

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

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59

60 **Abstract**

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

70

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

77

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

87

88 **Introduction**

89 Bipolar disorder (BPD) is a serious episodic neuropsychiatric disorder presenting with extreme
90 elation, or mania, and severe depressive states¹. In tandem, individuals with bipolar often
91 experience disturbances in thinking and behavior, as well as psychotic features such as
92 delusions and hallucinations¹. Estimates of the prevalence of BPD within the general population
93 range from 0.5-1.5%^{1,2}. Bipolar disorder is highly heritable, with siblings of probands at an 8-
94 fold increased risk of the disorder^{1,2}, and twin studies producing strikingly high estimates of
95 heritability, around 89-93%^{1,3,4}. More recently, genetic studies of BPD have indicated SNP
96 heritability estimates of 17-23%⁵.

97

98 Bipolar disorder encompasses diagnostically distinct subtypes; bipolar disorder type I (BD-I),
99 characterized by full manic episodes, and bipolar disorder type II (BD-II), which includes both
100 hypomania and recurrent depressive episodes^{1,6,7}. Individuals with diagnostic features of both
101 bipolar disorder and schizophrenia may additionally be diagnosed with schizoaffective disorder
102 (SAB)⁷. Recent studies have indicated that these diagnostic distinctions may be borne out
103 genetically; for example, BD-I is significantly more heritable than BD-II^{5,8}, and there are distinct
104 differences between polygenic risk profiles of individuals with BD-I compared to BD-II^{6,8}. These
105 diagnostic and genetic heterogeneities within bipolar disorder contribute to the complexity in
106 identifying genetic associations with bipolar disorder. Additional complications arise due to the
107 complex polygenic nature of the disorder, and the high degree of overlap, both diagnostically
108 and genetically, with other psychiatric disorders such as Schizophrenia and Major Depressive
109 Disorder⁹⁻¹¹.

110

111 Global collaborative efforts over the last decade have enabled large collections of samples from
112 individuals with BPD. Genome-wide associations studies (GWAS) of these collections have
113 identified multiple BPD-associated loci throughout the genome^{6,12-25}, most recently 30 novel
114 loci identified in the PGC-BD GWAS⁵. Despite these advances in locus discovery, little is
115 understood about the pathogenesis of bipolar disorder. It is likely that, in line with other
116 psychiatric disorders, larger sample sizes will be required in order to identify additional risk

117 loci²⁶. However, even elegantly designed and well-powered GWAS studies will not necessarily
118 identify biological mechanisms contributing to disease, as large lists of genomic loci may be
119 uninformative, and require careful dissection and downstream analyses to identify truly
120 disease-causing associations²⁷.

121
122 Transcriptomic Imputation (TI) analyses offer an opportunity to probe gene expression on a
123 large scale, using eQTL reference panel-derived prediction models^{28,29}. These approaches have
124 several attractive advantages to researchers studying genetics of complex traits. First, results
125 are readily biologically interpretable. Second, the large scale of GWAS studies means that TI
126 studies are powered to detect even modest changes in gene expression, which likely represent
127 a large portion of the risk in psychiatric disorders^{30,31}, and which cannot be identified with
128 traditional transcriptome approaches. Third, the use of genetically-regulated gene expression
129 ensures that any associations precede symptom onset, rather than being mediated by disease
130 status²⁸.

131
132 In this study, we present the largest analysis of transcriptomic imputation in Bipolar Disorder.
133 Our analysis included individuals from the most recent PGC-BD GWAS⁵ (19,986 cases/30,992
134 controls), as well as individuals from the iPSYCH consortium (1,502 cases/23,311 controls). We
135 calculated predicted genetically regulated gene expression (GREX) for ~20,000 genes across 13
136 brain regions, using prediction models derived from GTEX^{28,32} and CommonMind Consortium
137 data^{31,33}. We sought to identify associations between GREX and a diagnosis of bipolar disorder,
138 or one of three bipolar subtypes (BD-I, BD-II, SAB). We identified 125 significant gene-tissue
139 associations with BPD, constituting 53 independent associations. Of these, 29 gene-tissue
140 associations were novel; i.e., they did not lie within 1MB of a locus identified in the recent PGC-
141 BD GWAS⁵. Additionally, we identified 80 gene-tissue associations with BD-I (37 independent
142 associations, of which 12 were novel), two gene-tissue associations with BD-II (both novel), and
143 one gene-tissue association with SAB. Our associations were highly consistent with differential
144 gene expression analyses of bipolar cases and controls in the CommonMind Consortium. We
145 expound upon these results using a number of analyses, including gene set enrichment

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

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150

151 **Methods**

152

153 **Samples**

154 Genotype data were obtained from the Psychiatric Genomics Consortium Bipolar Disorder
155 (PGC-BD) collection. These data included 19,986 cases and 30,992 ancestry-matched controls
156 from the PGC-BD collection⁵. Three of these cohorts were available through summary statistics
157 only (Supplementary Figure 1). 1,502 BPD cases and 23,311 matched controls were additionally
158 analysed by collaborators at iPSYCH (supplementary information).

159

160 In order to be included in the study, cases were required to meet international diagnostic
161 criteria for BPD (ie, DSM-IV, ICD-9, ICD-10), or to have a lifetime diagnosis of BPD according to
162 structured diagnostic instruments⁵. Genotyping information for these samples can be found in
163 the flagship papers describing the initial sample collection⁵, and were processed in a
164 standardized manner using “ricopili”⁵.

165

166 The PGC-BD collection included 14,938 individuals with BD-I, 3,543 individuals with BD-II, and
167 1,500 individuals with SAB. No subtype data were available for individuals collected through
168 iPSYCH.

