

# Transcriptomic Imputation of Bipolar Disorder and Bipolar subtypes reveals 29 novel associated genes

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# **Abstract**

Bipolar disorder is a complex neuropsychiatric disorder presenting with episodic mood disturbances. In this study we use a transcriptomic imputation approach to identify novel genes and pathways associated with bipolar disorder, as well as three diagnostically and genetically distinct subtypes. Transcriptomic imputation approaches leverage well-curated and publicly available eQTL reference panels to create gene-expression prediction models, which may then be applied to “impute” genetically regulated gene expression (GREX) in large GWAS datasets. By testing for association between phenotype and GREX, rather than genotype, we hope to identify more biologically interpretable associations, and thus elucidate more of the genetic architecture of bipolar disorder.

We applied GREX prediction models for 13 brain regions (derived from CommonMind Consortium and GTEx eQTL reference panels) to 21,488 bipolar cases and 54,303 matched controls, constituting the largest transcriptomic imputation study of bipolar disorder (BPD) to date. Additionally, we analyzed three specific BPD subtypes, including 14,938 individuals with subtype 1 (BD-I), 3,543 individuals with subtype 2 (BD-II), and 1,500 individuals with schizoaffective subtype (SAB).

We identified 125 gene-tissue associations with BPD, of which 53 represent independent associations after FINEMAP analysis. 29/53 associations were novel; i.e., did not lie within 1Mb of a locus identified in the recent PGC-BD GWAS. We identified 37 independent BD-I gene-tissue associations (10 novel), 2 BD-II associations, and 2 SAB associations. Our BPD, BD-I and BD-II associations were significantly more likely to be differentially expressed in post-mortem brain tissue of BPD, BD-I and BD-II cases than we might expect by chance. Together with our pathway analysis, our results support long-standing hypotheses about bipolar disorder risk, including a role for oxidative stress and mitochondrial dysfunction, the post-synaptic density, and an enrichment of circadian rhythm and clock genes within our results.

## Introduction

Bipolar disorder (BPD) is a serious episodic neuropsychiatric disorder presenting with extreme elation, or mania, and severe depressive states<sup>1</sup>. In tandem, individuals with bipolar often experience disturbances in thinking and behavior, as well as psychotic features such as delusions and hallucinations<sup>1</sup>. Estimates of the prevalence of BPD within the general population range from 0.5-1.5%<sup>1,2</sup>. Bipolar disorder is highly heritable, with siblings of probands at an 8-fold increased risk of the disorder<sup>1,2</sup>, and twin studies producing strikingly high estimates of heritability, around 89-93%<sup>1,3,4</sup>. More recently, genetic studies of BPD have indicated SNP heritability estimates of 17-23%<sup>5</sup>.

Bipolar disorder encompasses diagnostically distinct subtypes; bipolar disorder type I (BD-I), characterized by full manic episodes, and bipolar disorder type II (BD-II), which includes both hypomania and recurrent depressive episodes<sup>1,6,7</sup>. Individuals with diagnostic features of both bipolar disorder and schizophrenia may additionally be diagnosed with schizoaffective disorder (SAB)<sup>7</sup>. Recent studies have indicated that these diagnostic distinctions may be borne out genetically; for example, BD-I is significantly more heritable than BD-II<sup>5,8</sup>, and there are distinct differences between polygenic risk profiles of individuals with BD-I compared to BD-II<sup>6,8</sup>. These diagnostic and genetic heterogeneities within bipolar disorder contribute to the complexity in identifying genetic associations with bipolar disorder. Additional complications arise due to the complex polygenic nature of the disorder, and the high degree of overlap, both diagnostically and genetically, with other psychiatric disorders such as Schizophrenia and Major Depressive Disorder<sup>9-11</sup>.

Global collaborative efforts over the last decade have enabled large collections of samples from individuals with BPD. Genome-wide associations studies (GWAS) of these collections have identified multiple BPD-associated loci throughout the genome<sup>6,12-25</sup>, most recently 30 novel loci identified in the PGC-BD GWAS<sup>5</sup>. Despite these advances in locus discovery, little is understood about the pathogenesis of bipolar disorder. It is likely that, in line with other psychiatric disorders, larger sample sizes will be required in order to identify additional risk

loci<sup>26</sup>. However, even elegantly designed and well-powered GWAS studies will not necessarily identify biological mechanisms contributing to disease, as large lists of genomic loci may be uninformative, and require careful dissection and downstream analyses to identify truly disease-causing associations<sup>27</sup>.

Transcriptomic Imputation (TI) analyses offer an opportunity to probe gene expression on a large scale, using eQTL reference panel-derived prediction models<sup>28,29</sup>. These approaches have several attractive advantages to researchers studying genetics of complex traits. First, results are readily biologically interpretable. Second, the large scale of GWAS studies means that TI studies are powered to detect even modest changes in gene expression, which likely represent a large portion of the risk in psychiatric disorders<sup>30,31</sup>, and which cannot be identified with traditional transcriptome approaches. Third, the use of genetically-regulated gene expression ensures that any associations precede symptom onset, rather than being mediated by disease status<sup>28</sup>.

In this study, we present the largest analysis of transcriptomic imputation in Bipolar Disorder. Our analysis included individuals from the most recent PGC-BD GWAS<sup>5</sup> (19,986 cases/30,992 controls), as well as individuals from the iPSYCH consortium (1,502 cases/23,311 controls). We calculated predicted genetically regulated gene expression (GREX) for ~20,000 genes across 13 brain regions, using prediction models derived from GTEX<sup>28,32</sup> and CommonMind Consortium data<sup>31,33</sup>. We sought to identify associations between GREX and a diagnosis of bipolar disorder, or one of three bipolar subtypes (BD-I, BD-II, SAB). We identified 125 significant gene-tissue associations with BPD, constituting 53 independent associations. Of these, 29 gene-tissue associations were novel; i.e., they did not lie within 1MB of a locus identified in the recent PGC-BD GWAS<sup>5</sup>. Additionally, we identified 80 gene-tissue associations with BD-I (37 independent associations, of which 12 were novel), two gene-tissue associations with BD-II (both novel), and one gene-tissue association with SAB. Our associations were highly consistent with differential gene expression analyses of bipolar cases and controls in the CommonMind Consortium. We expound upon these results using a number of analyses, including gene set enrichment

146 analyses, replication of previous transcriptome-based studies of bipolar disorder<sup>28,34</sup>, and an  
147 approach analogous to PHEWAS<sup>35,36</sup> to identify associations between these genes and specific  
148 endophenotypes of bipolar disorder.

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# **Methods**

## **Samples**

Genotype data were obtained from the Psychiatric Genomics Consortium Bipolar Disorder (PGC-BD) collection. These data included 19,986 cases and 30,992 ancestry-matched controls from the PGC-BD collection<sup>5</sup>. Three of these cohorts were available through summary statistics only (Supplementary Figure 1). 1,502 BPD cases and 23,311 matched controls were additionally analysed by collaborators at iPSYCH (supplementary information).

In order to be included in the study, cases were required to meet international diagnostic criteria for BPD (ie, DSM-IV, ICD-9, ICD-10), or to have a lifetime diagnosis of BPD according to structured diagnostic instruments<sup>5</sup>. Genotyping information for these samples can be found in the flagship papers describing the initial sample collection<sup>5</sup>, and were processed in a standardized manner using “ricopili”<sup>5</sup>.

The PGC-BD collection included 14,938 individuals with BD-I, 3,543 individuals with BD-II, and 1,500 individuals with SAB. No subtype data were available for individuals collected through iPSYCH.

## **Transcriptomic Imputation**

We imputed genetically regulated gene expression (GREX) using the CommonMind Consortium (CMC) derived Dorso-lateral pre-frontal cortex (DLPFC) predictor model<sup>33</sup>, and GTEx-derived brain tissue prediction models<sup>28,32</sup>. We imputed GREX in all cohorts for which we had access to raw data using PrediXcan<sup>28</sup> (Suppl. Figure 1).

For three cohorts, raw genotype data was not available. For these cohorts, and two cohorts with a trio structure, genic associations were computed using summary statistics, using MetaXcan<sup>37</sup>, a summary-statistic approach analogous to prediXcan<sup>28</sup>. Previous studies have shown that genic association p-values and effect sizes calculated using MetaXcan and PrediXcan

are highly correlated, provided that ethnically matched reference panels are used<sup>33,37</sup>. This was confirmed using three European PGC BD cohorts for which both summary statistics and raw genotype data were available.

### **iPsych-Gems Analysis**

iPSYCH-GEMS GWAS data was genotyped and imputed in 23 waves, and subsequently merged for association analyses. No subtype data were available for iPSYCH-GEMS data. Variants with imputation scores > 0.8 were included for the analysis. Genetically regulated gene expression levels were calculated using the CMC DLPFC predictor model<sup>33</sup>, as well as 12 GTEx-derived brain tissue databases<sup>28,32</sup>. Association tests on case-control status were carried out using a logistic regression in R, including wave membership as covariate.

Principal component analysis was done in order to remove genetic outliers. The phenotype specific PCs that are significantly different between cases and controls were included as covariates as well, to account for the population stratification. Related individuals were identified by pairwise IBD analysis and one of every pair (preferably controls) identified as related ( $\text{piHAT} > 0.2$ ) was removed.

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Regression formula: Disease ~ gene-expression + wave1 + wave2 +.....+ wave22 + PC1+PC2+...

The association analysis was done using R software.

### **Association Tests**

We tested for association between GREX and case-control status in each cohort separately, using a standard linear regression test in R. We included ten principal components as covariates. We repeated this analysis for BD-I, BD-II and SAB, including all controls. We required that a cohort include at least 50 individuals with a given subtype to be included in each analysis, and consequently removed one cohort with only 36 SAB cases.



We carried out an analysis comparing bipolar subtypes BD-I, BD-II, SAB. For each pair of subtypes, we compared GREX in cases only, including all cohorts with more than 50 individuals with each diagnosis.

Raw genotype-based and summary-statistics based cohorts were meta-analysed using an odds-ratio based approach in METAL<sup>38</sup>.

### **Establishing a threshold for genome-wide significance**

We applied two significance thresholds to the data. First, for each tissue, we applied a Bonferroni correction accounting for the total number of genes tested within that tissue (Suppl. table 1). Second, we applied a global genome-wide significance threshold, accounting for all genes tested across all tissues. These are denoted by dashed and solid lines respectively in the manhattan plots throughout this manuscript.

### **Identifying independent associations**

We identified 18 regions with multiple gene-tissue associations; regions were defined based on distance between genes, and were checked using visual inspection of associations across each chromosome. For each of these regions, we applied FINEMAP<sup>39</sup> to identify independently associated genes. We substituted the LD-matrix usually used in FINEMAP with an analogous GREX correlation matrix.

This matrix was calculated for each cohort with available raw data, and a weighted average calculated across all populations, weighting for effective sample size. We ensured that summary-statistic based cohorts were represented in this weighted average by selecting the geographically nearest cohort as a proxy, and increasing the weighting of that proxy cohort accordingly.

