

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

Douglas M Ruderfer<sup>1</sup>, Stephan Ripke<sup>2,3,4</sup>, Andrew McQuillin<sup>5</sup>, James Boocock<sup>6</sup>, Eli A Stahl<sup>7</sup>, Jennifer M Whitehead Pavlides<sup>8</sup>, Niamh Mullins<sup>9</sup>, Alexander W Charney<sup>10</sup>, Anil P S Ori<sup>11</sup>, Loes M Olde Loohuis<sup>11</sup>, Enrico Domenici<sup>12</sup>, Arianna Di Florio<sup>13</sup>, Sergi Papiol<sup>14,15</sup>, Janos L. Kalman<sup>14,15</sup>, Rolf Adolfsson<sup>16</sup>, Ingrid Agartz<sup>17,18,19</sup>, Esben Agerbo<sup>20,21,22</sup>, Huda Akil<sup>23</sup>, Diego Albani<sup>24</sup>, Margot Albus<sup>25</sup>, Martin Alda<sup>26,27</sup>, Madeline Alexander<sup>28</sup>, Judith Allardyce<sup>29</sup>, Ney Alliey-Rodriguez<sup>30</sup>, Thomas D Als<sup>31,22,32</sup>, Farooq Amin<sup>33,34</sup>, Adebayo Anjorin<sup>35</sup>, Maria J Arranz<sup>36,37</sup>, Swapnil Awasthi<sup>3</sup>, Silviu A Bacanu<sup>38</sup>, Judith A Badner<sup>39</sup>, Marie Baekvad-Hansen<sup>40</sup>, Steven Bakker<sup>41</sup>, Gavin Band<sup>42</sup>, Jack D Barchas<sup>43</sup>, Ines Barroso<sup>44</sup>, Nicholas Bass<sup>45</sup>, Michael Bauer<sup>46</sup>, Bernhard T Baune<sup>47</sup>, Martin Begemann<sup>48</sup>, Celine Bellenguez<sup>42</sup>, Richard A Belliveau Jr<sup>4</sup>, Frank Bellivier<sup>49,50,51,52</sup>, Stephan Bender<sup>53,54</sup>, Judit Bene<sup>55,56</sup>, Sarah E Bergen<sup>57,4</sup>, 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\*Authors contributed equally to this work

Affiliations are towards the end of the manuscript

**Corresponding author:** Douglas M. Ruderfer ([douglas.ruderfer@vanderbilt.edu](mailto:douglas.ruderfer@vanderbilt.edu))

## Abstract

Schizophrenia (SCZ) and bipolar disorder (BD) are highly heritable disorders that share a significant proportion of common risk variation. Understanding the genetic factors underlying the specific symptoms of these disorders will be crucial for improving diagnosis, intervention and treatment. In case-control data consisting of 53,555 cases (20,129 BD, 33,426 SCZ) and 54,065 controls, we identified 114 genome-wide significant loci (GWS) when comparing all cases to controls, of which 41 represented novel findings. Two genome-wide significant loci were identified when comparing SCZ to BD and a third was found when directly incorporating functional information. Regional joint association identified a genomic region of overlapping association in BD and SCZ with disease-independent causal variants indicating a fourth region contributing to differences between these disorders. Regional SNP-heritability analyses demonstrated that the estimated heritability of BD based on the SCZ GWS regions was significantly higher than that based on the average genomic region (91 regions,  $p = 1.2 \times 10^{-6}$ ) while the inverse was not significant (19 regions,  $p=0.89$ ). Using our BD and SCZ GWAS we calculated polygenic risk scores and identified several significant correlations with: 1) SCZ subphenotypes: negative symptoms (SCZ,  $p=3.6 \times 10^{-6}$ ) and manic symptoms (BD,  $p=2 \times 10^{-5}$ ), 2) BD subphenotypes: psychotic features (SCZ  $p=1.2 \times 10^{-10}$ , BD  $p=5.3 \times 10^{-5}$ ) and age of onset (SCZ  $p=7.9 \times 10^{-4}$ ). Finally, we show that psychotic features in BD has significant SNP-heritability ( $h^2_{\text{snp}}=0.15$ ,  $SE=0.06$ ), and a significant genetic correlation with SCZ ( $r_g=0.34$ ) in addition there is a significant sign test result between SCZ GWAS and a GWAS of BD cases contrasting those with and without psychotic features ( $p=0.0038$ , one-side binomial test). For the first time, we have identified specific loci pointing to a potential role of 4 genes (*DARS2*, *ARFGEF2*, *DCAKD* and *GATAD2A*) that distinguish between BD and SCZ, providing an opportunity to understand

the biology contributing to clinical differences of these disorders. Our results provide the best evidence so far of genomic components distinguishing between BD and SCZ that contribute directly to specific symptom dimensions.

## **Introduction**

Bipolar disorder (BD) and schizophrenia (SCZ) are severe psychiatric disorders and among the leading causes of disability worldwide<sup>1</sup>. Both disorders have significant genetic components with heritability estimates ranging from 60-80%<sup>2</sup>. A genetic-epidemiological genetic study demonstrated a substantial overlap between these two disorders with a genetic correlation from common variation near 0.6-0.7 and high relative risks (RR) among relatives of both BD and SCZ patients (RRs for parent/offspring: BD/BD: 6.4, BD/SCZ: 2.4; SCZ/BD: 5.2, SCZ/SCZ: 9.9)<sup>3</sup>. Despite shared genetics and symptomology, the current diagnostic systems<sup>4,5</sup> represent BD and SCZ as distinct categorical entities differentiated on the basis of their clinical presentation, with BD characterized by predominant mood symptoms, mood-congruent delusions and an episodic disease course and SCZ considered a prototypical psychotic disorder. Further, premorbid cognitive impairment and reduced intelligence are more frequent and severe in SCZ than BD<sup>6</sup>. The genetic contributors to these phenotypic distinctions have yet to be elucidated and could aid in understanding the underlying biology of their unique clinical presentation.

While the shared genetic component is large, studies to date have identified key genetic architecture differences between these two disorders. A polygenic risk score created from a case only SCZ vs BD genome-wide association study (GWAS) significantly correlated with SCZ vs BD diagnosis in an independent sample<sup>7</sup>, providing evidence that differences between the disorders also have a genetic basis. An enrichment of rare, moderate to highly penetrant copy

number variants (CNVs) and *de novo* CNVs are seen in SCZ patients<sup>8-12</sup>, while, the involvement of CNVs in BD is much less clear<sup>13</sup>. Although the role of *de novo* single nucleotide variants in BD and SCZ has been investigated in only a handful of studies so far, enrichment in pathways associated with the postsynaptic density has been reported for SCZ, but not BD<sup>14,15</sup>. Identifying disorder-specific variants or quantifying the contribution of variation to specific symptom dimensions remains an open question. For example, previous work by this group has demonstrated that SCZ patients with greater manic symptoms had higher polygenic risk for BD<sup>7</sup>. Here, we utilize the largest collection of genotyped samples of BD and SCZ along with 28 subphenotypes to assess variants and genomic regions that contribute differentially to the disorders and to specific symptoms dimensions or subphenotypes within them.

## **Methods**

### **Sample Description**

SCZ samples are those analyzed previously<sup>16</sup>. BD samples are the newest collection from Psychiatric Genomics Consortium Bipolar Disorder Working Group (*Stahl et al. submitted*). To ensure independence of the data sets, individuals were excluded until no individual showed a relatedness ( $\rho_{\text{hat}}$ ) value greater than 0.2 to any other individual in the collection, while preferentially keeping the case over the control for case-control related pairs. In total 2,181 BD cases, 1,604 SCZ cases and 27,308 controls were removed (most of which were previously known), leaving 20,129 BD cases 33,426 SCZ cases and 54,065 controls for the final meta-analysis.

For analyses directly comparing BD and SCZ, we matched cases from both phenotypes on genotyping platform and ancestry, resulting in 15,270 BD cases versus 23,585 SCZ cases. In other words, we were able to match 76% of BD cases and 71% of SCZ cases.

### **Sub-phenotype description**

BD sub-phenotypes were collected by each study site using a combination of diagnostic instruments, case records and participant interviews. Ascertainment details for each study site are described in the supplementary data of the PGC Bipolar Working Group paper (*Stahl et al. submitted*). The selection of phenotypes for collection by this group was determined by literature searches in order to determine phenotypes with prior evidence for heritability. It was further refined dependent on the availability of phenotype data across a range of study sites and the consistency by which the phenotypes were defined. Schizophrenia subphenotypes are the same as described previously but in a larger proportion of patients<sup>7</sup>.

