, eQTL
<i>GNL3</i>	1.40×10^{-92}	Frontal Cortex BA9	All 10	2.4 (Risk)	eQTL, Chromatin Int.
<i>SEMA3G</i>	2.70×10^{-73}	Cerebellum	8 (All except AlcsUD, BD2)	-18.1 (Protective)	Positional, eQTL
<i>WDR73</i>	3.60×10^{-61}	Frontal Cortex BA9	6 (Psychosis, SZA, BD1, PD, RC, OCD)	16.5 (Risk)	Positional
<i>ENSG00000259683</i>	3.90×10^{-57}	Fetal Tissue	All 10	-15.9 (Protective)	Positional
<i>FADS1</i>	2.11×10^{-32}	Cerebellum	6 (Psychosis, SZA, BD1, AlcsUD, RC, UM)	-12.0 (Protective)	Positional, eQTL
<i>SP4</i>	5.14×10^{-26}	Pituitary	All 10	1.6 (Risk)	Positional, eQTL
<i>CTSF</i>	2.01×10^{-23}	Substantia nigra	All 10	-1.0 (Protective)	Positional, eQTL
<i>ADD3</i>	6.12×10^{-22}	Cerebellar Hemisphere	All 10	9.7 (Risk)	Positional, eQTL
<i>DRD2</i>	6.45×10^{-18}	Nucleus accumbens	3 (Psychosis, SZA, BD1)	8.7 (Risk)	Positional, eQTL
<i>PTPRD</i>	9.01×10^{-18}	Putamen	5 (Psychosis, SZA, BD1, OCD, UM)	-8.6 (Protective)	Positional, eQTL
<i>NT5C</i>	3.01×10^{-14}	Pituitary	All 10	-7.6 (Protective)	Positional, eQTL
<i>WIPF3</i>	8.89×10^{-13}	Cortex	All 10	7.1 (Risk)	Positional
<i>MCHR1</i>	1.12×10^{-12}	Caudate	8 (All except BD2, PD)	7.1 (Risk)	eQTL
<i>TCF4</i>	2.30×10^{-12}	Frontal Cortex BA9	5 (Psychosis, SZA, BD1, OCD, UM)	7.0 (Risk)	Positional, eQTL
<i>GRIN2A</i>	8.11×10^{-11}	Frontal Cortex BA9	4 (Psychosis, SZA, BD1, OCD)	6.5 (Risk)	Positional
<i>ZSWIM6</i>	1.33×10^{-10}	Cortex	All 10	-6.4 (Protective)	Positional, eQTL
<i>SLC39A8</i>	3.45×10^{-10}	Caudate	7 (Psychosis, SZA, BD1, SA, PD, RC, AlcsUD)	6.3 (Risk)	Positional, eQTL
<i>KANSL1</i>	4.18×10^{-10}	Cerebellum	All 10	-6.3 (Protective)	Positional, eQTL
<i>AC008124.1</i>	8.79×10^{-10}	Hippocampus	All 10	6.1 (Risk)	Positional
<i>NEK4</i>	1.05×10^{-9}	Frontal Cortex BA9	All 10	-6.1 (Protective)	Positional, eQTL

Gene	Most Significant TWAS <i>P</i> -value (JOINT. <i>P</i>)	Associated Tissue	Associated Subphenotypes (MTAG)	Top TWAS Z-score (Direction)	FUMA Evidence
<i>PBRM1</i>	1.11 x 10 ⁻⁹	Frontal Cortex BA9	4 (Psychosis, SZ, BD1, SA)	6.1 (Risk)	Positional, eQTL
<i>TRANK1</i>	1.98 x 10 ⁻⁹	Hippocampus	5 (SZ, BD1, SA, RC, UM)	6.0 (Risk)	Positional, eQTL
<i>ZSCAN9</i>	2.50 x 10 ⁻⁹	Pituitary	All 10	-5.9 (Protective)	eQTL
<i>AC010894.2</i>	3.12 x 10 ⁻⁹	Cortex	All 10	5.9 (Risk)	Positional
<i>GATAD2A</i>	3.33 x 10 ⁻⁹	Cerebellum	All 10	5.9 (Risk)	Positional
<i>FAM114A2</i>	4.01 x 10 ⁻⁹	Nucleus accumbens	All 10	5.8 (Risk)	Positional
<i>SORCS3</i>	4.25 x 10 ⁻⁹	Amygdala	6 (Psychosis, SZ, BD1, OCD, PD, UM)	-5.8 (Protective)	Positional, eQTL
<i>GRM3</i>	4.88 x 10 ⁻⁹	Frontal Cortex BA9	4 (Psychosis, SZ, BD1, OCD)	5.8 (Risk)	Positional, eQTL
<i>AC005253.1</i>	5.15 x 10 ⁻⁹	Cerebellar Hemisphere	All 10	5.8 (Risk)	Positional
<i>STK4</i>	6.62 x 10 ⁻⁹	Putamen	8 (All except BD1, Psychosis)	5.7 (Risk)	Positional, eQTL
<i>MED8</i>	7.21 x 10 ⁻⁹	Caudate	All 10	5.7 (Risk)	Positional
<i>WDR82</i>	8.30 x 10 ⁻⁹	Caudate	All 10	-5.7 (Protective)	Positional
<i>LINC01103</i>	9.01 x 10 ⁻⁹	Nucleus accumbens	All 10	5.7 (Risk)	Positional
<i>ZEB2</i>	9.98 x 10 ⁻⁹	Cerebellum	5 (Psychosis, SZ, BD1, OCD, RC)	5.6 (Risk)	Positional
<i>SNX19</i>	1.01 x 10 ⁻⁸	Amygdala	7 (SZ, BD1, SA, RC, PD, OCD, UM)	5.6 (Risk)	Positional, eQTL
<i>LINC01021</i>	1.15 x 10 ⁻⁸	Fetal Tissue	All 10	5.6 (Risk)	Positional
<i>MSRA</i>	1.33 x 10 ⁻⁸	Caudate	All 10	5.6 (Risk)	Positional
<i>FADS2</i>	1.52 x 10 ⁻⁸	Cerebellum	6 (Psychosis, SZ, BD1, AlcsUD, RC, UM)	-5.5 (Protective)	Positional, eQTL
<i>TMEM258</i>	1.88 x 10 ⁻⁸	Caudate	All 10	5.5 (Risk)	Positional
<i>UBE2Q2L</i>	2.01 x 10 ⁻⁸	Frontal Cortex BA9	All 10	5.4 (Risk)	Positional
<i>RP11-476D1.5</i>	2.15 x 10 ⁻⁸	Hippocampus	All 10	5.4 (Risk)	Positional
<i>RP11-203G2.1</i>	2.30 x 10 ⁻⁸	Cortex	All 10	5.4 (Risk)	Positional
<i>CTD-2234N22.2</i>	2.51 x 10 ⁻⁸	Caudate	All 10	5.4 (Risk)	Positional
<i>NAPRT</i>	2.78 x 10 ⁻⁸	Cerebellum	All 10	5.3 (Risk)	Positional
<i>GPR139</i>	2.99 x 10 ⁻⁸	Pituitary	All 10	5.3 (Risk)	Positional, eQTL
<i>DARS</i>	3.10 x 10 ⁻⁸	Frontal Cortex BA9	All 10	5.3 (Risk)	Positional
<i>LINC01422</i>	3.33 x 10 ⁻⁸	Cortex	All 10	5.3 (Risk)	Positional
<i>LINC00478</i>	3.55 x 10 ⁻⁸	Cortex	All 10	-5.2 (Protective)	Positional
<i>CTD-3074O7.2</i>	3.75 x 10 ⁻⁸	Caudate	All 10	-5.2 (Protective)	Positional
<i>C1orf132</i>	4.01 x 10 ⁻⁸	Cerebellum	All 10	5.2 (Risk)	Positional

