Genomic dissection of bipolar disorder and schizophrenia including 28 subphenotypes

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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 = 1.2×10^{-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=3.6×10^{-6}) and manic symptoms (BD, p=2×10^{-5}), 2) BD subphenotypes: psychotic features (SCZ p=1.2×10^{-10}, BD p=5.3×10^{-5}) and age of onset (SCZ p=7.9×10^{-4}). Finally, we show that psychotic features in BD has significant SNP-heritability (h^2_{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[1]. Both disorders have significant genetic components with heritability estimates ranging from 60-80%[2]. 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)[3]. Despite shared genetics and symptomology, the current diagnostic systems[4,5] 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[6]. 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[7], 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[8–12], while, the involvement of CNVs in BD is much less clear[13]. 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[14,15]. 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[7]. 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[16]. 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 (pihat) 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[7].

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[17] / SHAPEIT[18] (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[19] 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 λ. Thirteen principal components namely 1,2,3,4,5,6,7,8,10,12,15,18,20 were included in all association analyses (λ=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)[20]

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_{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 ($p_{HET} < 0.05$). SMR analyses were conducted using eQTL data from whole peripheral blood[21], dorsolateral prefrontal cortex generated by the CommonMind Consortium[8], and 11 brain sub-regions from the GTEx consortium[22].

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 (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)[23,24]. 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[25] 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[26]. Unlike pw-gwas[23], 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[26]. 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[16] 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[27–30]. Here, we applied the summary-data-based Mendelian randomization (SMR) method[20] (see Methods) utilizing the cis-QTLs derived from peripheral blood[21], human dorsolateral prefrontal cortex (DLPFC)[31] from the Common Mind Consortium and 11 brain regions from the GTEx consortium[22]. 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 ($p_{GWAS} = 2.8x10^{-6}$) and is an eQTL for probe ILMN 1811648 ($p_{eQTL} = 2.9x10^{-168}$), resulting in $p_{SMR} = 4.1x10^{-6}$ in blood ($p_{eQTL} = 2.9x10^{-25}$, $p_{SMR} = 2.0x10^{-5}$ in DLFC, and $p_{eQTL} = 4.6x10^{-15}$, $p_{SMR} = 6.0x10^{-5}$ in GTEx cerebellar hemisphere) (Supplementary Table 2,

Supplementary Figure 6) and shows no evidence of heterogeneity (p_{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[23]. 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 = 8.67×10^{-10}) and for SCZ was rs2315283 (chr19:19480575, p=4.41×10^{-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=6.7x10^{-5}). We further calculated the probability of each variant in the region being causal for both BD and SCZ[32] 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[31] but in opposite directions (rs111444407 p_{eQTL} = 6x10^{-15}, beta = 0.105; rs2315283 p_{eQTL} = 1.5x10^{-28}, beta = -0.11).

Regional SNP-heritability estimation

Across the genome, regional SNP-heritabilities (h^2_{snp}) were estimated separately for SCZ and BD[25] 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[16] 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_{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_{snp} in SCZ, as expected (p = 1.1x10^{-22}), but also in BD (p = 1.2x10^{-6}). In risk regions specific to BD (n=19), significantly increased regional h^2_{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_{snp} in both disorders, as expected (BD p = 5.3x10^{-5}, SCZ p = 0.006), compared to non-risk regions. However, we observed a significant increase in BD h^2_{snp} in shared risk regions compared to BD

risk regions (BD p = 0.003) but not SCZ h^2_{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 < 5x10^{-6}), thereby substantially increasing the number of regions, resulted in similar results (Supplementary Figure 8). Seven regions contributed to substantially higher h^2_{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 $h^2_{snp}= 0.0019$ in SCZ and $h^2_{snp}=0.00063$ 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[7] 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[7] (p=2x10^{-5}, t=4.26) and psychotic features in BD patients (p=5.3x10^{-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_{snp} estimates using LD-score regression[33], psychotic features in BD ($h^2_{snp}=0.15$, SE=0.06) and suicide attempt ($h^2_{snp}=0.25$, 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[16], 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[34], 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[35]. 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[36]. 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[37]. 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,[38] although human genetic evidence is limited[39]. 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[40]. 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[41,42].

