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# 1 **Genomic dissection of bipolar disorder and schizophrenia including 28 subphenotypes**

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98

## 100 **Summary**

101 Schizophrenia and bipolar disorder are two distinct diagnoses that share symptomology.  
102 Understanding the genetic factors contributing to the shared and disorder-specific symptoms will  
103 be crucial for improving diagnosis and treatment. In genetic data consisting of 53,555 cases  
104 (20,129 BD, 33,426 SCZ) and 54,065 controls, we identified 114 genome-wide significant loci  
105 implicating synaptic and neuronal pathways shared between disorders. Comparing SCZ to BD  
106 (23,585 SCZ, 15,270 BD) identified four genomic regions including one with disorder-  
107 independent causal variants and potassium ion response genes as contributing to differences in  
108 biology between the disorders. Polygenic risk score (PRS) analyses identified several significant  
109 correlations within case-only phenotypes including SCZ PRS with psychotic features and age of  
110 onset in BD. For the first time, we discover specific loci that distinguish between BD and SCZ and  
111 identify polygenic components underlying multiple symptom dimensions. These results point to  
112 the utility of genetics to inform symptomology and potentially treatment.

113

114

## 115 **Introduction**

116 Bipolar disorder (BD) and schizophrenia (SCZ) are severe psychiatric disorders and among the  
117 leading causes of disability worldwide(Whiteford et al., 2013). Both disorders have significant  
118 genetic components with heritability estimates ranging from 60-80%(Nöthen et al., 2010). Recent  
119 genetic and epidemiological studies have demonstrated substantial overlap between these two  
120 disorders with a genetic correlation from common variation near 0.6-0.7(Cross-Disorder Group of  
121 the Psychiatric Genomics Consortium, 2013) and high relative risks (RR) among relatives of both  
122 BD and SCZ patients (RRs for parent/offspring: BD/BD: 6.4, BD/SCZ: 2.4; SCZ/BD: 5.2,

123 SCZ/SCZ: 9.9)(Lichtenstein et al., 2009). Despite shared genetics and symptomology, the current  
124 diagnostic systems(“Diagnostic and Statistical Manual of Mental Disorders | DSM Library,”  
125 n.d.)(“WHO | International Classification of Diseases,” n.d.) adhere to historical distinctions from  
126 the late 19<sup>th</sup> century and represent BD and SCZ as independent categorical entities differentiated  
127 on the basis of their clinical presentation, with BD characterized by predominant mood symptoms,  
128 mood-congruent delusions and an episodic disease course and SCZ considered a prototypical  
129 psychotic disorder. Identifying genetic components contributing to both disorders provides insight  
130 into the biology underlying the shared symptoms of the disorders.

131 While the shared genetic component is substantial, studies to date have also implicated genetic  
132 architecture differences between these two disorders(Curtis et al., 2011; Ruderfer et al., 2014). A  
133 polygenic risk score created from a case only SCZ vs BD genome-wide association study (GWAS)  
134 significantly correlated with SCZ or BD diagnosis in an independent sample(Ruderfer et al., 2014),  
135 providing the first evidence that differences between the disorders also have a genetic basis. An  
136 enrichment of rare, moderate to highly penetrant copy number variants (CNVs) and *de novo* CNVs  
137 are seen in SCZ patients(CNV and Schizophrenia Working Groups of the Psychiatric Genomics  
138 Consortium, 2017; Gulsuner and McClellan, 2015; Kirov et al., 2012; Stone et al., 2008;  
139 Szatkiewicz et al., 2014), while, the involvement of CNVs in BD is less clear(Green et al., 2016).  
140 Although the role of *de novo* single nucleotide variants in BD and SCZ has been investigated in  
141 only a handful of studies, enrichment in pathways associated with the postsynaptic density has  
142 been reported for SCZ, but not BD(Fromer et al., 2014; Kataoka et al., 2016). Identifying disorder-  
143 specific variants and quantifying the contribution of genetic variation to specific symptom  
144 dimensions remain important open questions. Characterizing these genetic differences will  
145 facilitate an understanding of the dimensions of the disorders instead of the dichotomous diagnosis.

146 For example, we have shown that SCZ patients with greater manic symptoms have higher  
147 polygenic risk for BD(Ruderfer et al., 2014). These findings demonstrate shared genetic  
148 underpinnings for symptoms across disorders and may enable us to characterize patients by genetic  
149 liability to symptom dimensions thereby informing disease course and treatment.

150 Here, we utilize large collections of genotyped samples for BD and SCZ along with clinically-  
151 relevant measures identifying 28 subphenotypes to address three questions: 1) Are there specific  
152 variants, genes or pathways that are either shared by, or differentiate BD and SCZ? 2) Are the  
153 shared symptoms between these disorders driven by the same underlying genetic profiles? and 3)  
154 Can we demonstrate independent genetic signatures for subphenotypes within these disorders?

155

## 156 **Results**

157

### 158 **Shared genetic contribution to BD and SCZ**

159 We performed association analysis of BD and SCZ combined into a single phenotype, totaling  
160 53,555 cases (20,129 BD, 33,426 SCZ) and 54,065 controls on 15.5 million SNP allele dosages  
161 imputed from 1000 genomes phase 3(The 1000 Genomes Project Consortium, 2015). Logistic  
162 regression was performed controlling for 13 principal components of ancestry, study sites and  
163 genotyping platform. We identified 11,231 SNPs with p-value below our genome-wide  
164 significance (GWS) threshold of  $5 \times 10^{-8}$ . After grouping SNPs in linkage disequilibrium with each  
165 other ( $r^2 > 0.2$ ), 114 genomic risk loci remained. For the most significant variant in each of the 114  
166 GWS loci, we performed conditional analysis with any GWS hit within 1Mb of the extent of the  
167 locus from the previously performed single disease GWAS of SCZ(Schizophrenia Working Group  
168 of the Psychiatric Genomics Consortium, 2014) and BD(Stahl et al., 2017) and identified 32 loci



169 that were independently significant defined strictly as no single disease locus within 1Mb or a  
170 GWS p-value after conditional analysis (Supplementary Table 1). We further performed gene-set  
171 based tests using MAGMA(Leeuw et al., 2015) across 10,891 curated pathways(Watanabe et al.,  
172 2017) and identified 8 pathways surpassing Bonferroni correction ( $p < 4.6 \times 10^{-6}$ ) with all but one  
173 pathway implicating synaptic and neuronal biology (Supplementary Table 2a). Establishing  
174 independent controls (see Methods) allowed us to perform disorder-specific GWAS in 20,129 BD  
175 cases vs 21,524 BD controls and 33,426 SCZ cases and 32,541 SCZ controls. Using these results,  
176 we compared effect sizes of these 114 loci across each disorder independently showing the subsets  
177 of variants that had larger effects in SCZ compared to BD and vice versa (Figure 1a).

178

### 179 **Differentiating genetic contribution to BD and SCZ**

180 To identify loci with divergent effects on BD and SCZ, we performed an association analysis  
181 comparing 23,585 SCZ cases with 15,270 BD cases matched for shared ancestry and genotyping  
182 platform (see Methods, Figure 1b, Table 1). Two genome-wide significant loci were identified, the  
183 most significant of which was rs56355601 located on chromosome 1 at position 173,811,455  
184 within an intron of *DARS2* (Supplementary Figure 1). The second most significant locus was  
185 rs200005157, a four base-pair insertion/deletion, on chromosome 20 at position 47638976 in an  
186 intron of *ARFGEF2* (Supplementary Figure 2). For both variants, the minor allele frequency was  
187 higher in BD cases than SCZ cases and disease-specific GWAS showed opposite directions of  
188 effect when compared to controls. We sought to identify additional disease-specific loci by  
189 comprehensively incorporating expression information with association results to perform fine-  
190 mapping and identify novel variants(Gamazon et al., 2015; Giambartolomei et al., 2014; Gusev et  
191 al., 2016; He et al., 2013). Here, we applied the summary-data-based Mendelian randomization

192 (SMR) method(Zhu et al., 2016) (see Methods) utilizing the cis-QTLs derived from peripheral  
193 blood(Westra et al., 2013), human dorsolateral prefrontal cortex (DLPFC)(Fromer et al., 2016)  
194 from the Common Mind Consortium and 11 brain regions from the GTEx consortium(Consortium,  
195 2015). We identified one SNP-probe combination that surpassed the threshold for genome-wide  
196 significance in blood but was also the most significant finding in brain. We found that SNP  
197 rs4793172 in gene *DKFZ* is associated with SCZ vs BD analysis ( $p_{\text{GWAS}} = 2.8 \times 10^{-6}$ ) and is an  
198 eQTL for probe ILMN 1811648 ( $p_{\text{eQTL}} = 2.9 \times 10^{-168}$ ), resulting in  $p_{\text{SMR}} = 4.1 \times 10^{-6}$  in blood ( $p_{\text{eQTL}}$   
199  $= 2.9 \times 10^{-25}$ ,  $p_{\text{SMR}} = 2.0 \times 10^{-5}$  in DLFC, and  $p_{\text{eQTL}} = 4.6 \times 10^{-15}$ ,  $p_{\text{SMR}} = 6.0 \times 10^{-5}$  in GTEx cerebellar  
200 hemisphere) (Supplementary Table 3, Supplementary Figure 3) and shows no evidence of  
201 heterogeneity ( $p_{\text{HET}} = 0.66$ ) which implies only a single causal variant in the locus.

202 In an effort to prioritize genes for the two GWS loci from the GWAS, we performed fine-  
203 mapping(Benner et al., 2016) using an LD map derived from a majority of the control samples.  
204 We then performed SMR on each of the variants with causal probability greater than 1% using all  
205 eQTLs from the CommonMind Consortium DLPFC reference. All the most likely causal variants  
206 were shown to most significantly regulate the same gene suggesting *CSEIL* is the most likely  
207 relevant gene on chromosome 20 (rs200005157: causal probability=0.21,  $p_{\text{GWAS}} = 2.4 \times 10^{-8}$ ,  $p_{\text{eQTL}}$   
208  $3 \times 10^{-8}$ ,  $p_{\text{SMR}} = 8.5 \times 10^{-5}$ ,  $p_{\text{HET}} = 0.34$ ). For the locus on chromosome 1, *SLC9C2* is the most  
209 significantly regulated gene. However, a highly significant heterogeneity test indicates a complex  
210 genetic architecture making it difficult to infer a causal role for the associated SNP. Therefore,  
211 *DARS2* presents as the most likely relevant gene on chromosome 1 (rs56355601:  $p_{\text{GWAS}} = 5.6 \times 10^{-9}$ ,  
212 causal probability=0.079,  $p_{\text{eQTL}} = 7.4 \times 10^{-13}$ ,  $p_{\text{SMR}} = 6.17 \times 10^{-6}$ ,  $p_{\text{HET}} = 0.03$ ). We note however, that in  
213 both cases there are less associated variants that are stronger eQTLs for these genes complicating  
214 a straightforward causal interpretation. Finally, using the same gene-set test used for the combined

215 analysis GO biological process “response to potassium ion” ( $p=1.6 \times 10^{-6}$ ) was the only pathway  
216 surpassing our Bonferroni corrected significance threshold (Supplementary Table 2b).

217

### 218 **Regional joint association**

219 We expanded our efforts to identify disorder-specific genomic regions by jointly analyzing  
220 independent GWAS results from BD and SCZ(Pickrell et al., 2016). The genome was split into  
221 1,703 previously defined approximately LD independent regions(Berisa and Pickrell, 2015).  
222 Thirteen percent, or 223 regions, had a posterior probability greater than 0.5 of having a causal  
223 variant for at least one disorder. Of these, 132 best fit the model of a shared causal variant  
224 influencing both BD and SCZ, 88 were most likely specific to SCZ, 3 demonstrated evidence of  
225 two independent variants (with one impacting each of the two disorders) and none were BD-  
226 specific. Of note, this approach calculates a prior probability that any given region is disease-  
227 specific and from these data the probability of having a BD specific region was 0.1% compared to  
228 15% for SCZ, likely a result of increased power from the larger SCZ sample size and/or a  
229 difference in genetic architecture between these disorders.