Gene	Most Significant TWAS <i>P</i> -value (JOINT. <i>P</i>)	Associated Tissue	Associated Subphenotypes (MTAG)	Top TWAS Z-score (Direction)	FUMA Evidence
<i>LINC01511</i>	4.18 x 10 ⁻⁸	Cortex	All 10	-5.2 (Protective)	Positional
<i>CLCN3</i>	4.39 x 10 ⁻⁸	Frontal Cortex BA9	All 10	-5.1 (Protective)	Positional
<i>RP11-474E11.1</i>	4.66 x 10 ⁻⁸	Hippocampus	All 10	5.1 (Risk)	Positional
<i>AC10482.2</i>	4.88 x 10 ⁻⁸	Nucleus accumbens	All 10	-5.1 (Protective)	Positional
<i>INO80E</i>	6.01 x 10 ⁻⁸	Cerebellum	All 10	-5.1 (Protective)	Positional
<i>MADD</i>	6.15 x 10 ⁻⁸	Caudate	All 10	-5.0 (Protective)	Positional
<i>MLEC</i>	6.30 x 10 ⁻⁸	Cortex	All 10	-5.0 (Protective)	Positional
<i>RP11-755F1.1</i>	6.66 x 10 ⁻⁸	Hippocampus	All 10	-5.0 (Protective)	Positional
<i>CARNMT1</i>	7.01 x 10 ⁻⁸	Frontal Cortex BA9	All 10	-4.9 (Protective)	Positional
<i>C20orf196</i>	7.22 x 10 ⁻⁸	Cerebellum	All 10	4.9 (Risk)	Positional
<i>DPY19L1</i>	7.50 x 10 ⁻⁸	Caudate	All 10	4.9 (Risk)	Positional
<i>RUNDC3A</i>	7.88 x 10 ⁻⁸	Frontal Cortex BA9	All 10	-4.9 (Protective)	Positional
<i>GLT8D1</i>	8.11 x 10 ⁻⁸	Cortex	All 10	4.9 (Risk)	Positional
<i>GLIS3</i>	8.33 x 10 ⁻⁸	Pituitary	All 10	-4.8 (Protective)	Positional
<i>CHRNA3</i>	8.55 x 10 ⁻⁸	Nucleus accumbens	All 10	4.8 (Risk)	Positional
<i>ATP6V1B1</i>	8.79 x 10 ⁻⁸	Cortex	All 10	-4.8 (Protective)	Positional

eTable 27. Additional Credible Genes from the MHC Region (BD-SCZ MTAG) (N=17).

See section S2 for a description of the methods and results of the credible gene set analyses.

Gene	Most Significant TWAS P-value (JOINT.P)	Associated Tissue	Associated Subphenotypes (MTAG)	Top TWAS Z-score (Direction)	FUMA Evidence
<i>HCG27</i>	2.80×10^{-285}	Hippocampus	9 (All except AlcSUD)	36.1 (Risk)	Positional
<i>ZNF184</i>	3.00×10^{-282}	Hypothalamus	All 10	-35.9 (Protective)	Positional
<i>HLA-DMB</i>	2.50×10^{-273}	Cerebellum	All 10	-35.3 (Protective)	eQTL, Chromatin Int.
<i>PRSS16</i>	8.20×10^{-246}	Cerebellum	8 (All except AlcSUD, BD2)	33.5 (Risk)	Positional, eQTL
<i>BTN3A2</i>	1.10×10^{-105}	Hypothalamus	All 10	22.0 (Risk)	Positional, eQTL
<i>HLA-C</i>	3.33×10^{-51}	Ant. Cingulate BA24	6 (Psychosis, SZ, BD1, PD, OCD, UM)	14.8 (Risk)	Positional, eQTL
<i>C4A</i>	2.15×10^{-36}	Nucleus accumbens	5 (Psychosis, SZ, BD1, SA, AlcSUD)	12.6 (Risk)	eQTL, Chromatin Int.
<i>CYP21A1P</i>	1.50×10^{-29}	Hippocampus	7 (SZ, BD1, SA, RC, PD, OCD, UM)	-11.4 (Protective)	Positional
<i>VAR2</i>	9.80×10^{-25}	Cerebellum	All 10	-1.3 (Protective)	Positional
<i>APOM</i>	6.70×10^{-21}	Cerebellum	All 10	9.4 (Risk)	Positional
<i>BAG6</i>	4.20×10^{-19}	Caudate	All 10	8.9 (Risk)	Positional
<i>CLIC1</i>	3.10×10^{-17}	Frontal Cortex BA9	All 10	8.4 (Risk)	Positional
<i>HIST1H2BK</i>	7.70×10^{-15}	Cortex	All 10	-7.7 (Protective)	Positional, eQTL
<i>GPANK1</i>	2.20×10^{-11}	Cerebellum	All 10	6.7 (Risk)	Positional
<i>EGFL8</i>	4.50×10^{-10}	Caudate	All 10	6.2 (Risk)	Positional
<i>FLOT1</i>	1.80×10^{-9}	Hippocampus	All 10	6.0 (Risk)	Positional
<i>HCG4B</i>	3.30×10^{-9}	Pituitary	All 10	5.9 (Risk)	Positional

eTable 28. Credible Gene Set from BD-Only MTAG Analysis (no MHC) (N=25).

See section S2 for a description of the methods and results of the credible gene set analyses.