### **Quality Control, Imputation, Association Analysis and Polygenic Risk Scoring**

Quality control and imputation were performed on each of the study cohort datasets (n=81), according to standards established by the Psychiatric Genomics Consortium (PGC). The quality control parameters for retaining SNPs and subjects were: SNP missingness < 0.05 (before sample removal); subject missingness ( $p < 0.02$ ); autosomal heterozygosity deviation ( $|F_{het}| < 0.2$ ); SNP missingness < 0.02 (after sample removal); difference in SNP missingness between cases and controls < 0.02; and SNP Hardy-Weinberg equilibrium ( $p > 10^{-6}$  in controls or  $p > 10^{-10}$  in cases). Genotype imputation was performed using the pre-phasing/imputation stepwise approach implemented in IMPUTE2<sup>17</sup> / SHAPEIT<sup>18</sup> (chunk size of 3 Mb and default



parameters). The imputation reference set consisted of 2,186 phased haplotypes from the full 1000 Genomes Project dataset (August 2012, 30,069,288 variants, release “v3.macGT1”). After imputation, we used the best guess genotypes, for further robust relatedness testing and population structure analysis. Here we required very high imputation quality ( $INFO > 0.8$ ) and low missingness ( $< 1\%$ ) for further quality control. After linkage disequilibrium (LD) pruning ( $r^2 < 0.02$ ) and frequency filtering ( $MAF > 0.05$ ), there were 14,473 autosomal SNPs in the data set. Relatedness testing was done with PLINK<sup>19</sup> and pairs of subjects with  $pihat > 0.2$  were identified and one member of each pair removed at random after preferentially retaining cases over controls. Principal component estimation was done with the same collection of autosomal SNPs. We tested the first 20 principal components for phenotype association (using logistic regression with study indicator variables included as covariates) and evaluated their impact on the genome-wide test statistics using  $\lambda$ . Thirteen principal components namely 1,2,3,4,5,6,7,8,10,12,15,18,20 were included in all association analyses ( $\lambda=1.45$ ). Analytical steps were repeated for SCZ vs BD analysis.

We performed four main association analyses, i.e. (i) GWAS of BD and SCZ as a single combined case phenotype, as well as disorder-specific GWAS using independent control sets in (ii) BD cases vs BD controls and (iii) SCZ cases vs SCZ controls, and (iv) association analysis of SCZ cases vs BD cases.

### **Summary-data-based Mendelian Randomization (SMR)<sup>20</sup>**

We used SMR as a statistical fine-mapping tool applied to the SCZ vs BD GWAS results to identify loci with strong evidence of causality via gene expression. SMR analysis is limited to significant ( $FDR < 0.05$ ) cis SNP-expression quantitative trait loci (eQTLs) with  $MAF > 0.01$ .

eQTLs passing these thresholds were combined with GWAS results in the SMR test, with significance ( $p_{\text{SMR}}$ ) reported at a Bonferroni-corrected threshold for each eQTL data set. The eQTL architecture may differ between genes. Through LD, many SNPs can generate significant associations with the same gene, but in some instances multiple SNPs may be independently associated with the expression of a gene. After identification of significant SNP-expression-trait association through the SMR test, a follow-up heterogeneity test aims to prioritize variants by excluding regions for which there is conservative evidence for multiple causal loci ( $p_{\text{HET}} < 0.05$ ). SMR analyses were conducted using eQTL data from whole peripheral blood<sup>21</sup>, dorsolateral prefrontal cortex generated by the CommonMind Consortium<sup>8</sup>, and 11 brain sub-regions from the GTEx consortium<sup>22</sup>.

### **Regional joint GWAS**

Summary statistic Z-scores were calculated for each marker in each of the four main GWAS results, using the logistic regression coefficient and its standard error. Rare SNPs ( $\text{MAF} < 0.01$ ), and SNPs with a low INFO score ( $< 0.3$ ) in either dataset were removed. The causal variant relationships between SCZ and BD were investigated using the Bayesian method software *pw-gwas* (v0.2.1), with quasi-independent regions determined by estimate LD blocks in an analysis of European individuals ( $n=1,702$ )<sup>23,24</sup>. Briefly, *pw-gwas* takes a Bayesian approach to determine the probability of five independent models of association. (1) There is no causal variant in BD or SCZ; (2) a causal variant in BD, but not SCZ (3); a causal variant in SCZ, but not BD; (4) a shared causal variant influencing both BD and SCZ; (5) two causal variants where one influences BD, and one influences SCZ. The posterior probability of each model is calculated using model



priors, estimated empirically within pw-gwas. Regions were considered to support a particular model when the posterior probability of the model was greater than 0.5.

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

We calculated local SNP-heritability independently for SCZ and BD using the Heritability Estimator from Summary Statistics (HESS) software<sup>25</sup> for each of the independent regions defined above. The sum of these regional estimates is the total SNP-heritability of the trait. To calculate local SNP-heritability HESS requires reference LD matrices representative of the population from which the GWAS samples were drawn. We utilized the 1000 genomes European individuals as the reference panel<sup>26</sup>. Unlike pw-gwas<sup>23</sup>, HESS does not assume that only one causal variant can be present in each region.

## **Results**

### **GWAS**

We performed association analysis of BD and SCZ as a combined phenotype, totaling 53,555 cases (20,129 BD, 33,426 SCZ) and 54,065 controls on 15.5 million dosages imputed from 1000 genomes phase 3<sup>26</sup>. Logistic regression was performed controlling for 13 components of ancestry, study sites and genotyping platform. One hundred and fourteen regions contained at least one variant for which the p-value was lower than our genome-wide significance (GWS) threshold of  $p < 5 \times 10^{-8}$ . Among these 114 loci, 41 had non-overlapping LD regions ( $r^2 > 0.6$ ) with the largest and most recently performed single disease GWAS of SCZ<sup>16</sup> and BD (*Stahl et al. submitted*). Establishing independent controls (see Methods) allowed us to perform disorder-

specific GWAS in 20,129 BD cases vs 21,524 BD controls and 33,426 SCZ cases and 32,541 SCZ controls. Using these results, we compared effect sizes of these 114 loci across each disorder independently (Figure 1a) showing that subsets of variants have larger effects in SCZ vs BD or vice versa.

To identify loci with divergent effects on BD and SCZ, we performed an association analysis on 23,585 SCZ cases and 15,270 BD cases matched for shared ancestry and genotyping platform (see Methods, Figure 1b Supplementary Figures 1-5, Supplementary Table 1). Two genome-wide significant loci were identified, the most significant of which was rs56355601 located on chromosome 1 at position 173,811,455 within an intron of *DARS2*. The second most significant locus was a four base indel on chromosome 20 at position 47638976 in an intron of *ARFGEF2*. For both variants, the minor allele frequency was higher in BD cases than SCZ cases and disease-specific GWAS showed opposite directions of effect. We sought to identify additional disease specific loci by incorporating expression information with association results to perform fine-mapping and identify novel variants<sup>27-30</sup>. Here, we applied the summary-data-based Mendelian randomization (SMR) method<sup>20</sup> (see Methods) utilizing the cis-QTLs derived from peripheral blood<sup>21</sup>, human dorsolateral prefrontal cortex (DLPFC)<sup>31</sup> from the Common Mind Consortium and 11 brain regions from the GTEx consortium<sup>22</sup>. We identified one SNP-probe combination that surpassed the threshold for genome-wide significance in blood but was also the most significant finding in brain. We found that SNP rs4793172 in gene *DCAKD* is associated with SCZ vs BD analysis ( $p_{\text{GWAS}} = 2.8 \times 10^{-6}$ ) and is an 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 ( $p_{\text{eQTL}} = 2.9 \times 10^{-25}$ ,  $p_{\text{SMR}} = 2.0 \times 10^{-5}$  in DLFC, and  $p_{\text{eQTL}} = 4.6 \times 10^{-15}$ ,  $p_{\text{SMR}} = 6.0 \times 10^{-5}$  in GTEx cerebellar hemisphere) (Supplementary Table 2,

Supplementary Figure 6) and shows no evidence of heterogeneity ( $p_{\text{HET}} = 0.66$ ) which implies only a single causal variant in the region.

### **Regional joint association**

We expanded our efforts to identify disorder specific genomic regions by jointly analyzing independent GWAS results from BD and SCZ<sup>23</sup>. Among 1,702 regions genome-wide (see Methods), 223 had a posterior probability of greater than 0.5 of having a causal variant in at least one disorder. Of these, 132 best fit the model of a shared causal variant influencing both BD and SCZ, 88 were most likely specific to SCZ, 3 demonstrated evidence of two independent variants (with one impacting each of the two disorders) and zero were BD specific. Of note, the data estimated prior probability of having a BD specific region was 0.1% compared to 15% for SCZ, potentially a result of increased power from the larger SCZ sample size.

The 114 GWS SNPs from the combined BD and SCZ GWAS localized into 99 independent regions, of which 78 (79%) were shared with a posterior probability of greater than 0.5. Sixty regions had at least one GWS SNP in the independent SCZ GWAS, of which 30 (50%) are shared and 8 regions contained a GWS SNP in the independent BD GWAS, of which 6 (75%) are shared using the same definition. For the three regions showing evidence for independent variants, two had highly non-overlapping association signals in the same region stemming from independent variants. The third, on chromosome 19 presented a different scenario where association signals were overlapping (Supplementary Figure 7). The most significant variant in BD was rs111444407 (chr19:19358207,  $p = 8.67 \times 10^{-10}$ ) and for SCZ was rs2315283 (chr19:19480575,  $p = 4.41 \times 10^{-7}$ ). After conditioning on the most significant variant in the other disorder, the association signals of the most significant variant in BD and SCZ were largely

unchanged (BD rs111444407 =  $1.3 \times 10^{-9}$ , SCZ rs2315283  $p = 6.7 \times 10^{-5}$ ). We further calculated the probability of each variant in the region being causal for both BD and SCZ<sup>32</sup> and found no correlation ( $r = -0.00016$ ). The most significant variants had the highest posterior probability of being causal (SCZ: rs2315283, prob = 0.02, BD: rs111444407, prob = 0.16). Both variants most significantly regulate the expression of *GATAD2A* in brain<sup>31</sup> but in opposite directions (rs111444407  $p_{eQTL} = 6 \times 10^{-15}$ , beta = 0.105; rs2315283  $p_{eQTL} = 1.5 \times 10^{-28}$ , beta = -0.11).