*Equation 1: Effective Sample Size*

$$N_{eff} = \frac{4}{\left(\frac{1}{N_{cases}} + \frac{1}{N_{controls}}\right)}$$

## Identifying genes associated with specific behaviours and clinical variables

We obtained data on 26 clinical variables relating to BPD, including for example rapid cycling, psychosis, panic attacks, and a variety of comorbid disorders. We used an approach analogous to PHEWAS, and an adaptation to the PHEWAS R package<sup>40</sup>, to test for associations between BD-I, BD-II and SAB-associated genes and these 26 endophenotypes.

Behavioural data was available for ~8,500 individuals, across 14 cohorts. We tested for association between GREX and all 26 endophenotypes in each cohort separately, controlling for ten principal components. Only endophenotypes with at least 20 cases, or 20 quantitative measures, were included within each cohort. Results were meta-analyzed across cohorts using an odds-ratio based approach in METAL<sup>41</sup>.

## Comparison with Differential Expression in CommonMind Consortium

We sought to compare putatively BPD-associated GREX changes to genes identified as differentially expressed in post-mortem brain samples. We obtained summary statistics on differential expression between Bipolar cases and healthy controls from the CommonMind Consortium Phase II analysis, across the dorso-lateral pre-frontal cortex (DLPFC; 55 cases, 296 controls) and anterior cingulate cortex (ACC; 48 cases, 246 controls).

We compared association statistics between these two analyses and each of our prediXcan BPD analyses; specifically, we tested whether genes reaching tissue-specific significance in each prediXcan analysis were more likely than expected by chance to be differentially expressed in the CMC analysis. We then repeated this test using all nominally significant genes in the prediXcan analyses. Additionally, we tested whether the degree of replication seen in each tissue was correlated with the number of genes tested, and/or with the sample size of the original eQTL reference panel used.

Since we did not have access to individual-level RNA-seq data in order to run a BD-I specific differential expression analysis, we compared BD-I DLPFC and ACC prediXcan association statistics to the CMC differential expression analysis.

We identified a small number of individuals within the CommonMind Consortium sample who were diagnosed with BD-II subtype. No RNA-seq data was available for these individuals; however, 11 had available microarray data. We therefore compared normalized microarray data between these 11 individuals and 204 controls, for the two top genes in our BD-II subtype analysis (*COLGALT2* and *NUP98*). No individuals with SAB were available for analysis.

### **Pathway Analysis**

Pathway analysis was carried out using an adaptation to MAGMA<sup>42</sup>. We performed three pathway analyses, as follows: 1) 174 drug-target gene sets; 2) 76 gene sets with prior evidence of involvement in BD<sup>31,43–45</sup>, including nervous-systems related pathways, gene sets relating to aberrant behavior in mice, circadian clock gene sets, calcium-gated voltage channels, as well as targets of FMRP; 3) ~8,500 pathways collated across six large publicly available datasets<sup>46–53</sup>. We included only gene sets with at least 10 genes.

For each of the four iterations, we analyzed BIP, BD-I, BD-II and SAB results separately. Analyses were carried out using genic p-values from our PrediXcan meta-analyses. In instances where a gene had multiple associations across different tissues, the best p-value was selected, and a Bonferroni correction applied to correct for the number of tissues tested. Gene-set enrichment results from the competitive (rather than self-contained) MAGMA analysis were used<sup>42</sup>, and FDR correction applied within each stratum of our analysis.

## Results

### Association Tests

We calculated predicted gene expression for thirteen brain regions (derived from CMC and GTEx data<sup>28,32,54,55</sup>) in 19,986 cases and 30,992 controls from the PGC-BPD<sup>5</sup> and 1,502 cases and 23,311 controls from the iPsych-GEMS consortium, and tested for association between predicted gene expression (GREX) and case-control status. Additionally, we used a summary-statistic based method to calculate genic associations in cases and controls for which raw genotypes were not available (Suppl. Figure 1A).

We identified 125 genes-tissue associations reaching tissue-specific significance (Suppl. Table 2; Figure 1A;  $\sim 5e-06$ ); 46/125 reached our stricter cross-tissue threshold ( $4.11e-07$ ). Within these associations, we identified 18 genomic regions with multiple associated genes, and where the same gene was associated across multiple tissues. We applied FINEMAP to each of these regions, and identified 53 independent associations (Table 1; Figure 1B), of which 29 are novel (i.e., they do not lie within 1Mb of a locus identified in the recent PGC-BD GWAS<sup>5</sup>). It should be noted that our sample includes all of the PGC-BD samples as well as an additional cohort, and so will have greater power to detect signals than the original GWAS.

### Comparison to previous transcriptome studies

Two previous studies have already identified BPD-associated genes using transcriptomic approaches, albeit using substantially smaller samples<sup>28,34</sup>. We sought to replicate these findings using the subset of our data not included in the original PGC-BD GWAS<sup>5</sup> (Table 2).

One gene, *PTPRE*, was identified as associated with Bipolar Disorder in the original prediXcan-based Transcriptomic Imputation analysis. Two genes, *SPCS1* and *CACNB3*, were identified using the SMR method<sup>34</sup>, which used eQTLs from peripheral blood. *PTPRE* reaches nominal significance in the putamen basal ganglia in our replication sample ( $p=0.024$ ). Both *SPCS1* and *CACNB3* were significant in our replication sample (after Bonferroni correction); *SPCS1* in the caudate basal ganglia ( $p=0.0011$ ), and *CACNB3* in the frontal cortex ( $p=0.0010$ ). Additionally,

*CACNB3* reaches nominal significance in seven other tissues. This level of replication is highly unlikely to occur by chance (binomial test:  $p=1.59 \times 10^{-7}$  at nominal significance threshold,  $p=0.0012$  at Bonferroni-corrected threshold).

## Subtypes

Bipolar disorder subtypes BD-I, BD-II and SAB have previously been shown to be diagnostically and genetically distinct<sup>6</sup>. We tested for association of GREX with case-control status for each of these three subtypes, using all available matched controls; BD-I (14,983 cases/controls), BD-II (3,543/22,155) and SAB (1,500/8,690).

We identified 80 BD-I gene-tissue associations reaching tissue-specific genome-wide significance ( $\sim 6 \times 10^{-6}$ ; Suppl. Table 3), constituting 37 independent associations following FINEMAP (Table 3; Figure 2A). 12 gene-tissue associations across 10 regions were novel, i.e., did not lie within 1Mb of a BD-I locus identified in the PGC-BD GWAS<sup>5</sup>. In line with our overall BPD analysis, the largest number of associations occur in the cortex and pre-frontal cortex (14 associations) and the limbic system (14 associations).

Two genes were associated with BD-II subtype, albeit not at the stricter cross-tissue significance threshold (Table 3). First, increased expression *NUP98* in the DLPFC was associated with BD-II ( $p=2.2 \times 10^{-6}$ ). Decreased expression of *COLGALT2* was associated with BD-II in the Putamen Basal Ganglia ( $p=3.5 \times 10^{-6}$ ) and neared significance in the Hippocampus ( $p=7.6 \times 10^{-6}$ ), the Caudate Basal Ganglia ( $p=1.4 \times 10^{-5}$ ) and the Nucleus Accumbens Basal Ganglia ( $p=8.9 \times 10^{-5}$ ). Neither of these BD-II genes lie within 1Mb of a BD-II locus identified in the recent PGC-BD GWAS, although other BD-II subthreshold associations do (Suppl. Table 4).

Increased expression of *FSIP2* in the Thyroid was associated with SAB ( $p=1.9 \times 10^{-6}$ ; Table 3). Increased expression of *ALDH1B1* in the Cerebellar Hemisphere was also associated with SAB, although at slightly below tissue-specific significance ( $p=8.4 \times 10^{-6}$ ). *FSIP2* lies  $\sim 0.5$ Mb from a locus also identified as potentially associated with SAB in the PGC-BD GWAS ( $p=6.9 \times 10^{-7}$ ). One

sub-threshold association (*SNX29*, in the Hypothalamus; Suppl. Table 4), also lies close to a PGC-BD GWAS SAB locus; all other SAB associations are novel.

There is a substantial overlap between association signals in our BD and BD-I analyses, likely due to the high proportion of BD-I cases within our sample, and a high proportion of overlapping controls. We examined association statistics ( $-\log_{10}$  p-values) of all associated genes across all four analyses (Figure 3) and noted that BD and BD-1 genes tend to be reciprocally associated, whereas genes identified in the BD-2 and SAB analyses tend to be associated only within those particular subtypes.

### **Comparison to Differential Expression in the CommonMind Consortium samples**

We compared our prediXcan GREX results to bipolar disorder differential expression analysis conducted in CommonMind Consortium post-mortem samples. Across all tissues, genes reaching nominal significance in our prediXcan analysis were significantly more likely to be differentially expressed in CMC DLPFC post-mortem samples (binomial test,  $p < 2.8 \times 10^{-73}$ ; Supplementary Table 5). The degree of replication was significantly correlated with the sample size of the original eQTL reference panel, even when controlling for the number of genes tested ( $p = 0.03$ ).

Genes reaching tissue-specific significance ( $p < 0.05/N$  genes tested) in the DLPFC, ACC, Cortex, and Nucleus Accumbens prediXcan analyses were more likely than expected by chance to be differentially expressed in the DLPFC CMC post-mortem samples (binomial test,  $p < 0.0038$ ).

There was no relationship between the likelihood of replication of significant genes and the number of genes tested, or eQTL reference panel sample size.

The vast majority of BPD cases in the CommonMind Consortium differential expression analysis were BD-I subtype; therefore, we also used the same CMC differential expression analysis to test for replication of our BD-I prediXcan results. As for the overall BPD analysis, nominally significant prediXcan genes were all significantly more likely to be differentially expressed in our

CMC analysis (binomial test,  $p < 4.57 \times 10^{-72}$ ), and the degree of replication was correlated with sample size of the original eQTL reference panel ( $p = 0.044$ ). Genes reaching tissue-specific significance in both the DLPFC and the Cortex were significantly more likely to be differentially expressed in the CMC analysis (binomial test,  $p < 0.0016$ ; Supplementary Table 5).

We identified a small number of individuals within the CommonMind Consortium sample who were diagnosed with BD-II subtype. No RNA-seq data was available for these individuals; however, 11 had available microarray expression data. We therefore compared normalized microarray data between these 11 individuals and 204 controls, for the two top genes in our BD-II subtype analysis (*COLGALT2* and *NUP98*). Both genes had the same directions of effect between cases and controls in our CMC Microarray data as in the prediXcan meta-analysis. In particular, the ratio of case:control expression for *COLGALT2* was strikingly similar in the microarray data (0.984) to the effect size estimated using prediXcan (0.980), and expression levels were significantly different between cases and controls ( $p = 0.0488$ ). However, the sample sizes in this analysis are small, and results should be taken as preliminary, exploratory findings, and further, larger analysis will be required.