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[43]. Their members, including *GATAD2A*, display preferential expression in fetal brain development[43] and in recent work has been implicated in SCZ through open chromatin[44]. Further, p66α (mouse *GATAD2A*) was recently shown to

participate in memory preservation through long-lasting histone modification in hippocampal memory-activated neurons[45]. 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.
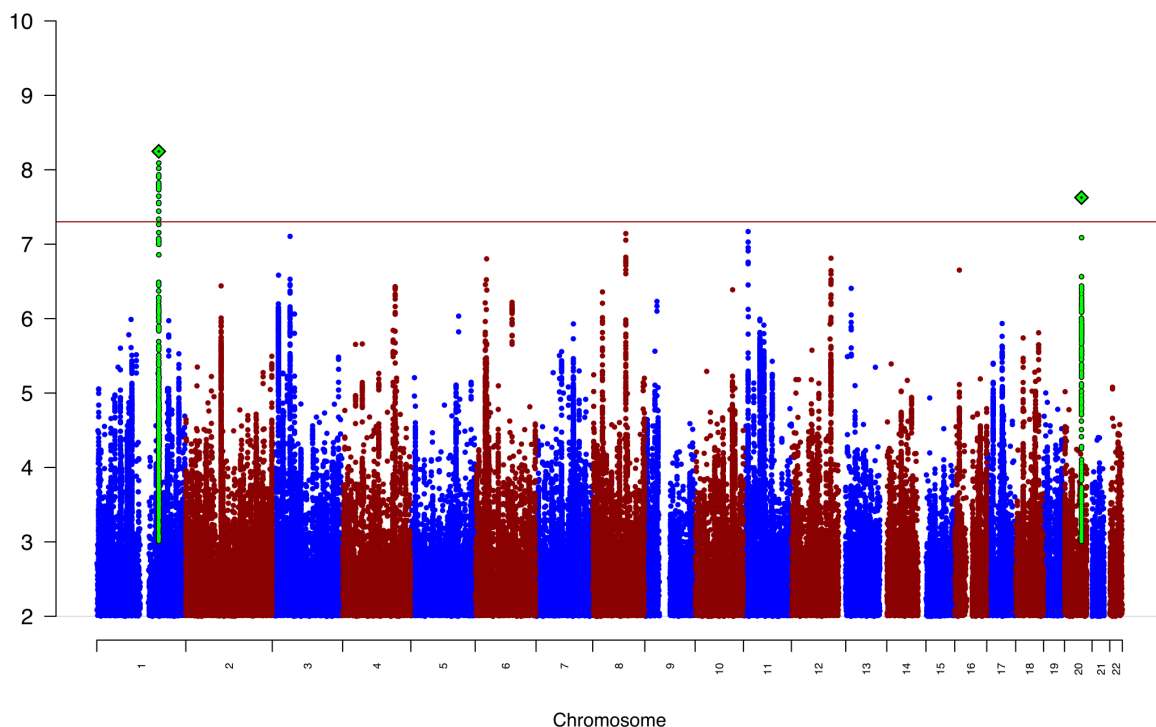
Figures