169

170 **Transcriptomic Imputation**

171 We imputed genetically regulated gene expression (GREX) using the CommonMind Consortium
172 (CMC) derived Dorso-lateral pre-frontal cortex (DLPFC) predictor model³³, and GTEx-derived
173 brain tissue prediction models^{28,32}. We imputed GREX in all cohorts for which we had access to
174 raw data using PrediXcan²⁸ (Suppl. Figure 1).

175

176 For three cohorts, raw genotype data was not available. For these cohorts, and two cohorts
177 with a trio structure, genic associations were computed using summary statistics, using
178 MetaXcan³⁷, a summary-statistic approach analogous to prediXcan²⁸. Previous studies have
179 shown that genic association p-values and effect sizes calculated using MetaXcan and PrediXcan

180 are highly correlated, provided that ethnically matched reference panels are used^{33,37}. This was
181 confirmed using three European PGC BD cohorts for which both summary statistics and raw
182 genotype data were available.

183

184 **iPsych-Gems Analysis**

185 iPSYCH-GEMS GWAS data was genotyped and imputed in 23 waves, and subsequently merged
186 for association analyses. No subtype data were available for iPSYCH-GEMS data. Variants with
187 imputation scores>0.8 were included for the analysis. Genetically regulated gene expression
188 levels were calculated using the CMC DLPFC predictor model³³, as well as 12 GTEx-derived brain
189 tissue databases^{28,32}. Association tests on case-control status were carried out using a logistic
190 regression in R, including wave membership as covariate.

191

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

197

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

199 The association analysis was done using R software.

200

201 **Association Tests**

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

207

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

211

212 Raw genotype-based and summary-statistics based cohorts were meta-analysed using an odds-
213 ratio based approach in METAL³⁸.

214

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

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

221

222 **Identifying independent associations**

223 We identified 18 regions with multiple gene-tissue associations; regions were defined based on
224 distance between genes, and were checked using visual inspection of associations across each
225 chromosome. For each of these regions, we applied FINEMAP³⁹ to identify independently
226 associated genes. We substituted the LD-matrix usually used in FINEMAP with an analogous
227 GREX correlation matrix.

228

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

234

Equation 1: Effective Sample Size

235

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

236 **Identifying genes associated with specific behaviours and clinical variables**

237 We obtained data on 26 clinical variables relating to BPD, including for example rapid cycling,
238 psychosis, panic attacks, and a variety of comorbid disorders. We used an approach analogous
239 to PHEWAS, and an adaptation to the PHEWAS R package⁴⁰, to test for associations between
240 BD-I, BD-II and SAB-associated genes and these 26 endophenotypes.

241

242 Behavioural data was available for ~8,500 individuals, across 14 cohorts. We tested for
243 association between GREX and all 26 endophenotypes in each cohort separately, controlling for
244 ten principal components. Only endophenotypes with at least 20 cases, or 20 quantitative
245 measures, were included within each cohort. Results were meta-analyzed across cohorts using
246 an odds-ratio based approach in METAL⁴¹.

247

248 **Comparison with Differential Expression in CommonMind Consortium**

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

254

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

262

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

266

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

272

273 **Pathway Analysis**

274 Pathway analysis was carried out using an adaptation to MAGMA⁴². We performed three
275 pathway analyses, as follows: 1) 174 drug-target gene sets; 2) 76 gene sets with prior evidence
276 of involvement in BD^{31,43–45}, including nervous-systems related pathways, gene sets relating to
277 aberrant behavior in mice, circadian clock gene sets, calcium-gated voltage channels, as well as
278 targets of FMRP; 3) ~8,500 pathways collated across six large publicly available datasets^{46–53}.
279 We included only gene sets with at least 10 genes.

280

281 For each of the four iterations, we analyzed BIP, BD-I, BD-II and SAB results separately. Analyses
282 were carried out using genic p-values from our PrediXcan meta-analyses. In instances where a
283 gene had multiple associations across different tissues, the best p-value was selected, and a
284 Bonferroni correction applied to correct for the number of tissues tested. Gene-set enrichment
285 results from the competitive (rather than self-contained) MAGMA analysis were used⁴², and
286 FDR correction applied within each stratum of our analysis.

287

288

289 **Results**

290 **Association Tests**

291 We calculated predicted gene expression for thirteen brain regions (derived from CMC and
292 GTEx data^{28,32,54,55}) in 19,986 cases and 30,992 controls from the PGC-BPD⁵ and 1,502 cases and
293 23,311 controls from the iPsych-GEMS consortium, and tested for association between
294 predicted gene expression (GREX) and case-control status. Additionally, we used a summary-
295 statistic based method to calculate genic associations in cases and controls for which raw
296 genotypes were not available (Suppl. Figure 1A).

297

298 We identified 125 genes-tissue associations reaching tissue-specific significance (Suppl. Table 2;
299 Figure 1A; ~5e-06); 46/125 reached our stricter cross-tissue threshold (4.11e-07). Within these
300 associations, we identified 18 genomic regions with multiple associated genes, and where the
301 same gene was associated across multiple tissues. We applied FINEMAP to each of these
302 regions, and identified 53 independent associations (Table 1; Figure 1B), of which 29 are novel
303 (i.e., they do not lie within 1Mb of a locus identified in the recent PGC-BD GWAS⁵). It should be
304 noted that our sample includes all of the PGC-BD samples as well as an additional cohort, and
305 so will have greater power to detect signals than the original GWAS.

306

307 **Comparison to previous transcriptome studies**

308 Two previous studies have already identified BPD-associated genes using transcriptomic
309 approaches, albeit using substantially smaller samples^{28,34}. We sought to replicate these
310 findings using the subset of our data not included in the original PGC-BD GWAS⁵ (Table 2).