Gene	Most Significant TWAS P-value (JOINT.P)	Associated Tissue	Associated Subphenotypes (MTAG)	Top TWAS Z-score (Direction)	FUMA Evidence
<i>CTSF</i>	7.91×10^{-24}	Substantia nigra	All 10	-1.0 (Protective)	Positional, eQTL
<i>GNL3</i>	2.15×10^{-22}	Pituitary	All 10	9.7 (Risk)	eQTL, Chromatin Int.
<i>PACSI1</i>	2.00×10^{-19}	Cortex	3 (BD1, Psychosis, SZA)	-9.0 (Protective)	Positional
<i>ADD3</i>	1.18×10^{-18}	Cerebellar Hemisphere	9 (All except AlcSUD)	8.8 (Risk)	Positional, eQTL
<i>FADS1</i>	3.01×10^{-17}	Cerebellum	4 (BD1, AlcSUD, RC, UM)	-8.4 (Protective)	Positional, eQTL
<i>SP4</i>	1.45×10^{-16}	Pituitary	All 10	8.2 (Risk)	Positional, eQTL
<i>STK4</i>	2.05×10^{-15}	Putamen	7 (All except BD1, SZA, Psychosis)	7.9 (Risk)	Positional, eQTL
<i>NT5C</i>	3.33×10^{-14}	Pituitary	9 (All except BD1)	-7.6 (Protective)	Positional, eQTL
<i>WIPF3</i>	7.21×10^{-13}	Cortex	9 (All except BD1)	7.2 (Risk)	Positional
<i>ZSWIM6</i>	2.22×10^{-10}	Cortex	All 10	-6.3 (Protective)	Positional, eQTL
<i>TRANK1</i>	5.15×10^{-9}	Hippocampus	4 (BD1, SA, Psychosis, SZA)	5.8 (Risk)	Positional, eQTL
<i>ZSCAN9</i>	8.82×10^{-9}	Cerebellum	4 (BD1, BD2, PD, OCD)	-5.7 (Protective)	eQTL
<i>PBRM1</i>	1.05×10^{-8}	Frontal Cortex BA9	3 (BD1, Psychosis, SZA)	5.7 (Risk)	Positional, eQTL
<i>FADS2</i>	1.48×10^{-8}	Cerebellum	4 (BD1, AlcSUD, RC, UM)	-5.6 (Protective)	Positional, eQTL
<i>TMEM258</i>	1.77×10^{-8}	Caudate	All 10	5.5 (Risk)	Positional
<i>SNX19</i>	4.88×10^{-8}	Amygdala	6 (BD1, SA, PD, RC, OCD, UM)	5.1 (Risk)	Positional, eQTL
<i>CLCN3</i>	5.01×10^{-8}	Frontal Cortex BA9	All 10	-5.1 (Protective)	Positional
<i>AC008124.1</i>	5.33×10^{-8}	Hippocampus	All 10	5.1 (Risk)	Positional
<i>LINC01103</i>	6.15×10^{-8}	Nucleus accumbens	All 10	5.0 (Risk)	Positional
<i>GATAD2A</i>	7.30×10^{-8}	Cerebellum	All 10	5.0 (Risk)	Positional
<i>DPY19L1</i>	7.55×10^{-8}	Caudate	All 10	4.9 (Risk)	Positional
<i>RP11-476D1.5</i>	8.90×10^{-8}	Hippocampus	All 10	4.9 (Risk)	Positional
<i>CHRNA3</i>	9.12×10^{-8}	Nucleus accumbens	All 10	4.8 (Risk)	Positional
<i>ATP6V1B1</i>	9.88×10^{-8}	Cortex	All 10	-4.8 (Protective)	Positional
<i>Clorf132</i>	1.01×10^{-7}	Cerebellum	All 10	4.8 (Risk)	Positional

eTable 29. Additional Credible Genes from the MHC Region (BD-Only MTAG) (N=2).

See section S2 for a description of the methods and results of the credible gene set analyses.

Gene	Most Significant TWAS P-value (JOINT.P)	Associated Tissue	Associated Subphenotypes (MTAG)	Top TWAS Z-score (Direction)	FUMA Evidence
C4A	3.11 x 10 ⁻⁸	Nucleus accumbens	Psychosis, SZA, BD1	5.5 (Risk)	eQTL, Chromatin Int.
HLA-DPA1	4.50 x 10 ⁻⁷	Cerebellum	SZA, Psychosis	-5.0 (Protective)	eQTL

eTable 30. Enrichment of Credible Gene Sets with SCHEMA Rare-Variant Genes (N=33).

See section S2 for a description of the methods and results of the credible gene set analyses.

Credible Set	N Genes in Set	Overlapping Genes with SCHEMA	P-value (Fisher's Exact)	Significant after Correction (P < .0125)
BD-SCZ_noMHC	68	3 (TCF4, PBRM1, ZEB2)	4.1 x 10 ⁻⁴	Yes
BD-SCZ_wMHC	85	3 (TCF4, PBRM1, ZEB2)	1.1 x 10 ⁻³	Yes
BD-Only_noMHC	25	1 (PBRM1)	.048	No
BD-Only_wMHC	27	1 (PBRM1)	.044	No

S9. Detailed Cohort Descriptions

This section provides detailed information on each cohort contributing to the study, including ascertainment procedures, diagnostic methods, and inclusion/exclusion criteria. For details on the references included below see O'Connell et al., (2025).²⁵

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

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

Cases for the BOMA-Bipolar Study were ascertained from consecutive admissions to the inpatient units of the Department of Psychiatry and Psychotherapy at the University of Bonn and at the Central Institute for Mental Health in Mannheim, University of Heidelberg, Germany. DSM-IV lifetime diagnoses of bipolar I disorder were assigned using a consensus best-estimate procedure, based on all available information, including a structured interview with the SCID and SADS-L, medical records, and the family history method. In addition, the OPCRIT⁶ checklist was used for the detailed polydiagnostic documentation of symptoms. Controls were ascertained from three population-based studies in Germany (PopGen, KORA, and Heinz-Nixdorf-Recall Study). The control subjects were not screened for mental illness. Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent.

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

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

Blackwood, D | 18711365 [PGC1] | Edinburgh, UK | bip_ed1_eur

This sample comprised Caucasian individuals contacted through the inpatient and outpatient services of hospitals in South East Scotland. A BD-I diagnosis was based on an interview with the patient using the SADS-L supplemented by case note review and frequently by information from medical staff, relatives and caregivers. Final diagnoses, based on DSM-IV criteria, were reached by consensus between two trained psychiatrists. Ethnically matched controls from the same region were recruited through the South of Scotland Blood Transfusion Service. Controls were not directly screened to exclude those with a personal or family history of psychiatric illness. The study was approved by the Multi-Centre Research Ethics Committee for Scotland and patients gave written informed consent for the collection of DNA samples for use in genetic studies.