a.
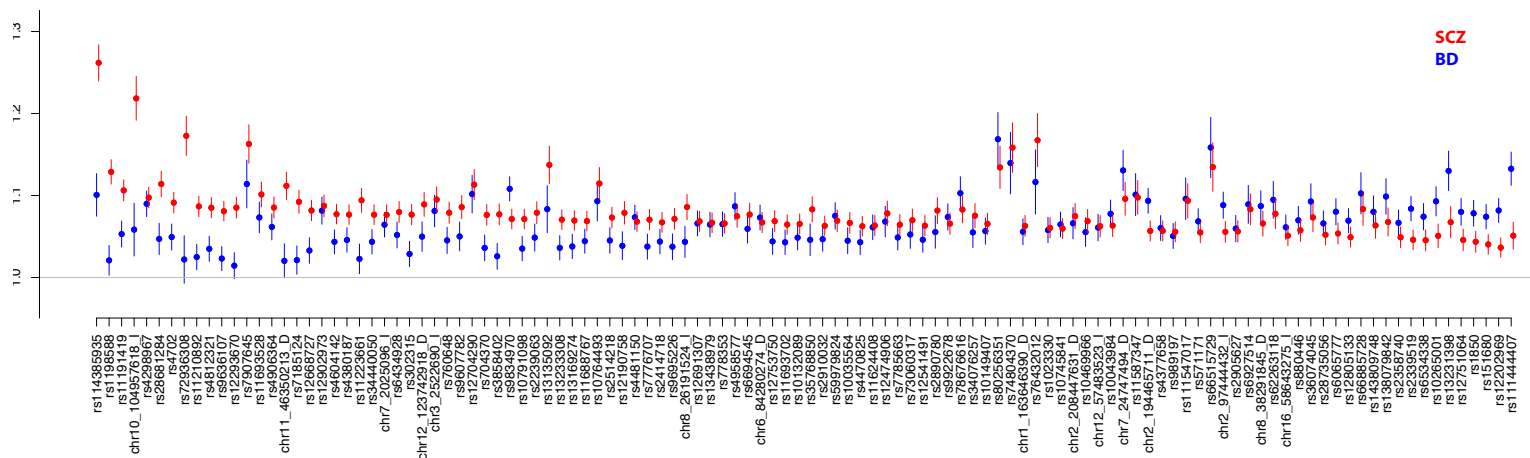
b.

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.
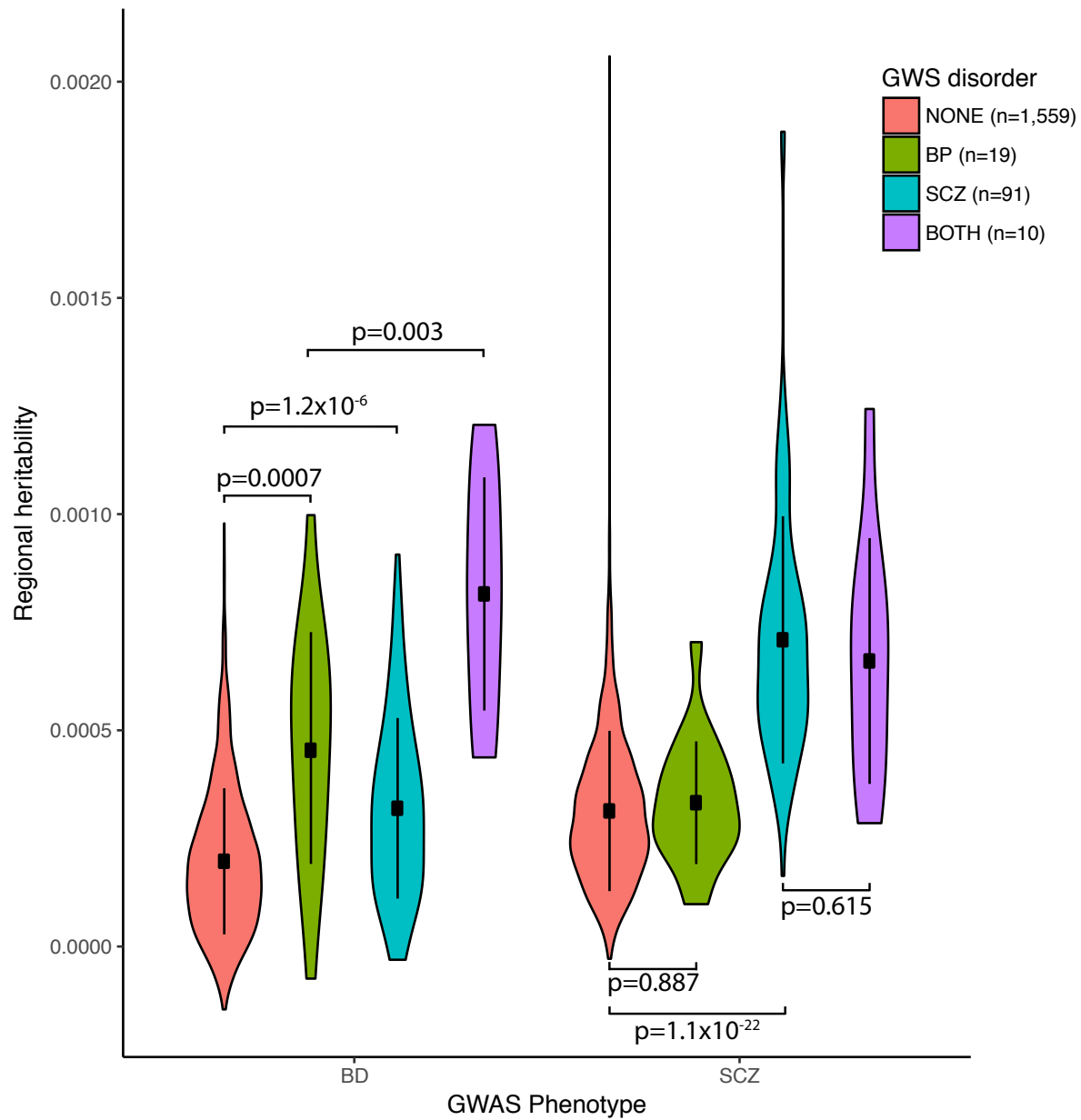
Figure 2. Regional SNP-heritability estimates for SCZ and BD stratified by whether the region