230 The 114 GWS SNPs from the combined BD and SCZ GWAS localized into 99 independent  
231 regions (13 regions had multiple GWS SNPs), of which 78 (79%) were shared with a posterior  
232 probability of greater than 0.5. Sixty regions had at least one GWS SNP in the independent SCZ  
233 GWAS, of which 30 (50%) are shared and 8 regions contained a GWS SNP in the independent  
234 BD GWAS, of which 6 (75%) are shared using the same definition. For the three regions showing  
235 evidence for independent variants, two had highly non-overlapping association signals in the same  
236 region stemming from independent variants. The third, on chromosome 19 presented a different  
237 scenario where association signals were overlapping. The most significant variant in BD was

238 rs111444407 (chr19:19358207,  $p = 8.67 \times 10^{-10}$ ) and for SCZ was rs2315283 (chr19:19480575,  
239  $p=4.41 \times 10^{-7}$ ). After conditioning on the most significant variant in the other disorder, the  
240 association signals of the most significant variant in BD and SCZ were largely unchanged (BD  
241 rs111444407  $=1.3 \times 10^{-9}$ , SCZ rs2315283  $p=6.7 \times 10^{-5}$ ). We further calculated the probability of each  
242 variant in the region being causal for both BD and SCZ (Benner et al., 2016) and found no  
243 correlation ( $r= -0.00016$ ). The most significant variants had the highest posterior probability of  
244 being causal (SCZ: rs2315283, prob = 0.02, BD: rs111444407, prob = 0.16). Both variants most  
245 significantly regulate the expression of *GATAD2A* in brain (Fromer et al., 2016) but in opposite  
246 directions (rs111444407  $p_{eQTL} = 6 \times 10^{-15}$ , beta = 0.105; rs2315283  $p_{eQTL} = 1.5 \times 10^{-28}$ , beta = -0.11).  
247

#### 248 **Regional SNP-heritability estimation**

249 Across the genome, regional SNP-heritabilities ( $h^2_{\text{snp}}$ ) were estimated separately for SCZ and  
250 BD (Shi et al., 2016) and were found to be moderately correlated ( $r=0.25$ ). We next defined risk  
251 regions as those containing the most associated SNP for each GWS locus. In total, there were 101  
252 SCZ risk regions from the 105 autosomal GWS loci reported previously (Schizophrenia Working  
253 Group of the Psychiatric Genomics Consortium, 2014) and 29 BD risk regions from 30 GWS loci  
254 reported previously (Stahl et al., 2017). Ten regions were risk regions for both BD and SCZ  
255 comprising 33% of BD risk regions and 10% of SCZ risk regions. We further stratified regional  
256  $h^2_{\text{snp}}$  by whether a region was a risk region in one disorder, none or both (Supplementary Figure  
257 4). Since the discovery data for the regions overlapped with the data used for the heritability  
258 estimation, we expected within-disorder analyses to show significant results. In risk regions  
259 specific to SCZ ( $n=91$ ) there was a significant increase in regional  $h^2_{\text{snp}}$  in SCZ, as expected ( $p =$   
260  $1.1 \times 10^{-22}$ ), but also in BD ( $p = 1.2 \times 10^{-6}$ ). In risk regions specific to BD ( $n=19$ ), significantly

261 increased regional  $h^2_{\text{snp}}$  was observed in BD, as expected ( $p = 0.0007$ ), but not in SCZ ( $p = 0.89$ ).  
262 Risk regions shared by both disorders had significantly higher  $h^2_{\text{snp}}$  in both disorders, as expected  
263 (BD  $p = 5.3 \times 10^{-5}$ , SCZ  $p = 0.006$ ), compared to non-risk regions. However, we observed a  
264 significant increase in BD  $h^2_{\text{snp}}$  in shared risk regions compared to BD risk regions (BD  $p = 0.003$ )  
265 but not SCZ  $h^2_{\text{snp}}$  for shared risk regions compared to SCZ risk regions ( $p = 0.62$ ). Using a less  
266 stringent p-value threshold for defining risk regions ( $p < 5 \times 10^{-6}$ ), thereby substantially increasing  
267 the number of regions, resulted in similar results. Seven regions contributed to substantially higher  
268  $h^2_{\text{snp}}$  in SCZ compared to BD but no region showed the inverse pattern. Of these regions, all but  
269 one was in the major histocompatibility region (MHC), the sole novel region was  
270 chr10:104380410-106695047 with regional  $h^2_{\text{snp}} = 0.0019$  in SCZ and  $h^2_{\text{snp}} = 0.00063$  in BD.

271

## 272 **Polygenic dissection of subphenotypes**

273 Subphenotypes were collected for a subset of patients with either BD or SCZ (see Methods). For  
274 SCZ, we had clinical quantitative measurements of manic, depressive, positive and negative  
275 symptoms generated from factor analysis of multiple instruments as described previously (Ruderfer  
276 et al., 2014) but in larger sample sizes ( $n = 6908, 6907, 8259, 8355$  respectively). For BD, 24  
277 subphenotypes were collected among nearly 13,000 cases in distinct categories including  
278 comorbidities, clinical information such as rapid cycling and psychotic features as well as  
279 additional disease course data such as age of onset and number of hospitalizations. For each BD  
280 or SCZ patient, we calculated a polygenic risk score (PRS) using all SNPs, from each of the four  
281 main GWAS analyses (BD+SCZ, BD, SCZ and SCZvsBD). We then used regression analysis  
282 including principal components and site to assess the relationship between each subphenotype and  
283 the 4 PRS. Specifically, we tested whether polygenic risk scores of BD+SCZ, BD, SCZ or

284 SCZvsBD were correlated with each of these subphenotypes separately within BD and SCZ cases.  
285 When testing if the variance explained by the PRS was different from zero, we applied a  
286 significance cutoff of  $p < 0.0004$  based on Bonferroni correction for 112 tests. In total, we  
287 identified 6 significant results after correction (Figure 2, Table 2).

288

289 A significant positive correlation existed between BD PRS and manic symptoms in SCZ cases as  
290 seen previously(Ruderfer et al., 2014) ( $p=2 \times 10^{-5}$ ,  $t=4.26$ ) and BD PRS and psychotic features in  
291 BD patients ( $p=5.3 \times 10^{-5}$ ,  $t=4.04$ ). A significant increase in SCZ PRS was seen for BD cases with  
292 versus without psychotic features ( $p=1.2 \times 10^{-10}$ ,  $t=6.45$ ) and patients with increased negative  
293 symptoms in SCZ patients ( $p=3.60 \times 10^{-6}$ ,  $t=4.64$ ). The BD+SCZ vs controls PRS was significantly  
294 associated with psychotic features in BD ( $p=7.9 \times 10^{-13}$ ,  $t=7.17$ ) and negative symptoms in SCZ  
295 ( $p=1.5 \times 10^{-5}$ ,  $t=4.33$ ). The next two most significant results which did not survive our conservative  
296 correction were both indicative of a more severe course in BD: increased BD+SCZ PRS with  
297 increased numbers of hospitalizations in BD cases ( $p=4.2 \times 10^{-4}$ ,  $t=3.53$ ) and increased SCZ PRS  
298 with earlier onset of BD ( $p=7.9 \times 10^{-4}$ ,  $t=-3.36$ ). We assessed the role of BD subtype on the  
299 correlation between SCZ PRS and psychotic features and identified a significant correlation when  
300 restricted to only BD type I cases indicating the result was not likely driven by BD patients with a  
301 schizoaffective subtype (BDI: 3,763 with psychosis, 2,629 without,  $p=1.55 \times 10^{-5}$ , Supplementary  
302 Table 4).

303

304 We performed a GWAS for all 8 quantitative subphenotypes and 9 binary subphenotypes with at  
305 least 1,000 cases and calculated heritability and genetic correlation with BD and SCZ. Only two  
306 subphenotypes had significant  $h^2_{\text{snp}}$  estimates using LD-score regression(Bulik-Sullivan et al.,

307 2015) both in BD: psychotic features in BD ( $h^2_{\text{snp}}=0.15$ ,  $SE=0.06$ ) and suicide attempt ( $h^2_{\text{snp}}=0.25$ ,  
308  $SE=0.1$ ). Only psychotic features demonstrated a significant genetic correlation with SCZ  
309 ( $r_g=0.34$ ,  $SE=0.13$ ,  $p=0.009$ ). The significant genetic correlation demonstrates a genome-wide  
310 relationship between common variants contributing to SCZ risk and those contributing to  
311 psychotic features in BD cases. We tested whether the most significantly associated SCZ loci  
312 contributed directly to psychotic features in BD. One hundred of the 105 autosomal genome-wide  
313 significant SCZ SNPs previously published (Schizophrenia Working Group of the Psychiatric  
314 Genomics Consortium, 2014) were in our dataset after QC and 60 were in the same direction of  
315 effect for risk of psychotic features in BD ( $p=0.028$ , one-sided binomial-test).

316  
317  
318

## Discussion

319 Here we present a genetic dissection of bipolar disorder and schizophrenia from over 100,000  
320 genotyped subjects. Consistent with earlier results (Cross-Disorder Group of the Psychiatric  
321 Genomics Consortium, 2013), we found extensive genetic sharing between these two disorders,  
322 identifying 114 genome-wide significant loci contributing to both disorders of which 32 are novel.  
323 These findings point to the relevance of neuronal and synaptic biology for the shared genetic  
324 substrate of these disorders. However, despite this degree of sharing, we identified several loci that  
325 significantly differentiated between the two disorders, having opposite directions of effect. We  
326 also found polygenic components that significantly correlated from one disorder to symptoms of  
327 the other.

328

329 Two GWS loci were identified from the case only SCZ versus BD analysis providing opportunities  
330 to inform the underlying biological distinctions between BD and SCZ. The most significant locus

331 implicates *DARS2* (coding for the mitochondrial Aspartate-tRNA ligase) which is highly expressed  
332 in the brain and significantly regulated by the most significant SNP rs56355601 ( $p_{eQTL}=2.5 \times 10^{-11}$ ).  
333 Homozygous mutations in *DARS2* are responsible for leukoencephalopathy with brainstem and  
334 spinal cord involvement and lactate elevation (LBSL), which was characterized by neurological  
335 symptoms such as psychomotor developmental delay, cerebellar ataxia and delayed mental  
336 development(Yamashita et al., 2013, p. 2). Based on methylation analysis from the prefrontal  
337 cortex of stress models (rats and monkeys) and from peripheral samples (in monkeys and human  
338 newborns), *DARS2*, among others, has been suggested as a potential molecular marker of early-  
339 life stress and vulnerability to psychiatric disorders(Luoni et al., 2016). The second most  
340 significant locus implicates *CSEIL*, a nuclear transport factor that plays a role in cellular  
341 proliferation as well as in apoptosis(Bera et al., 2001). Intronic SNPs in *CSEIL* have been  
342 associated with subjective well-being(Okbay et al., 2016) and, nominally to antidepressant  
343 response(Li et al., 2016). More interestingly, *CSEIL* is a potential target gene of miR-137, one of  
344 the well-known schizophrenia risk loci(Schizophrenia Working Group of the Psychiatric  
345 Genomics Consortium, 2014), which is able to negatively regulate *CSEIL* by interacting with  
346 complementary sequences in the 3' UTR of *CSEIL*(Li et al., 2013). Although falling short of  
347 genome-wide significance, the third most significant locus implicates *ARNTL* (Aryl Hydrocarbon  
348 Receptor Nuclear Translocator Like), which is a core component of the circadian clock. *ARNTL*  
349 has been previously hypothesized for relevance in bipolar disorder,(Yang et al., 2008) although  
350 human genetic evidence is currently limited(Byrne et al., 2014).

351

352 The ability to generate transcriptional data on multiple tissues across many individuals using RNA-  
353 sequencing has provided detailed information on the role common variants play in regulating



354 expression of specific genes in specific tissues. These eQTLs can be integrated with the genetic  
355 association data from GWAS to inform on the relationship between variant association and variant  
356 regulation of expression for each gene. Performing this integration, we identified a third genome-  
357 wide significant finding in DCAKD. The gene codes for Dephospho-CoA Kinase Domain  
358 Containing protein, a member of the human postsynaptic density proteome from human  
359 neocortex(Bayés et al., 2011). In the mouse cortical synaptoproteome DCAKD is among the  
360 proteins with the highest changes between juvenile postnatal days and adult stage, suggesting a  
361 putative role in brain development(Gonzalez-Lozano et al., 2016; Moczulska et al., 2014).  
362 Discerning between pleiotropy (variant independently regulates expression and alters risk to  
363 disease) from causality (variant regulates expression which thereby alters risk to disease) through  
364 statistical analysis alone is difficult, this analytical approach is stringent in excluding loci where  
365 colocalised SNP-phenotype and SNP-expression associations may reflect confounding driven by  
366 linkage disequilibrium (LD) (one variant regulates expression and a different variant alters risk but  
367 the variants in the region are in LD). Hence, this approach utilizes currently available data to  
368 prioritize genes, including direction of effect, for functional follow-up. These analyses will become  
369 more powered with increased sample sizes for both phenotype and eQTL data sets.

370

371 Performing pathway analysis based on the full association results shows enrichment of genes  
372 involved in response to potassium ions, including potassium voltage-gated channel subfamily  
373 members and a number of genes regulated by cellular potassium concentration. This is in line with  
374 previous genetic evidence pointing to a key etiologic role of potassium channels, in particular, in  
375 BD(Judy and Zandi, 2013), which could be explained by their role in multiple neurobiological

376 mechanisms involved in the development of psychiatric disorders such as regulation of the  
377 dopaminergic circuits, synaptic plasticity, and myelination(Balaraman et al., 2015).

378

379 We further assessed the contribution of regions of the genome to each disorder through joint  
380 regional association and heritability estimation. These results point to an additional locus that may  
381 contribute differentially to liability to BD and SCZ. The region on chr19 shows overlapping  
382 association peaks that are driven by independent causal variants for each disorder. Both variants  
383 significantly regulate the same gene *GATAD2A* but in opposite directions. *GATAD2A* is a  
384 transcriptional repressor, which is targeted by *MBD2* and is involved in methylation-dependent  
385 gene silencing. The protein is part of the large NuRD (nucleosome remodeling and deacetylase)  
386 complex, for which also HDAC1/2 are essential components. NurD complex proteins have been  
387 associated with autism(Li et al., 2015). Their members, including *GATAD2A*, display preferential  
388 expression in fetal brain development(Li et al., 2015) and in recent work has been implicated in  
389 SCZ through open chromatin(Fullard et al., n.d.). Further, p66 $\alpha$  (mouse *GATAD2A*) was recently  
390 shown to participate in memory preservation through long-lasting histone modification in  
391 hippocampal memory-activated neurons(Ding et al., 2017). SNP-heritability appears to be  
392 consistently shared across regions and chromosomes between these two disorders. Regions with  
393 GWS loci often explain higher proportions of heritability as expected. When looking at the effect  
394 on heritability of the presence of a GWS locus in the other disorder, we identified a significant  
395 increase in BD heritability for regions containing a GWS locus for SCZ but no significant increase  
396 in SCZ heritability in regions having a BD one. This result suggests a directionality to the genetic  
397 sharing of these disorders with a larger proportion of BD loci being specific to BD. However, we  
398 cannot exclude that the asymmetry of results may reflect less power of discovery for BD than SCZ.