311

312 One gene, *PTPRE*, was identified as associated with Bipolar Disorder in the original prediXcan-
313 based Transcriptomic Imputation analysis. Two genes, *SPCS1* and *CACNB3*, were identified using
314 the SMR method³⁴, which used eQTLs from peripheral blood. *PTPRE* reaches nominal
315 significance in the putamen basal ganglia in our replication sample ($p=0.024$). Both *SPCS1* and
316 *CACNB3* were significant in our replication sample (after Bonferroni correction); *SPCS1* in the
317 caudate basal ganglia ($p=0.0011$), and *CACNB3* in the frontal cortex ($p=0.0010$). Additionally,

318 *CACNB3* reaches nominal significance in seven other tissues. This level of replication is highly
319 unlikely to occur by chance (binomial test: $p=1.59\times10^{-7}$ at nominal significance threshold,
320 $p=0.0012$ at Bonferroni-corrected threshold).

321

322 **Subtypes**

323 Bipolar disorder subtypes BD-I, BD-II and SAB have previously been shown to be diagnostically
324 and genetically distinct⁶. We tested for association of GREX with case-control status for each of
325 these three subtypes, using all available matched controls; BD-I (14,983 cases/controls), BD-II
326 (3,543/22,155) and SAB (1,500/8,690).

327

328 We identified 80 BD-I gene-tissue associations reaching tissue-specific genome-wide
329 significance ($\sim6\times10^{-6}$; Suppl. Table 3), constituting 37 independent associations following
330 FINEMAP (Table 3; Figure 2A). 12 gene-tissue associations across 10 regions were novel, i.e., did
331 not lie within 1Mb of a BD-I locus identified in the PGC-BD GWAS⁵. In line with our overall BPD
332 analysis, the largest number of associations occur in the cortex and pre-frontal cortex (14
333 associations) and the limbic system (14 associations).

334

335 Two genes were associated with BD-II subtype, albeit not at the stricter cross-tissue significance
336 threshold (Table 3). First, increased expression *NUP98* in the DLPFC was associated with BD-II
337 ($p=2.2\times10^{-6}$). Decreased expression of *COLGALT2* was associated with BD-II in the Putamen Basal
338 Ganglia ($p=3.5\times10^{-6}$) and neared significance in the Hippocampus ($p=7.6\times10^{-6}$), the Caudate Basal
339 Ganglia ($p=1.4\times10^{-5}$) and the Nucleus Accumbens Basal Ganglia ($p=8.9\times10^{-5}$). Neither of these
340 BD-II genes lie within 1Mb of a BD-II locus identified in the recent PGC-BD GWAS, although
341 other BD-II subthreshold associations do (Suppl. Table 4).

342

343 Increased expression of *FSIP2* in the Thyroid was associated with SAB ($p=1.9\times10^{-6}$; Table 3).
344 Increased expression of *ALDH1B1* in the Cerebellar Hemisphere was also associated with SAB,
345 although at slightly below tissue-specific significance ($p=8.4\times10^{-6}$). *FSIP2* lies ~0.5 Mb from a
346 locus also identified as potentially associated with SAB in the PGC-BD GWAS ($p=6.9\times10^{-7}$). One

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

349

350 There is a substantial overlap between association signals in our BD and BD-I analyses, likely
351 due to the high proportion of BD-I cases within our sample, and a high proportion of
352 overlapping controls. We examined association statistics (-log10 p-values) of all associated
353 genes across all four analyses (Figure 3) and noted that BD and BD-1 genes tend to be
354 reciprocally associated, whereas genes identified in the BD-2 and SAB analyses tend to be
355 associated only within those particular subtypes.

356

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

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

365

366 Genes reaching tissue-specific significance ($p<0.05/N$ genes tested) in the DLPFC, ACC, Cortex,
367 and Nucleus Accumbens prediXcan analyses were more likely than expected by chance to be
368 differentially expressed in the DLPFC CMC post-mortem samples (binomial test, $p<0.0038$).
369 There was no relationship between the likelihood of replication of significant genes and the
370 number of genes tested, or eQTL reference panel sample size.

371

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

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

380

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

392 No individuals with SAB were available for analysis.

393

394 **Identifying genes associated with specific behaviours**

395 We tested whether any of the genes identified in our subtype analyses were particularly
396 associated with any specific BPD-endophenotype, using an approach analogous to PHEWAS^{35,36}.
397 We included all genes reaching tissue-specific significance in any subtype analysis.

398

399 We identified three significant associations (Table 4). We found that reduced expression of
400 *EIF1AD* in the DLPFC was associated with mixed states ($p=0.00197$) and panic attacks
401 ($p=0.0004948$). In our original analysis, decreased expression of the gene in the DLPFC was
402 associated with BD-I ($p=2.55\times 10^{-6}$). Additionally, decreased expression of *FSIP2* in the Pituitary
403 was associated with having a family history of BPD in our PHEWAS ($p=1e-05$).

404

405 **Pathway enrichment**

406 We tested for pathway enrichment using MAGMA⁴², for BD, BD-I, BD-II and SAB associations.
407 We carried out three stages of pathway analysis including the following gene sets 1) 174 sets of
408 drug targets; 2) 79 hypothesis-driven gene sets including targets of the FMRP protein, calcium-
409 gated voltage channels, pathways involved in aberrant mouse behavior, pathways pertaining to
410 chronotype and circadian rhythms 3) ~8,500 agnostic pathways obtained from large publicly
411 available databases. All FDR-corrected significant results for these analyses are shown in Table
412 5.

