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Characterizing the Genetic Overlap Between Psychiatric Disorders and Sleep-Related Phenotypes

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ABSTRACT

BACKGROUND: A range of sleep disturbances are commonly experienced by patients with psychiatric disorders, and genome-wide genetic analyses have shown some significant genetic correlations between these traits. Here, we applied novel statistical genetic methodologies to better characterize the potential shared genetic architecture between sleep-related phenotypes and psychiatric disorders.

METHODS: Using the MiXeR method, which can estimate polygenic overlap beyond genetic correlation, the shared genetic architecture between major psychiatric disorders (bipolar disorder [N = 51,710], depression [N = 480,359], and schizophrenia [N = 77,096]) and sleep-related phenotypes (chronotype [N = 449,734], insomnia [N = 386,533] and sleep duration [N = 446,118]) were quantified on the basis of genetic summary statistics. Furthermore, the conditional/conjunctional false discovery rate framework was used to identify specific shared loci between these phenotypes, for which positional and functional annotation were conducted with FUMA.

RESULTS: Extensive genetic overlap between the sleep-related phenotypes and bipolar disorder (63%–77%), depression (76%–79%), and schizophrenia (64%–79%) was identified, with moderate levels of congruence between most investigated traits (47%–58%). Specific shared loci were identified for all bivariate analyses, and a subset of 70 credible genes were mapped to these shared loci.

CONCLUSIONS: The current results provide evidence for substantial polygenic overlap between psychiatric disorders and sleep-related phenotypes, beyond genetic correlation ($|r_g|$ = 0.02 to 0.42). Moderate congruency within the shared genetic components suggests a complex genetic relationship and potential subgroups with higher or lower genetic concordance. This work provides new insights and understanding of the shared genetic etiology of sleep-related phenotypes and psychiatric disorders and highlights new opportunities and avenues for future investigation.

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Patients with psychiatric disorders frequently experience disturbed sleep (1–6). Sleep disturbances form part of the diagnostic criteria for mood disorders (7), are evident early in the course of psychosis (8), and are known to exacerbate positive psychotic symptoms (9). Numerous sleep disturbances are comorbid with psychiatric disorders, including insomnia, hypersomnia, reduced sleep need, circadian rhythm disruption, and nightmares (10). In addition to these sleep disturbances, evening circadian chronotype is associated with elevated rates of psychopathology (11,12). Evidence for the critical role of the circadian system in several psychiatric disorders, including bipolar disorder (BIP), major depressive disorder (MDD), and schizophrenia (SCZ), has also been summarized (13). Moreover, medications used in the treatment of psychiatric disorders are known to modify sleep, and treatments for sleep abnormalities impact psychiatric conditions (14). As such, a link between sleep disturbances and mental illness is well documented, but the underlying causal relationship has been difficult to establish from clinical and epidemiological data. The direction of effect is still unknown—whether sleep abnormalities are a causal factor or a result of the psychiatric disorder, or whether there are shared underlying mechanisms leading to both (13,15). An important reason for the difficulty in disentangling cause-and-effect is that sleep disturbances are both heterogeneous and vary over time and are present in different combinations of multiple phenotypes (16).

In support of the phenotypic relationship between sleep disturbances and psychiatric disorders, molecular studies suggest common underlying mechanisms. Initial studies of variants within candidate circadian/clock genes identified associations with psychiatric disorders, such as BIP (17), MDD (18), and SCZ (19). More recently, however, genome-wide association studies (GWASs) of sleep-related phenotypes, including chronotype (20), insomnia (21), and sleep duration (22), have shown that sleep-related phenotypes are complex

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traits, modulated by more than just the core circadian/clock genes. In support of the shared clinical picture and overlapping candidate genes, genome-wide genetic overlap has also been identified using standard tools. In major psychiatric disorders, there are reports of significant genetic correlations for chronotype with MDD and SCZ (20), for sleep duration with BIP and SCZ (22), and between insomnia and MDD (21). Moreover, Mendelian randomization results suggest that reduced sleep duration, evening type chronotype, and insomnia are potentially causal for SCZ, while bidirectional effects were identified between insomnia and depression (DEP) (20–22). Increased understanding of the genetic overlap between psychiatric disorder and sleep-related phenotypes may aid in the development of novel treatment strategies for psychiatric patients with comorbid sleep disturbances.