399 The degree to which power and subphenotypes contribute to this result requires further  
400 examination.

401

402 We note that as with nearly all GWAS findings, the calculated population-based effect sizes of the  
403 variants identified here are small and independently explain only a modest fraction to the  
404 heritability of these disorders. The identification of these variants is dependent on the ability to  
405 have highly accurate allele frequency estimates that can only be ascertained from large sample  
406 sizes. As sample sizes get larger the power to identify variants of smaller effect increases meaning  
407 that increasing sample size results in the identification of variants of smaller effect. However, a  
408 small population effect size does not exclude the possibility of a substantially larger effect on  
409 molecular phenotypes nor does it preclude the utility of association regions in understanding  
410 biology or having a clinical impact. Efforts following up GWAS results to date have demonstrated  
411 the value of these findings in pointing to genes that can aid in understanding the underlying biology  
412 of the trait(Claussnitzer et al., 2015; Mohanan et al., 2018; Sekar et al., 2016). Further, there is a  
413 clear relationship between GWAS results of a phenotype and gene targets of drugs that treat that  
414 phenotype pointing to the potential for improved therapeutic understanding(Nelson et al., 2015;  
415 Ruderfer et al., 2016). A major challenge of GWAS is the sheer number of findings and the  
416 substantial time/cost required for functional follow up of these findings in the classical paradigms  
417 used for genes causal for monogenic disorders. In silico bioinformatic analyses (such as SMR used  
418 here) that integrate GWAS results with ‘omics data (transcription, protein, epigenetic, etc.) have  
419 the potential to put a clearer biological focus on GWAS results. Such analyses can become more  
420 complex as more reference omics data sets (with genome-wide genotyping) become available.  
421 Additional analytical efforts will be required to facilitate the transition from GWAS to biology but

422 substantial data has shown there is much to be learned from these variants despite their small  
423 effects(Visscher et al., 2017).

424

425 We have now identified multiple genomic signatures that correlate between one disorder and a  
426 clinical symptom in the other disorder, illustrating genetic components underlying particular  
427 symptom dimensions within these disorders. Medical symptoms, including those seen in  
428 psychiatric disorders, can manifest through a multitude of causes. The classic example often used  
429 is headache for which many different paths lead to the same symptom. Psychiatric symptoms also  
430 have many potential causes. For example, symptoms of psychosis can be the result of highly  
431 heritable diseases such as BD and SCZ but also infectious and neurodegenerative diseases,  
432 sleep/sensory deprivation or psychedelic drugs. Demonstrating a shared biological underpinning  
433 to these symptoms suggests they could be treated through modulating the same pathway. As  
434 previously shown, we find a significant positive correlation between the PRS of BD and manic  
435 symptoms in SCZ. We also demonstrate that BD cases with psychotic features carry a significantly  
436 higher SCZ PRS than BD cases without psychotic features and this result is not driven by the  
437 schizoaffective BD subtype. Further, we show that increased PRS is associated with more severe  
438 illness. This is true for BD with psychotic features having increased SCZ PRS, earlier onset BD  
439 having higher SCZ PRS and cases with higher BD+SCZ PRS having a larger number of  
440 hospitalizations. We demonstrated that psychotic features within BD is a heritable trait and GWS  
441 loci for SCZ have a consistent direction of effect in psychotic features in BD, demonstrating the  
442 potential to study psychosis more directly to identify variants contributing to that symptom  
443 dimension.

444

445 This work illustrates the utility of genetic data, in aggregate, at dissecting symptom heterogeneity  
446 among related disorders and suggests that further work could aid in characterizing patients for  
447 more personalized treatment. Genetic risk scores have demonstrated their ability to inform and  
448 predict pathology(Cleynen et al., 2016) and more recently have been shown to be able to identify  
449 patients with risk equivalent to monogenic variants(Khera et al., 2017). In psychiatry, we lack  
450 objective biological measurements (biomarkers) with which to assess the ability of a genetic  
451 signature to predict or inform. Lacking diagnostic pathology for psychiatric disorders leaves a  
452 genuine opportunity for the genetics to drive diagnosis and treatment to a much larger degree than  
453 in other domains. One potential model assumes that each individual has a quantitative loading of  
454 a series of symptom dimensions (i.e. manic, psychotic, cognitive, etc.) and that these symptoms  
455 can be assessed at the genetic level to characterize a patient's dysfunction and used to inform  
456 disease course and optimal treatment. Making this a reality will require more detailed information  
457 on disease course and outcomes. For example, if treatment response data existed for these samples  
458 one could ask whether a genetic loading for psychosis was correlated with response to treatment.  
459 Initial work has already shown the potential of this approach using a SCZ PRS to inform lithium  
460 response in BD(Amare et al., 2018). Ultimately, the goal will be to quantify multiple genetic  
461 loadings of each individual's illness and use those measures to inform treatment based on the  
462 outcomes of previous individuals with similar profiles.

463  
464 In conclusion, we present a detailed genetic dissection of BD and SCZ pointing to substantial  
465 shared genetic risk but also demonstrating that specific loci contribute to the phenotypic  
466 differences of these disorders. We show that genetic risk scores can correspond to symptoms  
467 within and across disorders. Finally, we present data that points to these disorders being neither

468 independent nor the same but sharing particular symptom dimensions that can be captured from  
469 the genetics and used to characterize patients to ultimately inform diagnosis and treatment.

470

471 **Author Contributions:**

472 DMR, PS and KSK managed and organized the group. DMR, SR, JB, EAS, JMWP, NM, AWC,  
473 APSO, LMOL and VT contributed to analyses. Subphenotype collection and organization was led  
474 by AM and AHF. Initial manuscript was drafted by DMR, ED, ADF, SP, JLK. Manuscript  
475 contributions and interpretation of results was provided by DMR, ED, SHL, MCO, PFS, RAO,  
476 NRW, PS and KSK. The remaining authors contributed to the recruitment, genotyping, or data  
477 processing for the contributing components of the study. All other authors saw, had the opportunity  
478 to comment on, and approved the final draft.

479

480

481 **Consortia**

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578 The authors declare no competing interests.  
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## 899 **Figure Legends**

900

### 901 **Figure 1. Associated Genomic Loci Shared and Divergent Between BD and SCZ**

902 a) Odds ratios (OR) from independent data sets of BD (blue) and SCZ (red) for each of the 114  
903 genome-wide significant variants in the BD and SCZ vs controls GWAS. b) Manhattan plot for  
904 SCZ vs BD GWAS.

905

906 **Figure 2. Polygenic Risk Score Dissection of Clinical Symptom Dimensions**

907 Effect size (calculated by dividing regression estimate by standard error) from regression analysis  
908 including ancestry covariates for each subphenotype and PRS for BD (x-axis) and SCZ (y-axis).  
909 Point size represents  $-\log_{10}(\text{p-value})$  with SCZ (red) and BD (blue). Numbered subphenotypes  
910 are 1) comorbid migraine, 2) panic attacks 3) suicide attempt 4) mixed states 5) rapid cycling 6)  
911 comorbid eating disorder 7) comorbid OCD 8) year of birth 9) suicide ideation 10) panic disorder  
912 11) number of suicide attempts 12) depressive symptoms (SCZ) 13) episodes depressive 14)  
913 episodes total 15) positive symptoms (SCZ) 16) irritable mania 17) age of onset depression 18)  
914 family history 19) episodes mixed mania 20) unipolar mania 21) alcohol substance dependence  
915 22) age of onset mania 23) age at interview 24) number of hospitalizations. All subphenotypes are  
916 in BD except those labeled (SCZ).

917

918 **Table Legends**

919

920 **Table 1. Most Significant Associated Loci from SCZ vs BD GWAS**

921 Association results for the five most significant variants in the SCZ vs BD GWAS with the top  
922 two being genome-wide significant. Each variant includes results from the independent BD vs  
923 controls and SCZ vs controls GWAS and the comparable p-value from a heterogeneity test when  
924 performing a two cohort meta-analysis of SCZ and BD.

925

926 **Table 2. Complete Results of Polygenic Risk Score Dissection Analysis**



927 Polygenic scoring results of all four GWAS phenotypes (BD+SCZ vs controls, BD vs controls,  
928 SCZ vs controls and SCZ vs BD) and 24 subphenotypes from BD and 4 subphenotypes from SCZ,  
929 rows without case/control counts are quantitative measures. Significance and effects are from  
930 regression analysis of subphenotype on PRS including principal components of ancestry and site  
931 as covariates. Effect is the regression estimate divided by the standard error.

932

### 933 **Supplementary Figure Legends**

934

935 **Figure S1. Related to Figure 1b. Regional Association Plot and Forest Plot for the First**  
936 **Genome-wide Significant Hit in the SCZ vs BD GWAS.**

937 **Figure S2. Related to Figure 1b. Regional Association Plot and Forest Plot for the Second**  
938 **Genome-wide Significant Hit in the SCZ vs BD GWAS.**

939

940

941 **Figure S3. Related to Summary-data-based Mendelian Randomization. Detailed Association**  
942 **of DCAKD from SMR.**

943 Results at the *DCAKD* locus from SMR analysis of SCZ vs BD. Top plot, brown dots represent  
944 the *P* values for SNPs from SCZ vs BD GWAS, diamonds represent the *P* values for probes from  
945 the SMR test. Bottom plot, the eQTL *P* values of SNPs from the Westra study for the  
946 ILMN\_1811648 probe tagging *DCAKD*. The top and bottom plots include all the SNPs available  
947 in the region in the GWAS and eQTL summary data, respectively, rather than only the SNPs  
948 common to both data sets. Highlighted in red is the gene (*DCAKD*) that passed the SMR and  
949 HEIDI tests.

950

951 **Figure S4. Related to Regional SNP-heritability estimation. Heritability Estimates for BD**  
952 **and SCZ in Genome-wide Significant Regions of BD and SCZ.**

953 Regional SNP-heritability estimates for SCZ and BD stratified by whether the region contains the  
954 most significant variant in a genome-wide significant locus in BD, SCZ, neither or both.

955

956

957 **STAR Methods**

958 **CONTACT FOR REAGENT AND RESOURCE SHARING**

959 Genotype and phenotype data use is restricted and governed by the Psychiatric Genetics  
960 Consortium. Further information and requests for analytical results or additional information  
961 should be directed to and will be fulfilled by the Lead Contact, Douglas Ruderfer  
962 ([douglas.ruderfer@vanderbilt.edu](mailto:douglas.ruderfer@vanderbilt.edu)).

963

964 **SUBJECT DETAILS**

965 **Genotyped Sample Description**

966 SCZ samples are a substantial subset of those analyzed previously(Schizophrenia Working Group  
967 of the Psychiatric Genomics Consortium, 2014). BD samples are the newest collection from  
968 Psychiatric Genomics Consortium Bipolar Disorder Working Group(Stahl et al., 2017).

969 Below we provide information on the individual samples used here as provided by the original  
970 PGC disorder publications. Additionally, most studies have been described in detail in the citations  
971 provided. The boldfaced first line for each sample is study PI, PubMed ID, country (study name),  
972 and the PGC internal tag or study identifier.

973

974 **European ancestry, case-control design**

975 *Schizophrenia*

976 **Adolfsson, R | NP | Umeå, Sweden | scz\_umeb\_eur**

977 **Adolfsson, R | NP | Umeå, Sweden | scz\_umes\_eur**

978 Cases of European ancestry were ascertained from multiple different studies of schizophrenia  
979 (1992-2009). The diagnostic processes were similar between studies, and the final diagnosis is a  
980 best-estimate consensus lifetime diagnosis based on multiple sources of information such as  
981 clinical evaluation by research psychiatrists, different types of semi-structured interviews made by  
982 trained research nurses and research psychiatrists, medical records, course of the disease and data  
983 from multiple informants. Diagnosis was made in accordance with the Diagnostic and Statistical  
984 Manual of Mental Disorders-Version IV (DSM-IV) or International Classification of Diseases,  
985 10th Revision (ICD-10) criteria. Controls were recruited from the Betula study, an ongoing  
986 longitudinal, prospective, population-based study from the same geographic area (North Sweden)  
987 that is studying aging, health, and cognition in adults. All subjects (cases and controls) participated  
988 after giving written informed consent and the regional Ethical Review Board at the University of  
989 Umeå approved all original studies and participation in the PGC. GWAS genotyping was  
990 performed at Broad Institute.

991 **Andreassen, O | 19571808 | Norway (TOP) | scz\_top8\_eur**

992 In the TOP study (Tematisk område psykoser), cases of European ancestry, born in Norway, were  
993 recruited from psychiatric hospitals in the Oslo region. Patients were diagnosed according to SCID  
994 and further ascertainment details have been reported. Healthy control subjects were randomly  
995 selected from statistical records of persons from the same catchment area as the patient groups.

996 All participants provided written informed consent and the human subjects protocol was approved  
997 by the Norwegian Scientific-Ethical Committee and the Norwegian Data Protection Agency.

998 **Blackwood, D | 19571811 | Edinburgh, UK | scz\_edin\_eur**

999 Cases and controls were recruited from the southeast of Scotland, and ascertainment has been  
1000 previously described as part of the International Schizophrenia Consortium studies. All  
1001 participating subjects gave written, informed consent and the human subjects protocol was  
1002 approved by the Scotland A Research Ethics Committee. DNA samples were genotyped at the  
1003 Broad Institute.