413

414 We found significant enrichments between our BD associated genes and GWAS-derived gene
415 sets for schizophrenia ($p= 3.69E-13$; all p-values shown are FDR-corrected), bipolar disorder ($p=$
416 $2.59E-09$) and major mood disorder ($p=0.0040$). These results are reassuring rather than
417 illuminating, given the known genetic overlap between these disorders, the likely shared
418 samples with the previous BIP GWAS, and the potential for shared controls between all PGC
419 GWAS studies. Similar to the BD results, BD-I associated genes were significantly enriched for
420 GWAS-derived SCZ ($p= 5.39E-12$) and BD ($p= 1.78E-09$) gene sets. BD-II associated genes were
421 not significantly enriched with previous BP or schizophrenia GWAS results. SAB-associated
422 genes were significantly enriched with bipolar GWAS results ($p= 0.027$).

423

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

428

429 Four pathways in our 'hypothesis-driven' analysis were associated with BPD after FDR
430 correction, including genes associated with self-defined 'morning person' chronotype⁵⁸, genes
431 that were highly intolerant to deleterious mutation in EXAC, genes with non-synonymous
432 mutations linked to schizophrenia, and targets of the FMRP protein. FMRP pathways have
433 previously been associated with schizophrenia, autism, and intellectual disability^{33,59,60}. We

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

437

438 For BD-I, we identified two associated pathways in the hypothesis-driven analysis after FDR
439 correction; endoplasmic reticulum function (ER; $p=0.036$) and post synaptic density (PSD;
440 $p=0.046$). 49/8,500 molecular pathways from public databases were significant after FDR-
441 correction, with the most significant driven by methyltransferase activity (S-adenosylmethionine
442 – dependent methyltransferase activity; $p=3.0 \times 10^{-3}$). Four pathways involved in
443 methyltransferase activity are driven by TFB1M, a brain-expressed mitochondrial
444 methyltransferase gene involved in neurosensory mitochondrial deafness^{61,62}. Other significant
445 pathways include mitochondrial function (mitochondrial genome maintenance; $p=0.032$) which
446 was also validated in studies of the PSD proteins and associations with bipolar disorder⁶³.

447

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

454

455 Three hypothesis-driven pathways were enriched with SAB; including mitochondrion⁶⁴, non-
456 synonymous mutations associated with intellectual disability, and genes that have low-level
457 intolerance to EXAC mutations. Our large agnostic analysis revealed many neuron specific genes
458 sets including axonal regeneration, Schwann cell differentiation, and neuron projection
459 regeneration. Mitochondrion and mitochondrion localization were also significant further
460 emphasizing the involvement of mitochondrial genes in bipolar disorder^{65–67}. A total of 45
461 pathways were significantly enriched after FDR correction.

462

463 **Discussion**

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

471

472 We applied gene expression predictor models derived from GTEx and CMC data to 21,488
473 bipolar disorder cases and 54,303 controls from the PGC-BD and iPSYCH collections, and
474 obtained predicted genetically regulated gene expression levels (GREX) for 19,661 unique
475 genes, across 13 brain regions. We identified 53 independent BPD gene-tissue associations; of
476 these, 29 were novel, i.e., they did not occur within 1MB of a locus identified in the recent PGC-
477 BD GWAS⁵. Additionally, we identified 46 independent subtype-specific gene-tissue
478 associations.

479

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

487

488 BPD- and BD-I-associated genes identified in this study were significantly more likely to be
489 differentially expressed in post-mortem tissue from individuals with bipolar disorder than might
490 be expected by chance. Replication of highly associated genes was tissue-specific; for example,
491 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^{32,55}. 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^{69–71} and
511 caudate^{69,72–74} regions, decreased cerebellar volumes^{69,75–77}, and structural differences in the
512 prefrontal cortex of individuals with BPD^{69,78–81}.

513
514 We used genic associations for BD, BD-I, BD-II, and SAB to search for pathway enrichment with
515 MAGMA⁴² 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

521 these hormones are altered⁵⁷. Corticosteroids themselves are prescribed for a number of
522 different medical conditions and can cause symptoms in patients that include psychosis, mania,
523 depression, mixed features, delirium, and anxiety⁸². While these symptoms can arise after
524 corticosteroid use, we cannot be certain the mechanisms are unique and the shared
525 phenotypes in these overlapping gene sets suggest a similar genetic underpinning. Further
526 investigation is warranted to understand the pathways involved in corticosteroid induced
527 psychiatric symptoms and symptoms experienced by patients in bipolar disorder and
528 schizophrenia. Additionally, our pathway analysis results provide support for a number of
529 specific biological hypotheses.

530

531 **Oxidative Stress and Mitochondrial Dysfunction**

532 Collectively, our results indicate a potential role for oxidative stress and mitochondrial
533 dysfunction in bipolar disorder. This hypothesis has been explored in detail elsewhere⁸³⁻⁸⁶, and
534 has been implicated in BPD⁸³⁻⁸⁵ as well as a range of psychiatric disorders⁸⁷⁻⁹⁰, including anxiety
535 and panic disorders⁹¹, schizophrenia⁹²⁻⁹⁴, and major depressive disorder⁹⁵. Evidence for the
536 involvement of oxidative stress and mitochondrial dysfunction in BPD includes known
537 comorbidities between bipolar disorder and mitochondrial disease⁹⁶, the known antioxidant
538 properties of antipsychotic drugs⁸³, and the demonstrated benefit of antioxidant therapies in
539 individuals with schizophrenia and bipolar disorder⁸³.