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

Genetic Association Information Network (GAIN)/ The Bipolar Genome Study (BiGS) The BD sample was collected under the auspices of the NIMH Genetics Initiative for BD (<http://zork.wustl.edu/nimh/>), genotyped as part of GAIN and analyzed as part of a larger GWAS conducted by the BiGS consortium. Approximately half of the GAIN sample was collected as multiplex families or sib pair families (waves 1-4), the remainder were collected as individual cases (wave 5). Subjects were ascertained at 12 sites: Indiana University, John Hopkins University, the NIMH Intramural Research Program, Washington University at St. Louis, University of Pennsylvania, University of Chicago, Rush Medical School, University of Iowa, University of California, San Diego, University of California, San Francisco, Howard University, and University of Michigan. All investigations were carried out after the review of protocols by the IRB at each participating institution. At all sites, potential cases were identified from screening admissions to local treatment facilities and through publicity programs or advocacy groups. Potential cases were evaluated using the DIGS², FIGS⁸, and information from relatives and medical records. All information was reviewed through a best estimate diagnostic procedure by two independent and non-interviewing clinicians and a consensus best-estimate diagnosis was reached. In the event of a disagreement, a third review was done to break the tie. Controls were from the NIMH Genetic Repository sample obtained by Dr. P. Gejman through a contract to Knowledge Networks, Inc. Only individuals with complete or near-complete psychiatric questionnaire data who did not fulfill diagnostic criteria for major depression and denied a history of psychosis or BD were included as controls for BiGS analyses. Controls were matched for gender and ethnicity to the cases.

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

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

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

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

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

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

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

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

In the TOP study (Tematisk område psykoser), cases of European ancestry, born in Norway, were recruited from psychiatric hospitals in the Oslo region. Patients were diagnosed according to the ICD9 and further ascertainment details have been reported. Healthy control subjects were randomly selected from statistical records of persons from the same catchment area as the patient groups. The control subjects were screened by interview and with the Primary Care Evaluation of Mental Disorders (PRIME-MD). None of the control subjects had a history of moderate/severe head injury, neurological disorder, mental retardation or an age outside the age range of 18-60 years. Healthy subjects were excluded if they or any of their close relatives had a lifetime history of a severe psychiatric disorder. All participants provided written informed consent and the human subjects protocol was approved by the Norwegian Scientific-Ethical Committee and the Norwegian Data Protection Agency.

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

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

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

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

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

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

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

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

Clinical characterization of the patients included the Mini-International Neuropsychiatric Interview (MINI¹¹), the Diagnostic Interview for Genetic Studies (DIGS⁷), the Family Interview for Genetic Studies (FIGS⁸) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)¹². The final diagnoses were made according to the DSM-IV-TR and determined by consensus of 2 research psychiatrists. The unrelated Swedish control individuals, consisting of a large population-based sample representative of the general population of the region, were randomly selected from the 'Betula study'.

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

The case samples were recruited from patients longitudinally followed at specialty mood disorders clinics in Halifax and Ottawa (Canada). Cases were interviewed in a blind fashion with the Schedule of Affective Disorders and Schizophrenia-Lifetime version (SADS-L)¹³ and consensus diagnoses were made according to DSM-IV¹⁴ and Research Diagnostic Criteria (RDC)¹⁵. Protocols and procedures were approved by the local Ethics Committees and written informed consent was obtained from all patients before participation in the study. Control subjects were drawn from the I2B2 (Informatics for Integrating Biology and the Bedside) project¹⁶. The study consists of de-identified healthy individuals recruited from a healthcare system in the Boston, MA, US area. The de-identification process meant that the Massachusetts General Hospital Institutional

Review Board elected to waive the requirement of seeking informed consent as detailed by US Code of Federal Regulations, Title 45, Part 46, Section 116 (46.116).

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

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

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

Bipolar cases were drawn from the Mayo Clinic Bipolar Biobank¹⁷. Enrolment sites included Mayo Clinic, Rochester, Minnesota; Lindner Center of HOPE/University of Cincinnati College of Medicine, Cincinnati, Ohio; and the University of Minnesota, Minneapolis, Minnesota. Enrolment at each site was approved by the local Institutional Review Board, and all participants consented to use of their data for future genetic studies. Participants were identified through routine clinical appointments, from in-patients admitted in mood disorder units, and recruitment advertising. Participants were required to be between 18 and 80 years old and be able to speak English, provide informed consent, and have DSM-IV-TR diagnostic confirmation of type 1 or 2 bipolar disorder or schizoaffective bipolar disorder as determined using the SCID. Controls were selected from the Mayo Clinic Biobank¹⁸. Potential controls with ICD9 codes for bipolar disorder, schizophrenia or related diagnoses in their electronic medical record were excluded.

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

Cases were recruited from consecutive admissions to psychiatric in-patient units at the University Hospital Würzburg. All cases received a lifetime diagnosis of BD according to the DSM-IV criteria using a consensus best-estimate procedure based on all available information, including semi-structured diagnostic interviews using the Association for Methodology and Documentation in Psychiatry²³, medical records and the family history method. In addition, the OPCRIT system was used for the detailed poly diagnostic documentation of symptoms.

Control subjects were ascertained from the population-based Heinz Nixdorf Recall (HNR) Study²⁴. The controls were not screened for a history of mental illness. Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent.

Rietschel, M; Nöthen, MM; Schulze, TG; Bauer, M; Forstner, AJ; Müller-Myhsok, B | 24618891 | BOMA-Germany III | bip_bmg3_eur²⁵

Cases were recruited at the Central Institute of Mental Health in Mannheim, University of Heidelberg, and other collaborating psychiatric hospitals in Germany. All cases received a lifetime diagnosis of BD according to the DSM-IV criteria using a consensus best-estimate procedure based on all available information including structured diagnostic interviews using the AMDP, Composite International Diagnostic Screener (CID-S)²⁶, SADS-L and/or SCID, medical records, and the family history method. In addition, the OPCRIT system was used for the detailed poly diagnostic documentation of symptoms.

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

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

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

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

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

review of medical records; and interviews with first and/or second degree family members using the Family Informant Schedule and Criteria (FISC)²⁷. Consensus best estimate BD diagnoses were assigned by two or more independent senior psychiatrists and/or psychologists, and according to the RDC, and the DSM-IV. Controls were Spanish subjects drawn from a cohort of individuals recruited in the framework of the European Community Respiratory Health Survey (ECRHS, <http://www.ecrhs.org/>). The controls were not screened for a history of mental illness. Study protocols were reviewed and approved in advance by Institutional Review Boards of the participating institutions. All subjects provided written informed consent.

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

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

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

Cases were recruited from consecutive admissions to the Obregia Clinical Psychiatric Hospital, Bucharest, Romania. Patients were administered the DIGS²⁸ and FIGS⁸ interviews. Information was also obtained from medical records and close relatives. The diagnosis of BP-I was assigned according to DSM-IV criteria using the best estimate procedure. All patients had at least two hospitalized illness episodes. Population-based controls were evaluated using the DIGS to exclude a lifetime history of major affective disorders, schizophrenia, schizoaffective disorders, and other psychoses, obsessive-compulsive disorder, eating disorders, and alcohol or drug addiction.