### Regional SNP-heritability estimation

Across the genome, regional SNP-heritabilities ( $h^2_{\text{snp}}$ ) were estimated separately for SCZ and BD<sup>25</sup> and were found to be moderately correlated ( $r = 0.25$ ). We next defined risk regions as those containing the most associated SNP for each GWS locus. In total, there were 101 SCZ risk regions from the 105 autosomal GWS loci reported previously<sup>16</sup> and 29 BD risk regions from 30 GWS loci reported in a companion paper (*Stahl et al. submitted*). Ten regions were risk regions for both BD and SCZ comprising 33% of BD risk regions and 10% of SCZ risk regions. We further stratified regional  $h^2_{\text{snp}}$  by whether a region was a risk region in one disorder, none or both (Figure 2). Since the discovery data for the regions overlapped with the data used for the heritability estimation, we expected within-disorder analyses to show significant results. In risk regions specific to SCZ ( $n = 91$ ) there was a significant increase in regional  $h^2_{\text{snp}}$  in SCZ, as expected ( $p = 1.1 \times 10^{-22}$ ), but also in BD ( $p = 1.2 \times 10^{-6}$ ). In risk regions specific to BD ( $n = 19$ ), significantly increased regional  $h^2_{\text{snp}}$  was observed in BD, as expected ( $p = 0.0007$ ), but not in SCZ ( $p = 0.89$ ). Risk regions shared by both disorders had significantly higher  $h^2_{\text{snp}}$  in both disorders, as expected (BD  $p = 5.3 \times 10^{-5}$ , SCZ  $p = 0.006$ ), compared to non-risk regions. However, we observed a significant increase in BD  $h^2_{\text{snp}}$  in shared risk regions compared to BD

risk regions (BD  $p = 0.003$ ) but not SCZ  $h^2_{\text{snp}}$  for shared risk regions compared to SCZ risk regions ( $p = 0.62$ ). Using a less stringent p-value threshold for defining risk regions ( $p < 5 \times 10^{-6}$ ), thereby substantially increasing the number of regions, resulted in similar results (Supplementary Figure 8). Seven regions contributed to substantially higher  $h^2_{\text{snp}}$  in SCZ compared to BD but no region showed the inverse pattern. Of these regions, all but one was in the major histocompatibility region (MHC), the sole novel region was chr10:104380410-106695047 with regional  $h^2_{\text{snp}} = 0.0019$  in SCZ and  $h^2_{\text{snp}} = 0.00063$  in BD.

### **Polygenic dissection of subphenotypes**

Subphenotypes were collected for a subset of patients in both BD and SCZ (see Methods). For SCZ, we had clinical quantitative measurements of manic, depressive, positive and negative symptoms generated from factor analysis of multiple instruments as described previously<sup>7</sup> but in larger sample sizes ( $n=6908, 6907, 8259, 8355$  respectively). For BD, 24 subphenotypes were collected among nearly 13,000 cases in distinct categories including comorbidities, clinical information such as rapid cycling and psychotic features as well as additional disease course data such as age of onset and number of hospitalizations. For each BD and SCZ patient, we calculated a polygenic risk score (PRS) using all SNPs, from each of the four main GWAS analyses (BD+SCZ, BD, SCZ and SCZvsBD). We then used regression analysis including principal components and site to assess the relationship between each subphenotype and the 4 PRS. We applied a significance cutoff of  $p < 0.0004$  based on Bonferroni correction for 112 tests. In total, we identified 6 significant results after correction (Figure 3, Table 1). For BD PRS we see a significant positive correlation between PRS and manic symptoms in SCZ cases as seen previously<sup>7</sup> ( $p=2 \times 10^{-5}$ ,  $t=4.26$ ) and psychotic features in BD patients ( $p=5.3 \times 10^{-5}$ ,  $t=4.04$ ). For

SCZ PRS, we see a significant increase in PRS for BD cases with versus without psychotic features ( $p=1.2 \times 10^{-10}$ ,  $t=6.45$ ) and negative symptoms in SCZ patients ( $p=3.60 \times 10^{-6}$ ,  $t=4.64$ ). As with the SCZ PRS, BD+SCZ PRS is also significantly associated with psychotic features in BD ( $p=7.9 \times 10^{-13}$ ,  $t=7.17$ ) and negative symptoms in SCZ ( $p=1.5 \times 10^{-5}$ ,  $t=4.33$ ). While not surpassing conservative correction, the next two most significant results are both indicative of a more severe course in BD: increased BD+SCZ PRS with increased numbers of hospitalizations in BD cases ( $p=4.2 \times 10^{-4}$ ,  $t=3.53$ ) and increased SCZ PRS with earlier onset of BD ( $p=7.9 \times 10^{-4}$ ,  $t=-3.36$ ). We assessed the role of BD subtype on correlation between SCZ PRS and psychotic features and identified significant correlation when restricted to only BD type I cases (BDI: 3,763 with psychosis, 2,629 without,  $p=1.55 \times 10^{-5}$ , Supplementary Table 3).

For all 8 quantitative subphenotypes and 9 binary subphenotypes having at least 1,000 cases, we performed a GWAS within cases to calculate heritability and genetic correlation with BD and SCZ. Only two subphenotypes had significant  $h^2_{\text{snp}}$  estimates using LD-score regression<sup>33</sup>, psychotic features in BD ( $h^2_{\text{snp}}=0.15$ ,  $SE=0.06$ ) and suicide attempt ( $h^2_{\text{snp}}=0.25$ ,  $SE=0.1$ ). Only psychotic features demonstrated significant genetic correlation with SCZ ( $r_g=0.34$ ,  $SE=0.13$ ,  $p=0.009$ ). While the genetic correlation demonstrates a genome-wide relationship between common variants contributing to SCZ and those contributing to psychotic features in BD cases, we sought to assess whether this could be demonstrated among the most significantly associated SCZ loci. Of the 105 autosomal genome-wide significant SCZ loci previously published<sup>16</sup>, 60 out of 100 variants in our dataset after QC demonstrated the same direction of effect for psychotic features in BD ( $p=0.028$ , one-sided binomial-test).



## Discussion

Here we present a genetic dissection of bipolar disorder and schizophrenia from over 100,000 genotyped subjects. As previously shown<sup>34</sup>, we found an extensive degree of genetic sharing between these two disorders. We identified 114 genome-wide significant loci contributing to both disorders of which 37 are novel to this analysis. Despite the high degree of sharing, we identified several loci that significantly differentiated between the two disorders, having opposite directions of effect, and polygenic components that significantly correlated from one disorder to symptoms of the other.

Two GWS loci were identified from the case only SCZ versus BD analysis providing opportunities to inform the underlying biological distinctions between BD and SCZ. The most significant locus is in *DARS2* (coding for the mitochondrial Aspartate-tRNA ligase) which is highly expressed in the brain and significantly regulated by the most significant SNP rs56355601 ( $p_{eQTL}=2.5 \times 10^{-11}$ ). Homozygous mutations in *DARS2* are responsible for leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), which was characterized by neurological symptoms such as psychomotor developmental delay, cerebellar ataxia and delayed mental development<sup>35</sup>. Interestingly, based on methylation analysis from the prefrontal cortex of stress models (rats and monkeys) and from peripheral samples (in monkeys and human newborns), *DARS2*, among others, has been suggested as a potential molecular marker of early-life stress and vulnerability to psychiatric disorders<sup>36</sup>. The second most significant locus maps to *ARFGEF2*, which codes for ADP Ribosylation Factor Guanine Nucleotide Exchange Factor 2 (also known as BIG2), a protein involved in vesicular trafficking from the trans-Golgi network. Mutations in *ARFGEF2* have been shown to underlie an

autosomal recessive condition characterized by microcephaly and periventricular heterotopia, a disorder caused by abnormal neural proliferation and migration<sup>37</sup>. Although not genome-wide significant, the third most significant locus implicates *ARNTL* (Aryl Hydrocarbon Receptor Nuclear Translocator Like), which is a core component of the circadian clock. *ARNTL* has been previously hypothesized for relevance in bipolar disorder,<sup>38</sup> although human genetic evidence is limited<sup>39</sup>. Incorporating transcriptional data identified a third genome-wide significant finding in *DCAKD*. The gene codes for Dephospho-CoA Kinase Domain Containing, a member of the human postsynaptic density proteome from human neocortex<sup>40</sup>. In the mouse cortical synaptoproteome *DCAKD* has been found to be among the proteins with the highest changes between juvenile postnatal days and adult stage, which suggests a putative role in brain development<sup>41,42</sup>.