540

541 A substantial number of the genes identified in our meta-analyses also have a role in oxidative
542 stress and mitochondrial dysfunction (including for example, *AIFM3*, *CHDH*, *EDEM2*, *EIF1AD*,
543 *FADS1*, *TARS2*). In particular, our PHEWAS results implicate a gene, *EIF1AD*, which has a wel-
544 described role in response to oxidative stress⁹⁷. Reduced expression of *EIF1AD* (eukaryotic
545 translation initiation factor 1A domain containing; also known as haponin) in the DLPFC was
546 associated with panic attacks, mixed states, and BD-I; in line with this, a recent study found
547 increased RNA damage due to oxidative stress in individuals with BD-I and mixed states,
548 compared to controls, and a decrease in levels of RNA damage after remission from an
549 episode⁸⁴. A large number of associations in our pathway analyses (Table 5) also point to

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

552

553 Common with BD-I and BD-II are the methyltransferase pathways with the most significant
554 genes involved in mitochondrial methyltransferase. These genes are responsible for
555 neurological phenotypes and associated with bipolar disorder^{65,66}. A study of human induced
556 pluripotent stem cells found early mitochondrial abnormalities in lithium responsive patients
557 with bipolar disorder suggesting these mitochondrial abnormalities are present at the earliest
558 stages of cell development⁶⁷. SAB significant pathways reinforce the relationship between
559 bipolar disorder with mitochondrial and neuronal function.

560

561 **Post-synaptic Density**

562 Multiple studies and hypotheses have implicated the post-synaptic density (PSD) as having a
563 role for Bipolar Disorder, Schizophrenia, and other psychiatric disorders^{63,64}. The PSD is a key
564 location for a host of dopamine and glutamate signaling interactions, and has a key role in
565 axonal growth and guidance. Further, proteins located in the PSD are involved in NMDA
566 receptor trafficking, and underlie energy pathways and mitochondrial function. Our BD-I
567 results are significantly enriched for genes related to PSD-95, a scaffolding protein within the
568 PSD ($p=5.2e-04$). This enrichment is not driven by a single highly associated gene, but rather a
569 large number of sub-threshold associations. The most significant post synaptic density (PSD)
570 gene PACS1 ($p=5.57e-05$) codes for MHC-1 removal of membrane proteins in the trans golgi
571 network and is overexpressed in brain; other subthreshold PSD-95 and glutamatergic
572 associations include *TUBA1B* ($p=3.1e-04$), *SHANK1* ($p=5.4e-04$), *BSN* ($p=6.5e-04$), and *AP2B1*
573 ($p=6.7e-04$). Additionally, our results are enriched for targets of the FMRP (fragile-X mental
574 retardation protein; $p=0.0015$), in line with previous studies of Bipolar Disorder and
575 schizophrenia^{59,98}, as well as the original CommonMind Consortium analysis³¹. FMRP is encoded
576 by *FMR1*, which is required at synapses for normal glutamate receptor signaling⁹⁹.

577

578

579 **Circadian Rhythms**

580 Longstanding hypotheses implicate the disruption of circadian rhythms in bipolar disorder. In
581 particular, sleep disruption is included among bipolar disorder diagnostic criteria and is cited as
582 a particular concern for individuals with BPD. Addressing circadian rhythm disruption is a key
583 factor in treatment of bipolar disorder^{100,101}, and in identifying individuals at risk of relapse^{102–}
584 ¹⁰⁶. Even among healthy individuals, circadian entrainment and sleep patterns are deeply
585 entwined with mood regulation^{100,107–112}. These relationships have been discussed in detail
586 elsewhere, including detailed discussions of plausible neurobiological mechanisms^{100,113–126}.
587 Consequently, studies of the genetics of bipolar disorder have included an emphasis on “clock”
588 genes, i.e., genes involved in regulating circadian rhythmicity^{100,125,127,128}, and the genetics of
589 chronicity and sleep traits¹²⁴.

590

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

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702 Potential Conflicts of Interest: TW has acted as advisor and lecturer to H. Lundbeck A/S
703

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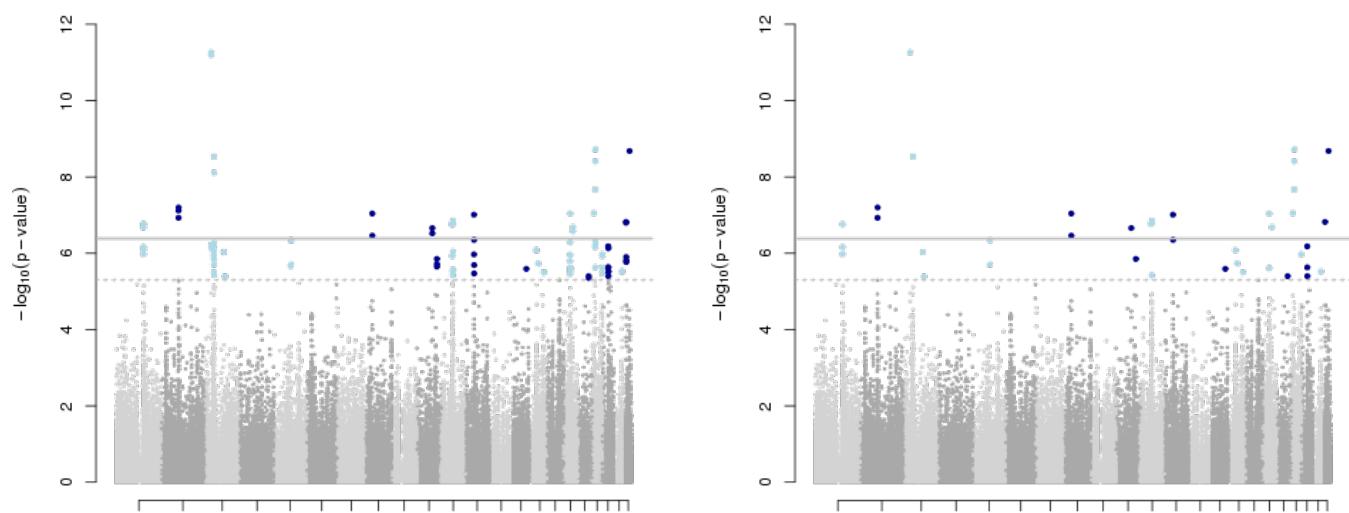