contains the most significant variant in a genome-wide significant locus in BD, SCZ, neither or
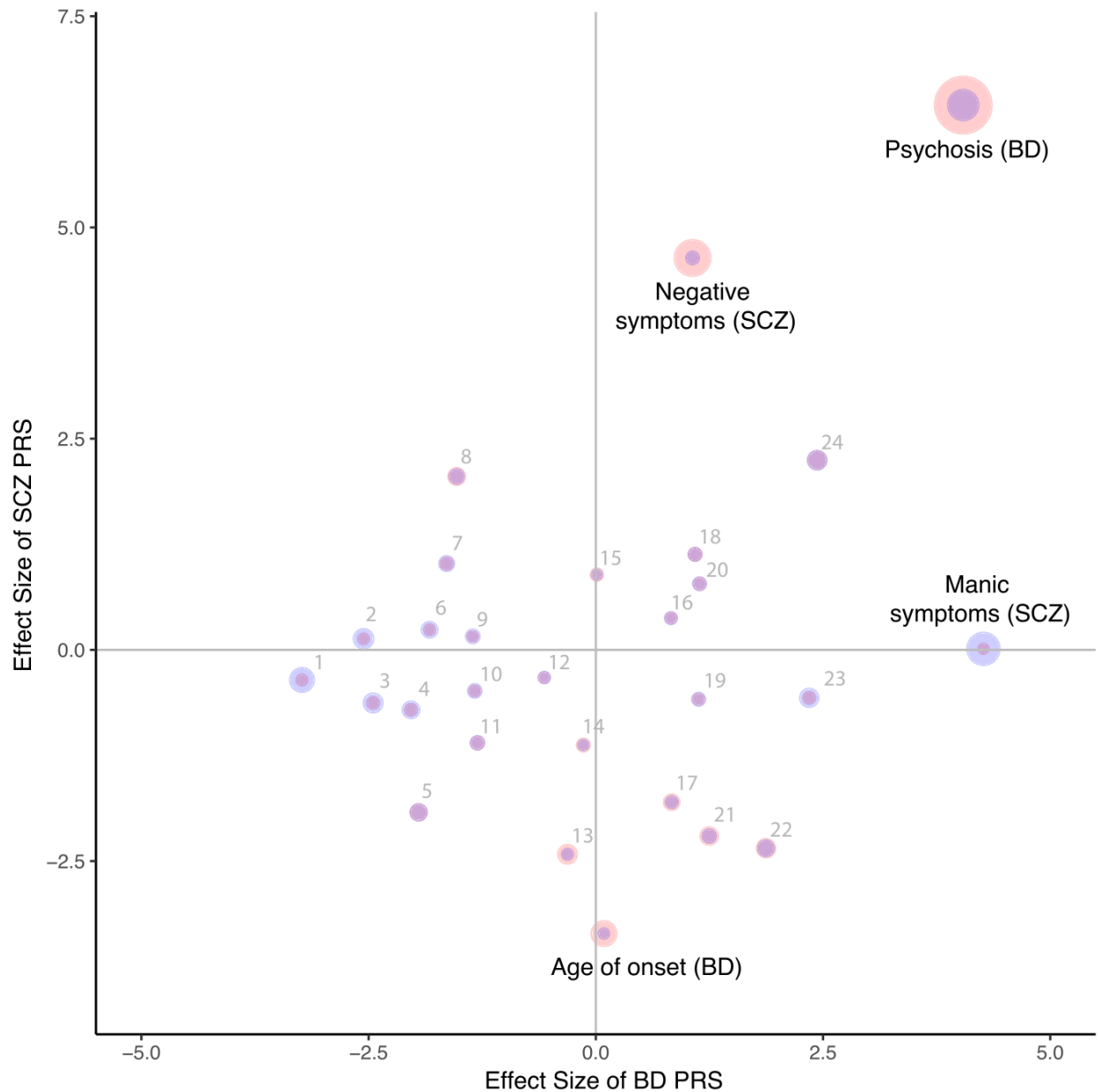
both.