We further assessed the contribution of regions of the genome to each disorder through joint regional association and regional heritability estimation. These results point to two additional loci that may contribute differentially to liability to BD and SCZ. The region on chr19 shows overlapping association peaks that are driven by independent causal variants for each disorder. Both variants significantly regulate the same gene *GATAD2A* but in opposite directions. *GATAD2A* is a transcriptional repressor, which is targeted by *MBD2* and is involved in methylation-dependent gene silencing. The protein is part of the large NuRD (nucleosome remodeling and deacetylase) complex, for which also HDAC1/2 are essential components. NurD complex proteins have been associated to autism<sup>43</sup>. Their members, including *GATAD2A*, display preferential expression in fetal brain development<sup>43</sup> and in recent work has been implicated in SCZ through open chromatin<sup>44</sup>. Further, p66 $\alpha$  (mouse *GATAD2A*) was recently shown to

participate in memory preservation through long-lasting histone modification in hippocampal memory-activated neurons<sup>45</sup>. The region on chromosome 10 appears to be shared across both disorders; however, there are additional independent contributing variants to SCZ and not BD, indicating another region of interest, although biological interpretation remains unknown.

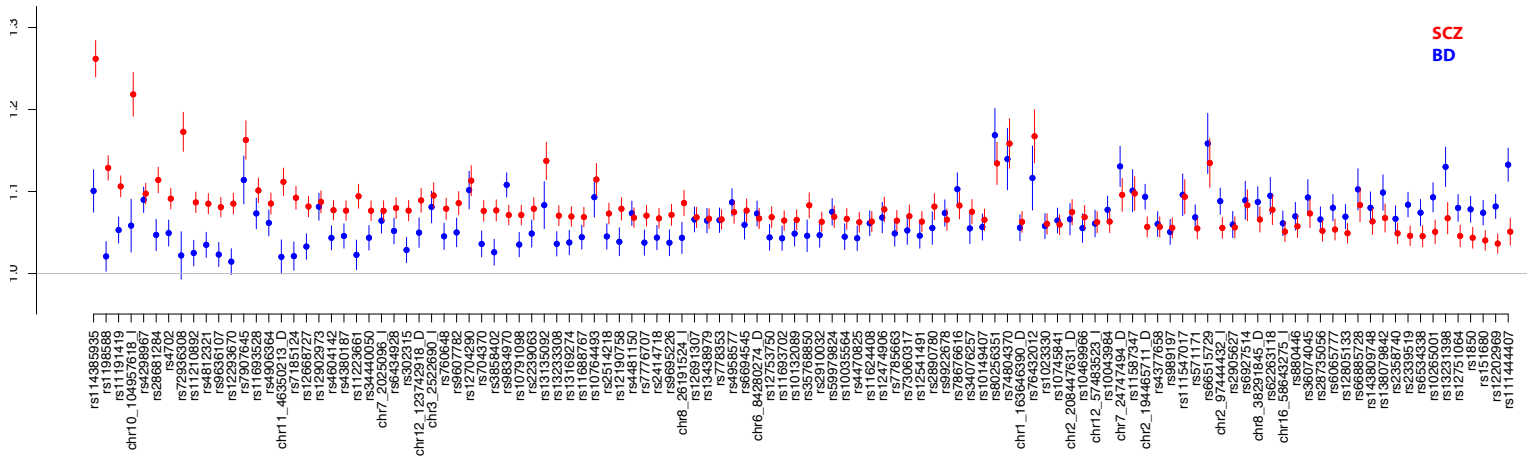
More broadly, SNP-heritability appears to be consistently shared across regions and chromosomes between these two disorders. Regions with GWS loci often explain higher proportions of heritability as expected. When looking at the effect on heritability of the presence of a GWS locus in the other disorder, we identified a significant increase in BD heritability for regions containing a GWS locus for SCZ but no significant increase in SCZ heritability in regions having a BD one. This result suggests a directionality to the genetic sharing of these disorders with a larger proportion of BD loci being specific to BD. However, we cannot exclude that the asymmetry of results may reflect less power of discovery for BD than SCZ. The degree to which power and subphenotypes contribute to this result requires further examination.

We have now identified multiple genomic signatures that correlate between one disorder and a clinical symptom in the other disorder, demonstrating that there are genetic components underlying particular symptom dimensions within these disorders. As previously shown, we find a significant positive correlation between PRS of BD and manic symptoms in SCZ. We also demonstrate that BD cases with psychotic features carry a significantly higher SCZ PRS than BD cases without psychotic features and this result is not driven by schizoaffective BD subtype. Further, we show evidence that increased PRS is associated with more severe illness. This is true for BD with psychotic features having increased SCZ PRS, earlier onset BD having higher SCZ

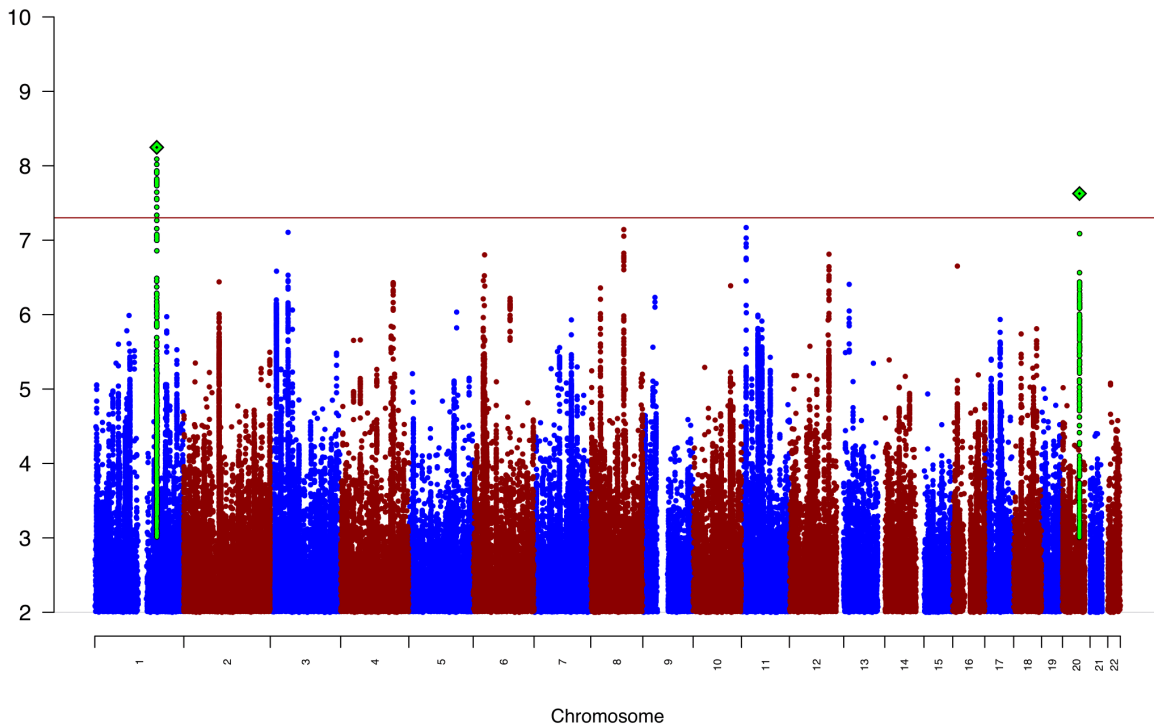
PRS and cases with higher BD+SCZ PRS having a larger number of hospitalizations. We demonstrated that psychotic features within BD is an independently heritable trait and that GWS loci for SCZ have a consistent direction of effect in psychotic features in BD, demonstrating the potential to study psychosis more directly to identify variants contributing to that symptom dimension. All in all, this work illustrates the utility of genetic data to dissect symptom heterogeneity among correlated disorders and suggests that further work could potentially aid in defining subgroups of patients for more personalized treatment.