1004 **Børglum, A | 19571808 | Denmark | scz\_aarh\_eur**

1005 DNA samples for all subjects were collected from blood spots systematically collected by the  
1006 Danish Newborn Screening Biobank), with case/control status established using the Danish  
1007 Psychiatric Central Register. Cases were diagnosed clinically according to ICD-10 criteria.  
1008 Controls were selected to match the cases by birth cohort. The Danish Data Protection Agency and  
1009 the ethics committees in Denmark approved the human subjects protocol.

1010 **Bramon | 23871474 | Seven countries (PEIC, WTCCC2) | scz\_pewb\_eur**

1011 **Bramon | 23871474 | Spain (PEIC, WTCCC2) | scz\_pewb\_eur**

1012 The Psychosis Endophenotypes International Consortium (PEIC) was part of WTCCC2. Samples  
1013 were collected through seven centers in Europe and Australia (the Institute of Psychiatry, King's  
1014 College London, London; GROUP (consisting of the University of Amsterdam, Amsterdam; the  
1015 University of Groningen, Groningen; Maastricht University Medical Centre, Maastricht; and the  
1016 University of Utrecht, Utrecht); the University of Western Australia, Perth; the Universidad de  
1017 Cantabria, Santander; the University of Edinburgh, Edinburgh; Heidelberg University, Heidelberg  
1018 and Ludwig-Maximilians-Universität München, Munich). To allow for a DSM-IV diagnosis to be

1019 ascertained or ruled out, all participants (including controls and unaffected family members)  
1020 underwent a structured clinical interview with the Schedule for Affective Disorders and  
1021 Schizophrenia (SADS), the Structured Clinical Interview for DSM Disorders (SCID), or the  
1022 Schedules for Clinical Assessment in Neuropsychiatry (SCAN). We included cases with  
1023 schizophrenia and schizoaffective disorder. Participants in all groups were excluded if they had a  
1024 history of neurological disease or head injury resulting in loss of consciousness.

1025 **Buxbaum, J | 20489179 | New York, US & Israel | scz\_msaf\_eur**

1026 Samples contributed by Mount Sinai were derived from three cohorts. In all cohorts, ethical  
1027 approval was obtained from all participating sites, and all subjects provided informed consent.  
1028 Two of the cohorts were in a prior paper on copy number variation. One of the cohorts was from  
1029 the Mount Sinai brain bank, where DNA was extracted from postmortem samples, and another  
1030 comprised of patients ascertained in Israel. The third cohort included subjects more recently  
1031 recruited through the Mount Sinai Conte Center.

1032 **Corvin, A | 19571811 | Ireland | scz\_dubl\_eur**

1033 The case sample was collected primarily in the Dublin area and the ascertainment procedure has  
1034 been previously described. The controls were recruited, from the same region through the Irish  
1035 Blood Transfusion Services. All participants gave written, informed consent and the collections  
1036 were approved through the Federated Dublin Hospitals and Irish Blood Transfusion Services  
1037 Research Ethics Committees, respectively. DNA samples were genotyped at the Broad Institute.

1038 **Corvin, A; Riley, B | 22883433 | Ireland (WTCCC2) | scz\_irwt\_eur**

1039 The case sample was recruited from the Republic of Ireland and Northern Ireland. All cases had  
1040 four Irish grandparents and ascertainment details have been reported elsewhere. Ethics approval  
1041 was obtained from all participating hospitals and centers. Controls were blood donors from the

1042 Irish Blood Transfusion Service, whose Ethics Committee approved the human subjects protocol.  
1043 All participants gave written informed consent. Samples were genotyped at Affymetrix (Santa  
1044 Clara, California, US) laboratory as part of the WTCCC2 genotyping pipeline.

1045 **Ehrenreich, H | 20819981 | Germany (GRAS) | scz\_gras**

1046 The Gottingen Research Association for Schizophrenia (GRAS) collection included cases  
1047 recruited across 23 German hospitals. Controls were unscreened blood donors recruited at the  
1048 Georg-August-University according to national blood donation guidelines. Cases completed a  
1049 structured clinical interview and were diagnosed with DSM-IV schizophrenia or schizoaffective  
1050 disorder. The study was approved by the Georg-August-University ethics committee and local  
1051 internal review boards of the participating centers. All participants gave written informed consent.

1052 **Esko, T | 15133739 | Estonia (EGCUT) | scz\_egcu\_eur**

1053 The Estonian cohort comes from the population-based biobank of the Estonian Genome Project of  
1054 University of Tartu (EGCUT). The project was conducted according to the Estonian Gene  
1055 Research Act and all participants provided informed consent ([www.biobank.ee](http://www.biobank.ee)). In total, 52,000  
1056 individuals aged 18 years or older participated in this cohort (33% men, 67% women). The  
1057 population distributions of the cohort reflect those of the Estonian population (83% Estonians,  
1058 14% Russians and 3% other). General practitioners (GP) and physicians in the hospitals randomly  
1059 recruited the participants. A Computer-Assisted Personal interview was conducted over 1-2 ours  
1060 at doctors' offices. Data on demographics, genealogy, educational and occupational history,  
1061 lifestyle and anthropometric and physiological data were assessed. Schizophrenia was diagnosed  
1062 prior to the recruitment by a psychiatrist according to ICD-10 criteria and identified from the  
1063 Estonian Biobank phenotype database. Controls were drawn from a larger pool of genotyped

1064 biobank samples by matching on gender, age and genetic ancestry. All the controls were  
1065 population-based and have not been sampled for any specific disease.

1066 **Esko, T; Li, Q; Domenici E | 15133739, 24166486 | J&J and Roche cases, EGCUT controls |**  
1067 **scz\_jr3a\_eur**

1068 **Esko, T; Li, Q; Domenici E | 15133739, 24166486 | J&J and Roche cases, EGCUT controls |**  
1069 **scz\_jr3b\_eur**

1070 **Esko, T; Li, Q; Domenici E | 15133739, 24166486 | J&J and Roche cases, EGCUT controls |**  
1071 **scz\_jri6\_eur**

1072 **Esko, T; Li, Q; Domenici E | 15133739, 24166486 | J&J and Roche cases cases, EGCUT**  
1073 **controls | scz\_jrsa\_eur**

1074 Cases were collected by Johnson and Johnson (J&J) and Roche as part of clinical collaborations  
1075 with hospitals and outpatient centers. Cases were diagnosed according to DSMIV criteria, with  
1076 medical record review by a trained psychiatrist. There were reliability trials across centers for the  
1077 J&J studies. The J& J cases were mostly collected in Eastern Europe, with most coming from  
1078 Estonian and Russia (>100); intermediate numbers from Austria, the Czech Republic, Latvia,  
1079 Lithuania, and Spain (50-100); and smaller collections from Bulgaria, Hungary, and Poland (<50).  
1080 The Roche cases were assessed with a structured psychiatric assessment by trained interviewers.  
1081 Most of the Eastern European controls were from the Estonian Biobank project (EGCUT) and  
1082 were ancestrally matched with cases from the J&J sample.

1083 **Gejman, P | 19571809 | US, Australia (MGS) | scz\_mgs2\_eur**

1084 European ancestry case samples were collected by the Molecular Genetics of Schizophrenia  
1085 (MGS) collaboration across multiple sites in the USA and Australia as described in detail  
1086 elsewhere. Cases gave written informed consent, and IRBs at each collecting site approved the

1087 human subjects protocol. A survey company (Knowledge Networks, under MGS guidance)  
1088 collected the European ancestry control sample and ascertainment is described in detail elsewhere.  
1089 DNA samples were genotyped at the Broad Institute.

1090 **Gurling, H | 19571811 | London, UK | scz\_uclou\_eur**

1091 All cases and controls were collected by University College London and had both parents from  
1092 England, Scotland or Wales. All participants gave written informed consent and the U.K. National  
1093 Health Service multicenter and local research ethics committee approved the human subjects  
1094 protocol. Further details on ascertainment are available elsewhere. The samples were genotyped  
1095 at the Broad Institute.

1096 **Jönsson, E | 19571808 | Sweden (Hubin) | scz\_ersw\_eur**

1097 Cases were recruited from northwestern Stockholm County and ascertainment has been described  
1098 previously. Cases gave informed consent and the human subjects protocol was approved by the  
1099 ethical committees of the Karolinska Hospital and the Stockholm Regional Ethical Committee.  
1100 Controls were recruited either among subjects previously participating in biological research at the  
1101 Karolinska Institute or drawn from a representative register of the population of Stockholm  
1102 County. All participants provided informed consent.

1103 **Kirov, G | Not published | Bulgaria | scz\_buls\_eur**

1104 All cases were recruited from Bulgaria and had a history of hospitalization for treatment of  
1105 schizophrenia. Controls were recruited from the two largest cities in Bulgaria as previously  
1106 described. All participants gave written informed consent and the study was approved by local  
1107 ethics committees at the participating centers.

1108 **Knight, J; Collier DA; Nisenbaum L | Not published | Canada (Toronto) -US(Lilly)-US  
1109 (MIGen)| scz\_lktu\_eur**



1110 Toronto cases were recruited by referral and advertisement. Diagnoses were made according to  
1111 DSM-III or DSM-IV criteria following interview and medical record review. US cases were  
1112 recruited from schizophrenia clinical trials in a range of settings as part of a trial with Eli Lilly.  
1113 Diagnoses were made according to DSM-III or DSM-IV criteria following interview by  
1114 psychiatrist and medical record review. No controls were sampled as part of the study, and  
1115 ancestrally-matched controls were chosen from the Myocardial Infarction Genetics Consortium  
1116 (MIGen, dbGaP ID phs000294.v1.p1) that was genotyped with the same SNP array.

1117 **Lencz, T; Darvasi A | 23325106 | Israel | scz\_ajsz\_eur**

1118 Cases and controls were sampled from an Ashkenazi Jewish repository (Hebrew University  
1119 Genetic Resource, <http://hugr.huji.ac.il>). Patients were recruited from hospitalized inpatients at 7  
1120 medical centers in Israel and were diagnosed with DSM-IV schizophrenia or schizoaffective  
1121 disorder. Controls were sampled through the Israeli Blood Bank and did not report any chronic  
1122 disease or regularly prescribed medication at the time of assessment. Full ascertainment details  
1123 have previously been reported. Local ethics committees and the National Genetic Committee of  
1124 the Israeli Ministry of Health approved the studies and all participants gave informed, written  
1125 consent.

1126 **Levinson, D | 22885689 | Six countries, WTCCC controls | scz\_lacw\_eur**

1127 Cases collected as part of a larger pedigree-based study were partitioned into two subsamples.  
1128 Cases with two genotyped parents were analyzed as trios (see PI Levinson, ms.scz\_lemu\_eur in  
1129 the Trio section below). Unrelated cases who could not be used as part of a trio were included as  
1130 a separate case-control analysis, using independent controls, matched by ancestry and genotyping  
1131 array, from the Wellcome Trust Case Control Consortium. Cases were identified from different  
1132 clinical settings (e.g. inpatients, outpatients and community facilities) in six countries (Australia,

1133 France, Germany, Ireland, UK, and the US). Diagnoses were established using semi-structured  
1134 interviews, psychiatric records and informant reports. Case subjects were diagnosed with  
1135 schizophrenia or schizoaffective disorder according to DSM-III-R criteria. All protocols were  
1136 approved by local IRBs, and all cases provided written informed consent.

1137 **Malhotra, A | 17522711 | New York, US | scz\_zhh1\_eur**

1138 The case and control subjects were recruited in the New York metropolitan area and ascertainment  
1139 methods have been described previously. All participants gave written, informed consent and the  
1140 IRB of the North Shore-Long Island Jewish Health System approved the human subjects protocols.  
1141 DNA was genotyped at Zucker Hillside.

1142 **Mowry, B | 21034186 | Australia | scz\_asrb\_eur**

1143 These subjects were part of the Australian Schizophrenia Research Bank. The case sample was  
1144 recruited in four Australian States (New South Wales, Queensland, Western Australia and  
1145 Victoria) through hospital inpatient units, community mental health services, outpatient clinics and  
1146 rehabilitation services, non-government mental illness support organizations, and, in the initial  
1147 stages, through a large-scale, national, multi-media advertising campaign. This sample is  
1148 comprised of 509 cases from larger metropolitan centers of Brisbane, Newcastle, Sydney,  
1149 Melbourne, and Perth. Cases gave written informed consent, and the human subjects protocol was  
1150 initially approved by the Hunter New England Area Health Research Committee and subsequently  
1151 approved by relevant Institutional Ethics Committees in Brisbane, Sydney, Melbourne and Perth.  
1152 Healthy controls were recruited through multi-media advertisements, and other sources. Controls  
1153 were from the metropolitan centers of Brisbane, Newcastle, Sydney, Melbourne, and Perth.  
1154 Controls gave written informed consent, and the human subjects protocol was approved by the  
1155 Hunter New England Area Health Research Committee and Institutional Ethics Committees in

1156 Brisbane, Sydney, Melbourne and Perth. The samples were genotyped in two stages at the Hunter  
1157 Medical Research Institute, University of Newcastle, Newcastle, Australia.

1158 **O'Donovan, M: Owen, M | 19571811 | Cardiff, UK | scz\_caws\_eur**

1159 The case sample included European ancestry schizophrenia cases recruited in the British Isles and  
1160 described previously. All cases gave written informed consent to. The study was approved by the  
1161 Multicentre Research Ethics Committee in Wales and Local Research Ethics Committees from all  
1162 participating sites. The control sample used the Wellcome Trust CaseControl Consortium  
1163 (WTCCC) sample described elsewhere, but included similar numbers of individuals from the 1958  
1164 British Birth Cohort and a panel of consenting blood donors (UK Blood Service). Samples were  
1165 genotyped at Affymetrix service lab (San Francisco, USA).