No individuals with SAB were available for analysis.

### Identifying genes associated with specific behaviours

We tested whether any of the genes identified in our subtype analyses were particularly associated with any specific BPD-endophenotype, using an approach analogous to PHEWAS<sup>35,36</sup>. We included all genes reaching tissue-specific significance in any subtype analysis.

We identified three significant associations (Table 4). We found that reduced expression of *EIF1AD* in the DLPFC was associated with mixed states ( $p = 0.00197$ ) and panic attacks ( $p = 0.0004948$ ). In our original analysis, decreased expression of the gene in the DLPFC was associated with BD-I ( $p = 2.55 \times 10^{-6}$ ). Additionally, decreased expression of *FSIP2* in the Pituitary was associated with having a family history of BPD in our PHEWAS ( $p = 1 \times 10^{-5}$ ).

## Pathway enrichment

We tested for pathway enrichment using MAGMA<sup>42</sup>, for BD, BD-I, BD-II and SAB associations. We carried out three stages of pathway analysis including the following gene sets 1) 174 sets of drug targets; 2) 79 hypothesis-driven gene sets including targets of the FMRP protein, calcium-gated voltage channels, pathways involved in aberrant mouse behavior, pathways pertaining to chronotype and circadian rhythms 3) ~8,500 agnostic pathways obtained from large publicly available databases. All FDR-corrected significant results for these analyses are shown in Table 5.

We found significant enrichments between our BD associated genes and GWAS-derived gene sets for schizophrenia ( $p=3.69E-13$ ; all  $p$ -values shown are FDR-corrected), bipolar disorder ( $p=2.59E-09$ ) and major mood disorder ( $p=0.0040$ ). These results are reassuring rather than illuminating, given the known genetic overlap between these disorders, the likely shared samples with the previous BIP GWAS, and the potential for shared controls between all PGC GWAS studies. Similar to the BD results, BD-I associated genes were significantly enriched for GWAS-derived SCZ ( $p=5.39E-12$ ) and BD ( $p=1.78E-09$ ) gene sets. BD-II associated genes were not significantly enriched with previous BP or schizophrenia GWAS results. SAB-associated genes were significantly enriched with bipolar GWAS results ( $p=0.027$ ).

We identified three drug target gene sets enriched in our BPD associated genes; anabolic steroids ( $p=5.84E-4$ ), androgens ( $p=0.025$ ) and corticosteroids for systemic use ( $p=0.012$ ). Corticosteroids when given in high doses can cause symptoms of mania, psychosis, impulsivity, irritability, anxiety, and depression<sup>56,57</sup>.

Four pathways in our 'hypothesis-driven' analysis were associated with BPD after FDR correction, including genes associated with self-defined 'morning person' chronotype<sup>58</sup>, genes that were highly intolerant to deleterious mutation in EXAC, genes with non-synonymous mutations linked to schizophrenia, and targets of the FMRP protein. FMRP pathways have previously been associated with schizophrenia, autism, and intellectual disability<sup>33,59,60</sup>. We



identified five further pathways with nominally significant competitive MAGMA p-values, but which did not survive FDR-correction, relating to pre- and post- synaptic density, circadian clock genes, and loss of function mutations associated with intellectual disability.

For BD-I, we identified two associated pathways in the hypothesis-driven analysis after FDR correction; endoplasmic reticulum function (ER;  $p=0.036$ ) and post synaptic density (PSD;  $p=0.046$ ). 49/8,500 molecular pathways from public databases were significant after FDR-correction, with the most significant driven by methyltransferase activity (S-adenosylmethionine – dependent methyltransferase activity;  $p=3.0 \times 10^{-3}$ ). Four pathways involved in methyltransferase activity are driven by TFB1M, a brain-expressed mitochondrial methyltransferase gene involved in neurosensory mitochondrial deafness<sup>61,62</sup>. Other significant pathways include mitochondrial function (mitochondrial genome maintenance;  $p=0.032$ ) which was also validated in studies of the PSD proteins and associations with bipolar disorder<sup>63</sup>.

For BD-2 there were no significant hypothesis-driven pathways; however, 34 agnostic pathways were significantly enriched. S-adenosylmethionine-dependent methyltransferase activity pathway was the most significant ( $p=0.0029$ ), in line with our BD-I analysis. Other significant pathways and potentially interesting pathways include metabolism of porphyrins, heme biosynthesis, abnormal neuronal migration, and negative regulation of systemic arterial blood pressure.

Three hypothesis-driven pathways were enriched with SAB; including mitochondrion<sup>64</sup>, non-synonymous mutations associated with intellectual disability, and genes that have low-level intolerance to EXAC mutations. Our large agnostic analysis revealed many neuron specific genes sets including axonal regeneration, Schwann cell differentiation, and neuron projection regeneration. Mitochondrion and mitochondrion localization were also significant further emphasizing the involvement of mitochondrial genes in bipolar disorder<sup>65–67</sup>. A total of 45 pathways were significantly enriched after FDR correction.

## Discussion

In this study, we present the largest analysis to date of transcriptomic imputation in Bipolar Disorder, and three bipolar disorder subtypes. Transcriptomic Imputation approaches leverage carefully curated eQTL reference panels to create prediction models of genetically-regulated gene expression<sup>28,32,33,68</sup> (GREX). These models are then used to predict GREX in genotyped samples (for example, those obtained through GWAS), thus providing large, well-powered gene-expression datasets, while circumventing the difficulties and complications inherent in traditional transcriptome studies.

We applied gene expression predictor models derived from GTEX and CMC data to 21,488 bipolar disorder cases and 54,303 controls from the PGC-BD and iPSYCH collections, and obtained predicted genetically regulated gene expression levels (GREX) for 19,661 unique genes, across 13 brain regions. We identified 53 independent BPD gene-tissue associations; of these, 29 were novel, i.e., they did not occur within 1MB of a locus identified in the recent PGC-BD GWAS<sup>5</sup>. Additionally, we identified 46 independent subtype-specific gene-tissue associations.

Our study includes an additional 1,503 BPD cases and ~23,000 controls from the iPSYCH consortium, which were not included in the discovery stage of the recent PGC-BD GWAS, and so some proportion of these novel associations likely stem from both the increased power of our sample, as well as the increased power of prediXcan over GWAS<sup>28,33</sup>. It should be noted that our BD-II, SAB, and cross-subtype analyses are small, and power to detect true associations is therefore low. These analyses should be taken as preliminary, exploratory findings, and larger, more well-powered studies should be carried out.

BPD- and BD-I-associated genes identified in this study were significantly more likely to be differentially expressed in post-mortem tissue from individuals with bipolar disorder than might be expected by chance. Replication of highly associated genes was tissue-specific; for example, genes discovered in the DLPFC were differentially expressed in the DLPFC. When testing only

492 nominally significant genes (i.e., all genes reaching  $p < 0.05$ ), replication was highly similar across  
 493 all tissues, and degree of replication seemed to be driven by the power of the original eQTL  
 494 reference panel (taking sample size as a proxy). This might indicate a large group of genes with  
 495 broad, multi-region implications, while smaller groups of genes confer region-specific BPD risk.  
 496 It is likely that some of the cross-brain signal also arises from highly correlated gene expression  
 497 patterns and shared eQTLs between brain regions<sup>32,55</sup>. We used microarray data from a small  
 498 sample of individuals with BD-II to visualize expression of our two BD-II associated genes,  
 499 *NUP98* and *COLGALT1*, in cases compared to controls. For both genes, the observed direction of  
 500 effect matches our prediXcan results. Although these results are encouraging, this analysis is  
 501 based on a very small number of cases; as such, these results should be interpreted as early,  
 502 preliminary indications, which should be followed with larger and more detailed investigations.

503  
 504 An interesting feature of transcriptomic analysis is the ability to probe associations across  
 505 specific brain regions (Suppl. Table 1). In our BPD meta-analysis, we identified 20 pre-frontal  
 506 cortex associations (nine in the DLPFC), 13 in the striatum (Caudate, Nucleus Accumbens, and  
 507 Putamen Basal Ganglia), 11 in the cerebellum and cerebellar hemisphere, and 2 in the  
 508 hippocampus. These results imply prominent roles for the frontal cortex, striatum and  
 509 cerebellum in bipolar disorder, consistent with previous neuro-anatomical studies. For  
 510 example, imaging studies have repeatedly demonstrated enlarged putamen<sup>69-71</sup> and  
 511 caudate<sup>69,72-74</sup> regions, decreased cerebellar volumes<sup>69,75-77</sup>, and structural differences in the  
 512 prefrontal cortex of individuals with BPD<sup>69,78-81</sup>.

513  
 514 We used genic associations for BD, BD-I, BD-II, and SAB to search for pathway enrichment with  
 515 MAGMA<sup>42</sup> using gene sets for drug targets, hypothesis driven, and agnostic gene sets. Our drug  
 516 target genes revealed sets for anabolic steroids, corticosteroids, and androgens which have  
 517 common precursors and similar effects on hormone receptors. Hormone imbalance has been  
 518 hypothesized in patients with BD and schizophrenia. Altered hypothalamic-pituitary-adrenal  
 519 (HPA) axis and increased systemic cortisol metabolism was found by measuring cortisol  
 520 metabolizing enzymes in urine of patients vs controls suggesting the synthesis pathways for

these hormones are altered<sup>57</sup>. Corticosteroids themselves are prescribed for a number of different medical conditions and can cause symptoms in patients that include psychosis, mania, depression, mixed features, delirium, and anxiety<sup>82</sup>. While these symptoms can arise after corticosteroid use, we cannot be certain the mechanisms are unique and the shared phenotypes in these overlapping gene sets suggest a similar genetic underpinning. Further investigation is warranted to understand the pathways involved in corticosteroid induced psychiatric symptoms and symptoms experienced by patients in bipolar disorder and schizophrenia. Additionally, our pathway analysis results provide support for a number of specific biological hypotheses.

### **Oxidative Stress and Mitochondrial Dysfunction**

Collectively, our results indicate a potential role for oxidative stress and mitochondrial dysfunction in bipolar disorder. This hypothesis has been explored in detail elsewhere<sup>83–86</sup>, and has been implicated in BPD<sup>83–85</sup> as well as a range of psychiatric disorders<sup>87–90</sup>, including anxiety and panic disorders<sup>91</sup>, schizophrenia<sup>92–94</sup>, and major depressive disorder<sup>95</sup>. Evidence for the involvement of oxidative stress and mitochondrial dysfunction in BPD includes known comorbidities between bipolar disorder and mitochondrial disease<sup>96</sup>, the known antioxidant properties of antipsychotic drugs<sup>83</sup>, and the demonstrated benefit of antioxidant therapies in individuals with schizophrenia and bipolar disorder<sup>83</sup>.