## Figures

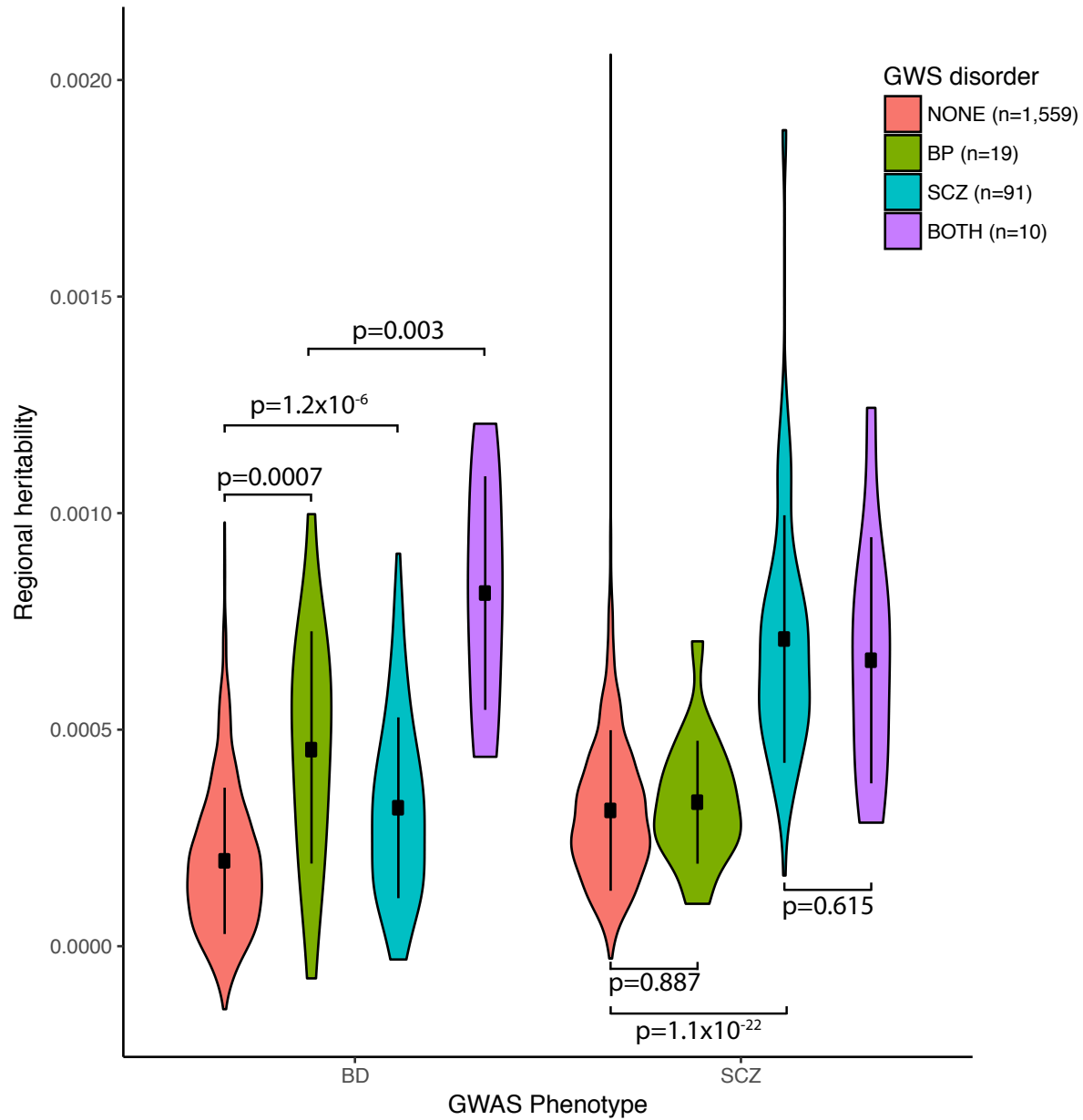
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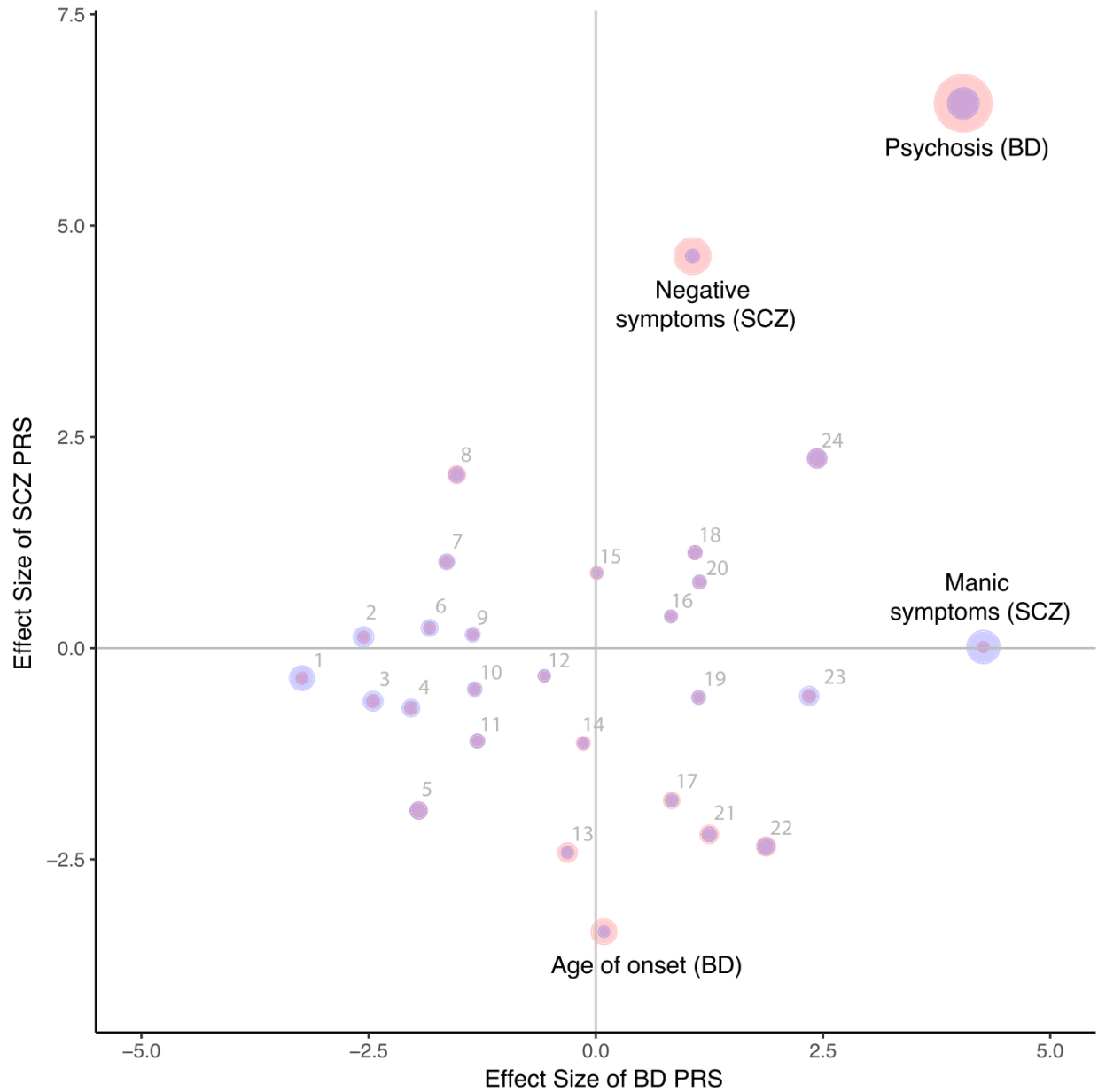


**Figure 1.** a) Odds ratios (OR) from independent data sets of BD (blue) and SCZ (red) for each of the 114 genome-wide significant variants in the BD and SCZ vs controls GWAS. b) Manhattan plot for SCZ vs BD GWAS.



**Figure 2.** Regional SNP-heritability estimates for SCZ and BD stratified by whether the region contains the most significant variant in a genome-wide significant locus in BD, SCZ, neither or both.





**Figure 3.** Effect size (calculated by dividing regression estimate by standard error) from regression analysis including ancestry covariates for each subphenotype and PRS for BD (x-axis) and SCZ (y-axis). Point size represents  $-\log_{10}(p\text{-value})$  with SCZ (red) and BD (blue). Numbered subphenotypes are 1) comorbid migraine, 2) panic attacks 3) suicide attempt 4) mixed states 5) rapid cycling 6) comorbid eating disorder 7) comorbid OCD 8) year of birth 9) suicide ideation 10) panic disorder 11) number of suicide attempts 12) depressive symptoms (SCZ) 13)

episodes depressive 14) episodes total 15) positive symptoms (SCZ) 16) irritable mania 17) age of onset depression 18) family history 19) episodes mixed mania 20) unipolar mania 21) alcohol substance dependence 22) age of onset mania 23) age at interview 24) number of hospitalizations. All subphenotypes are in BD except those labeled (SCZ).

**Table 1.** Polygenic scoring results of all four GWAS phenotypes (BD+SCZ vs controls, BD vs controls, SCZ vs controls and SCZ vs BD) and 24 subphenotypes from BD and 4 subphenotypes from SCZ, rows without case/control counts are quantitative measures. Significance and effects are from regression analysis of subphenotype on PRS including ancestry and site as covariates. Effect is the regression estimate divided by the standard error.