1166 **O'Donovan, M: Owen, M: Walters, J | 22614287 | UK (CLOZUK) | scz\_clm2\_eur**

1167 **O'Donovan, M: Owen, M: Walters, J | 22614287 | UK (CLOZUK) | scz\_clo3\_eur**

1168 CLOZUK cases were taking the antipsychotic clozapine and had received a clinical diagnosis of  
1169 treatment-resistant schizophrenia. Patients taking clozapine provide blood samples to allow  
1170 detection of adverse drug-effects. Through collaboration with Novartis (the manufacturer of a  
1171 proprietary form of clozapine, Clozaril), we acquired blood from people with treatment-resistant  
1172 schizophrenia according to the clozapine registration forms completed by treating psychiatrists as  
1173 previously reported. The samples were genotyped at the Broad Institute. The UK Multicentre  
1174 Research Ethics Committee (MREC) approved the study. The controls were drawn from the  
1175 WTCCC2 control samples (~3,000 from the 1958 British Birth Cohort and ~3,000 samples from  
1176 the UK Blood Service Control Group). An additional 900 controls, held by Cardiff University,  
1177 were recruited from the UK National Blood Transfusion Service. They were not specifically

1178 screened for psychiatric illness. All control samples were from participants who provided informed  
1179 consent.

1180 **Ophoff, R | 19571808 | Netherlands | scz\_ucla\_eur**

1181 The case sample consisted of inpatients and outpatients recruited through psychiatric hospitals and  
1182 institutions throughout the Netherlands. Cases with DSM-IV schizophrenia were included in the  
1183 analysis. Further details on ascertainment are provided elsewhere. Controls came from the  
1184 University Medical Centre Utrecht and were volunteers with no psychiatric history. Ethical  
1185 approval was provided by local ethics committees and all participants gave written informed  
1186 consent.

1187 **Palotie, A | 19571808 | Finland | scz\_fi3m\_eur**

1188 **Palotie, A | Not published | Finnish | scz\_fii6\_eur**

1189 Finnish cases were drawn from a nationwide collection of families with schizophrenia spectrum  
1190 disorders. The control sample was derived from the Finnish Health 2000 survey. All participants  
1191 provided written informed consent and approval was obtained from the ethics committees at each  
1192 location.

1193 **Pato, C | 19571811 | Portugal | scz\_port\_eur**

1194 Cases and controls lived in Portugal, the Azorean and Madeiran islands, or were the direct (firstor  
1195 second-generation) Portugese immigrant population in the US, as previously described. Controls  
1196 were not biologically related to cases. All participants gave written informed consent and the IRB  
1197 of SUNY Upstate Medical University approved the protocol. The samples were genotyped at the  
1198 Broad Institute.

1199 **Petryshen, T | 24424392| Boston, US (CIDAR) | scz\_cims\_eur**

1200 Cases were recruited from inpatient and outpatient settings in the Boston area by clinician referral,  
1201 through review of medical records, or through advertisements in local media. Cases were  
1202 diagnosed with DSM-IV schizophrenia through a structured clinical interview (SCID) by trained  
1203 interviewers with review of medical records and a best estimate diagnostic procedure including  
1204 reliability trials across interviewers. A psychiatrist or a PhD-level mental health professional made  
1205 the final diagnostic determination. Controls were ascertained through local advertisements from  
1206 the same geographical area. Ethical approval was provided by local ethics committees and all  
1207 participants gave written informed consent.

1208 **Rietschel/Rujescu/Nöthen | 19571808 | Bonn/Mannheim, Germany | scz\_boco\_eur**

1209 These German samples were collected by separate groups within the MoodS Consortium in  
1210 Mannheim, Bonn, Munich and Jena. For the PGC analyses, the samples were combined by chip  
1211 and ancestry. In Bonn/Mannheim, cases were ascertained as previously described. Controls were  
1212 drawn from three population-based epidemiological studies (PopGen), the Cooperative Health  
1213 Research in the Region of Augsburg (KORA) study, and the Heinz Nixdorf Recall (HNR) study.  
1214 All participants gave written informed consent and the local ethics committees approved the  
1215 human subjects protocols. Additional controls were randomly selected from a Munich-based  
1216 community sample and screened for the presence of anxiety and affective disorders using the  
1217 Composite International Diagnostic Screener. Only individuals negative for the above mentioned  
1218 disorders were included in the sample.

1219 **Rujescu, D | 19571808 | Munich, Germany | scz\_munc\_eur**

1220 For the Munich sample, cases were ascertained from the Munich area of Germany, as described  
1221 previously. The controls were unrelated volunteers randomly selected from the general population  
1222 of Munich. All were screened to exclude a history of psychosis/central neurological disease either

1223 personally or in a first-degree relative. All participants gave written informed consent and the local  
1224 ethics committees approved the human subjects protocols.

1225 **St Clair, D | 19571811 | Aberdeen, UK | scz\_aber\_eur**

1226 Ascertainment and inclusion/exclusion criteria for cases and controls have been previously  
1227 described. All participating subjects were born in the UK (95% Scotland) and gave written  
1228 informed consent. Both local and multiregional academic ethical committee approved the human  
1229 subjects protocol. The samples were genotyped at the Broad Institute.

1230 **Sullivan, PF | 18347602 | US (CATIE) | scz\_cati\_eur**

1231 Cases were collected as part of the Clinical Antipsychotics Trials of Intervention Effectiveness  
1232 (CATIE) project and ascertainment was previously described. Participants were recruited from  
1233 multiple sites in the USA with informed written consent and approval from the IRBs at each  
1234 CATIE site and the University of North Carolina (Chapel Hill). The control subjects were collected  
1235 by MGS (described above) and gave online informed consent and were fully anonymized. There  
1236 was no overlap with controls included in the MGS collaboration sample.

1237 **Sullivan, PF; Sklar P; Hultman C | 23974872 | Sweden | scz\_swe1\_eur**

1238 **Sullivan, PF; Sklar P; Hultman C | 23974872 | Sweden | scz\_s234\_eur**

1239 **Sullivan, PF; Sklar P; Hultman C | 23974872 | Sweden | scz\_swe5\_eur**

1240 **Sullivan, PF; Sklar P; Hultman C | 23974872 | Sweden | scz\_swe6\_eur**

1241 Samples from the Swedish Schizophrenia Study were collected in a multi-year project and  
1242 genotypes in six batches (sw1-6). All procedures were approved by ethical committees at the  
1243 Karolinska Institutet and the University of North Carolina, and all subjects provided written  
1244 informed consent (or legal guardian consent and subject assent). All samples were genotyped at  
1245 the Broad Institute. Cases with schizophrenia were identified via the Swedish Hospital Discharge

1246 Register which captures all public and private inpatient hospitalizations. The register is complete  
1247 from 1987 and is augmented by psychiatric data from 1973-1986. The register contains  
1248 International Classification of Disease discharge diagnoses made by attending physicians for each  
1249 hospitalization. Case inclusion criteria included  $\geq 2$  hospitalizations with a discharge diagnosis of  
1250 schizophrenia, both parents born in Scandinavia and age  $\geq 18$  years. Case exclusion criteria  
1251 included hospital register diagnosis of any medical or psychiatric disorder mitigating a confident  
1252 diagnosis of schizophrenia as determined by expert review. The validity of this case definition of  
1253 schizophrenia was strongly supported by clinical, epidemiological, genetic epidemiological and  
1254 genetic evidence. Controls were selected at random from Swedish population registers, with the  
1255 goal of obtaining an appropriate control group and avoiding ‘super-normal’ controls. Control  
1256 inclusion criteria included never being hospitalized for schizophrenia or bipolar disorder (given  
1257 evidence of genetic overlap with schizophrenia), both parents born in Scandinavia and age of  $\geq 18$   
1258 years.

1259 **Walters, J | 21850710 | Cardiff, UK (CogUK) | scz\_cou3\_eur**

1260 Cases were recruited from community mental health teams in Wales and England on the basis of  
1261 a clinical diagnosis of schizophrenia or schizoaffective disorder (depressed sub-type) as described  
1262 previously. 35 Diagnosis was confirmed following a SCAN interview and review of case notes  
1263 followed by consensus diagnosis according to DSM-IV criteria. The samples were genotyped at  
1264 the Broad Institute. The UK Multicentre Research Ethics Committee (MREC) approved the study  
1265 and all participants provided valid informed consent.

1266 **Weinberger, D | 11381111 | NIMH CBDB | scz\_lie2\_eur**

1267 **Weinberger, D | 11381111 | NIMH CBDB | scz\_lie5\_eur**

1268 Subjects were recruited from the Clinical Brain Disorders Branch of the NIMH ‘Sibling Study’ as  
1269 previously described. In brief, cases and controls gave informed consent and only participants of  
1270 European ancestry were included in the current analysis. Cases completed a structured clinical  
1271 interview and were diagnosed with schizophrenia-spectrum disorders. Samples were genotyped at  
1272 the NIMH.

1273 **Wendland/Schubert | Pfizer | Not Published | Multiple countries | scz\_pfla\_eur**

1274 Pfizer contributed anonymized individual genotypes for cases from seven multi-center  
1275 randomized, double-blind efficacy and safety clinical trials (A1281063, A1281134, A1281148,  
1276 A245-102, NRA7500001, NRA7500002, NRA7500003, and NRA7500004) as well as a set of  
1277 purchased samples (NRA9000099). Trial samples were collected for antipsychotic medications  
1278 across outpatient and inpatient treatment settings. All participating cases had a diagnosis of  
1279 schizophrenia and were assessed using a structural clinical interview by trained interviewers, with  
1280 systematic procedures to quality-control diagnostic accuracy and reliability trials across  
1281 participating sites in the United States and internationally. Purchased blood samples were obtained  
1282 from PrecisionMed International by Pharmacia and Upjohn Corporation, and were collected from  
1283 diagnosed subjects with schizophrenia and schizoaffective disorder. All studies were reviewed by  
1284 both central and local institutional review boards, depending on the study site, before recruitment  
1285 of subjects started. Protocol amendments were approved while the study was in progress and  
1286 before the data were unblinded. The studies were conducted in conformity with the U.S. Food and  
1287 Drug Administration Code of Federal Regulations (21CFR, Part 50) and the Declaration of  
1288 Helsinki and its amendments, and were consistent with Good Clinical Practice and the applicable  
1289 regulatory requirements. Participants provided written informed consent before enrollment. An  
1290 optional blood sample was collected from clinical trial subjects for pharmacogenetic analysis to



1291 investigate potential associations between genetic variant drug response and general characteristics  
1292 of schizophrenia and related disorders. Sample collection was not required for participation in the  
1293 original clinical trials. The controls (A9011027) were recruited in a multi-site, cross-sectional,  
1294 non-treatment prospective trial to collect data, including DNA, from cognitive normal and free of  
1295 psychiatric diseases elderly subjects in the US. Subjects were specifically recruited to match the  
1296 gender, age, and ethnicity information from the LEADe and UCSD MCI studies. The study  
1297 described here is within the scope of patient consent.

1298 **Werge, T | 19571808 | Denmark | scz\_denm\_eur**

1299 Cases were ascertained through psychiatric departments and twin pair studies, and were of Danish  
1300 parentage for at least the prior three generations. The controls were collected at the University of  
1301 Aarhus, and included 500 medical students, all of Danish parentage for at least three generations.  
1302 All subjects gave written informed consent and the Danish Data Protection Agency and the ethics  
1303 committees of Denmark approved the human subjects protocol.

1304

1305 *Bipolar Disorder*

1306 **Adolfsson, R | Not published | Umeå, Sweden | bip\_ume4\_eur**

1307 Clinical characterization of the patients included the Mini-International Neuropsychiatric  
1308 Interview (MINI), the Diagnostic Interview for Genetic Studies (DIGS), the Family Interview for  
1309 Genetic Studies (FIGS) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).  
1310 The final diagnoses were made according to the DSM-IV-TR and determined by consensus of 2  
1311 research psychiatrists. The unrelated Swedish control individuals, consisting of a large population-  
1312 based sample representative of the general population of the region, were randomly selected from  
1313 the 'Betula study'.

1314 **Alda, M; Smoller, J | Not published | Nova Scotia, Canada; I2B2 controls | bip\_hal2\_eur**

1315 The case samples were recruited from patients longitudinally followed at specialty mood disorders  
1316 clinics in Halifax and Ottawa (Canada). Cases were interviewed in a blind fashion with the  
1317 Schedule of Affective Disorders and Schizophrenia-Lifetime version (SADS-L) and consensus  
1318 diagnoses were made according to DSM-IV and Research Diagnostic Criteria (RDC). Protocols  
1319 and procedures were approved by the local Ethics Committees and written informed consent was  
1320 obtained from all patients before participation in the study. Control subjects were drawn from the  
1321 I2B2 (Informatics for Integrating Biology and the Bedside) project. The study consists of de-  
1322 identified healthy individuals recruited from a healthcare system in the Boston, MA, US area. The  
1323 de-identification process meant that the Massachusetts General Hospital Institutional Review  
1324 Board elected to waive the requirement of seeking informed consent as detailed by US Code of  
1325 Federal Regulations, Title 45, Part 46, Section 116 (46.116).