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 –log10(p-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	*P-value*				*Effect*			
					BP+SCZ	BP	SCZ	SCZvsBD	BP+SCZ	BP	SCZ	SCZvsBD
BD	psychosis	8131	4632	3499	**7.9E-13**	**5.3E-05**	**1.2E-10**	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
SCZ	Manic	6908			2.4E-02	**2.0E-05**	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			**1.5E-05**	2.9E-01	**3.6E-06**	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

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References

1. Whiteford, H. A. *et al.* Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *The Lancet* **382,** 1575–1586 (2013).
2. Nöthen, M. M., Nieratschker, V., Cichon, S. & Rietschel, M. New findings in the genetics of major psychoses. *Dialogues Clin. Neurosci.* **12,** 85–93 (2010).
3. Lichtenstein, P. *et al.* Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *The Lancet* **373,** 234–239 (2009).

4. Diagnostic and Statistical Manual of Mental Disorders | DSM Library. Available at: http://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596. (Accessed: 14th March 2017)

5. WHO | International Classification of Diseases. *WHO* Available at: http://www.who.int/classifications/icd/en/. (Accessed: 14th March 2017)

6. Bortolato, B., Miskowiak, K. W., Köhler, C. A., Vieta, E. & Carvalho, A. F. Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatr. Dis. Treat.* **11,** 3111–3125 (2015).

7. Ruderfer, D. M. *et al.* Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Mol. Psychiatry* **19,** 1017–1024 (2014).

8. Kirov, G. *et al.* De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Mol. Psychiatry* **17,** 142–153 (2012).

9. Szatkiewicz, J. P. *et al.* Copy number variation in schizophrenia in Sweden. *Mol. Psychiatry* **19,** 762–773 (2014).

10. CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nat. Genet.* **49,** 27–35 (2017).

11. Stone, J. L. *et al.* Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature* **455,** 237–241 (2008).

12. Gulsuner, S. & McClellan, J. M. Copy Number Variation in Schizophrenia. *Neuropsychopharmacology* **40,** 252–254 (2015).

13. Green, E. K. *et al.* Copy number variation in bipolar disorder. *Mol. Psychiatry* **21,** 89–93 (2016).

14. Kataoka, M. *et al.* Exome sequencing for bipolar disorder points to roles of de novo loss-of-function and protein-altering mutations. *Mol. Psychiatry* **21,** 885–893 (2016).

15. Fromer, M. *et al.* De novo mutations in schizophrenia implicate synaptic networks. *Nature* **506,** 179–184 (2014).

16. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511,** 421–427 (2014).

17. Howie, B., Marchini, J. & Stephens, M. Genotype Imputation with Thousands of Genomes. *G3 GenesGenomesGenetics* **1,** 457–470 (2011).

18. Delaneau, O., Zagury, J.-F. & Marchini, J. Improved whole-chromosome phasing for disease and population genetic studies. *Nat. Methods* **10,** 5–6 (2013).

19. Purcell, S. *et al.* PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. *Am. J. Hum. Genet.* **81,** 559–575 (2007).