The aim of the present study was therefore to further characterize the overlapping genetic architecture [the number of genomic loci contributing to risk, the distribution of their allelic frequencies and effect sizes, and the interactions of alleles in and between genes (23,24)] of sleep-related phenotypes and psychiatric disorders, beyond genetic correlation, by utilizing results from large GWASs and relevant statistical genetics tools. To do so, we employed a stepwise approach. First, MiXeR (25) was used to quantify the trait-specific and shared polygenic architecture of sleep-related phenotypes and psychiatric disorders. Second, we utilized the conditional false discovery rate/conjunctional false discovery rate (condFDR/conjFDR) approach (26–28) to detect novel phenotype-specific variants and shared loci between sleep-related phenotypes and psychiatric disorders. Finally, we performed functional annotation and gene mapping of these identified specific loci. While genetic correlation provides an aggregate measure for the balance of variants with the same and opposite effects on a given pair of traits, both MiXeR and condFDR/conjFDR are able to identify genetic overlap regardless of effect direction (25,28,29). These methods, therefore, complement genetic correlation to provide a more comprehensive overview of the genetic relationships between traits.

METHODS AND MATERIALS

GWAS Data

GWAS summary statistics for BIP and SCZ were obtained from the Psychiatric Genomics Consortium. The BIP sample comprised 20,352 cases and 31,358 controls (30). Data for the SCZ sample included 33,640 cases and 43,456 controls (31). Data on DEP were obtained from the Psychiatric Genomics Consortium and 23andMe, Inc., and included 135,458 cases and 344,901 controls (32). Detailed description of each sample is provided in the corresponding publications (30–32).

GWAS data for insomnia, chronotype, and sleep duration were obtained from publicly available summary statistics, derived from the UK Biobank (detailed definition of each phenotype is provided in Supplement 1). The insomnia sample included 109,402 cases and 277,131 controls (21), and the chronotype sample included 449,734 individuals (20). Owing to data sharing restrictions, the insomnia (944,477) and chronotype (248,100) cohorts from 23andMe could not be included (20,21). The chronotype GWAS was analyzed such that reported allelic effects are specific to morningness. Finally, sleep duration was treated as a continuous variable and included a sample of 446,118 individuals (22).

For all GWAS samples used, summary statistics were generated only from individuals of European ancestry. All GWASs investigated in the present study were approved by the relevant ethics committees, and informed consent was obtained from all participants. The Norwegian Institutional Review Board for the South-East Norway Region has evaluated the current protocol and found that no additional institutional review board approval was needed because no individual data were used.

Data Analysis

We generated conditional quantile-quantile plots to visually assess the cross-phenotype polygenic enrichment, conditioning each of the psychiatric disorders on the sleep phenotypes and vice versa. After observing cross-phenotype polygenic enrichment, we sought to quantify the genetic overlap between investigated phenotypes. To do so, we applied causal mixture models (25) to the GWAS summary statistics, using MiXeR (version 1.3). MiXeR provides univariate estimates of the number of trait-influencing loci for each trait of interest as well as bivariate estimates of genome-wide genetic overlap between pairs of traits. In these cross-trait analyses, MiXeR models additive genetic effects as a mixture of four components, representing single nucleotide polymorphisms (SNPs) not affecting either trait, SNPs affecting only one of the traits, and SNPs affecting both traits. These components are then plotted in Venn diagrams. After fitting parameters of the model, the Dice coefficient (DC) (the proportion of SNPs shared by two traits out of the total number of SNPs estimated to influence both traits) and genetic correlation were also calculated. In addition to the MiXeR analyses of psychiatric disorders and sleep-related phenotypes, we included two additional comparisons as positive and negative controls (Table S1 in Supplement 2). To illustrate substantial genetic overlap estimates between two traits with high genetic correlation (positive control), we included MiXeR estimates for overlap between SCZ and BIP. Similarly, to illustrate little genetic overlap estimates between two traits with low genetic correlation (negative control), we included MiXeR estimates for the overlap between SCZ and height (33). Further details are provided in the Supplemental Methods in Supplement 1 and in the original publication (25), and all code is available online (https://github.com/precimed/mixer).