1326 **Andreassen, OA | PMID:21926972 [PGC1], PMID:20451256 | Norway (TOP) | bip\_top7\_eur**

1327 In the TOP study (Tematisk område psykoser), cases of European ancestry, born in Norway, were  
1328 recruited from psychiatric hospitals in the Oslo region. Patients were diagnosed according to the  
1329 SCID and further ascertainment details have been reported. Healthy control subjects were  
1330 randomly selected from statistical records of persons from the same catchment area as the patient  
1331 groups. The control subjects were screened by interview and with the Primary Care Evaluation of  
1332 Mental Disorders (PRIME-MD). None of the control subjects had a history of moderate/severe  
1333 head injury, neurological disorder, mental retardation or an age outside the age range of 18-60  
1334 years. Healthy subjects were excluded if they or any of their close relatives had a lifetime history  
1335 of a severe psychiatric disorder. All participants provided written informed consent and the human  
1336 subjects protocol was approved by the Norwegian Scientific-Ethical Committee and the

1337 Norwegian Data Protection Agency.

1338 **Andreassen, OA | Not published | Norway (TOP) | bip\_top8\_eur**

1339 The TOP8 bipolar disorder cases and controls were ascertained in the same way as the  
1340 bip\_top7\_eur (TOP7) samples described above, and recruited from hospitals across Norway.

1341 **Biernacka, JM; Frye, MA | 27769005 | Mayo Clinic, USA | bip\_may1\_eur**

1342 Bipolar cases were drawn from the Mayo Clinic Bipolar Biobank. Enrolment sites included Mayo  
1343 Clinic, Rochester, Minnesota; Lindner Center of HOPE/University of Cincinnati College of  
1344 Medicine, Cincinnati, Ohio; and the University of Minnesota, Minneapolis, Minnesota. Enrolment  
1345 at each site was approved by the local Institutional Review Board approval, and all participants  
1346 consented to use of their data for future genetic studies. Participants were identified through routine  
1347 clinical appointments, from in-patients admitted in mood disorder units, and recruitment  
1348 advertising. Participants were required to be between 18 and 80 years old and be able to speak  
1349 English, provide informed consent, and have DSM-IV-TR diagnostic confirmation of type 1 or 2  
1350 bipolar disorder or schizoaffective bipolar disorder as determined using the SCID. Controls were  
1351 selected from the Mayo Clinic Biobank. Potential controls with ICD9 codes for bipolar disorder,  
1352 schizophrenia or related diagnoses in their electronic medical record were excluded.

1353 **Blackwood, D | 18711365 [PGC1] | Edinburgh, UK | bip\_edi1\_eur**

1354 This sample comprised Caucasian individuals contacted through the inpatient and outpatient  
1355 services of hospitals in South East Scotland. A BD-I diagnosis was based on an interview with the  
1356 patient using the SADS-L supplemented by case note review and frequently by information from  
1357 medical staff, relatives and caregivers. Final diagnoses, based on DSM-IV criteria were reached  
1358 by consensus between two trained psychiatrists. Ethnically-matched controls from the same region  
1359 were recruited through the South of Scotland Blood Transfusion Service. Controls were not

1360 directly screened to exclude those with a personal or family history of psychiatric illness. The  
1361 study was approved by the Multi-Centre Research Ethics Committee for Scotland and patients  
1362 gave written informed consent for the collection of DNA samples for use in genetic studies.

1363 **Breen, G; Vincent, JB | 24387768; 19416921; 21926972 [PGC1] |London, UK; Toronto,**  
1364 **Canada [BACC] | bip\_bac1\_eur**

1365 The total case/control cohort (N=1922) includes 871 subjects from Toronto, Canada (N=431 cases  
1366 (160 male; 271 female); N=440 controls (176 male; 264 female)), 1051 subjects from London, UK  
1367 (N=538 cases (180 male; 358 female); N=513 controls (192 male; 321 female)). A summary of  
1368 mean and median age at interview, age of onset (AOO), diagnostic subtypes (BD 1 versus BD 2),  
1369 presence of psychotic symptoms, suicide attempt and family history of psychiatric disorders has  
1370 been provided previously for both the Toronto and London cohorts. From the Toronto site (Centre  
1371 for Addiction & Mental Health (CAMH)), BD individuals and unrelated healthy controls matched  
1372 for age, gender and ethnicity were recruited. Inclusion criteria for patients: a) diagnosed with  
1373 DSMIV/ICD 10 BD 1 or 2; b) 18 years old or over; c) Caucasian, of Northern and Western  
1374 European origin, and three out of four grandparents also N.W. European Caucasian. Exclusion  
1375 criteria include: a) Use of intravenous drugs; b) Evidence of intellectual disability; c) Related to  
1376 an individual already in the study; d) Manias that only ever occurred in relation to or resulting  
1377 from alcohol or substance abuse/dependence, or medical illness; e) Manias resulting from non-  
1378 psychotropic substance usage. The SCAN interview (Schedule for Clinical Assessments in  
1379 Neuropsychiatry) was used for subject assessment. Using the SCAN interview along with case  
1380 note review, each case was assigned DSM-IV and ICD 10 diagnoses by two independent  
1381 diagnosticians, according to lifetime consensus best-estimate diagnosis. Lifetime occurrence of  
1382 psychiatric symptoms was also recorded using the OPCRIT checklist, modified for use with mood

1383 disorders. Similar methods and criteria were also used to collect a sample of 538 BD cases and  
1384 513 controls for the London cohort (King's College London; KCL). Both studies were approved  
1385 by respective institutional research ethics committees (the CAMH Research Ethics Board (REB)  
1386 in Toronto, and the College Research Ethics Committee (CREC) at KCL), and informed written  
1387 consent was obtained from all participants. GWAS results have previously been published for the  
1388 entire KCL/CAMH cohort.

1389 **Corvin, A | 18711365 [PGC1] | Ireland | bip\_dub1\_eur**

1390 Samples were collected as part of a larger study of the genetics of psychotic disorders in the  
1391 Republic of Ireland, under protocols approved by the relevant IRBs and with written informed  
1392 consent that permitted repository use. Cases were recruited from Hospitals and Community  
1393 psychiatric facilities in Ireland by a psychiatrist or psychiatric nurse trained to use the SCID.  
1394 Diagnosis was based on the structured interview supplemented by case note review and collateral  
1395 history where available. All diagnoses were reviewed by an independent reviewer. Controls were  
1396 ascertained with informed consent from the Irish GeneBank and represented blood donors who  
1397 met the same ethnicity criteria as cases. Controls were not specifically screened for psychiatric  
1398 illness.

1399 **Rietschel, M; Nöthen, MM, Cichon, S | 21926972 [PGC1] | BOMA-Germany I |**  
1400 **bip\_bonn\_eur**

1401 Cases for the BOMA-Bipolar Study were ascertained from consecutive admissions to the inpatient  
1402 units of the Department of Psychiatry and Psychotherapy at the University of Bonn and at the  
1403 Central Institute for Mental Health in Mannheim, University of Heidelberg, Germany. DSM-IV  
1404 lifetime diagnoses of bipolar I disorder were assigned using a consensus best-estimate procedure,  
1405 based on all available information, including a structured interview with the SCID and SADS-L,

1406 medical records, and the family history method. In addition, the OPCRIT checklist was used for  
1407 the detailed polydiagnostic documentation of symptoms. Controls were ascertained from three  
1408 population-based studies in Germany (PopGen, KORA, and Heinz-Nixdorf-Recall Study). The  
1409 control subjects were not screened for mental illness. Study protocols were reviewed and approved  
1410 in advance by Institutional Review Boards of the participating institutions. All subjects provided  
1411 written informed consent.

1412 **Rietschel, M; Nöthen, MM; Schulze, TG; Reif, A; Forstner, AJ | 24618891 | BOMA-Germany**  
1413 **II | bip\_bmg2\_eur**

1414 Cases were recruited from consecutive admissions to psychiatric in-patient units at the University  
1415 Hospital Würzburg. All cases received a lifetime diagnosis of BD according to the DSM-IV criteria  
1416 using a consensus best-estimate procedure based on all available information, including semi-  
1417 structured diagnostic interviews using the Association for Methodology and Documentation in  
1418 Psychiatry, medical records and the family history method. In addition, the OPCRIT system was  
1419 used for the detailed polydiagnostic documentation of symptoms.

1420 Control subjects were ascertained from the population-based Heinz Nixdorf Recall (HNR) Study.  
1421 The controls were not screened for a history of mental illness. Study protocols were reviewed and  
1422 approved in advance by Institutional Review Boards of the participating institutions. All subjects  
1423 provided written informed consent.

1424 **Rietschel, M; Nöthen, MM; Schulze, TG; Bauer, M; Forstner, AJ; Müller-Myhsok, B |**  
1425 **24618891 | BOMA-Germany III | bip\_bmg3\_eur**

1426 Cases were recruited at the Central Institute of Mental Health in Mannheim, University of  
1427 Heidelberg, and other collaborating psychiatric hospitals in Germany. All cases received a lifetime  
1428 diagnosis of BD according to the DSM-IV criteria using a consensus best-estimate procedure based

1429 on all available information including structured diagnostic interviews using the AMDP,  
1430 Composite International Diagnostic Screener (CID-S), SADS-L and/or SCID, medical records,  
1431 and the family history method. In addition, the OPCRIT system was used for the detailed  
1432 polydiagnostic documentation of symptoms. Controls were selected randomly from a Munich-  
1433 based community sample and recruited at the Max-Planck Institute of Psychiatry. They were  
1434 screened for the presence of anxiety and mood disorders using the CID-S. Only individuals without  
1435 mood and anxiety disorders were collected as controls. Study protocols were reviewed and  
1436 approved in advance by Institutional Review Boards of the participating institutions. All subjects  
1437 provided written informed consent.

1438 **Hauser, J; Lissowska, J; Forstner, AJ | 24618891 | BOMA-Poland | bip\_bmpo\_eur**

1439 Cases were recruited at the Department of Psychiatry, Poznan University of Medical Sciences,  
1440 Poznan, Poland. All cases received a lifetime diagnosis of BD according to the DSM-IV criteria  
1441 on the basis of a consensus best-estimate procedure and structured diagnostic interviews using the  
1442 SCID. Controls were drawn from a population-based case-control sample recruited by the Cancer-  
1443 Center and Institute of Oncology, Warsaw, Poland and a hospital-based case-control sample  
1444 recruited by the Nofer Institute of Occupational Medicine, Lodz, Poland. The Polish controls were  
1445 produced by the International Agency for Research on Cancer (IARC) and the Centre National de  
1446 Génotypage (CNG) GWAS Initiative for a study of upper aerodigestive tract cancers. The controls  
1447 were not screened for a history of mental illness. Study protocols were reviewed and approved in  
1448 advance by Institutional Review Boards of the participating institutions. All subjects provided  
1449 written informed consent.

1450 **Rietschel, M; Nöthen, MM; Rivas, F; Mayoral, F; Kogevinas, M; others | 24618891 | BOMA-**  
1451 **Spain | bip\_bmsp\_eur**

1452 Cases were recruited at the mental health departments of the following five centers in Andalusia,  
1453 Spain: University Hospital Reina Sofia of Córdoba, Provincial Hospital of Jaen; Hospital of Jerez  
1454 de la Frontera (Cádiz); Hospital of Puerto Real (Cádiz); Hospital Punta Europa of Algeciras  
1455 (Cádiz); and Hospital Universitario San Cecilio (Granada). Diagnostic assessment was performed  
1456 using the SADS-L; the OPCRIT; a review of medical records; and interviews with first and/or  
1457 second degree family members using the Family Informant Schedule and Criteria (FISC).  
1458 Consensus best estimate BD diagnoses were assigned by two or more independent senior  
1459 psychiatrists and/or psychologists, and according to the RDC, and the DSM-IV. Controls were  
1460 Spanish subjects drawn from a cohort of individuals recruited in the framework of the European  
1461 Community Respiratory Health Survey (ECRHS, <http://www.ecrhs.org/>). The controls were not  
1462 screened for a history of mental illness. Study protocols were reviewed and approved in advance  
1463 by Institutional Review Boards of the participating institutions. All subjects provided written  
1464 informed consent.

1465 **Fullerton, J.M.; Mitchell, P.B.; Schofield, P.R.; Martin N.G.; Cichon, S. | 24618891 | BOMA-**  
1466 **Australia | bip\_bmau\_eur**

1467 Cases were recruited at the Mood Disorder Unit, Prince of Wales Hospital in Sydney. All cases  
1468 received a lifetime diagnosis of BD according to the DSM-IV criteria on the basis of a consensus  
1469 best-estimate procedure and structured diagnostic interviews using the DIGS, FIGS, and the SCID.  
1470 Controls were parents of unselected adolescent twins from the Brisbane Longitudinal Twin Study.  
1471 The controls were not screened for a history of mental illness. Study protocols were reviewed and  
1472 approved in advance by Institutional Review Boards of the participating institutions. All subjects  
1473 provided written informed consent.

1474 **Grigoriu-Serbanescu, M; Nöthen, MM | 21353194 | BOMA-Romania | bip\_rom3\_eur**



1475 Cases were recruited from consecutive admissions to the Obregia Clinical Psychiatric Hospital,  
1476 Bucharest. Patients were administered the DIGS and FIGS interviews. Information was also  
1477 obtained from medical records and close relatives. The diagnosis of BP-I was assigned according  
1478 to DSM-IV criteria using the best estimate procedure. All patients had at least two hospitalized  
1479 illness episodes. Population-based controls were evaluated using the DIGS to exclude a lifetime  
1480 history of major affective disorders, schizophrenia, schizoaffective disorders, and other psychoses,  
1481 obsessive-compulsive disorder, eating disorders, and alcohol or drug addiction.