Subphenotype	N	Cases	Controls	<i>P-value</i>				<i>Effect</i>			
				BP+SCZ	BP	SCZ	SCZvsBD	BP+SCZ	BP	SCZ	SCZvsBD
psychosis	8131	4632	3499	<b>7.9E-13</b>	<b>5.3E-05</b>	<b>1.2E-10</b>	5.8E-01	7.17	4.04	6.45	0.55
suicide ideation	5399	3801	1598	7.8E-01	1.8E-01	8.7E-01	1.7E-01	-0.28	-1.35	0.16	1.37
family history	4971	2730	2241	6.1E-02	2.8E-01	2.6E-01	6.9E-01	1.87	1.09	1.13	-0.39
irritable mania	4230	2401	1829	3.8E-01	4.1E-01	7.1E-01	1.0E-01	0.88	0.83	0.38	-1.63
rapid cycling	5214	1744	3470	7.9E-03	5.1E-02	5.5E-02	3.1E-01	-2.66	-1.95	-1.92	1.01
alcohol substance dependence	5440	1494	3946	4.5E-01	2.1E-01	2.8E-02	1.7E-01	-0.75	1.25	-2.20	-1.36
panic disorder	4647	863	3784	2.8E-01	1.8E-01	6.3E-01	4.0E-01	-1.07	-1.33	-0.49	0.83
panic attacks	3976	851	3125	1.3E-01	1.1E-02	9.0E-01	4.7E-02	-1.50	-2.56	0.13	1.98
mixed states	4044	826	3218	1.0E-01	4.2E-02	4.8E-01	6.0E-02	-1.64	-2.03	-0.71	1.88
unipolar mania	4863	461	4402	2.4E-02	2.5E-01	4.3E-01	6.1E-01	2.26	1.14	0.78	0.51
comorbid migraine	2652	410	2242	1.3E-02	1.2E-03	7.2E-01	4.4E-01	-2.48	-3.23	-0.36	0.77
comorbid OCD	4215	386	3829	9.7E-01	1.0E-01	3.1E-01	1.9E-01	-0.04	-1.64	1.02	1.30
comorbid eating disorder	3839	331	3508	2.1E-01	6.7E-02	8.1E-01	6.3E-01	-1.25	-1.83	0.24	0.48
age of onset	8610			6.2E-03	9.3E-01	7.9E-04	6.2E-01	-2.74	0.09	-3.36	-0.50
age at interview	8062			5.9E-01	1.9E-02	5.7E-01	4.4E-01	0.54	2.35	-0.57	-0.78
episodes mixed mania	6587			6.3E-01	2.6E-01	5.6E-01	3.2E-01	-0.48	1.13	-0.58	-1.00
suicide attempt	6308			1.2E-01	1.4E-02	5.3E-01	2.8E-01	-1.54	-2.45	-0.63	1.09
episodes depressive	6252			7.4E-03	7.6E-01	1.6E-02	9.6E-01	-2.68	-0.31	-2.42	-0.05
episodes total	5958			1.3E-01	8.9E-01	2.6E-01	3.9E-01	-1.51	-0.14	-1.13	-0.87
year of birth	5317			1.7E-01	1.3E-01	4.0E-02	3.6E-02	1.39	-1.53	2.05	2.10
number of suicide attempts	5015			6.2E-02	1.9E-01	2.7E-01	4.9E-01	-1.87	-1.30	-1.10	-0.69
number of hospitalizations	3944			4.2E-04	1.5E-02	2.5E-02	7.4E-01	3.53	2.43	2.25	-0.33
age of onset depression	3467			2.3E-01	4.0E-01	7.2E-02	2.2E-01	-1.19	0.83	-1.80	1.24
age of onset mania	3395			2.5E-01	6.1E-02	1.9E-02	2.2E-01	-1.14	1.87	-2.35	-1.23
Manic	6908			2.4E-02	<b>2.0E-05</b>	9.9E-01	3.5E-02	2.26	4.26	0.01	-2.10
Depressive	6907			9.0E-01	5.7E-01	7.4E-01	1.8E-01	0.13	-0.57	-0.33	-1.36
Negative	8355			<b>1.5E-05</b>	2.9E-01	<b>3.6E-06</b>	2.1E-02	4.33	1.06	4.64	2.31
Positive	8259			4.1E-01	9.9E-01	3.7E-01	5.1E-01	0.82	0.01	0.89	0.65

## Author Affiliations

- 1 Division of Genetic Medicine, Departments of Medicine, Psychiatry, Biomedical Informatics, Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA
- 2 Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA
- 3 Department of Psychiatry and Psychotherapy, Charite - Universitätsmedizin, Berlin, Germany
- 4 Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
- 5 Molecular Psychiatry Laboratory, Division of Psychiatry, University College London, London, UK
- 6 Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, California, USA
- 7 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY USA
- 8 Queensland Brain Institute, The University of Queensland, Brisbane, Australia
- 9 MRC Social, Genetic and Developmental Psychiatry Centre, King's College London, London, UK
- 10 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA
- 11 Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, California, USA
- 12 Centre for Integrative Biology, University of Trento, Trento, Italy
- 13 MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK
- 14 Institute of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich, Munich, Germany
- 15 Department of Psychiatry and Psychotherapy, Ludwig Maximilian University, Munich, Germany
- 16 Department of Clinical Sciences, Psychiatry, Umea University, Umea, Sweden
- 17 Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, Stockholm, Sweden
- 18 Department of Psychiatry, Diakonhjemmet Hospital, Oslo, Norway
- 19 NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
- 20 Centre for Integrative Register-based Research, CIRRAU, Aarhus University, Aarhus, Denmark
- 21 National Centre for Register-based Research, Aarhus University, Aarhus, Denmark
- 22 The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark
- 23 Molecular & Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI USA
- 24 NEUROSCIENCE, Istituto Di Ricerche Farmacologiche Mario Negri, Milano, Italy
- 25 State Mental Hospital, Haar, Germany
- 26 Department of Psychiatry, Dalhousie University, Halifax, NS Canada
- 27 National Institute of Mental Health, Klecany, Czech Republic
- 28 Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, USA
- 29 Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK
- 30 Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, Illinois, USA
- 31 Department of Biomedicine, Aarhus University, Aarhus, Denmark
- 32 iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, Denmark
- 33 Department of Psychiatry and Behavioral Sciences, Atlanta Veterans Affairs Medical Center, Atlanta, Georgia, USA
- 34 Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, Georgia, USA
- 35 Psychiatry, Berkshire Healthcare NHS Foundation Trust, Bracknell, UK
- 36 Fundacio de Docencia i Recerca Mutua de Terrassa, Universitat de Barcelona, Spain
- 37 Institute of Psychiatry at King's College London, London, UK
- 38 Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia, USA
- 39 Psychiatry, Rush University Medical Center, Chicago, IL USA
- 40 Statens Serum Institut, Copenhagen, Denmark
- 41 Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, The Netherlands
- 42 Wellcome Trust Centre for Human Genetics, Oxford, UK
- 43 Department of Psychiatry, Weill Cornell Medical College, New York, NY USA
- 44 Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK
- 45 Division of Psychiatry, University College London, London, GB
- 46 Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
- 47 Discipline of Psychiatry, University of Adelaide, Adelaide, Australia
- 48 Clinical Neuroscience, Max Planck Institute of Experimental Medicine, Göttingen, Germany
- 49 Department of Psychiatry and Addiction Medicine, Assistance Publique - Hôpitaux de Paris, Paris, France
- 50 Paris Bipolar and TRD Expert Centres, FondaMental Foundation, Paris, France
- 51 Psychiatry, Université Paris Diderot, Paris, France
- 52 UMR-S1144 Team 1 : Biomarkers of relapse and therapeutic response in addiction and mood disorders, INSERM, Paris, France
- 53 Child and Adolescent Psychiatry, University of Technology Dresden, Dresden, Germany
- 54 Section for Experimental Psychopathology, General Psychiatry, Heidelberg, Germany
- 55 Department of Medical Genetics, University of Pécs, Pécs, Hungary
- 56 Szentagothai Research Center, University of Pécs, Pécs, Hungary
- 57 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
- 58 Psychiatry, University of Pennsylvania, Philadelphia, PA USA
- 59 Health Sciences Research, Mayo Clinic, Rochester, Minnesota USA
- 60 Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA
- 61 Cambridge Institute for Medical Research, University of Cambridge School of Clinical Medicine, Cambridge, UK

- 62 Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Subiaco, Western Australia, Australia
- 63 Division of Psychiatry, University of Edinburgh, Edinburgh, UK
- 64 Center for Statistical Genetics and Department of Biostatistics, University of Michigan, Ann Arbor, Michigan USA
- 65 Department of Biomedicine, Aarhus University, Aarhus C, Denmark
- 66 Institute of Cognitive Neuroscience, University College London, London, UK
- 67 Mental Health Sciences Unit, University College London, London, UK
- 68 NIHR BRC for Mental Health, King's College London, London, UK
- 69 Diamantina Institute of Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Brisbane, Queensland, Australia
- 70 University Medical Center Groningen, Department of Psychiatry, University of Groningen, RB, The Netherlands
- 71 School of Nursing, Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA
- 72 Athinoula A. Martinos Center, Massachusetts General Hospital, Boston, Massachusetts, USA
- 73 Center for Brain Science, Harvard University, Cambridge, Massachusetts, USA
- 74 Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA
- 75 Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, California USA
- 76 Molecular & Behavioral Neuroscience Institute and Department of Computational Medicine & Bioinformatics, University of Michigan, Ann Arbor, Michigan USA
- 77 Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York, USA
- 78 Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York, USA
- 79 Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA
- 80 Neonatal Genetik, Statens Serum Institut, Copenhagen, Denmark
- 81 Department of Psychiatry, University of California San Francisco, San Francisco, California, USA
- 82 Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia
- 83 Schizophrenia Research Institute, Sydney, Australia
- 84 School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia
- 85 Centre Hospitalier du Rouvray and INSERM U1079 Faculty of Medicine, Rouen, France
- 86 School of Psychiatry, University of New South Wales, Sydney, Australia
- 87 MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK
- 88 Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK
- 89 Department of Epidemiology and Public Health, University College London, London, UK
- 90 Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
- 91 Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Spain
- 92 Instituto de Salud Carlos III, Biomedical Network Research Centre on Mental Health (CIBERSAM), Madrid, Spain
- 93 Psychiatric Genetics Unit, Group of Psychiatry Mental Health and Addictions, Vall d'Hebron Research Institut (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain
- 94 Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, Australia
- 95 Department of Psychiatry, Mood Disorders Program, McGill University Health Center, Montreal, QC Canada
- 96 Institute of Psychology, Chinese Academy of Science, Beijing, China
- 97 Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
- 98 State Key Laboratory for Brain and Cognitive Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China
- 99 Department of Computer Science, University of North Carolina, Chapel Hill, North Carolina, USA
- 100 Castle Peak Hospital, Hong Kong, China
- 101 Institute of Mental Health, Singapore, Singapore
- 102 Department of Psychiatry, Washington University, St. Louis, Missouri, USA
- 103 Department of Child and Adolescent Psychiatry, Assistance Publique Hôpitaux de Paris, Pierre and Marie Curie Faculty of Medicine and Institute for Intelligent Systems and Robotics, Paris, France
- 104 Blue Note Biosciences, Princeton, New Jersey, USA
- 105 Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, UK
- 106 Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK
- 107 Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin, Ireland
- 108 University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA
- 109 National Centre for Mental Health, Cardiff University, Cardiff, UK
- 110 Translational Genomics, USAC, Phoenix, Arizona, USA
- 111 Centro Investigación Biomedica en Red Salud Mental, Madrid, Spain
- 112 University Hospital Marques de Valdecilla, Instituto de Formación e Investigación Marques de Valdecilla, University of Cantabria, Santander, Spain
- 113 Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA
- 114 Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany
- 115 Centre for Psychiatry, Queen Mary University of London, London, UK
- 116 UCL Genetics Institute, University College London, London, UK
- 117 Department of Psychiatry, Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland
- 118 Neurosciences, Radiology, Psychiatry, Cognitive Science, University of California San Diego, La Jolla, California USA
- 119 Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
- 120 Department of Psychiatry, University of Munster, Munster, Germany
- 121 Department of Genetics, The Hebrew University of Jerusalem, Jerusalem, Israel
- 122 Sheba Medical Center, Tel Hashomer, Israel
- 123 Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