A substantial number of the genes identified in our meta-analyses also have a role in oxidative stress and mitochondrial dysfunction (including for example, *AIFM3*, *CHDH*, *EDEM2*, *EIF1AD*, *FADS1*, *TARS2*). In particular, our PHEWAS results implicate a gene, *EIF1AD*, which has a well-described role in response to oxidative stress<sup>97</sup>. Reduced expression of *EIF1AD* (eukaryotic translation initiation factor 1A domain containing; also known as haponin) in the DLPFC was associated with panic attacks, mixed states, and BD-I; in line with this, a recent study found increased RNA damage due to oxidative stress in individuals with BD-I and mixed states, compared to controls, and a decrease in levels of RNA damage after remission from an episode<sup>84</sup>. A large number of associations in our pathway analyses (Table 5) also point to

mitochondrial methyltransferase pathways, endoplasmic reticulum function, mitochondrial function, and mitochondrion location.

Common with BD-I and BD-II are the methyltransferase pathways with the most significant genes involved in mitochondrial methyltransferase. These genes are responsible for neurological phenotypes and associated with bipolar disorder<sup>65,66</sup>. A study of human induced pluripotent stem cells found early mitochondrial abnormalities in lithium responsive patients with bipolar disorder suggesting these mitochondrial abnormalities are present at the earliest stages of cell development<sup>67</sup>. SAB significant pathways reinforce the relationship between bipolar disorder with mitochondrial and neuronal function.

### **Post-synaptic Density**

Multiple studies and hypotheses have implicated the post-synaptic density (PSD) as having a role for Bipolar Disorder, Schizophrenia, and other psychiatric disorders<sup>63,64</sup>. The PSD is a key location for a host of dopamine and glutamate signaling interactions, and has a key role in axonal growth and guidance. Further, proteins located in the PSD are involved in NMDA receptor trafficking, and underlie energy pathways and mitochondrial function. Our BD-I results are significantly enriched for genes related to PSD-95, a scaffolding protein within the PSD ( $p=5.2e-04$ ). This enrichment is not driven by a single highly associated gene, but rather a large number of sub-threshold associations. The most significant post synaptic density (PSD) gene PACS1 ( $p=5.57e-05$ ) codes for MHC-1 removal of membrane proteins in the trans golgi network and is overexpressed in brain; other subthreshold PSD-95 and glutamatergic associations include *TUBA1B* ( $p=3.1e-04$ ), *SHANK1* ( $p=5.4e-04$ ), *BSN* ( $p=6.5e-04$ ), and *AP2B1* ( $p=6.7e-04$ ). Additionally, our results are enriched for targets of the FMRP (fragile-X mental retardation protein;  $p=0.0015$ ), in line with previous studies of Bipolar Disorder and schizophrenia<sup>59,98</sup>, as well as the original CommonMind Consortium analysis<sup>31</sup>. FMRP is encoded by *FMR1*, which is required at synapses for normal glutamate receptor signaling<sup>99</sup>.

## Circadian Rhythms

Longstanding hypotheses implicate the disruption of circadian rhythms in bipolar disorder. In particular, sleep disruption is included among bipolar disorder diagnostic criteria and is cited as a particular concern for individuals with BPD. Addressing circadian rhythm disruption is a key factor in treatment of bipolar disorder<sup>100,101</sup>, and in identifying individuals at risk of relapse<sup>102–106</sup>. Even among healthy individuals, circadian entrainment and sleep patterns are deeply entwined with mood regulation<sup>100,107–112</sup>. These relationships have been discussed in detail elsewhere, including detailed discussions of plausible neurobiological mechanisms<sup>100,113–126</sup>. Consequently, studies of the genetics of bipolar disorder have included an emphasis on “clock” genes, i.e., genes involved in regulating circadian rhythmicity<sup>100,125,127,128</sup>, and the genetics of chronicity and sleep traits<sup>124</sup>.

Our BPD-association results include genes with a role in regulation of circadian rhythm; *CIART* (Circadian Associated Repressor Of Transcription), *CNNM4*, *ZSWIM3*, *RPRD2*, *TARS2*, *HSPD1*, *VPS45* and *PHLPP1*, as well as *ASCC3*<sup>129</sup>, *DUSP7*, *ITGA9*, *VPS4A*, *MAPRE2*, *RRP12* and *CSE1L*, associated with BD-I; and *NUP98*, associated with BD-II, as well as ~30 other sub-threshold associated circadian rhythm genes ( $p < 1e-03$ ), including genes identified in a recent GWAS of self-identified ‘morning-ness’. These ‘morning-ness’ genes constituted the most significantly enriched set in our hypothesis-driven pathway analysis ( $p = 3.27e-05$ ) within the full bipolar meta-analysis; additionally, we identified enrichments for circadian clock genes ( $p = 0.012$ ) and clock modulators ( $p = 0.023$ ), although these did not remain significant after FDR-correction. ‘Morning-ness’ genes were also enriched among SAB prediXcan associations ( $p = 2.3e-04$ ) and BD-I associations ( $p = 0.0012$ ), although the latter does not survive FDR-correction ( $p = 0.069$ ).

# Acknowledgements

Data were generated as part of the CommonMind Consortium supported by funding from Takeda Pharmaceuticals Company Limited, F. Hoffman-La Roche Ltd and NIH grants R01MH085542, R01MH093725, P50MH066392, P50MH080405, R01MH097276, RO1-MH-075916, P50M096891, P50MH084053S1, R37MH057881 and R37MH057881S1, HHSN271201300031C, AG02219, AG05138 and MH06692.

Brain tissue for the study was obtained from the following brain bank collections: the Mount Sinai NIH Brain and Tissue Repository, the University of Pennsylvania Alzheimer's Disease Core Center, the University of Pittsburgh NeuroBioBank and Brain and Tissue Repositories and the NIMH Human Brain Collection Core. CMC Leadership: Pamela Sklar, Joseph Buxbaum (Icahn School of Medicine at Mount Sinai), Bernie Devlin, David Lewis (University of Pittsburgh), Raquel Gur, Chang-Gyu Hahn (University of Pennsylvania), Keisuke Hirai, Hiroyoshi Toyoshiba (Takeda Pharmaceuticals Company Limited), Enrico Domenici, Laurent Essioux (F. Hoffman-La Roche Ltd), Lara Mangravite, Mette Peters (Sage Bionetworks), Thomas Lehner, Barbara Lipska (NIMH).

The iPSYCH-GEMS team would like to acknowledge funding from the Lundbeck Foundation (grant no R102-A9118 and R155-2014-1724), the Stanley Medical Research Institute, an Advanced Grant from the European Research Council (project no: 294838), the Danish Strategic Research Council the Novo Nordisk Foundation for supporting the Danish National Biobank resource, and grants from Aarhus and Copenhagen Universities and University Hospitals, including support to the iSEQ Center, the GenomeDK HPC facility, and the CIRRAU Center.

The Genotype-Tissue Expression (GTEx) Project was supported by the [Common Fund](#) of the Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS. The data used for the analyses described in this manuscript were obtained from the [GTEx Portal](#) on 09/05/16. BrainSpan: Atlas of the Developing Human Brain [Internet]. Funded by ARRA Awards 1RC2MH089921-01, 1RC2MH090047-01, and 1RC2MH089929-01.

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Potential Conflicts of Interest: TW has acted as advisor and lecturer to H. Lundbeck A/S