1482 **Craddock, N, Jones, I, Jones, L | 17554300 | WTCCC | bip\_wtcc\_eur\_sr-qc**

1483 Cases were all over the age of 17 yr, living in the UK and of European descent. Recruitment was  
1484 undertaken throughout the UK and included individuals who had been in contact with mental  
1485 health services and had a lifetime history of high mood. After providing written informed consent,  
1486 participants were interviewed by a trained psychologist or psychiatrist using a semi-structured  
1487 lifetime diagnostic psychiatric interview (Schedules for Clinical Assessment in Neuropsychiatry)  
1488 and available psychiatric medical records were reviewed. Using all available data, best-estimate  
1489 life-time diagnoses were made according to the RDC. In the current study we included cases with  
1490 a lifetime diagnosis of RDC bipolar 1 disorder, bipolar 2 disorder or schizo-affective disorder,  
1491 bipolar type. Controls were recruited from two sources: the 1958 Birth Cohort study and the UK  
1492 Blood Service (blood donors) and were not screened for history of mental illness. All cases and  
1493 controls were recruited under protocols approved by the appropriate IRBs. All subjects gave  
1494 written informed consent.

1495 **Kelsoe, J | 21926972 [PGC1] | USA (GAIN) | bip\_gain\_eur**

1496 *Genetic Association Information Network (GAIN)/ The Bipolar Genome Study (BiGS)* The BD  
1497 sample was collected under the auspices of the NIMH Genetics Initiative for BD

1498 (<http://zork.wustl.edu/nimh/>), genotyped as part of GAIN and analyzed as part of a larger GWAS  
1499 conducted by the BiGS consortium. Approximately half of the GAIN sample was collected as  
1500 multiplex families or sib pair families (waves 1-4), the remainder were collected as individual  
1501 cases (wave 5). Subjects were ascertained at 11 sites: Indiana University, John Hopkins University,  
1502 the NIMH Intramural Research Program, Washington University at St. Louis, University of  
1503 Pennsylvania, University of Chicago, Rush Medical School, University of Iowa, University of  
1504 California, San Diego, University of California, San Francisco, and University of Michigan. All  
1505 investigations were carried out after the review of protocols by the IRB at each participating  
1506 institution. At all sites, potential cases were identified from screening admissions to local treatment  
1507 facilities and through publicity programs or advocacy groups. Potential cases were evaluated using  
1508 the DIGS, FIGS, and information from relatives and medical records. All information was  
1509 reviewed through a best estimate diagnostic procedure by two independent and non-interviewing  
1510 clinicians and a consensus best-estimate diagnosis was reached. In the event of a disagreement, a  
1511 third review was done to break the tie. Controls were from the NIMH Genetic Repository sample  
1512 obtained by Dr. P. Gejman through a contract to Knowledge Networks, Inc. Only individuals with  
1513 complete or near-complete psychiatric questionnaire data who did not fulfill diagnostic criteria for  
1514 major depression and denied a history of psychosis or BD were included as controls for BiGS  
1515 analyses. Controls were matched for gender and ethnicity to the cases.

1516 **Kelsoe, J; Sklar, P; Smoller, J | [PGC1 Replication] | USA (FAT2; FaST, BiGS, TGEN) |**  
1517 **bip\_fat2\_eur**

1518 Cases were collected from individuals at the 11 U.S. sites described for the GAIN sample. Eligible  
1519 participants were age 18 or older meeting DSM-IV criteria for BD-I or BD-II by consensus  
1520 diagnosis based on interviews with the Affective Disorders Evaluation (ADE) and MINI. All

1521 participants provided written informed consent and the study protocol was approved by IRBs at  
1522 each site. Collection of phenotypic data and DNA samples were supported by NIMH grants  
1523 MH063445 (JW Smoller); MH067288 (PI: P Sklar), and MH63420 (PI: V Nimgaonkar). The  
1524 control samples were NIMH controls that were using the methods described in that section. The  
1525 case and control samples were independent of those included in the GAIN sample.

1526 **Kirov, G | 25055870 | Bulgarian trios | bip\_butr\_eur**

1527 All cases were recruited in Bulgaria from psychiatric inpatient and outpatient services. Each  
1528 proband had a history of hospitalisation and was interviewed with an abbreviated version of the  
1529 SCAN. Consensus best-estimate diagnoses were made according to DSM-IV criteria by two  
1530 researchers. All participants gave written informed consent and the study was approved by local  
1531 ethics committees at the participating centers.

1532 **Kirov, G | 25055870 | UK trios | bip\_uktr\_eur**

1533 The BD subjects were recruited from lithium clinics and interviewed in person by a senior  
1534 psychiatrist, using abbreviated version of the SCAN. Consensus best-estimate diagnoses were  
1535 made based on the interview and hospital notes. Ethics committee approval for the study was  
1536 obtained from the relevant research ethics committees and all individuals provided written  
1537 informed consent for participation.

1538 **Landén, M; Sullivan, PF; Sklar, P | [ICCBD] | Sweden (ICCBD) | bip\_swa2\_eur**

1539 The BD subjects were identified using the Swedish National Quality Register for Bipolar Disorders  
1540 (Bipolär) and the Swedish National Patient Register (using a validated algorithm requiring at least  
1541 two hospitalizations with a BD diagnosis). A confirmatory telephone interview with a diagnostic  
1542 review was conducted. Additional subjects were recruited from the St. Göran Bipolar Project  
1543 (Affective Center at Northern Stockholm Psychiatry Clinic, Sweden), enrolling new and ongoing

1544 patients diagnosed with BD using structured clinical interviews. Diagnoses were made according  
1545 to the DSM-IV criteria (Bipolär and St. Göran Bipolar Project) and ICD-10 (National Patient  
1546 Register). The control subjects used were the same as for the SCZ analyses described above. All  
1547 ascertainment procedures were approved by the Regional Ethical Committees in Sweden.

1548 **Landén, M; Sullivan, PF; Sklar, P | [ICCBD] | Sweden (ICCBD) | bip\_swei\_eur**

1549 The cases and controls in the bip\_swei\_eur sample were recruited using the same ascertainment  
1550 methods described for the bip\_swa2\_eur sample.

1551 **Leboyer, M | [PGC1 replication] | France | bip\_fran\_eur**

1552 Cases with BD1 or BD2 and control samples were recruited as part of a large study of genetics of  
1553 BD in France (Paris-Creteil, Bordeaux, Nancy) with a protocol approved by relevant IRBs and  
1554 with written informed consent. Cases of French descent for more than 3 generations were  
1555 assessed by a trained psychiatrist or psychologist using structured interviews supplemented by  
1556 medical case notes, mood scales and self-rating questionnaire assessing dimensions.

1557 **Li, Q | 24166486; 27769005 | USA (Janssen), SAGE controls | bip\_jst5\_eur**

1558 The study included unrelated patients with bipolar 1 disorder from 6 clinical trials (IDs:  
1559 NCT00253162, NCT00257075, NCT00076115, NCT00299715, NCT00309699, and  
1560 NCT00309686). Participant recruitment was conducted by Janssen Research & Development,  
1561 LLC (formerly known as Johnson & Johnson Pharmaceutical Research & Development, LLC) to  
1562 assess the efficacy and safety of risperidone. Bipolar cases were diagnosed according to DSM-IV-  
1563 TR criteria. The diagnosis of bipolar disorder was confirmed by the Schedule for Affective  
1564 Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-  
1565 PL) in NCT00076115, by the SCID in NCT00257075 and NCT00253162, or by the MINI in  
1566 NCT00299715 and NCT00309699, and NCT00309686, respectively. Additional detailed

1567 descriptions of these clinical trials can be found at ClinicalTrials.gov. Only patients of European  
1568 ancestry with matching controls were included in the current analysis. Controls subjects were  
1569 drawn from the Study of Addiction: Genetics and Environment (SAGE, dbGaP Study Accession:  
1570 phs000092.v1.p1). Control subjects did not have alcohol dependence or drug dependence  
1571 diagnoses; however, mood disorders were not an exclusion criterion.

1572 **McQuillin, A; Gurling, H | 18317468 [PGC1] | UCL (University College London), London,**  
1573 **UK | bip\_uclo\_eur**

1574 The UCL sample comprised Caucasian individuals who were ascertained and received clinical  
1575 diagnoses of bipolar 1 disorder according to UK National Health Service (NHS) psychiatrists at  
1576 interview using the categories of the International Classification of Disease version 10. In addition  
1577 bipolar subjects were included only if both parents were of English, Irish, Welsh or Scottish  
1578 descent and if three out of four grandparents were of the same descent. All volunteers read an  
1579 information sheet approved by the Metropolitan Medical Research Ethics Committee who also  
1580 approved the project for all NHS hospitals. Written informed consent was obtained from each  
1581 volunteer. The UCL control subjects were recruited from London branches of the National Blood  
1582 Service, from local NHS family doctor clinics and from university student volunteers. All control  
1583 subjects were interviewed with the SADS-L to exclude all psychiatric disorders.

1584 **Craddock, N; Jones, I; Jones, L | [ICCBD] | Cardiff and Worcester, UK (ICCBD-BDRN) |**  
1585 **bip\_icuk\_eur**

1586 Cases were all over the age of 17 yr, living in the UK and of European descent. Cases were  
1587 recruited via systematic and not systematic methods as part of the Bipolar Disorder Research  
1588 Network project ([www.bdrn.org](http://www.bdrn.org)), provided written informed consent and were interviewed using  
1589 a semi-structured diagnostic interview, the Schedules for Clinical Assessment in Neuropsychiatry.

1590 Based on the information gathered from the interview and case notes review, best-estimate lifetime  
1591 diagnosis was made according to DSM-IV. Inter-rater reliability was formally assessed using 20  
1592 randomly selected cases (mean  $\kappa$  Statistic = 0.85). In the current study we included cases with a  
1593 lifetime diagnosis of DSM-IV bipolar disorder or schizo-affective disorder, bipolar type. The  
1594 BDRN study has UK National Health Service (NHS) Research Ethics Committee approval and  
1595 local Research and Development approval in all participating NHS Trusts/Health Boards. Controls  
1596 were part of the Wellcome Trust Case Control Consortium common control set, which comprised  
1597 healthy blood donors recruited from the UK Blood Service and samples from the 1958 British  
1598 Birth Cohort. Controls were not screened for a history of mental illness. All cases and controls  
1599 were recruited under protocols approved by the appropriate IRBs. All subjects gave written  
1600 informed consent.

1601 **Ophoff, RA | Not Published | Netherlands | bip\_ucla\_eur**

1602 The case sample consisted of inpatients and outpatients recruited through psychiatric hospitals and  
1603 institutions throughout the Netherlands. Cases with DSM-IV bipolar disorder, determined after  
1604 interview with the SCID, were included in the analysis. Controls were collected in parallel at  
1605 different sites in the Netherlands and were volunteers with no psychiatric history after screening  
1606 with the (MINI). Ethical approval was provided by UCLA and local ethics committees and all  
1607 participants gave written informed consent.

1608 **Paciga, S | [PGC1] | USA (Pfizer) | bip\_pf1e\_eur**

1609 This sample comprised Caucasian individuals recruited into one of three Geodon (ziprasidone)  
1610 clinical trials (NCT00141271, NCT00282464, NCT00483548). Subjects were diagnosed by a  
1611 clinician with a primary diagnosis of Bipolar 1 Disorder, most recent episode depressed, with or  
1612 without rapid cycling, without psychotic features, as defined in the DSM-IV-TR (296.5x) and

1613 confirmed by the MINI (version 5.0.0). Subjects also were assessed as having a HAM-D-17 total  
1614 score of >20 at the screening visit. The trials were conducted in accordance with the protocols,  
1615 International Conference on Harmonization of Good Clinical Practice Guidelines, and applicable  
1616 local regulatory requirements and laws. Patients gave written informed consent for the collection  
1617 of blood samples for DNA for use in genetic studies.

1618 **Pato, C | [ICCBD] | Los Angeles, USA (ICCBD-GPC)| bip\_usc2\_eur**

1619 Genomic Psychiatry Consortium (GPC) cases and controls were collected via the University of  
1620 Southern California healthcare system, as previously described. Using a combination of focused,  
1621 direct interviews and data extraction from medical records, diagnoses were established using the  
1622 OPCRIT and were based on DSM-IV-TR criteria. Age and gender-matched controls were  
1623 ascertained from the University of Southern California health system and assessed using a  
1624 validated screening instrument and medical records.

1625 **Scott, L; Myer, RM; Boehnke, M | 19416921 [PGC1] | Michigan, USA (Pritzker and NIMH)**  
1626 **| bip\_mich\_eur**

1627 The Pritzker Neuropsychiatric Disorders Research Consortium (NIMH/Pritzker) case and controls  
1628 samples were from the NIMH Genetics Initiative Genetics Initiative Repository. Cases were  
1629 diagnosed according to DMS-III or DSM-IV criteria using diagnostic interviews and/or medical  
1630 record review. Cases with low confidence diagnoses were excluded. From each wave 1-5 available  
1631 non-Ashkenazi European-origin family, two BD1 siblings were included when possible and the  
1632 proband was preferentially included if available (n=946 individuals in 473 sibling pairs); otherwise  
1633 a single BD1 case was included (n=184). The bipolar sibling pairs were retained within the  
1634 NIMH/Pritzker sample when individuals in more than one study were uniquely assigned to a study  
1635 set. Controls had non-Ashkenazi European-origin, were aged 20-70 years and reported no

1636 diagnosis with or treatment for BD or schizophrenia, and that they had not heard voices that others  
1637 could not hear. Individuals with suspected major depression were excluded based on answers to  
1638 questions related to depressive mood. NIMH controls were further selected as the best match(es)  
1639 to NIMH cases based on self-reported ancestry.