- 124 Life&Brain Center, Department of Genomics, University of Bonn, Bonn, Germany
- 125 Institute of Human Genetics, University of Bonn, Bonn, Germany
- 126 Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium
- 127 Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA
- 128 VA Boston Health Care System, Brockton, Massachusetts, USA
- 129 Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
- 130 King's College London, London, UK
- 131 First Department of Psychiatry, University of Athens Medical School, Athens, Greece
- 132 Department of Psychiatry, University College Cork, Co. Cork, Ireland
- 133 Department of Medical Genetics, Oslo University Hospital, Oslo, Norway
- 134 Division of Psychiatric Genomics, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA
- 135 Department of Statistics, University of Oxford, Oxford, UK
- 136 Cognitive Genetics and Therapy Group, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Co. Galway, Ireland
- 137 Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, Illinois, USA
- 138 Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
- 139 Molecular and Physiological Sciences, The Wellcome Trust, London, UK
- 140 Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana USA
- 141 Department of Psychiatry, University of Regensburg, Regensburg, Germany
- 142 Department of Neurology, Oslo University Hospital, Oslo, Norway
- 143 Department of General Practice, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland
- 144 Folkhalsan Research Center, Helsinki, Finland, Biomedicum Helsinki 1, Haartmaninkatu 8, Helsinki, Finland
- 145 National Institute for Health and Welfare, Helsinki, Finland
- 146 Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA
- 147 Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, Massachusetts, USA
- 148 Estonian Genome Center, University of Tartu, Tartu, Estonia
- 149 Translational Technologies and Bioinformatics, Pharma Research and Early Development, F.Hoffman-La Roche, Basel, Switzerland
- 150 Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, London, UK
- 151 Cognitive Science, University of California San Diego, La Jolla, California USA
- 152 Department of Medical & Molecular Genetics, Indiana University, Indianapolis, Indiana USA
- 153 Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Mannheim, Germany
- 154 Department of Genetics, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands
- 155 Department of Psychiatry, University of Colorado Denver, Aurora, Colorado, USA
- 156 Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA
- 157 Department of Psychiatry & Psychology, Mayo Clinic, Rochester, Minnesota USA
- 158 Neuroscience Research Australia, Sydney, Australia
- 159 School of Medical Sciences, University of New South Wales, Sydney, Australia
- 160 Department of Psychiatry and Psychotherapy, University Medical Center Gottingen, Gottingen, Germany
- 161 Department of Psychiatry, University of Halle, Halle, Germany
- 162 Department of Psychiatry, University of Munich, Munich, Germany
- 163 Neuropsychiatric Genetics Research Group, Dept of Psychiatry and Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland
- 164 Department of Economics and Business Economics, National Centre for Register-based Research, Aarhus University, Aarhus, Denmark
- 165 Departments of Psychiatry and Human and Molecular Genetics, INSERM, Institut de Myologie, Hopital de la Pitie-Salpetriere, Paris, France
- 166 Neuroscience Therapeutic Area, Janssen Research and Development, Raritan, New Jersey, USA
- 167 Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Australia
- 168 Department of Psychological Medicine, University of Worcester, Worcester, UK
- 169 School of Biomedical and Healthcare Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, UK
- 170 Department of Psychiatry, University of California San Diego, La Jolla, California USA
- 171 Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania
- 172 Bioinformatics Research Centre (BiRC), Aarhus University, Aarhus, Denmark
- 173 Biostatistics, University of Minnesota System, Minneapolis, MN USA
- 174 Mental Health Department, University Regional Hospital. Biomedicine Institute (IBIMA), Malaga, Spain
- 175 Academic Medical Centre University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands
- 176 Mclean Hospital, Harvard Medical School, 115 Mill St, Belmont Massachusetts, USA
- 177 Illumina, La Jolla, California, California, USA
- 178 Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Mental Health Services Copenhagen, Denmark
- 179 J.J. Peters VA Medical Center, Bronx, New York, New York, USA
- 180 Department of Psychology, Eberhard Karls Universitat Tübingen, Tübingen, Germany
- 181 Priority Centre for Health Behaviour, University of Newcastle, Newcastle, Australia
- 182 School of Electrical Engineering and Computer Science, University of Newcastle, Newcastle, Australia
- 183 Department of Biomedicine, University of Basel, Basel, Switzerland
- 184 Department of Psychiatry and Behavioral Sciences, Howard University Hospital, Washington, DC USA
- 185 Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland
- 186 Section of Neonatal Screening and Hormones, Department of Clinical Biochemistry, Immunology and Genetics, Statens Serum Institut, Copenhagen, Denmark
- 187 Department for Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark
- 188 Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, Japan



- 189 Centre for Clinical Research in Neuropsychiatry, School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Medical Research Foundation Building, Perth, Australia
- 190 School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Perth, Australia
- 191 The Perkins Institute for Medical Research, The University of Western Australia, Perth, Australia
- 192 Faculte de Medecine, Universite Paris Est, Creteil, France
- 193 Psychiatrie Translationnelle, Inserm U955, Creteil, France
- 194 Peninsula School of Medicine and Dentistry, Plymouth University, Plymouth, UK
- 195 Regional Centre for Clinical Research in Psychosis, Department of Psychiatry, Stavanger University Hospital, Stavanger, Norway
- 196 Rheumatology Research Group, Vall d'Hebron Research Institute, Barcelona, Spain
- 197 Centre for Medical Research, The University of Western Australia, Perth, Western Australia, Australia
- 198 Western Australian Institute for Medical Research, The University of Western Australia, Perth, Western Australia, Australia
- 199 Department of Medical Genetics, Medical University, Sofia, Bulgaria
- 200 Department of Psychology, University of Colorado Boulder, Boulder, Colorado, USA
- 201 Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
- 202 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
- 203 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada
- 204 Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, Russia
- 205 Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany
- 206 Latvian Biomedical Research and Study Centre, Riga, Latvia
- 207 Cell Biology, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY USA
- 208 Department of Psychiatry and Zilkha Neurogenetics Institute, Keck School of Medicine at University of Southern California, Los Angeles, California, USA
- 209 Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY USA
- 210 Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
- 211 Faculty of Medicine, Vilnius University, Vilnius, Lithuania
- 212 Psychiatry, GGZ inGeest, Amsterdam, The Netherlands
- 213 Psychiatry, VU medisch centrum, Amsterdam, The Netherlands
- 214 Department of Biology and Medical Genetics, 2nd Faculty of Medicine and University Hospital Motol, Prague, Czech Republic
- 215 Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden
- 216 Department of Child and Adolescent Psychiatry, Pierre and Marie Curie Faculty of Medicine, Paris, France
- 217 Psychiatry, North East London NHS Foundation Trust, Ilford, UK
- 218 Clinic for Psychiatry and Psychotherapy, University Hospital Cologne, Cologne, Germany
- 219 INSERM, Paris, France
- 220 Duke-NUSA Graduate Medical School, Singapore, Singapore
- 221 Hofstra Northwell School of Medicine, Hempstead, New York, USA
- 222 The Feinstein Institute for Medical Research, Manhasset, New York, USA
- 223 The Hofstra NS-LIJ School of Medicine, Hempstead, New York, USA
- 224 Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
- 225 HudsonAlpha Institute for Biotechnology, Huntsville, AL USA
- 226 Department of Medical & Molecular Genetics, King's College London, London, UK
- 227 Department of Human Genetics, University of Michigan, Ann Arbor, MI USA
- 228 Centre for Genomic Sciences, The University of Hong Kong, Hong Kong, China
- 229 Mental Health Centre and Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan, China
- 230 Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA
- 231 Department of Psychiatry, Columbia University, New York, New York, USA
- 232 Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
- 233 Cancer Epidemiology and Prevention, M. Skłodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland
- 234 Psychiatry, University of Illinois at Chicago College of Medicine, Chicago, IL USA
- 235 Human Genetics, Genome Institute of Singapore, A\*STAR, Singapore, Singapore
- 236 Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore
- 237 Department of Mental Health and Substance Abuse Services; National Institute for Health and Welfare, Helsinki, Finland
- 238 Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University in Szczecin, Szczecin, Poland
- 239 Max Planck Institute of Psychiatry, Munich, Germany
- 240 Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
- 241 Mental Health, NHS 24, Glasgow, UK
- 242 Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA
- 243 Psychiatry, Brigham and Women's Hospital, Boston, MA USA
- 244 Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany
- 245 The Zucker Hillside Hospital, Glen Oaks, New York, USA
- 246 Centre National de la Recherche Scientifique, Laboratoire de Genetique Moleculaire de la Neurotransmission et des Processus Neurodegeneratifs, Hopital de la Pitie Salpetriere, Paris, France
- 247 Research and Education, Division of Clinical Neuroscience, Oslo Universitetssykehus, Oslo, Norway
- 248 Clinical Neurosciences, St George's University of London, London, UK
- 249 School of Psychology, The University of Queensland, Brisbane, Australia
- 250 Department of Medical and Molecular Genetics, School of Medicine, King's College London, Guy's Hospital, London, UK
- 251 Department of Genomics Mathematics, University of Bonn, D-53127 Bonn, Germany
- 252 Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden
- 253 Research Unit, Sorlandet Hospital, Kristiansand, Norway
- 254 Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK



255 Department of Psychiatry, National University of Ireland Galway, Co. Galway, Ireland  
256 Research Institute, Lindner Center of HOPE, Mason, OH USA  
257 Department of Psychiatry, University of Michigan, Ann Arbor, MI USA  
258 Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK  
259 Genetic Cancer Susceptibility Group, International Agency for Research on Cancer, Lyon, France  
260 Human Genetics Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD USA  
261 Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway  
262 Massachusetts Mental Health Center Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA  
263 Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia  
264 School of Psychology, University of Newcastle, Newcastle, Australia  
265 First Psychiatric Clinic, Medical University, Sofia, Bulgaria  
266 Institute for Molecular Bioscience, The University of Queensland, Brisbane, Australia  
267 Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology - NTNU, Trondheim, Norway  
268 Psychiatry, St Olavs University Hospital, Trondheim, Norway  
269 Discipline of Biochemistry, Neuroimaging and Cognitive Genomics (NICOG) Centre, National University of Ireland, Galway, Ireland  
270 Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Australia  
271 Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, Germany  
272 Institute of Translational Medicine, University of Liverpool, Liverpool, UK  
273 Munich Cluster for Systems Neurology (SyNergy), Munich, Germany  
274 Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland  
275 Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht, The Netherlands  
276 Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany  
277 Department of Psychiatry, Trinity College Dublin, Dublin, Ireland  
278 Research/Psychiatry, Veterans Affairs San Diego Healthcare System, San Diego, California USA  
279 Psychiatry and Human Genetics, University of Pittsburgh, Pittsburgh, PA USA  
280 Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana, USA  
281 Mental Health Centre Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark  
282 DETECT Early Intervention Service for Psychosis, Blackrock, Co. Dublin, Ireland  
283 Centre for Public Health, Institute of Clinical Sciences, Queen's University Belfast, Belfast, UK  
284 Division of Psychiatry, Haukeland Universitetssjukehus, Bergen, Norway  
285 Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway  
286 Lawrence Berkeley National Laboratory, University of California at Berkeley, Berkeley, California, USA  
287 Department of Clinical Psychiatry, Psychiatry Clinic, Clinical Center University of Sarajevo, Sarajevo, Bosnia  
288 Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, Connecticut, USA  
289 Biomedical Research Centre, Ninewells Hospital and Medical School, Dundee, UK  
290 Institute for Molecular Medicine Finland, FIMM, University of Helsinki, Helsinki, Finland  
291 Melbourne Neuropsychiatry Centre, University of Melbourne & Melbourne Health, Melbourne, Australia  
292 College of Medicine Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY USA  
293 Department of Psychiatry, University of Helsinki, Helsinki, Finland  
294 Public Health Genomics Unit, National Institute for Health and Welfare, Helsinki, Finland  
295 PEIC  
296 Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina USA  
297 Division of Clinical Research, Massachusetts General Hospital, Boston, MA USA  
298 Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark, Denmark  
299 Center for Human Genetic Research and Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA  
300 Department of Child and Adolescent Psychiatry, Erasmus University Medical Centre, Rotterdam, The Netherlands  
301 Department of Complex Trait Genetics, Neuroscience Campus Amsterdam, VU University Medical Center Amsterdam, Amsterdam, The Netherlands  
302 Department of Functional Genomics, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, VU University, Amsterdam, The Netherlands  
303 Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA  
304 Department of Psychiatry, University of Oxford, Oxford, UK  
305 Outpatient Clinic for Bipolar Disorder, Altrecht, Utrecht, The Netherlands  
306 Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, USA  
307 Virginia Institute for Psychiatric and Behavioral Genetics, Departments of Psychiatry and Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia, USA  
308 Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, Spain  
309 Montreal Neurological Institute and Hospital, Montreal, QC Canada  
310 Department of Neurology and Neurosurgery, McGill University, Faculty of Medicine, Montreal, QC Canada  
311 Institute for Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, New York, USA  
312 Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK  
313 Rush University Medical Center, Chicago, IL USA  
314 Scripps Translational Science Institute, La Jolla, California USA  
315 Faculty of Science, Medicine & Health, University of Wollongong, Australia  
316 Hunter New England Health Service, Newcastle, Australia  
317 Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy  
318 Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA

319 Faculty of Medicine, Department of Psychiatry, School of Health Sciences, University of Iceland, Reykjavik, Iceland  
320 Research and Development, Bronx Veterans Affairs Medical Center, New York, New York, USA  
321 Department of Neurosciences, University of California San Diego, La Jolla, California USA  
322 Psychiatry and the Behavioral Sciences, University of Southern California, Los Angeles, California USA  
323 Mood Disorders, PsyQ, Rotterdam, The Netherlands  
324 University of Aberdeen, Institute of Medical Sciences, Aberdeen, UK  
325 deCODE Genetics / Amgen, Reykjavik, Iceland  
326 Faculty of Medicine, University of Iceland, Reykjavik, Iceland  
327 Department of Clinical Neurology, Medical University of Vienna, Wien, Austria  
328 Department of Neuroscience, Norges Teknisk Naturvitenskapelige Universitet Fakultet for naturvitenskap og teknologi, Trondheim, Norway  
329 Department of Psychiatry, Hospital Namsos, Namsos, Norway  
330 Lieber Institute for Brain Development, Baltimore, Maryland, USA  
331 Centre for Addiction and Mental Health, Toronto, ON Canada  
332 Department of Medical Genetics, University Medical Centre Utrecht, Universiteitsweg, Utrecht, The Netherlands  
333 Institute of Mental Health, Singapore, Singapore  
334 Neurogenomics, TGen, Los Angeles, AZ USA  
335 Berkshire Healthcare NHS Foundation Trust, Bracknell, UK  
336 Priority Research Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia  
337 Section of Psychiatry, University of Verona, Verona, Italy  
338 Department of Psychology, The Jockey Club Tower, 6/F, the Centennial Campus, Pokfulam Road, The University of Hong Kong, Hong Kong, China  
339 Department of Psychiatry, McGill University, Montreal, QC Canada  
340 Dept of Psychiatry, Sankt Olavs Hospital Universitetssykehuset i Trondheim, Trondheim, Norway  
341 Psychiatry, Psychiatrisches Zentrum Nordbaden, Wiesloch, Germany  
342 Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain  
343 Institute of Ophthalmology, University College London, London, UK  
344 National Institute for Health Research, Biomedical Research Centre at Moorfields Eye Hospital, National Health Service Foundation Trust, London, UK  
345 Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland  
346 Health Research Board, Dublin, Ireland  
347 Institute of Clinical Medicine, University of Oslo, Oslo, Norway  
348 Departments of Psychiatry, Neurology, Neuroscience and Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA  
349 Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark  
350 Department of Psychiatry, University Medical Center Groningen, University of Groningen, The Netherlands  
351 Department of Molecular Neuroscience, Institute of Neurology, London, UK  
352 WTCCC2  
353 Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA USA  
354 Dalla Lana School of Public Health, University of Toronto, Toronto, ON Canada  
355 Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON Canada  
356 Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK  
357 Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD USA  
358 Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD USA  
359 Department of Psychiatry, Institute for Genomic Health SUNY Downstate Medical Center Brooklyn, NY, USA  
360 Departments of Psychiatry and Human Genetics, University of Chicago, Chicago, Illinois, USA  
361 Universidad Autonoma de Nuevo Leon, Department of Psychiatry, Monterrey, Mexico; Department of Psychiatry, Mayo Clinic, MN, USA.  
362 Department of Psychiatry (UPK), University of Basel, Basel, Switzerland  
363 Department of Psychiatry and Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN USA  
364 Virginia Institute for Psychiatric and Behavioral Genetics and Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia, USA

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