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749 Sebastian Zollner 134 ; Weihua Guan 135 ; Melissa J Green 136 ; Cynthia Shannon  
750 Weickert 136 ; Thomas W Weickert 136 ; Olav B Smeland 137 ; David Craig 138 ; Janet L Sobell  
751 139 ; Lili Milani 140 ; James L Kennedy 141,142 ; John S Strauss 141 ; Wei Xu 143 ; Katherine  
752 Gordon-Smith 144 ; Sarah V Knott 144 ; Amy Perry 144 ; José Guzman Parra 145 ; Fermin  
753 Mayoral 145 ; Fabio Rivas 145 ; Miquel Casas 146 ; Cristina Sánchez-Mora 146 ; Caroline M  
754 Nievergelt 147 ; Ralph Kupka 148 ; John P Rice 149 ; Jack D Barchas 150 ; Anders D Børglum  
755 11,12 ; Preben Bo Mortensen 151 ; Ole Mors 152 ; Maria Grigoriou-Serbanescu 153 ; Frank  
756 Bellivier 154 ; Bruno Etain 154 ; Marion Leboyer 154 ; Josep Antoni Ramos-Quiroga 40 ; Marta  
757 Ribasés 40 ; Tõnu Esko 25 ; Jordan W Smoller 8 ; Nicholas Craddock 26 ; Ian Jones 26 ; Michael J  
758 Owen 26 ; Marcella Rietschel 43 ; Thomas G Schulze 43 ; John Vincent 46 ; Tõnu Esko 155 ;  
759 Eduard Vieta 156 ; Merete Nordentoft 157 ; Martin Alda 47 ; Hreinn Stefansson 48 ; Kari  
760 Stefansson 48 ; Danielle Posthuma 158,159 ; Ingrid Agartz 160 ; Frank Bellivier 161 ;  
761 Tõnu Esko 52 ; Ketil J Oedegaard 162 ; Eystein Stordal 163 ; Josep Antoni Ramos-Quiroga 54 ;  
762 Marta Ribasés 54 ; Richard M Myers 56 ; René S Kahn 16 ; Frank Bellivier 164 ; Bruno Etain 164 ;  
763 Marion Leboyer 165 ; Bruno Etain 166 ; Anders D Børglum 13 ; Ole Mors 167 ; Thomas Werge  
764 168 ; Qingqin S Li 169 ; Thomas G Schulze 63 ; Fernando Goes 65 ; Ingrid Agartz 14 ; Christina M  
765 Hultman 66 ; Mikael Landén 66 ; Patrick F Sullivan 66,66 ; Cathryn M Lewis 19,170 ; Susan L  
766 McElroy 171 ; Jordan W Smoller 172,173 ; Bertram Müller-Myhsok 69 ; Joanna M Biernacka 174  
767 ; Mark Frye 175 ; Gustavo Turecki 176 ; Guy A Rouleau 177 ; Thomas G Schulze 71 ; Thomas  
768 Werge 178 ; Guy A Rouleau 179 ; Bertram Müller-Myhsok 180 ; Martin Alda 181 ; Francis J  
769 McMahon 182 ; Thomas G Schulze 182 ; Janice M Fullerton 75 ; Peter R Schofield 75 ; Eystein  
770 Stordal 183 ; Gunnar Morken 184 ; Ulrik F Malt 185 ; Ingrid Melle 186 ; Sara A Paciga 187 ;  
771 Nicholas G Martin 89 ; Arne E Vaaler 188 ; Gunnar Morken 189 ; David M Hougaard 190 ; Carlos  
772 Pato 100,191 ; Michele T Pato 100 ; Nicholas G Martin 192 ; Aiden Corvin 103 ; Michael Gill 103  
773 ; René S Kahn 104 ; Rolf Adolfsson 105 ; Josep Antoni Ramos-Quiroga 106 ; Frank Bellivier 193 ;  
774 Bruno Etain 193 ; Marion Leboyer 107 ; Thomas G Schulze 113 ; Bernhard T Baune 194 ; Ketil J  
775 Oedegaard 195 ; Alessandro Serretti 196 ; Markus M Nöthen 5,6 ; Elliot S Gershon 124,197 ;  
776 Thomas Werge 198 ; Andrew M McIntosh 125,199 ; Mikael Landén 200 ; Kari Stefansson 201 ;  
777 Bertram Müller-Myhsok 202 ; Michael Boehnke 132 ; Udo Dannlowski 203 ; Janice M  
778 Fullerton 204 ; Philip B Mitchell 136 ; Peter R Schofield 204 ; Patrick F Sullivan 205,206 ; Ingrid  
779 Agartz 207 ; Ingrid Melle 208 ; Wade H Berrettini 209 ; Vishwajit Nimgaonkar 210 ; Tõnu Esko  
780 140 ; Andres Metspalu 140,211 ; Lisa A Jones 144 ; Josep Antoni Ramos-Quiroga 146 ; Marta  
781 Ribasés 146 ; John Nurnberger 212 ; Naomi R Wray 22,102 ; Arianna Di Florio 26,206 ; Michael C  
782 O'Donovan 26 ; Howard Edenberg 213 ; Roel A Ophoff 104,214 ; Laura J Scott 132 ; Sven Cichon  
783 3,5,92,109 ; Ole A Andreassen 80,137 ; Pamela Sklar 2,16,33,215 ; John Kelsoe 119 ; Jerome  
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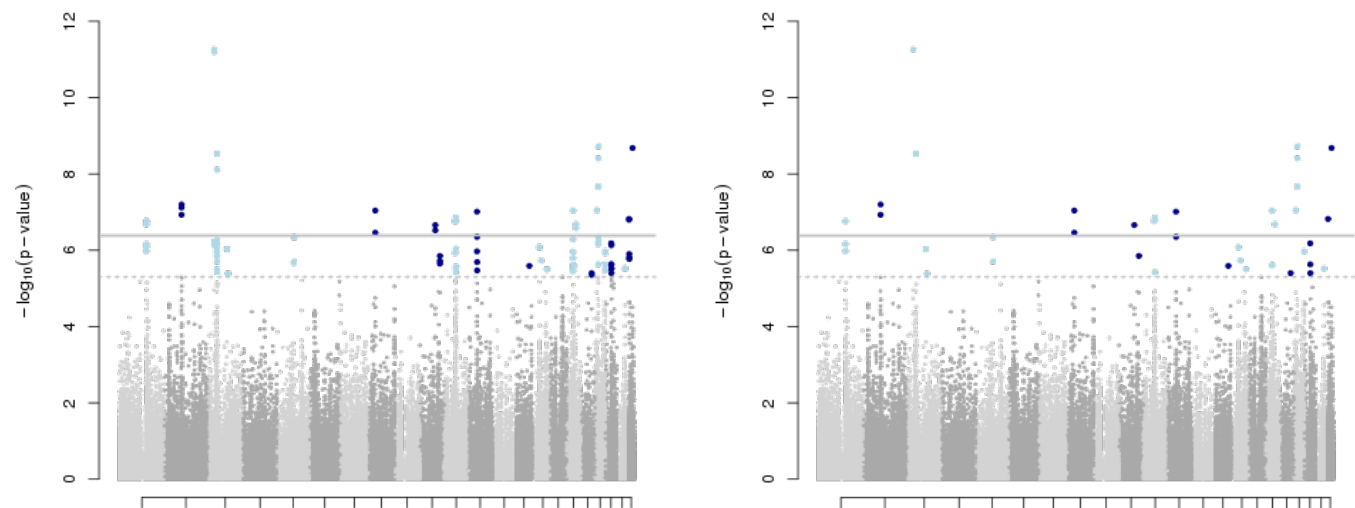
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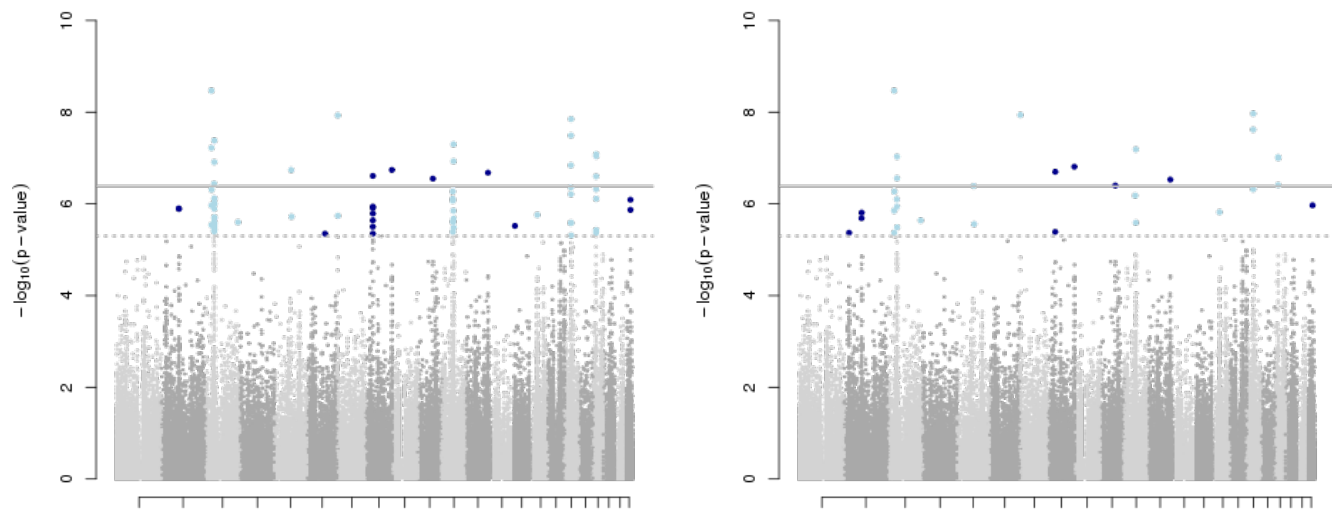
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**Figure 1: Genic associations identified across full Bipolar sample**

- A) 125 gene-tissue associations are identified in the full BPD meta-analysis
- B) FINEMAP analysis identifies 53 independent associations





**Figure 2: Genic associations identified in three bipolar subtypes.**

A) 80 gene-tissue associations are identified in the Bipolar-I sample.

B) FINEMAP and Stepwise conditional analysis identify 37 independent associations

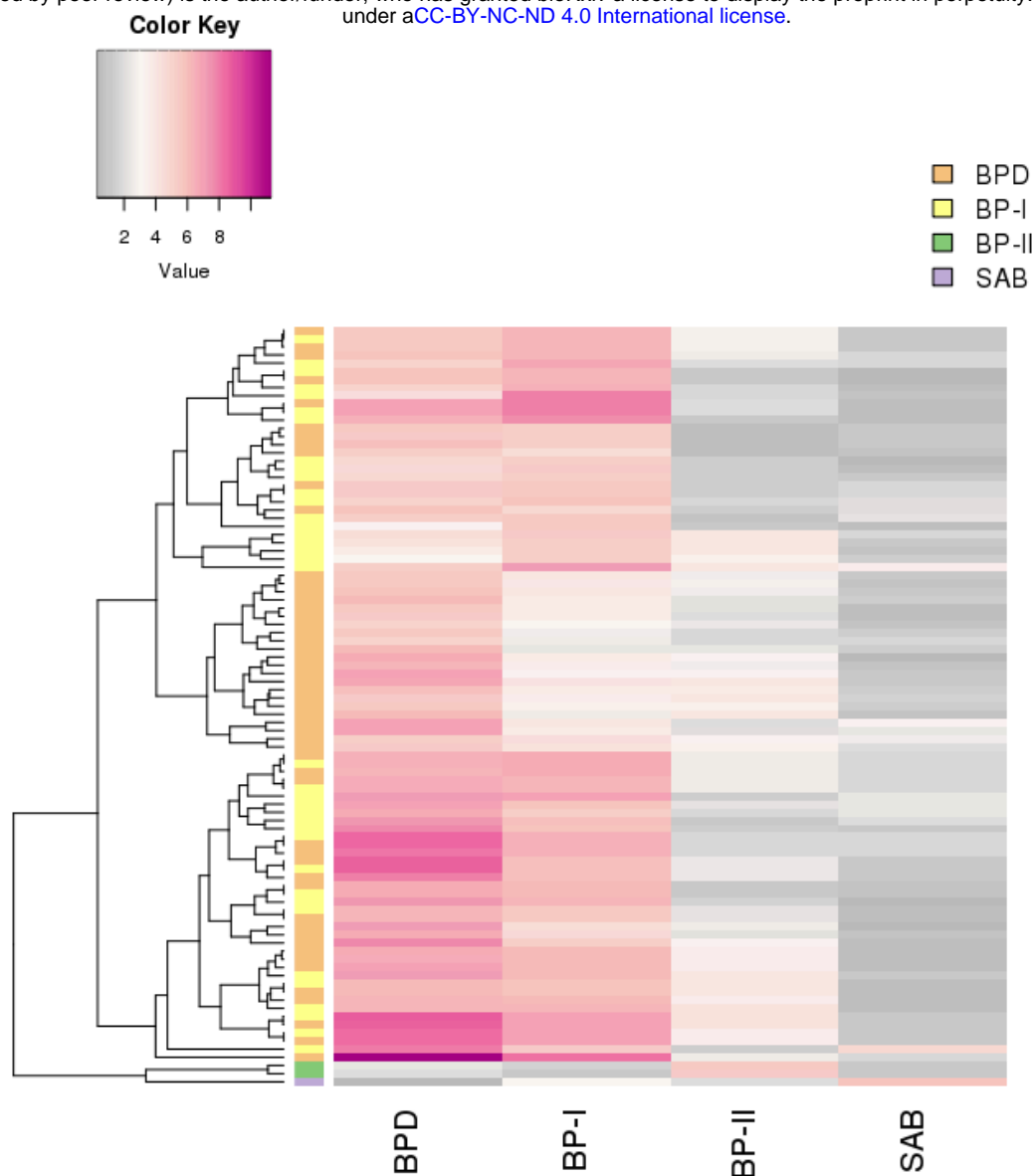
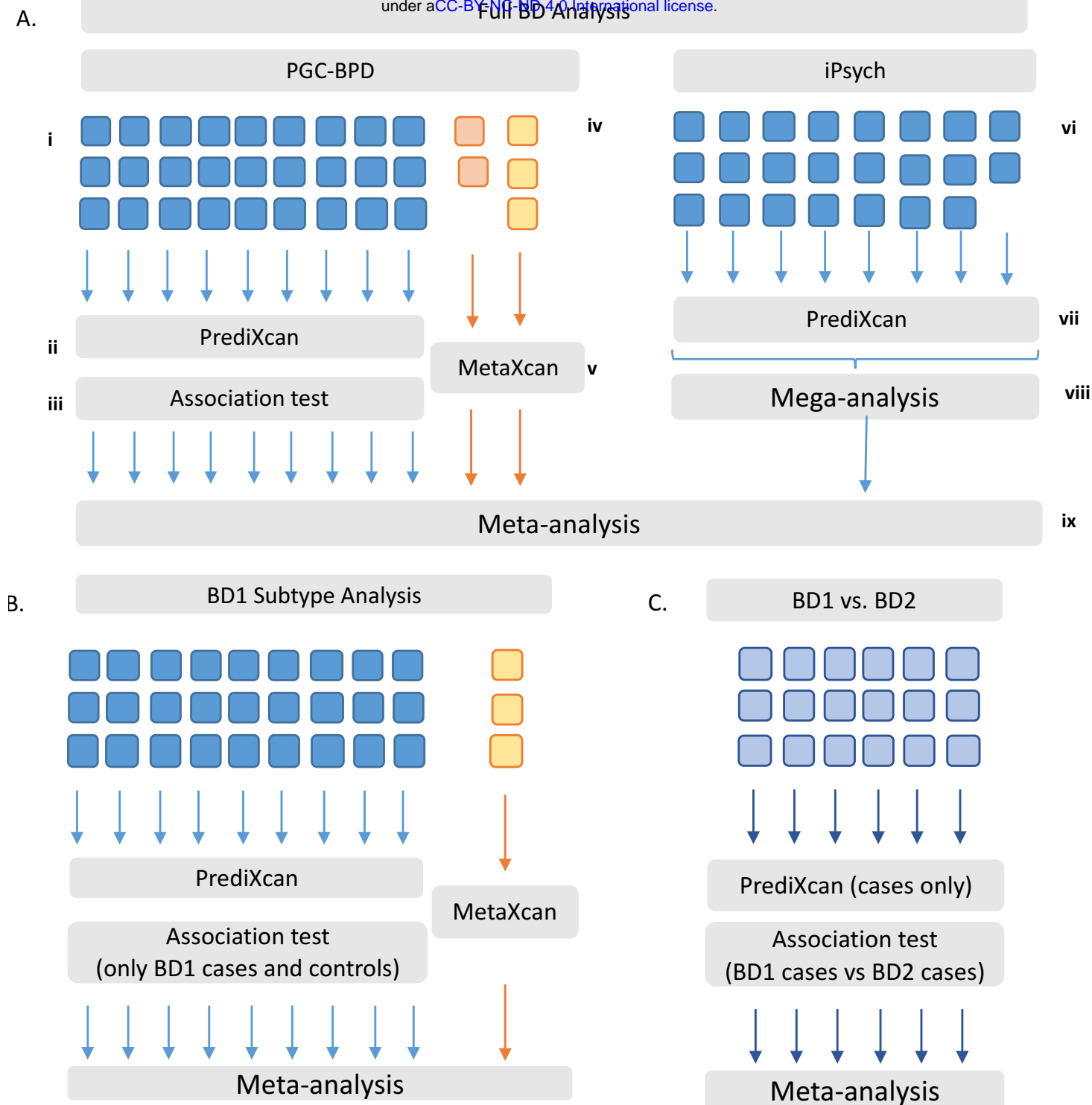