1640 **Sklar, P; Smoller, J | 18317468 [PGC1] | USA (STEP1) | bip\_stp1\_eur**

1641 The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) was a seven-  
1642 site, national U.S., longitudinal cohort study designed to examine the effectiveness of treatments  
1643 and their impact on the course of BD that enrolled 4,361 participants who met DSM-IV criteria  
1644 for BD1, BD2, bipolar not otherwise specified (NOS), schizoaffective manic or bipolar type, or  
1645 cyclothymic disorder based on diagnostic interviews. From the parent study, 2,089 individuals  
1646 who were over 18 years of age with BD1 and BD2 diagnoses consented to the collection of blood  
1647 samples for DNA. BD samples with a consensus diagnosis of BD1 were selected for inclusion in  
1648 STEP1. Two groups of controls samples from the NIMH repository were used. One comprised  
1649 DNA samples derived from US Caucasian anonymous cord blood donors. The second were  
1650 controls who completed the online self-administered psychiatric screen and were ascertained as  
1651 described above, by Knowledge Networks Inc. For the second sample of controls only those  
1652 without history of schizophrenia, psychosis, BD or major depression with functional impairment  
1653 were used.

1654 **Sklar, P; Smoller, J | 18711365 [PGC1] | USA (STEP2) | bip\_stp2\_eur**

1655 The STEP2 sample included BD-1 and BD-2 samples from the STEP-BD study described above  
1656 along with BD-2 subjects from UCL study also described above. The controls samples for this  
1657 study were from the NIMH repository as described above for the STEP1 study.

1658



1659 **European ancestry, trio design**

1660 *Schizophrenia*

1661 **Kirov, G: Owen M | 22083728| Bulgaria | ms.scz\_butr\_eur**

1662 Families from Bulgaria were recruited if a proband had schizophrenia or schizoaffective disorder,  
1663 both parents were available, and all members of the trio agreed to participate in the study.  
1664 Recruitment took place between 1999 and 2004 in several psychiatric hospitals in Bulgaria. Ethical  
1665 Committee approval was obtained from each of these hospitals. All probands and all parents  
1666 received an Information Sheet and signed Informed Consent Forms. All participants had attended  
1667 mainstream schools, which at the time in Bulgaria, excluded people with mental retardation.  
1668 Probands were either in- or out-patients at the time of the study but each had a history of  
1669 hospitalization. A team of psychiatrists was trained in using the rating scales and methods of the  
1670 study. We used the SCAN instrument to perform an interview for psychotic and mood symptoms.  
1671 This instrument has been translated into Bulgarian and validated by one of its authors (A.  
1672 Jablensky). Consensus diagnoses were made according to DSM-IV criteria on the basis of an  
1673 interview and inspection of hospital notes by two clinicians. If consensus was not attained, the  
1674 patient was re-interviewed by a research interview trained clinician and was excluded if consensus  
1675 could still not be reached. In addition, approximately 23% of the sample was selected at random  
1676 and re-interviewed by a research interview trained clinician. Hospital notes were also collected for  
1677 affected relatives in order to confirm diagnoses.

1678 **Levinson, D | 22885689 | Six countries | ms.scz\_lemu\_eur**

1679 Schizophrenia cases were included from the family sample of European-ancestry pedigrees  
1680 described by Levinson et al. Participants and their families in this trio study, probands were  
1681 ascertained and recruited from different clinical settings (e.g. inpatients, outpatients and

1682 community facilities) in six countries (Australia, France, Germany, Ireland, UK, and the US).  
1683 (Unrelated individuals were included as part of a case-control design, see Levinson, D,  
1684 scz\_lacw\_eur above.) Diagnoses were established using semi-structured interviews, psychiatric  
1685 records and informant reports. Case probands were diagnosed with schizophrenia or  
1686 schizoaffective disorder according to DSM-III-R criteria. The trio-based analysis included families  
1687 where there was at least one affected proband and two available parents. Each affected sibling in  
1688 such families was included, with the parents, as an independent trio. All protocols were approved  
1689 by loci IRBs, and all cases provided written informed consent.

1690 **Kirov, G: Owen, M | Not Published | Bulgaria | ms.scz\_uktr\_eur**

1691 All cases and parents were recruited from UK and had a history of hospitalization for treatment of  
1692 schizophrenia. Diagnosis was confirmed following a SCAN interview and review of case notes  
1693 followed by consensus diagnosis according to DSM-IV criteria. The samples were genotyped at  
1694 the Broad Institute. All participants gave written informed consent and the study was approved by  
1695 local ethics committees at the participating centers. The samples were genotyped at the Broad  
1696 Institute.

1697

### 1698 **Genotype Quality Control**

1699 To ensure independence of the data sets, individuals were excluded until no individual showed a  
1700 relatedness (pihat) value greater than 0.2 to any other individual in the collection, while  
1701 preferentially keeping the case over the control for case-control related pairs. In total 1,795 BD  
1702 cases, 1,165 SCZ cases and 27,274 controls were removed (most of which were previously  
1703 known), leaving 20,129 BD cases 33,426 SCZ cases and 54,065 controls for the final meta-  
1704 analysis.

1705 For analyses directly comparing BD and SCZ, we matched cases from both phenotypes on  
1706 genotyping platform and ancestry, resulting in 15,270 BD cases versus 23,585 SCZ cases. Hence,  
1707 we were able to match 76% of BD cases and 71% of SCZ cases for this case vs case analysis.  
1708 Among our entire dataset, 44% of the sample was female, 51% was male and 5% were unreported  
1709 by the collection site. This work focused explicitly on the autosomes and sought maximal power  
1710 across the analyses, sex was not used except for during quality control and sex-specific analyses  
1711 were not performed in this effort. Individual ages were not provided. For a subset of cases, we had  
1712 information for age of onset which were used in subphenotype specific analyses only.

1713

#### 1714 **Sub-phenotype Description**

1715 BD sub-phenotypes were collected by each study site using a combination of diagnostic  
1716 instruments, case records and participant interviews. Ascertainment details for each study site are  
1717 described in the supplementary data of the PGC Bipolar Working Group paper(Stahl et al., 2017).  
1718 The selection of phenotypes for collection by this group was determined by literature searches in  
1719 order to determine phenotypes with prior evidence for heritability. It was further refined dependent  
1720 on the availability of phenotype data across a range of study sites and the consistency by which  
1721 the phenotypes were defined. Schizophrenia subphenotypes represent quantitative traits extracted  
1722 using factor analysis from a set of standard psychiatric assessments and represent four symptom  
1723 dimensions (manic, depressive, positive and negative). These subphenotypes were used  
1724 previously(Ruderfer et al., 2014) but in this work we have increased the sample size with additional  
1725 cohorts being added.

1726

#### 1727 **METHOD DETAILS**

1728

1729 **QUANTIFICATION AND STATISTICAL ANALYSIS**

1730

1731 **Quality Control, Imputation, Association Analysis and Polygenic Risk Score Testing**

1732 Quality control and imputation were performed on each of the study cohort datasets (n=81),  
1733 according to standards established by the Psychiatric Genomics Consortium (PGC). The quality  
1734 control parameters for retaining SNPs and subjects were: SNP missingness < 0.05 (before sample  
1735 removal); subject missingness ( $p < 0.02$ ); autosomal heterozygosity deviation ( $|F_{het}| < 0.2$ ); SNP  
1736 missingness < 0.02 (after sample removal); difference in SNP missingness between cases and  
1737 controls < 0.02; and SNP Hardy-Weinberg equilibrium ( $p > 10^{-6}$  in controls or  $p > 10^{-10}$  in cases).  
1738 Genotype imputation was performed using the pre-phasing/imputation stepwise approach  
1739 implemented in IMPUTE2(Howie et al., 2011) / SHAPEIT(Delaneau et al., 2013) (chunk size of  
1740 3 Mb and default parameters). The imputation reference set consisted of 2,186 phased haplotypes  
1741 from the full 1000 Genomes Project dataset (August 2012, 30,069,288 variants, release  
1742 “v3.macGT1”), all variants align to human genome build 19 (hg19). After imputation, we used the  
1743 best guess genotypes (genotype probability > 0.8), for further robust relatedness testing and  
1744 population structure analysis. Here we required very high imputation quality (INFO > 0.8) and low  
1745 missingness (<1%) for further quality control. After linkage disequilibrium (LD) pruning ( $r^2 <$   
1746 0.02) and frequency filtering (MAF > 0.05), there were 14,473 autosomal SNPs in the data set.  
1747 Principal component estimation was done with the same collection of autosomal SNPs. We tested  
1748 the first 20 principal components for phenotype association (using logistic regression with study  
1749 indicator variables included as covariates) and evaluated their impact on the genome-wide test  
1750 statistics using  $\lambda$ . Thirteen principal components namely 1,2,3,4,5,6,7,8,10,12,15,18,20 were

1751 included in all association analyses ( $\lambda=1.45$ ). Analytical steps were repeated for SCZ vs BD  
1752 analysis.

1753 We performed four main association analyses (Figure 1), i.e. (i) GWAS of BD and SCZ as a single  
1754 combined case phenotype, as well as disorder-specific GWAS using independent control sets in  
1755 (ii) BD cases vs BD controls and (iii) SCZ cases vs SCZ controls, and (iv) association analysis of  
1756 SCZ cases vs BD cases. For all GWS loci from the GWAS of BD and SCZ vs controls we identified  
1757 any GWS loci within 1Mb from the extent of the locus in the previously published PGC SCZ vs  
1758 controls(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and the  
1759 most recent PGC GWAS of BD vs controls(Stahl et al., 2017) and performed conditional analysis.  
1760 Specifically, we transformed the genotype probabilities of the disease variant into dosages and  
1761 used it as an additional covariate for the association analysis for the BD+SCZ vs controls index  
1762 SNP. This was done within each cohort and an OR based inverse SE weighted meta-analysis was  
1763 performed for the final result. All datasets were included except for those with trios.

1764

### 1765 **Summary-data-based Mendelian Randomization (SMR)**

1766 SMR(Zhu et al., 2016) is a method that integrates summary level GWAS data with gene expression  
1767 quantitative trait loci (eQTL) identified in independent data sets. This integration aims to identify  
1768 variants that have pleiotropic effects on expression of a given gene and the phenotype. While  
1769 significant findings may indeed reflect a causal path from variant to phenotype through expression,  
1770 it is impossible to discern statistically between pleiotropy and causality. However, the method can  
1771 remove linkage as driving the result, and uses the data available to prioritise amongst genes in  
1772 genomic regions that show association with disease. We used SMR as a statistical fine-mapping  
1773 tool applied to the SCZ vs BD GWAS results to identify loci with strong evidence of causality via

1774 gene expression. SMR analysis is limited to significant ( $FDR < 0.05$ ) cis SNP-expression  
1775 quantitative trait loci (eQTLs) with  $MAF > 0.01$ . eQTLs passing these thresholds were combined  
1776 with GWAS results in the SMR test, with significance ( $p_{SMR}$ ) reported at a Bonferroni-corrected  
1777 threshold for each eQTL data set. The eQTL architecture may differ between genes. For example,  
1778 through LD, many SNPs can generate significant associations with the same gene, but in some  
1779 instances multiple SNPs may be independently associated with the expression of a gene. After  
1780 identification of significant SNP-expression-trait association through the SMR test, a follow-up  
1781 heterogeneity test aims to prioritize variants by excluding regions for which there is conservative  
1782 evidence for multiple causal loci ( $p_{HET} < 0.05$ ). SMR analyses were conducted using eQTL data  
1783 from whole peripheral blood(Westra et al., 2013), dorsolateral prefrontal cortex generated by the  
1784 CommonMind Consortium<sup>8</sup>, and 11 brain sub-regions from the GTEx consortium(Consortium,  
1785 2015).

1786

### 1787 **Regional joint GWAS**

1788 Summary statistic Z-scores were calculated for each marker in each of the four main GWAS  
1789 results, using the logistic regression coefficient and its standard error. Rare SNPs ( $MAF < 0.01$ ),  
1790 and SNPs with a low INFO score ( $< 0.3$ ) in either dataset were removed. The causal variant  
1791 relationships between SCZ and BD were investigated using the Bayesian method software pw-  
1792 gwas (v0.2.1), with quasi-independent regions determined by estimate LD blocks in an analysis of  
1793 European individuals ( $n=1,703$ )(Berisa and Pickrell, 2015; Pickrell et al., 2016). Briefly, pw-gwas  
1794 takes a Bayesian approach to determine the probability of five independent models of association.  
1795 (1) There is no causal variant in BD or SCZ; (2) a causal variant in BD, but not SCZ (3); a causal  
1796 variant in SCZ, but not BD; (4) a shared causal variant influencing both BD and SCZ; (5) two

1797 causal variants where one influences BD, and one influences SCZ (Figure 2). The posterior  
1798 probability of each model is calculated using model priors, estimated empirically within pw-gwas.  
1799 Regions were considered to support a particular model when the posterior probability of the model  
1800 was greater than 0.5.

1801

### 1802 **Regional SNP-heritability estimation**

1803 We calculated local SNP-heritability independently for SCZ and BD using the Heritability  
1804 Estimator from Summary Statistics (HESS) software(Shi et al., 2016) for each of the independent  
1805 regions defined above. The sum of these regional estimates is the total SNP-heritability of the trait.  
1806 To calculate local SNP-heritability HESS requires reference LD matrices representative of the  
1807 population from which the GWAS samples were drawn. We utilized the 1000 genomes European  
1808 individuals as the reference panel(The 1000 Genomes Project Consortium, 2015). Unlike pw-  
1809 gwas(Pickrell et al., 2016), HESS does not assume that only one causal variant can be present in  
1810 each region.

1811

### 1812 **DATA AND SOFTWARE AVAILABILITY**

1813 Summary statistics from GWAS are publically available at [https://www.med.unc.edu/pgc/results-](https://www.med.unc.edu/pgc/results-and-downloads/downloads)  
1814 [and-downloads/downloads](https://www.med.unc.edu/pgc/results-and-downloads/downloads).

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