Figure 1: Genic associations identified across full Bipolar sample

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

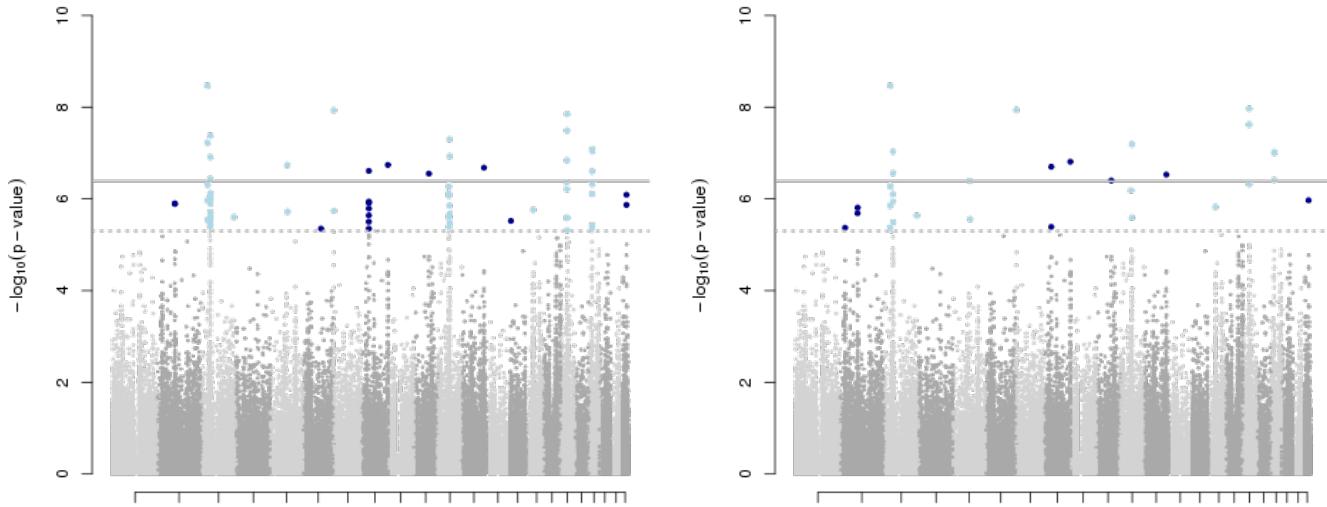


Figure 2: Genic associations identified in three bipolar subtypes.

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

B) FINEMAP and Stepwise conditional analysis identify 37 independent associations