Figure 3: Substantial overlap between BPD and BP-I associated genes.

$-\log_{10}$  p-values are shown for all genes reaching genome-wide significance in any discovery analysis. The row side colour bar indicates the original discovery analysis identifying the gene. The four row values indicate the best p-value achieved by that gene in each subtype analysis.

e.g.: the bottom row shows a gene (*FSIP2*) identified in the SAB subtype analysis, and the best p-value achieved by *FSIP2* across all tissues in the overall BPD analysis, BP-I, BP-II and SAB analyses.

# Full BD Analysis



## Supplementary Figure 1: Analysis outline.

A) Discovery Samples. 27 PGC-SCZ cohorts had available raw genotypes (i). Predicted DLPFC gene expression was calculated in each cohort using prediXcan (ii) and tested for association with case-control status (iii). 5 PGC cohorts (2 trio, 3 case-control) had only summary statistics available (iv). MetaXcan was used to calculate DLPFC associations for each cohort (v). iPsych samples were collected in 23 waves (vi). Predicted DLPFC gene expression was calculated in each wave separately using prediXcan (vii) and merged for association testing. A mega-analysis was run across all 23 waves, using wave membership as a covariate in the regression (viii). Results were meta-analysed across all 32 cohorts and the iPsych MEGA-analysis results (ix). This procedure was repeated for 12 GTEx prediction models.

B) Subtype Analyses. Subtype information was available only for PGC-BD samples. Analysis was carried out in the same way as for the full BD analysis (A), including only BD1 cases.

C) Cross-subtype analysis. Analysis was carried out for cases only, in the same way as A and B.

Table 1: Gene-Tissue Associations results

Gene name	Tissue	CHR	pos1	pos2	BETA	SE	P
DCLK3	DLPFC_preds2	3	36753913	36781352	-0.2047	0.0297	5.49E-12
MCHR1	DLPFC_preds2	22	41074754	41078818	-0.0731	0.0129	1.29E-08
FADS1	DLPFC_preds2	11	61567099	61596790	-0.0549	0.0105	1.68E-07
CDHR1	DLPFC_preds2	10	85954410	85979377	-0.0254	0.0049	2.18E-07
DDHD2	DLPFC_preds2	8	38082736	38133076	-0.1334	0.0257	2.20E-07
TARS2	DLPFC_preds2	1	150459887	150480078	-2.8641	0.5865	1.04E-06
FAM172A	DLPFC_preds2	5	92953775	93447404	-0.2763	0.0581	1.98E-06
EIF1AD	DLPFC_preds2	11	65764016	65769647	-0.1719	0.0372	3.81E-06
HLF	DLPFC_preds2	17	53342373	53402426	-2.4336	0.4688	2.10E-07
ANKRD36	Hypothalamus	2	97779233	97930258	-0.0687	0.0127	6.32E-08
ASIP	Hypothalamus	20	32782375	32857150	-0.2119	0.0426	6.55E-07
RPRD2	Hypothalamus	1	150335567	150449042	-0.164	0.0331	6.96E-07
NCOA6	Hypothalamus	20	33563206	33590240	-0.0272	0.0058	2.33E-06
LPAR2	Cerebellar_Hemisphere	19	19649057	19657468	0.1546	0.0263	3.92E-09
GNL3	Cerebellar_Hemisphere	3	52715172	52728508	0.0267	0.0046	6.68E-09
DDHD2	Cerebellar_Hemisphere	8	38082736	38133076	-0.0914	0.0171	9.04E-08
RP5-1028K7	Cerebellar_Hemisphere	17	38785049	38821393	0.1614	0.0302	9.07E-08
ADD3	Cerebellar_Hemisphere	10	85954410	85979377	0.0217	0.0045	1.42E-06
MCM3AP	Cerebellar_Hemisphere	21	47655047	47706211	-0.1719	0.0368	2.99E-06
KCNN3	Cerebellar_Hemisphere	1	154669931	154842756	-0.0539	0.012	7.17E-06
ZNF80	Cerebellar_Hemisphere	3	113953483	113956425	-0.1061	0.023	4.07E-06
DDHD2	Pituitary	8	38082736	38133076	-0.029	0.0055	1.77E-07
CHDH	Pituitary	3	53846362	53880417	0.1584	0.0354	7.68E-06
PLPP5	Cortex	8	38082736	38133076	-0.0859	0.0169	3.48E-07
MED24	Cortex	17	37894180	37903544	0.0285	0.0061	2.85E-06
CIART	Putamen_Basal_Ganglia	1	150254953	150259505	0.0862	0.0165	1.75E-07
ZNF584	Putamen_Basal_Ganglia	19	58912871	58929694	0.0435	0.0092	2.47E-06
DOCK6	Hippocampus	19	11309971	11373157	0.2862	0.0535	8.87E-08

<b>LEO1</b>	Hippocampus	15	52230222	52264003	-0.1459	0.0306	1.86E-06
<b>PHLPP1</b>	Hippocampus	18	60382672	60647666	-0.0472	0.0102	3.99E-06
<b>CILP2</b>	Nucleus_Accumbens_Basal_Ganglia	19	19303008	19312678	0.0949	0.0158	1.90E-09
<b>AIFM3</b>	Nucleus_Accumbens_Basal_Ganglia	22	21319396	21335649	-0.0914	0.0174	1.50E-07
<b>ZNF584</b>	Nucleus_Accumbens_Basal_Ganglia	19	58912871	58929694	0.0366	0.0075	1.06E-06
<b>MED24</b>	Nucleus_Accumbens_Basal_Ganglia	17	37313147	37323737	0.0383	0.0081	2.44E-06
<b>DDHD2</b>	Caudate_Basal_Ganglia	8	38120648	38126761	-0.0326	0.0064	4.37E-07
<b>UBR1</b>	Caudate_Basal_Ganglia	15	43235095	43398311	-0.1468	0.0298	8.39E-07
<b>CATSPERB</b>	Caudate_Basal_Ganglia	14	92047040	92247051	-0.0343	0.0073	2.60E-06
<b>AC024257.1</b>	Frontal_Cortex_BA9	12	48759919	48761738	0.0693	0.013	9.78E-08
<b>SEMA4C</b>	Frontal_Cortex_BA9	2	97525453	97536494	0.1046	0.0197	1.17E-07
<b>RHEBL1</b>	Frontal_Cortex_BA9	12	49458468	49463808	0.1061	0.021	4.44E-07
<b>CDHR1</b>	Frontal_Cortex_BA9	10	85980254	85985345	-0.036	0.0075	1.87E-06
<b>ZNF584</b>	Frontal_Cortex_BA9	19	58912871	58929694	0.0845	0.0183	3.95E-06
<b>TSSK6</b>	Thyroid	19	19734477	19739739	0.1638	0.0292	2.12E-08
<b>HHLA2</b>	Thyroid	3	108015376	108097132	0.1106	0.0225	9.23E-07
<b>UBE2Q2L</b>	Thyroid	15	84841242	84850986	0.0436	0.0094	3.16E-06
<b>SNTB2</b>	Thyroid	16	69221032	69342955	-0.0265	0.0058	5.16E-06
<b>MCHR1</b>	Anterior_Cingulate_Cortex_BA24	22	41074754	41078818	-0.1785	0.0298	2.10E-09
<b>FAM81B</b>	Anterior_Cingulate_Cortex_BA24	5	94727048	94786158	0.4376	0.0868	4.62E-07
<b>EDEM2</b>	Anterior_Cingulate_Cortex_BA24	20	33284722	33413452	-0.0445	0.0097	4.01E-06
<b>TMEM127</b>	Anterior_Cingulate_Cortex_BA24	2	96914254	96931732	-0.0378	0.0083	5.09E-06
<b>GNL3</b>	Cerebellum	3	52715172	52728508	0.0368	0.0062	2.93E-09
<b>PLPP5</b>	Cerebellum	8	38082736	38133076	-0.0427	0.0085	5.17E-07
<b>ADD3</b>	Cerebellum	10	111756126	111895323	0.0268	0.0057	2.36E-06