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

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

Kirov, G | 25055870 | Bulgarian trios | bip_butr_eur

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

Kirov, G | 25055870 | UK trios | bip_uktr_eur

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

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

The BD subjects were identified using the Swedish National Quality Register for Bipolar Disorders (Bipolär) and the Swedish National Patient Register (using a validated algorithm²⁹ requiring at least two hospitalizations with a BD diagnosis). A confirmatory telephone interview with a diagnostic review was conducted. Additional subjects were recruited from the St. Göran Bipolar Project (Affective Center at Northern Stockholm Psychiatry Clinic, Sweden), enrolling new and ongoing patients diagnosed with BD using structured clinical interviews. Diagnoses were made according to the DSM-IV criteria (Bipolär and St. Göran Bipolar Project) and ICD-10 (National Patient Register). The control subjects used were the same as for the SCZ analyses described above. All ascertainment procedures were approved by the Regional Ethical Committees in Sweden.

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

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

Leboyer, M^[30]; [PGC1 replication] | France | bip_fran_eur

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

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

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

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

Cases were all over the age of 17 yr, living in the UK and of European descent. Cases were recruited via systematic and not systematic methods as part of the Bipolar Disorder Research Network project (www.bdrn.org), provided written informed consent and were interviewed using a semi-structured diagnostic interview, the Schedules for Clinical Assessment in Neuropsychiatry. Based on the information gathered from the interview and case notes review, best-estimate lifetime diagnosis was made according to DSM-IV. Inter-rater reliability was formally assessed using 20 randomly selected cases (mean κ Statistic = .85). In the current study we included cases with a lifetime diagnosis of DSM-IV bipolar disorder or schizo-affective disorder, bipolar type. The BDRN study has UK National Health Service (NHS) Research Ethics Committee approval and local Research and Development approval in all participating NHS Trusts/Health Boards. Controls were part of the Wellcome Trust Case Control Consortium common control set, which comprised healthy blood donors recruited from the UK Blood Service and samples from the 1958 British Birth Cohort. Controls were not screened for a history of mental illness. All cases and controls were recruited under protocols approved by the appropriate IRBs. All subjects gave written informed consent.

Ophoff, RA | Not Published | Netherlands | bip_ucla_eur

The case sample consisted of inpatients and outpatients recruited through psychiatric hospitals and institutions throughout the Netherlands. Cases with DSM-IV bipolar disorder, determined after interview with the SCID, were included in the analysis. Controls were collected in parallel at different sites in the Netherlands and were volunteers with no psychiatric history after screening with the (MINI¹¹). Ethical approval was provided by UCLA and local ethics committees and all participants gave written informed consent.

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

This sample comprised Caucasian individuals recruited into one of three Geodon (ziprasidone) clinical trials (NCT00141271, NCT00282464, NCT00483548). Subjects were diagnosed by a clinician with a primary diagnosis of Bipolar 1 Disorder, most recent episode depressed, with or without rapid cycling, without psychotic features, as defined in the DSM-IV-TR (296.5x) and confirmed by the MINI (version 5.0). Subjects also were assessed as having a HAM-D-17 total score of >20 at the screening visit. The trials were conducted in accordance with the protocols, International Conference on Harmonization of Good Clinical Practice Guidelines, and applicable local regulatory requirements and laws. Patients gave written informed consent for the collection of blood samples for DNA for use in genetic studies.

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

Genomic Psychiatry Consortium (GPC) cases and controls were collected via the University of Southern California healthcare system, as previously described³¹. Using a combination of focused, direct interviews and data extraction from medical records, diagnoses were established using the OPCRIT and were based on DSM-IV-TR criteria. Age and gender-matched controls were ascertained from the University of Southern California health system and assessed using a validated screening instrument and medical records.

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

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

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

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

The cases were drawn from the same six clinical studies described for bip_jst5_eur except that only patients of east European ancestry with matching controls were included in this cohort. Most of the Eastern European controls were from the Estonian Biobank project (EGCUT)³² and were ancestrally matched with cases.

Schulze, T | [ConLiGen] | Germany | BIP_KFO_eur

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

===== External studies PGC3 =====

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

The Icelandic sample consisted of 2,908 subjects with BD (1661 SNP typed) and 344,848 controls (141,854 SNP typed). DNA was isolated from blood samples provided by patients and controls that were recruited throughout Iceland. Approval for the study was granted by the National Bioethics Committee of Iceland and the Icelandic Data Protection Authority and informed consent was obtained for all participants providing a sample for the study. Diagnoses were assigned according to Research Diagnostic Criteria³⁸ through the use of the SADS-L³⁹ for 303 subjects. DSM-IV BD diagnoses were obtained through the use of the Composite International Diagnostic Interview (CIDI-Auto) for 82 subjects. The remaining BD subjects were diagnosed by ICD 9 or ICD 10 at Landspítali University Hospital in the years 1987-2018. Controls were recruited as a part of various genetic programs at deCODE and were not screened for psychiatric disorders. Whole genome sequencing was performed on samples from 541 BD cases and 26,014 controls. Two types of imputations were performed; into SNP-typed individuals based on long-range phasing, followed by a familial imputation step into un-typed relatives of SNP-typed individuals. Cases of bipolar I disorder were defined using ICD-10 codes 31.1 and 31.2 and ICD-9 codes 296.0 and 296.2. Cases of bipolar II disorder were defined using the ICD-10 code 31.0 in the absence of ICD-10 codes F31.1 and F31.2 and ICD-9 codes 296.0 and 296.2.

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

The Estonian Biobank (EstBB) is a population-based cohort of 200,000 participants with a rich variety of phenotypic and health-related information collected for each individual³². At recruitment, all participants signed a consent to allow follow-up linkage of their electronic health records (EHR), thereby providing a longitudinal collection of phenotypic information. Health records have been extracted from the national Health Insurance Fund Treatment Bills (from 2004), Tartu University Hospital (from 2008), and North Estonia Medical Center (from 2005). The diagnoses are coded in ICD-10 format and drug dispensing data include drug ATC codes, prescription status and purchase date (if available). For the current study, cases of bipolar disease were determined by searching the EHRs for data on F31* ICD-10 diagnosis. All remaining participants who did not have any ICD-10 F* group diagnoses were defined as controls. Cases with bipolar I disorder were those with ICD codes of F31.1 and F31.2.

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

The HUNT sample consisted of 905 subjects with BD and 41,914 population controls⁴¹. Patients and controls were of European ancestry and were recruited from the Nord-Trøndelag County, Norway. Diagnoses were assigned according to ICD-9 or ICD-10. The controls included individuals not diagnosed with substance use disorders, schizophrenia, bipolar disorder, major depressive disorder, anxiety disorders, eating disorders, personality disorders, or ADHD in hospitals (ICD-9 or ICD-10) or general practice (ICPC2). They also were >40 years of age, had low self-reported levels of anxiety and depression (HADS-A and HADS-D < 11), and reported no use of antidepressants, anxiolytics, or hypnotics. Approval for the study was granted by the Data Inspectorate of Norway, the Health Directorate and the Regional Committee for Medical and Health Research Ethics. Cases of bipolar I disorder were those with ICD codes of F31.1, F31.2 or F31.6 and individuals with an ICD-9 code of 295 or ICD-10 codes F20-F29 were excluded. Cases of bipolar II disorder were those with ICD codes of F31.8 and individuals with an ICD-9 code of 295 or ICD-10 codes F20-F29, F31.1-.2 or F31.6 were excluded.