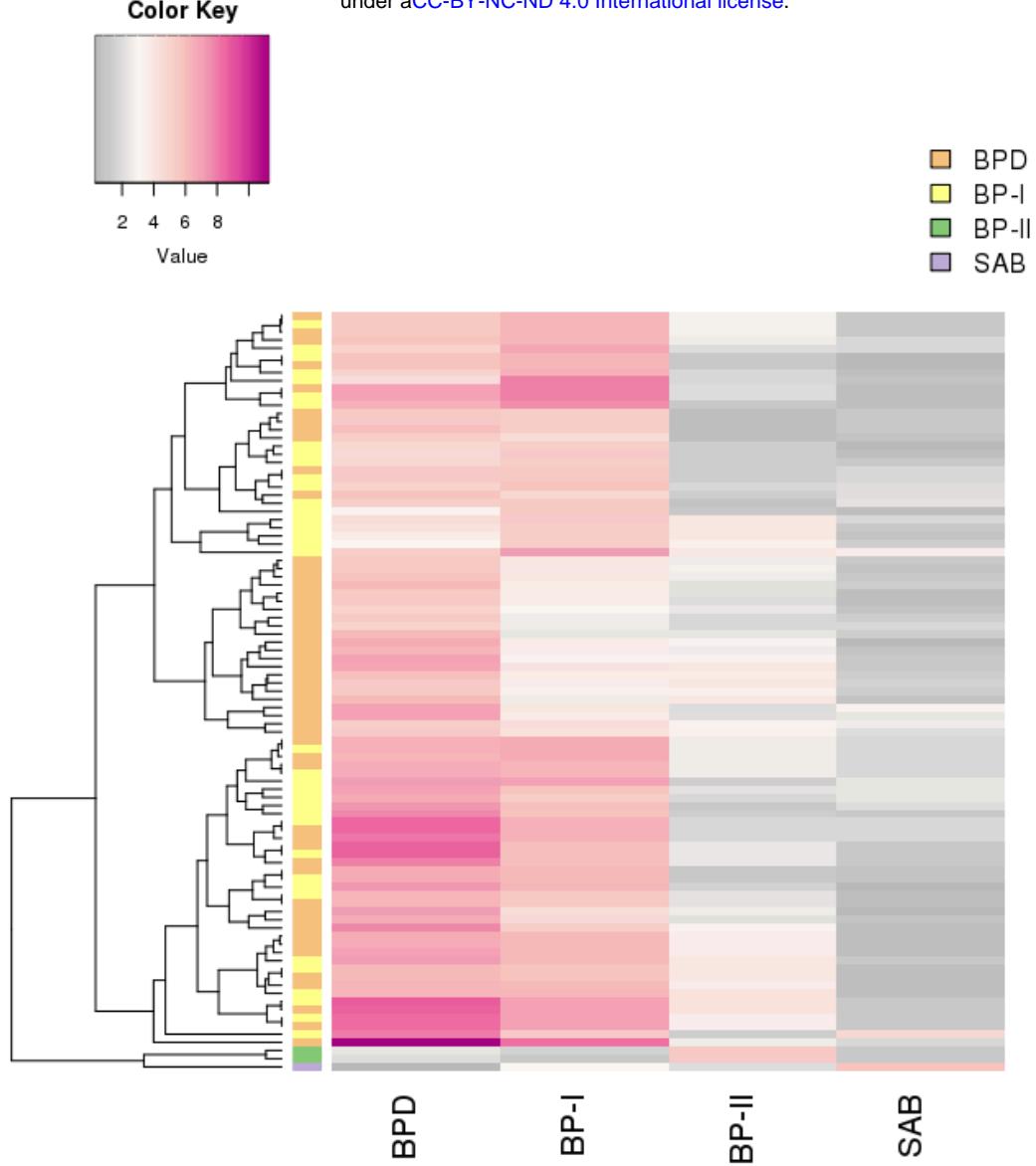
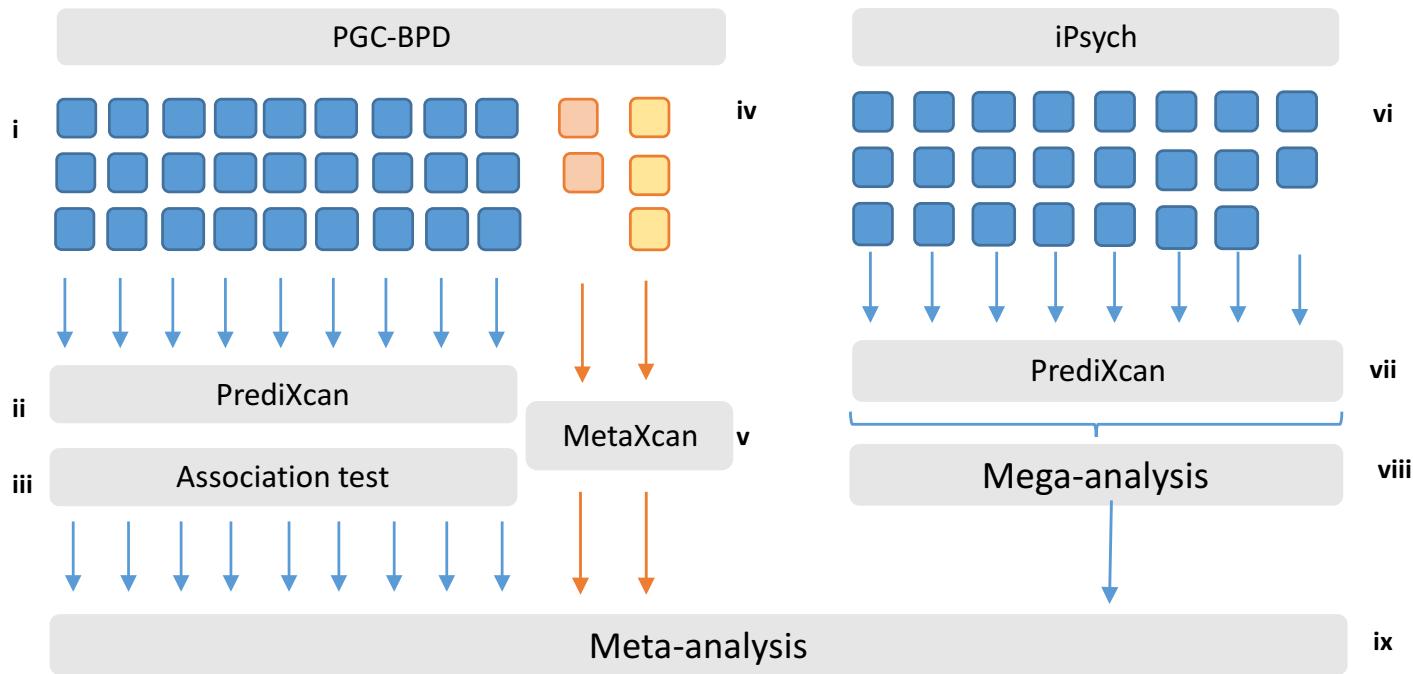


Figure 3: Substantial overlap between BPD and BP-I associated genes.

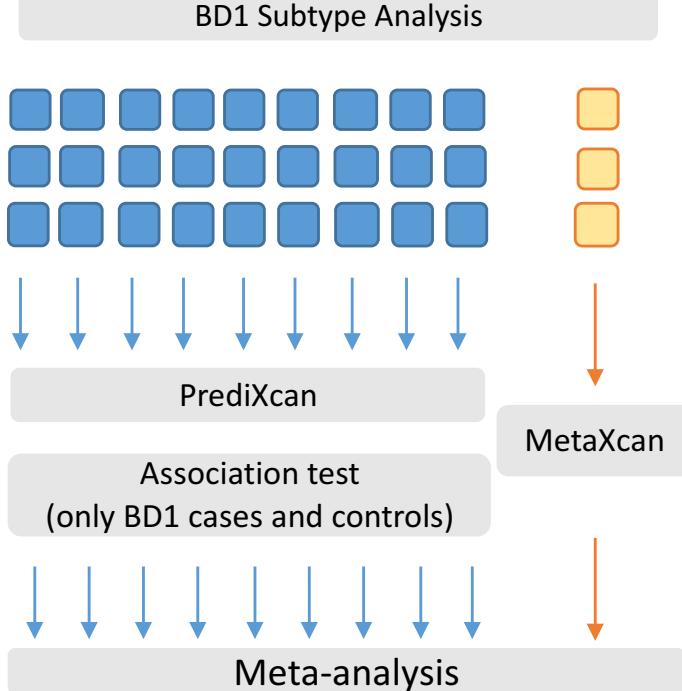
-log10 p-values are shown for all genes reaching genome-wide significance in any discovery analysis. The row side colour bar indicates the original discovery analysis identifying the gene. The four row values indicate the best p-value achieved by that gene in each subtype analysis.