Table 2: Replication p-values of genes identified in previous Transcriptome Analysis of BPD

Gene	Tissue	p-value	Direction of Effect
PTPRE	Putamen Basal Ganglia	0.024	-
SPCS1	<b>Caudate Basal Ganglia</b>	<b>0.0011</b>	<b>+</b>
CACNB3	<b>Frontal Cortex BA9</b>	<b>0.0010</b>	-
	Anterior Cingulate Cortex	0.0032	-
	Whole Blood	0.0042	+
	Cerebellum	0.0044	-
	Cerebellar Hemisphere	0.0080	-
	Caudate Basal Ganglia	0.012	-
	DLPFC	0.019	-
	Nucleus Accumbens Basal Ganglia	0.027	-
	Putamen Basal Ganglia	0.077	-

Table 3: Gene-Tissue Associations results for subtype analyses

Analysis	Tissue	Gene	CHR	POS1	POS2	BETA	SE	P
BD-I	Cerebellar Hemisphere	<i>RP5-1028K7.3</i>	17	38785049	38821393	0.1643	0.0287	1.06E-08
BD-I	Thyroid	<i>AC110781.3</i>	7	1878222	1889567	0.2924	0.0512	1.15E-08
BD-I	Caudate Basal Ganglia	<i>MIEN1</i>	17	37884749	37887040	-0.3695	0.0662	2.42E-08
BD-I	Anterior Cingulate Cortex BA24	<i>PACSI1</i>	11	65837834	66012218	0.0583	0.0108	6.45E-08
BD-I	Cerebellum	<i>SFMBT1</i>	3	52937588	53080766	-0.0774	0.0145	9.37E-08
BD-I	Nucleus Accumbens Basal Ganglia	<i>CILP2</i>	19	19649057	19657468	0.08	0.015	9.57E-08
BD-I	Cerebellar Hemisphere	<i>LPAR2</i>	19	19734477	19739739	0.1323	0.0248	1.01E-07
BD-I	Hippocampus	<i>ZC3H3</i>	8	144519825	144623623	-0.1936	0.0369	1.56E-07
BD-I	Cerebellum	<i>PLPP5</i>	8	38120648	38126761	-0.0419	0.0081	2.00E-07
BD-I	Cerebellum	<i>GNL3</i>	3	52715172	52728508	0.0302	0.0059	2.74E-07
BD-I	Putamen Basal Ganglia	<i>CCDC62</i>	12	123258874	123312075	-0.0411	0.008	2.94E-07
BD-I	Nucleus Accumbens Basal Ganglia	<i>HAPLN4</i>	19	19366450	19373605	0.1086	0.0214	3.91E-07
BD-I	DLPFC	<i>CDHR1</i>	10	85954410	85979377	-0.0236	0.0047	3.95E-07
BD-I	DLPFC	<i>FAM172A</i>	5	92953775	93447404	-0.2788	0.0551	4.12E-07
BD-I	Cortex	<i>MED24</i>	17	38175350	38217468	0.0291	0.0058	4.77E-07
BD-I	Putamen Basal Ganglia	<i>ITGA9</i>	3	37493606	37865005	-0.2048	0.0408	5.35E-07
BD-I	Putamen Basal Ganglia	<i>FADS1</i>	11	61567099	61596790	-0.0383	0.0077	6.62E-07
BD-I	Hypothalamus	<i>DUSP7</i>	3	52082935	52090566	0.0505	0.0102	7.98E-07
BD-I	Anterior Cingulate Cortex BA25	<i>MCHR1</i>	22	41074754	41078818	-0.1379	0.0282	1.06E-06
BD-I	Thyroid	<i>NEK4</i>	3	52744800	52804965	0.0305	0.0063	1.15E-06
BD-I	DLPFC	<i>TRANK1</i>	3	36868311	36986548	-0.0637	0.0132	1.42E-06
BD-I	Caudate Basal Ganglia	<i>UBR1</i>	15	43235095	43398311	-0.1353	0.0281	1.50E-06
BD-I	Cortex	<i>ACTR1B</i>	2	98272431	98280570	-0.0339	0.0071	1.54E-06
BD-I	Anterior Cingulate Cortex BA26	<i>ANKRD23</i>	2	97490263	97523671	0.0864	0.0182	2.03E-06
BD-I	Thyroid	<i>IGF2BP2-AS1</i>	3	185430316	185447575	-0.0772	0.0164	2.28E-06
BD-I	DLPFC	<i>EIF1AD</i>	11	65764016	65769647	-0.166	0.0353	2.55E-06
BD-I	Anterior Cingulate Cortex BA27	<i>FAM81B</i>	5	94727048	94786158	0.3838	0.0818	2.73E-06
BD-I	Caudate Basal Ganglia	<i>RFT1</i>	3	53122499	53164478	0.0333	0.0072	3.27E-06



BD-I	Nucleus Accumbens Basal Ganglia	<i>BRF2</i>	8	37700786	37707422	0.0299	0.0065	4.05E-06
BD-I	Thyroid	<i>GCKR</i>	2	27719709	27746554	-0.0349	0.0076	4.25E-06
BD-I	DLPFC	<i>MLH1</i>	3	37034823	37107380	2.1685	0.4718	4.30E-06
BD-I	Anterior Cingulate Cortex BA28	<i>LYZL4</i>	3	42438570	42452092	-0.0219	0.0048	5.24E-06
BD-I	Anterior Cingulate Cortex BA29	<i>CYP1A2</i>	15	75041185	75048543	0.0832	0.0184	6.04E-06
BD-I	Nucleus Accumbens Basal Ganglia	<i>CA1</i>	8	86239837	86291243	-0.1265	0.028	6.20E-06
BD-I	DLPFC	<i>ASCC3</i>	6	100956070	101329248	0.0854	0.0189	6.48E-06
BD-I	Nucleus Accumbens Basal Ganglia	<i>WWP2</i>	16	69796209	69975644	0.0579	0.0128	6.66E-06
BD-I	Nucleus Accumbens Basal Ganglia	<i>GLYCTK</i>	3	52321105	52329272	0.1337	0.0297	6.80E-06
BD-II	DLPFC	<i>NUP98</i>	11	3692313	3819022	9.9344	2.0969	2.16E-06
BD-II	Putamen Basal Ganglia	<i>COLGALT2</i>	1	183898796	184006863	-0.0206	0.0044	3.50E-06
BD-II	Hippocampus	<i>COLGALT2</i>	1	183898796	184006863	-0.0234	0.0052	7.55E-06
BD-II	Caudate Basal Ganglia	<i>COLGALT2</i>	1	183898796	184006863	-0.0238	0.0055	1.44E-05
BD-II	Nucleus Accumbens Basal Ganglia	<i>COLGALT2</i>	1	183898796	184006863	-0.0221	0.0056	8.92E-05
SAB	Pituitary	<i>FS/P2</i>	2	186603355	186698017	0.0001	0	1.86E-06
SAB	Cerebellar Hemisphere	<i>ALDH1B1</i>	9	38392661	38398658	0.1521	0.0342	8.55E-06

Table 4: Endophenotype-wide association study (enPHEWAS). All genes reaching tissue-wide significance in any subphenotype-based analysis were included.

Gene	Tissue	enPHEWAS Analysis					Subtype-specific meta-analysis				
		Endophenotype	beta	se	p	OR	Subtype	beta	se	p	OR
<i>EIF1AD</i>	DLPFC	mixedstates	-0.3873	0.1252	1.97E-03	0.68	BD-I	-0.166	0.0353	2.55E-06	0.85
<i>EIF1AD</i>	DLPFC	panic.attacks	-0.2861	0.0821	4.95E-04	0.75	BD-I	-0.166	0.0353	2.55E-06	0.85
<i>FAM172A</i>	DLPFC	bp2	0.127	0.0393	1.24E-03	1.14	BD-I	-0.2788	0.0551	4.12E-07	0.76
<i>FSIP2</i>	Pituitary	<i>famhistory</i>	-0.0009	0.0002	1.09E-05	1.00	SAB	0.0001	0	1.86E-06	1.00

Table 5: Pathway Results

Association statistics	Analysis type	SET	NGENES	COMP P	FDR
BPD	Drug targets	ANABOLIC STEROIDS	34	4.02E-06	0.001
BPD	Drug targets	CORTICOSTEROIDS FOR SYSTEMIC USE PLAIN	43	8.84E-05	0.013
BPD	Drug targets	ANDROGENS	47	1.72E-04	0.025
BPD	Drug targets	ANTIFUNGALS FOR TOPICAL USE	92	4.48E-04	0.064
BPD	Hypothesis driven	MORNING	109	3.27E-05	0.003
BPD	Hypothesis driven	HIGH	2718	1.08E-03	0.029
BPD	Hypothesis driven	SCZ-NS	567	1.29E-03	0.029
BPD	Hypothesis driven	FMRP-targets	735	1.47E-03	0.029
BPD	Hypothesis driven	Pre-synaptic active zone	156	4.20E-03	0.066
BPD	Hypothesis driven	Circadian clock genes	380	1.21E-02	0.159
BPD	Hypothesis driven	CLOCK-MODULATORS	254	2.32E-02	0.262
BPD	Hypothesis driven	PSD-95 (core)	56	3.52E-02	0.348
BPD	Hypothesis driven	ID-LoF	26	4.34E-02	0.381
BPD	Hypothesis driven	ARC+NMDAR+PSD95+mGluR5	122	5.45E-02	0.416
BPD	Hypothesis driven	SCZ-LoF	79	5.79E-02	0.416
BPD	Hypothesis driven	Cav2::kinases & phosph...	20	8.99E-02	0.504
BPD	Hypothesis driven	ID-NS	116	9.92E-02	0.504
BD-I	Agnostic	S-adenosylmethionine-dependent methyltransfe	91	3.76E-08	0.000
BD-I	Agnostic	mitochondrial nucleoid	33	5.64E-07	0.001
BD-I	Agnostic	nucleoid	34	8.11E-07	0.001
BD-I	Agnostic	RNA methylation	27	9.35E-07	0.001
BD-I	Agnostic	N-methyltransferase activity	59	9.64E-07	0.001
BD-I	Agnostic	RNA methyltransferase activity	26	9.73E-07	0.001
BD-I	Agnostic	regulation of transcription from RNA polymerase	16	5.25E-06	0.006
BD-I	Agnostic	impaired wound healing	25	8.91E-06	0.010