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

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

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

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

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

Intelligence Test ²⁴⁴. Study protocols were reviewed and approved by the ethical committee of the Medical Faculty of the University of Würzburg. All subjects provided written informed consent.

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

The sample includes 267 BD subjects (Spanish Wave2 Serretti PsychChip QC Summary), of which 180 Spanish and 87 Italian. Spanish sample: 180 subjects were enrolled in a naturalistic cohort study, consecutively admitted to the out-patient Bipolar Disorders Unit, Hospital Clinic, University of Barcelona. This is a systematic cross-sectional analysis deeply described in a previous paper on the same sample investigating rs10997870 SIRT1 gene variant⁴⁵. Inclusion criteria were a diagnosis of bipolar disorder (type 1 or 2) according to DSM-IV TR criteria and age of 18 years or older. The study was approved by the local ethical committee and carried out in accordance with the ethical standards laid down in the Declaration of Helsinki. Signed informed consent was obtained from all participants after a detailed and extensive description of the study and patient's confidentiality was preserved. The current and lifetime diagnoses of mental disorders were formulated by independent senior psychiatrists (diagnostic concordance: Kappa=.80) according to DSM-IV TR clinical criteria and confirmed through the semi-structured interviews for Axis I disorders according to DSM IV TR criteria (SCID I). Furthermore, all available clinical data coming from follow-up at our unit and collateral information concerning illness history were cross-referred in order to ensure accuracy and obtain complete clinical information. Specific psychopathological dimensions were assessed by means of rating scales and clinical questionnaires administered by clinicians, adequately trained to enhance inter-rater reliability. Mood episodes were defined according to DSM-IV TR criteria and their severity was measured through the administration of the 21-item Hamilton Depression Rating Scale (HDRS-21, Spanish version). The most severe depressive episode was defined on the basis of the severity at the HDRS (total score > 14) and clinical judgment. Italian sample: 87 subjects with bipolar depression were enrolled into the study when admitted at the Department of Psychiatry, University of Bologna, Italy. A description of the subjects has been previously reported when analyzing clinical features⁴⁶. Inclusion criteria were a diagnosis of bipolar disorder, most recent episode depressive as assessed by DSM-IV-TR criteria; Young Mania Rating Scale (YMRS) score <12; Hamilton Depression Rating Scale (HAM-D) <12. Exclusion criteria were presence of a bipolar disorder, most recent episode manic or hypomanic; presence of severe medical conditions; presence of moderate to severe dementia (Mini Mental State Examination score <20). The following scales were administered biweekly during the hospitalization: HAM-D, Hamilton Anxiety Rating Scale (HAM-A), YMRS and Dosage Record and Treatment Emergent Symptom Scale (DOTES). Written informed consent was obtained for each patient recruited. The study protocol was approved by the local Ethical Committee and it has been performed in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki.

The Spanish controls were part of the Mental-Cat clinical sample or the INSchool population-based cohort. A total of 1,774 controls from the Mental-Cat cohort (6.5% males) were evaluated and recruited prospectively from a restricted geographic area at the Hospital Universitari Vall d'Hebron of Barcelona (Spain) and consisted of unrelated healthy blood donors. The INSchool sample consisting of 771 children (76.2% males) from schools in Catalonia were involved for screening using the Achenbach System of Empirically Based Assessment (ASEBA) with the Child Behavior Checklist CBCL/4-18 (completed by parents or surrogates), the Teacher Report Form TRF/5-18 (completed by teachers and other school staff) and the Youth Self-Report YSR/11-18 (completed by youths); the Strengths and Difficulties Questionnaire (SDQ) and the Conner's ADHD Rating Scales (Parents and Teachers). Genomic DNA samples were obtained either from peripheral blood lymphocytes by the salting out procedure or from saliva using the Oragene DNA Self-Collection Kit (DNA Genotek, Kanata, Ontario Canada). DNA concentrations were determined using the Pico- Green dsDNA Quantitation Kit (Molecular Probes, Eugene, OR) and genotyped with the Illumina Infinium PsychArray-24 v1.1 at the Genomics Platform of the Broad Institute. The study was approved by the Clinical Research Ethics Committee (CREC) of Hospital Universitari Vall d'Hebron, all methods were performed in accordance with the relevant guidelines and regulations and written informed consent was obtained from participant parents before inclusion into the study. Detailed information has been published previously⁴⁷.

Perlis, R; Sklar, P; Smoller, J, Goes F, Mathews CA, Waldman I | Not published | [PGC Psychchip] | usaw4

Perlis, R; Sklar, P; Smoller, J: EHR data were obtained from a health care system of more than 4.6 million patients⁴⁸ spanning more than 20 years. Experienced clinicians reviewed charts to identify text features and coded data consistent or inconsistent with a diagnosis of bipolar disorder. Natural language processing was used to train a diagnostic algorithm with 95% specificity for classifying bipolar disorder. Filtered coded data were used to derive three additional classification rules for case subjects and one for control subjects. The positive predictive value (PPV) of EHR-based bipolar disorder and subphenotype diagnoses was calculated against diagnoses from direct semistructured interviews of 190 patients by trained clinicians blind to EHR diagnosis. The PPV of bipolar disorder defined by natural language processing was .86. Coded classification based on strict filtering achieved a value of .84, but classifications based on less stringent criteria performed less well. No EHR-classified control subject received a diagnosis of bipolar disorder on the basis of direct interview

(PPV=1.0). For most subphenotypes, PPV exceeded .8. The EHR-based classifications were used to accrue bipolar disorder cases and controls for genetic analyses. Samples were genotyped on the Psychchip array. Goes, FS: Cases represented independent probands from a European American family sample that was collected at Johns Hopkins University from 1988-201. Families had at least 2 additional relatives with a major mood disorder (defined as bipolar disorder type 1, bipolar type 2 or recurrent major depressive disorder). Diagnostic interviews were performed using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (N=81) and the Diagnostic Instrument for Genetics Studies (N=161). All cases underwent best-estimate diagnostic procedures. After genotyping quality control there were 242 cases, of which 240 were diagnosed as bipolar disorder type 1 and 2 as schizoaffective disorder, bipolar type. Diagnoses were based on DSM-III and DSM-IV criteria. Probands from this sample have been previously studied in family based linkage and exome studies.⁴⁹⁻⁵¹

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

Waldman I: Control samples were ascertained as part of an ongoing genetic study of ADHD and other Externalizing disorders (i.e., Oppositional Defiant Disorder and Conduct Disorder). Controls reported no current diagnoses of Externalizing or Internalizing disorders at the time of ascertainment. Controls were assessed for psychiatric conditions using the Emory Diagnostic Rating Scale (EDRS)⁵², a questionnaire that assessed parent ratings of symptoms of common DSM-IV Externalizing and Internalizing disorders (e.g., Major Depressive Disorder and various anxiety disorders). Samples were genotyped on the Psychchip array. Ethical approvals were obtained from the Emory University and University of Arizona Human Subjects Review Boards.