20. Zhu, Z. *et al.* Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48,** 481–487 (2016).

21. Westra, H.-J. *et al.* Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nat. Genet.* **45,** 1238–1243 (2013).

22. Consortium, T. Gte. The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. *Science* **348,** 648–660 (2015).

23. Pickrell, J. K. *et al.* Detection and interpretation of shared genetic influences on 42 human traits. *Nat. Genet.* **48,** 709–717 (2016).

24. Berisa, T. & Pickrell, J. K. Approximately independent linkage disequilibrium blocks in human populations. *Bioinformatics* **32,** 283–285 (2015).

25. Shi, H., Kichaev, G. & Pasaniuc, B. Contrasting the Genetic Architecture of 30 Complex Traits from Summary Association Data. *Am. J. Hum. Genet.* **99,** 139–153 (2016).

26. The 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature* **526,** 68–74 (2015).

27. Giambartolomei, C. *et al.* Bayesian Test for Colocalisation between Pairs of Genetic Association Studies Using Summary Statistics. *PLOS Genet.* **10,** e1004383 (2014).

28. He, X. *et al.* Sherlock: Detecting Gene-Disease Associations by Matching Patterns of Expression QTL and GWAS. *Am. J. Hum. Genet.* **92,** 667–680 (2013).

29. Gamazon, E. R. *et al.* A gene-based association method for mapping traits using reference transcriptome data. *Nat. Genet.* **47,** 1091–1098 (2015).

30. Gusev, A. *et al.* Integrative approaches for large-scale transcriptome-wide association studies. *Nat. Genet.* **48,** 245–252 (2016).

31. Fromer, M. *et al.* Gene expression elucidates functional impact of polygenic risk for schizophrenia. *Nat. Neurosci.* **19,** 1442–1453 (2016).

32. Benner, C. *et al.* FINEMAP: efficient variable selection using summary data from genome-wide association studies. *Bioinformatics* **32,** 1493–1501 (2016).

33. Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47,** 291–295 (2015).

34. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* **45,** 984–994 (2013).

35. Yamashita, S. *et al.* Neuropathology of leukoencephalopathy with brainstem and spinal cord involvement and high lactate caused by a homozygous mutation of DARS2. *Brain Dev.* **35,** 312–316 (2013).

36. Luoni, A. *et al.* Ankyrin-3 as a molecular marker of early-life stress and vulnerability to psychiatric disorders. *Transl. Psychiatry* **6,** e943 (2016).

37. Sheen, V. L. *et al.* Mutations in ARFGEF2 implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex. *Nat. Genet.* **36,** 69–76 (2004).

38. Yang, S., Van Dongen, H. P. A., Wang, K., Berrettini, W. & Bućan, M. Assessment of circadian function in fibroblasts of patients with bipolar disorder. *Mol. Psychiatry* **14,** 143–155 (2008).

39. Byrne, E. M. *et al.* Testing the role of circadian genes in conferring risk for psychiatric disorders. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet.* **0,** 254–260 (2014).

40. Bayés, À. *et al.* Characterization of the proteome, diseases and evolution of the human postsynaptic density. *Nat. Neurosci.* **14,** 19–21 (2011).

41. Moczulska, K. E. *et al.* Deep and Precise Quantification of the Mouse Synaptosomal Proteome Reveals Substantial Remodeling during Postnatal Maturation. *J. Proteome Res.* **13,** 4310–4324 (2014).

42. Gonzalez-Lozano, M. A. *et al.* Dynamics of the mouse brain cortical synaptic proteome during postnatal brain development. *Sci. Rep.* **6,** (2016).

43. Li, J. *et al.* Identification of Human Neuronal Protein Complexes Reveals Biochemical Activities and Convergent Mechanisms of Action in Autism Spectrum Disorders. *Cell Syst.* **1,** 361–374 (2015).

44.   Fullard, J. F. *et al.* Open chromatin profiling of human postmortem brain infers functional roles for non-coding schizophrenia loci. *Hum. Mol. Genet.* doi:10.1093/hmg/ddx103

45.   Ding, X. *et al.* Activity-induced histone modifications govern Neurexin-1 mRNA splicing and memory preservation. *Nat. Neurosci.* **advance online publication,** (2017).