BD-I	Agnostic	Downregulation of ERBB2:ERBB3 signaling	13	2.53E-05	0.020
BD-I	Agnostic	extracellular regulation of signal transduction	15	2.55E-05	0.020
BD-I	Agnostic	extracellular negative regulation of signal transd	15	2.55E-05	0.020
BD-I	Agnostic	abnormal cellular respiration	66	2.92E-05	0.021
BD-I	Agnostic	male meiosis	32	3.91E-05	0.026
BD-I	Agnostic	Fanconi Anemia pathway	21	5.83E-05	0.036
BD-I	Agnostic	Golgi-associated vesicle	56	7.65E-05	0.043
BD-I	Agnostic	regulation of T cell migration	13	8.00E-05	0.043
BD-I	Agnostic	positive regulation of T cell migration	11	1.01E-04	0.051
BD-I	Agnostic	failure of tooth eruption	16	1.34E-04	0.064
BD-I	Agnostic	viral assembly	29	1.43E-04	0.064
BD-I	Agnostic	macromolecule methylation	138	1.61E-04	0.066
BD-I	Agnostic	viral infectious cycle	121	1.67E-04	0.066
BD-I	Agnostic	negative regulation by host of viral transcription	12	1.69E-04	0.066
BD-I	Agnostic	skeletal muscle contraction	16	1.93E-04	0.072
BD-I	Agnostic	toxin metabolic process	10	2.77E-04	0.096
BD-I	Agnostic	granulomatous inflammation	24	2.79E-04	0.096
BD-I	Hypothesis driven	Endoplasmic Reticulum (core)	87	2.04E-04	0.036
BD-I	Hypothesis driven	PSD (human core)	624	5.16E-04	0.046
BD-I	Hypothesis driven	MORNING	109	1.16E-03	0.069
BD-II	Agnostic	S-adenosylmethionine-dependent methyltransfe	91	3.46E-07	0.003
BD-II	Agnostic	negative regulation of systemic arterial blood pr	11	2.09E-06	0.009
BD-II	Agnostic	Metabolism of porphyrins	15	4.92E-06	0.014
BD-II	Agnostic	RNA polymerase activity	37	9.47E-06	0.016
BD-II	Agnostic	DNA-directed RNA polymerase activity	37	9.47E-06	0.016
BD-II	Agnostic	Endogenous sterols	15	1.83E-05	0.026
BD-II	Agnostic	Heme biosynthesis	12	2.38E-05	0.027
BD-II	Agnostic	protein methyltransferase activity	58	2.54E-05	0.027
BD-II	Agnostic	condensed chromosome	145	4.07E-05	0.032

BD-II	Agnostic	mitochondrial genome maintenance	12	4.08E-05	0.032
BD-II	Agnostic	nuclear envelope organization	52	4.46E-05	0.032
BD-II	Agnostic	centrosome localization	12	5.04E-05	0.032
BD-II	Agnostic	abnormal nucleotide metabolism	10	5.28E-05	0.032
BD-II	Agnostic	chondroitin sulfate metabolic process	50	5.28E-05	0.032
BD-II	Agnostic	heme metabolic process	29	6.75E-05	0.038
BD-II	Agnostic	porphyrin-containing compound metabolic process	38	7.74E-05	0.038
BD-II	Agnostic	protoporphyrinogen IX metabolic process	10	7.83E-05	0.038
BD-II	Agnostic	chondroitin sulfate biosynthetic process	23	9.52E-05	0.038
BD-II	Agnostic	abnormal spinal cord morphology	193	9.60E-05	0.038
BD-II	Agnostic	Heme biosynthesis	10	9.78E-05	0.038
BD-II	Agnostic	N-methyltransferase activity	59	1.01E-04	0.038
BD-II	Agnostic	chondroitin sulfate proteoglycan metabolic process	52	1.07E-04	0.038
BD-II	Agnostic	abnormal neuronal migration	75	1.09E-04	0.038
BD-II	Agnostic	nucleotidyltransferase activity	106	1.10E-04	0.038
BD-II	Agnostic	Chondroitin sulfate	43	1.12E-04	0.038
BD-II	Agnostic	nucleoside kinase activity	11	1.14E-04	0.038
BD-II	Agnostic	KEGG PYRIMIDINE METABOLISM	90	1.50E-04	0.048
BD-II	Agnostic	oxidoreductase activity	11	1.56E-04	0.048
BD-II	Agnostic	Transport of Mature mRNA Derived from an Intr	34	1.94E-04	0.057
BD-II	Agnostic	nucleoside salvage	12	2.06E-04	0.059
BD-II	Agnostic	neuron spine	69	2.47E-04	0.068
BD-II	Agnostic	protein methylation	82	2.71E-04	0.070
BD-II	Agnostic	protein alkylation	82	2.71E-04	0.070
BD-II	Agnostic	dendritic spine	67	2.83E-04	0.071
BD-II	Agnostic	chondroitin sulfate proteoglycan biosynthetic process	26	2.95E-04	0.072
BD-II	Agnostic	RNA splicing	179	3.66E-04	0.085
BD-II	Agnostic	mRNA splicing	179	3.66E-04	0.085
BD-II	Agnostic	abnormal mitochondrion morphology	55	3.89E-04	0.088

BD-II	Drug targets	THYROID PREPARATIONS	11	1.65E-09	0.000
SAB	Agnostic	laminin complex	10	6.64E-08	0.001
SAB	Agnostic	abnormal miniature endplate potential	21	1.54E-07	0.001
SAB	Agnostic	ab6b1 ab6b4 integrin pathway	46	1.78E-07	0.001
SAB	Agnostic	Schwann cell development	20	2.59E-07	0.001
SAB	Agnostic	astrocyte development	12	3.19E-07	0.001
SAB	Agnostic	abnormal amacrine cell number	11	4.32E-07	0.001
SAB	Agnostic	glomerular basement membrane development	10	8.59E-07	0.001
SAB	Agnostic	cellular amide metabolic process	138	1.05E-06	0.001
SAB	Agnostic	abnormal PNS synaptic transmission	28	1.92E-06	0.002
SAB	Agnostic	short photoreceptor inner segment	13	2.74E-06	0.002
SAB	Agnostic	renal filtration cell differentiation	13	3.54E-06	0.003
SAB	Agnostic	glomerular visceral epithelial cell differentiation	13	3.54E-06	0.003
SAB	Agnostic	abnormal photoreceptor inner segment morpho	33	4.01E-06	0.003
SAB	Agnostic	Schwann cell differentiation	26	4.70E-06	0.003
SAB	Agnostic	axon regeneration	15	4.71E-06	0.003
SAB	Agnostic	abnormal Muller cell morphology	10	5.16E-06	0.003
SAB	Agnostic	glomerular epithelium development	14	6.23E-06	0.003
SAB	Agnostic	glomerular epithelial cell differentiation	14	6.23E-06	0.003
SAB	Agnostic	myofilament	17	9.13E-06	0.004
SAB	Agnostic	striated muscle thin filament	14	1.28E-05	0.005
SAB	Agnostic	mitochondrion localization	17	2.53E-05	0.010
SAB	Agnostic	abnormal retinal apoptosis	31	2.79E-05	0.011
SAB	Agnostic	neuron projection regeneration	21	3.25E-05	0.012
SAB	Agnostic	abnormal amacrine cell morphology	19	3.37E-05	0.012
SAB	Agnostic	neuromuscular junction development	33	5.04E-05	0.017
SAB	Agnostic	integral to lumenal side of endoplasmic reticular	24	5.87E-05	0.019
SAB	Agnostic	endoplasmic reticulum-Golgi intermediate comp	24	8.57E-05	0.027
SAB	Agnostic	negative regulation of ion transmembrane trans	11	9.33E-05	0.029

SAB	Agnostic	biotin metabolic process	10	1.06E-04	0.030
SAB	Agnostic	Biotin transport and metabolism	10	1.06E-04	0.030
SAB	Agnostic	Methylation	10	1.18E-04	0.033
SAB	Agnostic	abnormal retinal rod cell morphology	36	1.30E-04	0.035
SAB	Agnostic	cell differentiation involved in metanephros dev	11	1.33E-04	0.035
SAB	Agnostic	secondary metabolic process	68	1.52E-04	0.038
SAB	Agnostic	branched-chain amino acid catabolic process	18	1.76E-04	0.042
SAB	Agnostic	negative regulation of transmembrane transport	13	1.78E-04	0.042
SAB	Agnostic	metanephric glomerulus development	10	2.27E-04	0.052
SAB	Agnostic	regulation of DNA-dependent transcription in re:	41	2.32E-04	0.052
SAB	Agnostic	branched-chain amino acid metabolic process	22	2.42E-04	0.053
SAB	Agnostic	tropomyosin binding	14	2.74E-04	0.058
SAB	Agnostic	positive regulation of receptor biosynthetic proc	10	2.85E-04	0.058
SAB	Agnostic	cellular amino acid biosynthetic process	97	2.95E-04	0.058
SAB	Agnostic	skeletal muscle fiber development	44	3.04E-04	0.058
SAB	Agnostic	Branched-chain amino acid catabolism	16	3.07E-04	0.058
SAB	Agnostic	KEGG TOXOPLASMOSIS	110	3.07E-04	0.058
SAB	Agnostic	negative regulation of GTPase activity	15	3.29E-04	0.061
SAB	Agnostic	BIOCARTA ERK5 PATHWAY	17	3.35E-04	0.061
SAB	Agnostic	decreased cellular sensitivity to gamma-irradiati	18	3.48E-04	0.061
SAB	Agnostic	astrocyte differentiation	23	3.50E-04	0.061
SAB	Agnostic	positive regulation of glucose import	27	3.82E-04	0.065
SAB	Agnostic	photoreceptor connecting cilium	21	3.96E-04	0.066
SAB	Agnostic	short photoreceptor outer segment	27	4.03E-04	0.066
SAB	Agnostic	14-3-3 protein binding	16	4.51E-04	0.073
SAB	Agnostic	protein phosphatase 2A binding	16	4.98E-04	0.079
SAB	Agnostic	fatty acid derivative metabolic process	74	5.28E-04	0.081
SAB	Agnostic	icosanoid metabolic process	74	5.28E-04	0.081
SAB	Agnostic	KEGG GLYCOSYLPHOSPHATIDYLINOSITOL(GPI)-A	23	5.41E-04	0.081



SAB	Agnostic	KEGG HISTIDINE METABOLISM	24	5.54E-04	0.082
SAB	Agnostic	abnormal physiological response to xenobiotic	402	5.91E-04	0.085
SAB	Agnostic	regulation of stress-activated MAPK cascade	140	5.94E-04	0.085
SAB	Agnostic	Metabolism of amino acids and derivatives	171	6.39E-04	0.089
SAB	Agnostic	epithelial cell differentiation involved in kidney c	20	6.46E-04	0.089
SAB	Agnostic	regulation of stress-activated protein kinase sign	141	7.20E-04	0.098
SAB	Hypothesis driven	MORNING	109	2.29E-04	0.018
SAB	Hypothesis driven	LOW	8153	2.53E-04	0.018
SAB	Hypothesis driven	Mitochondrion_(core)	174	2.94E-04	0.018
SAB	Hypothesis driven	ID-NS	116	5.62E-04	0.025