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

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

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

Ophoff R: Cases and controls were collected using the same protocol as described above for the “ucla” sample. Lochner C: Controls include South African Caucasian population based-controls ascertained from blood banks and controls recruited through university campuses and newspaper advertisements, who underwent a psychiatric interview and had no current or lifetime psychiatric disorder ⁵³⁻⁵⁴.

Franke B: The controls included are healthy individuals from the Dutch part of the International Multicenter ADHD Genetics (IMAGE) project ⁵⁵⁻⁵⁶.

Posthuma D: Data were provided for 960 unscreened Dutch population controls from the Netherlands Study of Cognition, Environment and Genes (NESCOG)⁵⁷. The study was approved by the institutional review board of Vrije Universiteit Amsterdam and participants provided informed consent.

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

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

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

The NeuRA collection comprised BD cases from three cohorts ascertained in Australia: the bipolar high risk study⁵⁸ (n=97), the Imaging Genetics in Psychosis Study (IGP; n=47)⁵⁹ and a clinic sample (n=109) recruited via the Sydney Bipolar Disorders Clinic. The clinic sample used the same ascertainment procedures as described for the bip_bmau_eur sample. The bipolar high risk study is a collaborative study with 4 US and one Australian groups, with young participants aged 12-3. The IGP sample was recruited from outpatient services of the South Eastern Sydney-Illawarra Area Health Service (SESAHS), the Sydney Bipolar Disorders Clinic and the

Australian Schizophrenia Research Bank. Healthy controls were sourced from the high risk, IGP and the Cognitive and Affective Symptoms of Schizophrenia Intervention (CASSI) trial⁶¹ studies, and were recruited from the community, had no personal lifetime history of a DSM-IV Axis-I diagnosis as determined by psychiatric interview, and no history of psychotic disorders among first-degree biological relatives. Additional controls were recruited as part of the strategy to develop an Australian Schizophrenia Research Biobank for studies into the genetics of this disease. The ascertainment of these controls has been previously described⁶².

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

The cases in the swed1 sample were recruited using the same ascertainment methods described for the bip_swa2_eur sample. Population-based healthy controls, randomly selected from the Swedish national population register, were collected as part of two case-control studies of multiple sclerosis: GEMS (Genes and Environment in Multiple Sclerosis) and EIMS (Epidemiological Investigation of Multiple Sclerosis)⁶³.

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

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

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

McIntosh AM: BD cases were recruited from the clinical case loads of treating psychiatrists from Edinburgh and across the central belt of Scotland. Controls were identified from non-genetic family members and from the extended networks of the participants themselves. All participants were of European ancestry and diagnosis was confirmed using an established battery developed for ICCBD. Breen G: Controls were drawn from blood donors to the UK Motor Neuron Disease Association DNA Biobank⁶⁴.

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

Kelsoe, J: The Pharmacogenomics of Bipolar Disorder (PGBD) study was a prospective assessment of lithium response in BDI patients. The goal was to identify genes for lithium response. Subjects were recruited from clinics at 11 international sites and followed for up to 2.5 years. Diagnosis was obtained by DIGS interview and medical records reviewed by blind experienced clinicians. As the comparison was between lithium responders and non-responders, no controls were collected. All subjects provided written informed consent.

Perlis R: Cases of bipolar disorder were Individuals treated with lithium drawn from the Partners Healthcare electronic health record (EHR) database, which spans two large academic medical centers, Massachusetts General Hospital and Brigham and Women's Hospital in addition to community and specialty outpatient clinics⁶⁵. Any patients aged 18 years or older with at least one lithium prescription between 2006 and 2013 based on e-prescribing data were included. The Partners Institutional Review Board approved all aspects of this study. Individuals with a diagnosis of schizophrenia based on ICD9 codes were excluded.

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

===== **PGC3 Samples** =====

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

All adult patients with a DSM-IV-TR/DSM-5 diagnosis of bipolar disorder hospitalized at the inpatient unit or followed-up at the specialized 'Affective disorders and Suicide' outpatient clinic of the 2nd Department of Psychiatry, National and Kapodistrian University of Athens, Attikon General Hospital, Athens, Greece from 2012 to 2017 were recruited for the current study. Patients were referred to the specialized 'Affective disorders and Suicide' outpatient clinic either from the inpatient unit after hospitalization or from the community. Diagnosis was established and demographic (age, gender, family status, profession, employment status, education) and relevant clinical features (e.g. age at onset, polarity of first and most recent episode, number of lifetime depressive and manic/hypomanic episodes, number of hospitalizations, lifetime suicidality, lifetime psychosis) were extracted through a M.I.N.I.-5.0-based semi-structured diagnostic interview, which was administered during patients' initial clinical assessment and regularly updated ever since, interviews of primary caregivers and inspection of medical records. Lifetime presence of any DSM-IV-TR axis I psychiatric comorbidities (dysthymia, panic disorder, agoraphobia, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, alcohol and substance abuse and dependence, anorexia nervosa, bulimia nervosa) was similarly extracted. Family history of major psychiatric disorders and suicidality in first and second degree relatives was recorded with a specific questionnaire based on the Family Interview for Genetic Studies. Medical comorbidities were recorded with the Cumulative Illness Rating Scale, completed on the basis of interview with patient and primary caregivers, inspection of patient's medical records and laboratory exams (basic or specific, if considered necessary). Presence of selected medical diseases was specifically recorded.

Control (unaffected) participants were a convenient sample drawn from the same geographic area as case participants, either within health care facilities or as community volunteers. All of them went through a brief clinical interview including items on psychiatric and medical history, psychiatric family history, past and current medical or psychiatric therapies, and a brief mental state examination. Only participants found to be free of lifetime major mental disorders (MDD, BD, schizophrenia, or other psychotic disorders) and with no family history of major mental disorder in their first-degree relatives were recruited as controls.