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, BD-I, BD-II and SAB analyses.

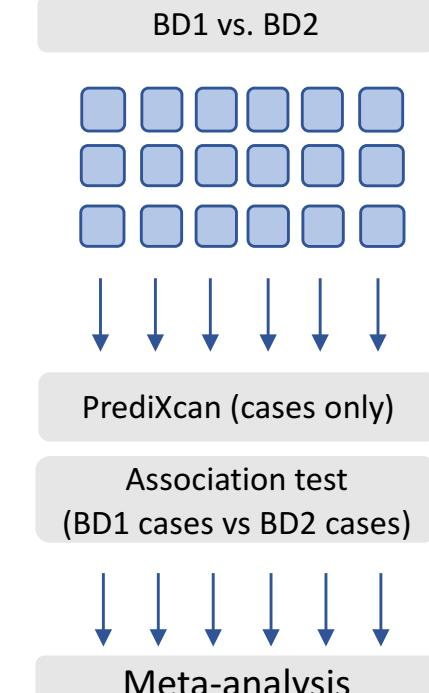
A.



B.



C.



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.

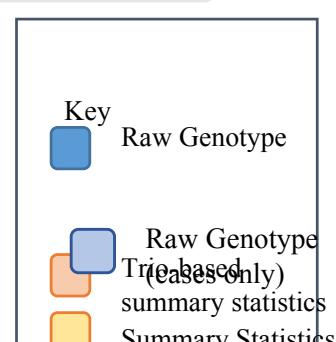


Table 1: Gene-Tissue Associations results

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
NCOA6	Hypothalamus	20	32782375	32857150	-0.2119	0.0426	6.55E-07
RPRD2	Hypothalamus	1	150335567	150449042	-0.164	0.0331	6.96E-07
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

LEO1	Hippocampus	15	52230222	52264003	-0.1459	0.0306	1.86E-06
PHLPP1	Hippocampus	18	60382672	60647666	-0.0472	0.0102	3.99E-06
CILP2	Nucleus_Accumbens_Basal_Ganglia	19	19303008	19312678	0.0949	0.0158	1.90E-09
AIFM3	Nucleus_Accumbens_Basal_Ganglia	22	21319396	21335649	-0.0914	0.0174	1.50E-07
ZNF584	Nucleus_Accumbens_Basal_Ganglia	19	58912871	58929694	0.0366	0.0075	1.06E-06
MED24	Nucleus_Accumbens_Basal_Ganglia	17	37313147	37323737	0.0383	0.0081	2.44E-06
DDHD2	Caudate_Basal_Ganglia	8	38120648	38126761	-0.0326	0.0064	4.37E-07
UBR1	Caudate_Basal_Ganglia	15	43235095	43398311	-0.1468	0.0298	8.39E-07
CATSPERB	Caudate_Basal_Ganglia	14	92047040	92247051	-0.0343	0.0073	2.60E-06
AC024257.1	Frontal_Cortex_BA9	12	48759919	48761738	0.0693	0.013	9.78E-08
SEMA4C	Frontal_Cortex_BA9	2	97525453	97536494	0.1046	0.0197	1.17E-07
RHEBL1	Frontal_Cortex_BA9	12	49458468	49463808	0.1061	0.021	4.44E-07
CDHR1	Frontal_Cortex_BA9	10	85980254	85985345	-0.036	0.0075	1.87E-06
ZNF584	Frontal_Cortex_BA9	19	58912871	58929694	0.0845	0.0183	3.95E-06
TSSK6	Thyroid	19	1973477	19739739	0.1638	0.0292	2.12E-08
HHLA2	Thyroid	3	108015376	108097132	0.1106	0.0225	9.23E-07
UBE2Q2L	Thyroid	15	84841242	84850986	0.0436	0.0094	3.16E-06
SNTB2	Thyroid	16	69221032	69342955	-0.0265	0.0058	5.16E-06
MCHR1	Anterior_Cingulate_Cortex_BA24	22	41074754	41078818	-0.1785	0.0298	2.10E-09
FAM81B	Anterior_Cingulate_Cortex_BA24	5	94727048	94786158	0.4376	0.0868	4.62E-07
EDEM2	Anterior_Cingulate_Cortex_BA24	20	33284722	33413452	-0.0445	0.0097	4.01E-06
TMEM127	Anterior_Cingulate_Cortex_BA24	2	96914254	96931732	-0.0378	0.0083	5.09E-06
GNL3	Cerebellum	3	52715172	52728508	0.0368	0.0062	2.93E-09
PLPP5	Cerebellum	8	38082736	38133076	-0.0427	0.0085	5.17E-07
ADD3	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	Caudate Basal Ganglia	0.0011	+
CACNB3	Frontal Cortex BA9	0.0010	-
	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>MEN1</i>	17	37884749	37887040	-0.3695	0.0662	2.42E-08
BD-I	Anterior Cingulate Cortex BA24	<i>PACS1</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>FSIP2</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>familyhistory</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+NMNDAR+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 transduction	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	Fancconi 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	Agnostic	Endoplasmic Reticulum (core)	87	2.04E-04	0.036
BD-I	Agnostic	PSD (human core)	624	5.16E-04	0.046
BD-I	Agnostic	MORN1G	109	1.16E-03	0.069
BD-II	Agnostic	S-adenosylmethionine-dependent methyltransferase	91	3.46E-07	0.003
BD-II	Agnostic	negative regulation of systemic arterial blood pressure	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 proc	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 Int	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 pr	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	a6b1 a6b4 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 reticul	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 development	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 involved 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 process	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-irradiation	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	Agnostic	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