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

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

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

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

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

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

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

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

This sample includes the BOMA-Romania sample and additional cases from the ConLiGen-Romania sample. For the BOMA-Romania sample, unrelated BP-I patients were recruited from consecutive admissions in the Obregia Psychiatric Hospital of Bucharest, Romania. All participants provided written informed consent following a detailed explanation of the study aims and procedures. The study was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants were of Romanian descent according to self-reported ancestry. Genealogical information about parents and all four grandparents was obtained through direct interview of the subjects. The patients were investigated with the Diagnostic Interview for Genetic Studies (DIGS)²⁸ and the Family Interview for Genetic Studies (FIGS)⁸. The diagnosis of BP-I was assigned according to DSM-IV criteria on the basis of both the DIGS and medical records. Patients were included in the sample if they had at least two documented hospitalized illness episodes (one manic/mixed and one depressive or two manic episodes) and no residual mood incongruent psychotic symptoms during remissions. This information was also confirmed by first degree relatives for 64% of the cases. The illness age-of-onset was defined as the age at which the proband first met DSM-IV criteria for a manic, mixed, or major depressive episode. Family history of psychiatric illness was obtained with FIGS administered both to the patients and to all available relatives.

Cases in the ConLiGen-Romania study were ascertained in the same manner as for BOMA-Romania. Cases were required to have taken lithium for at least two years and lithium treatment response was evaluated with the Alda scale⁶⁶.

Population-based controls were evaluated using the DIGS and FIGS to screen for a lifetime history of major affective disorders, schizoaffective disorders, SCZ and other psychoses, obsessive-compulsive disorder, eating disorders, and alcohol or drug addiction. Unaffected individuals were included as controls in the present study.

===== PGC4 Samples =====

Grigoriou-Serbanescu M | PMID : 31791676 | Romania (BOMA-Romania) | rom4

Cases were recruited from consecutive admissions to the Obregia Clinical Psychiatric Hospital, Bucharest, Romania. Patients were administered the DIG 28 and FIGS⁸ interviews. Information was also obtained from medical records and close relatives. The diagnosis of BP-I was assigned according to DSM-IV-R criteria using the best estimate procedure. All patients had at least two hospitalized illness episodes. Population-based controls were evaluated using the DIGS to exclude a lifetime history of major affective disorders, schizophrenia, schizoaffective disorders, and other psychoses, obsessive-compulsive disorder, eating disorders, and alcohol or drug addiction.

McQuillin A | PMID: 37643680 | UCL (University College London), London, UK | amq1

Case and controls were collected using the protocol described above for bip_uclo_cur.

Squassina A, | PMID: 21961650 | Italy | ital1

Patients with bipolar I or bipolar II disorder were recruited at the outpatient unit (Lithium Clinic) of the Clinical Psychopharmacology Centre at the Department of Biomedical Science, Section of Neuroscience & Clinical Pharmacology, University of Cagliari, University Hospital Agency of Cagliari, Italy. Clinical assessments followed a strict procedure. After providing informed consent, participants were interviewed using one of the structured or semistructured interviews SADS-L. Clinical diagnosis was confirmed by DSM-IV criteria. We also used available medical records, narrative summaries of all interviews, and details such as baseline assessments, clinical course, response to treatment, treatment adherence, psychiatric and medical comorbidities, history of suicidal behavior, and symptom profiles in OPCRIT format.⁶

For uniform evaluation of treatment response, we used all available information including data from clinical records, diagnostic interviews, and prospective follow-up assessed by NIMH Life-Chart Method⁶⁷. We used the Alda scale to assess lithium response⁶⁶.

Manchia M, Carpiniello B, Squassina A | PMID: 35566641 | Italy | ital2

The case samples were recruited among patients attending the outpatient clinic of the community mental health center of the Unit of Clinical Psychiatry within the University Hospital of Cagliari, Italy. Patients were enrolled in the genetic study if they met the following inclusion criteria: diagnosis of either Bipolar I or Bipolar II disorder according to DSM 5⁶⁸ criteria validated through the Italian version of the SCID-5-CV (Structured Clinical Interview for DSM-5 Clinical Version); being in euthymic phase.

All patients provided a written consent form regarding the use of their biological and clinical data for research purposes. Blood samples were gathered at the beginning of the study along with the relevant demographic and biometric data. All the clinical documents are stored in an anonymized database, accessible only by authorized personnel.

The recruited subjects were phenotypically characterized with the use of the following standardized tests:

- Brief Assessment of Cognition in Affective Disorders (BACA)
- Brief Assessment of Cognition in Schizophrenia to assess baseline cognitive capacities
- Hamilton Depression Rating Scale (HDRS)
- Young Mania Rating Scale (YMRS)
- Hamilton Anxiety Rating Scale (HAM-A)
- Barratt Impulsivity scale (BIS)
- Clinical Global Impression Scale – Severity (CGI-S)
- Alda score for Lithium response (clinical response defined as a score >7)
- OPCRIT

Tondo L, Squassina A | PMID: 20348464 | Italy | ital3

Our sample population encompasses a cohort of patients followed at the Mood Disorder Lucio Bini Center in Cagliari (Italy), a specialized outpatient clinic for the diagnosis, treatment and research of affective disorders. Since the founding of this outpatient clinic in 1977, all demographic and clinical information about patients have been recorded systematically by means of semi-structured initial and follow-up interviews, a life chart, extensive clinical evaluation and repeated assessments with standard rating scales for mood such as the Hamilton Depression Rating Scale (HDRS)⁶⁹, and Young Mania Rating Scale⁷⁰, typically every 4–6 weeks. Diagnoses were updated to meet the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria⁶⁸ after the year 2013. Written informed consent was obtained for collection and analysis of patient data to be presented anonymously in aggregate form, in accordance with the requirements of Italian law and following review by a local ethical committee. Required data were entered into a computerized database in coded form to protect subject identity.

Patients were included in the study if they had at least 12 months of treatment with lithium and if they had a diagnosis of bipolar disorder (BD) or major depressive disorder (MDD) according to DSM-5. The clinical response to lithium treatment was characterized using the "Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder" scale, also known as Alda Scale⁶⁶.

Alda M | Not published | Nova Scotia, Canada | hal3

The case samples were recruited from patients longitudinally followed at a specialty mood disorders clinic in Halifax (Canada). Cases were interviewed in a blind fashion with the Schedule of Affective Disorders and Schizophrenia-Lifetime version (SADS-L)¹³ by pairs of clinician researchers (psychiatrists and/or nurses). The interviews together with medical records were subsequently reviewed in a blind fashion by a panel of senior

clinical researchers. Consensus diagnoses were made according to DSM-IV¹⁴ and Research Diagnostic Criteria (RDC)¹⁵ Protocols and procedures were approved by the local Ethics Committees and written informed consent was obtained from all patients before participation in the study.

===== External Samples PGC4 =====

Genomic Psychiatry Cohort (GPC) (USA) | 33169155

Details of ascertainment and diagnosis, genotyping and quality control have been described in detail previously⁸². Briefly, cases were ascertained using the Diagnostic Interview for Psychosis and Affective Disorders (DI-PAD), a semi-structured clinical interview administered by mental health professionals, which was developed specifically for the GPC study. Individuals reporting no lifetime symptoms indicative of psychosis or mania and who have no first-degree relatives with these symptoms are included as control participants.

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