Next, we employed the condFDR/conjFDR method (26–28), which allows for the identification of specific shared loci between pairs of traits, thus complementing the genome-wide genetic overlap observed with MiXeR. The condFDR method utilizes genetic association summary statistics from a trait of interest (psychiatric) together with those of a conditional trait (sleep-related) to estimate the posterior probability that an SNP has no association with the primary trait, given that the p values for that SNP in both the primary and conditional traits are lower than the observed p values. This method increases the power to identify loci associated with the primary trait by leveraging associations with conditional traits, thereby re-ranking SNPs compared with the original GWAS p value

ranking. The conjFDR statistic is defined as the maximum of the two mutual condFDR values and is a conservative estimate of the posterior probability that an SNP has no association with either trait, given that the *p* values for that SNP in both the primary and conditional traits are lower than the observed *p* values. The conjFDR method thus allows the identification of loci associated with both traits. An FDR level of .01 per pairwise comparison was set for condFDR and conjFDR, corresponding to 1 false positive per 100 reported associations. We excluded SNPs around the extended major histocompatibility complex region and chromosome 8p23.1 (genome build 19 locations chr6:25119106–33854733 and chr8:7200000–12500000, respectively) before fitting the FDR model, because their intricate regional linkage disequilibrium (LD) may bias condFDR/conjFDR estimation (34). All code used to perform the described analyses is available online (https://github.com/precimed/pleiofdr). More details about the condFDR/conjFDR methods can be found in the original publications (26,27) and subsequent review (28).

Genomic Loci Definition

Independent genomic loci were defined according to the FUMA protocol (Supplemental Methods in Supplement 1) (35). We evaluated the directional effects of shared loci by comparing *z* scores from the respective GWAS summary statistics.

Functional Annotation

Positional and functional annotation of all candidate SNPs, in the genomic loci with a conjFDR value $< .10$ having an LD $r^2 \geq 0.6$ with one of the independent significant SNPs, was performed using multiple tools, implemented in FUMA (Supplemental Methods in Supplement 1) (35). In addition, we linked lead SNPs to genes using three gene-mapping strategies (35): 1) positional mapping to align SNPs to genes based on their physical proximity, 2) expression quantitative trait locus (eQTL) mapping to match cis-eQTL SNPs to genes whose expression is associated with allelic variation at the SNP level, and 3) chromatin interaction mapping to link SNPs to genes based on three-dimensional DNA–DNA interactions between each SNP's genomic region and nearby or distant genes. All gene-mapping strategies were limited to brain tissues, otherwise all other default settings in FUMA were used (35). Finally, we queried SNPs for known QTLs in brain tissues using the GTEx portal (GTEx, version 8) (36) and PsychEncode database (37).

RESULTS

Cross-trait Polygenic Enrichment

We observed cross-trait polygenic enrichment within stratified conditional quantile-quantile plots when conditioning the investigated psychiatric disorders on each of the sleep-related phenotypes and vice versa (Figure S1 in Supplement 1), indicative of polygenic overlap.

Quantification of Genetic Overlap With MiXeR

MiXeR estimated a wide range ($|r_g|$ = 0.04 to 0.42) in the measure of genetic correlation between each of the psychiatric disorders and sleep-related phenotypes (Figure 1), consistent with previous studies (20–22). Despite this range in correlation strengths, considerable genetic overlap was observed between all psychiatric and sleep-related traits (Figure 1 and Table 1). The largest amount of genetic overlap was observed between SCZ and chronotype (DC = 80%), while the set of variants influencing DEP was shown to fully encompass the variants estimated to influence sleep duration. Both SCZ (DCs: SCZ and chronotype = 80%, SCZ and insomnia = 76%, SCZ and sleep duration = 78%) and BIP (DCs: BIP and chronotype = 64%, BIP and insomnia = 78%, BIP and sleep duration = 76%) showed considerable overlap with all sleep-related phenotypes despite a wide range of genetic correlation results ($r_g = -0.12$ to 0.19). The highest genetic correlation was observed between DEP and insomnia ($r_g = 0.42$); however, MiXeR was unable to accurately quantify the genetic overlap between DEP and insomnia, as evidenced by the negative Akaike information criterion scores indicative of poor model fit. This is likely due to the high polygenicity and low heritability estimated for these traits (Table S1 in Supplement 2). Despite identifying large genetic overlap between the investigated sleep-related phenotypes and psychiatric disorders, moderate congruency of variant effects within the shared component was observed for most bivariate analyses (Table 1). As expected, MiXeR estimated considerable overlap between the SCZ and BIP (DC = 87%) and little overlap between SCZ and height (DC = 18%) (Table S1 in Supplement 2). Log-likelihood and bivariate density plots, illustrating the relationship between the GWAS test statistics, for each pairwise comparison are presented in the Supplemental data (Figure S2 in Supplement 1).

When considering the number of shared SNPs as a proportion of the total polygenicity of each trait (Table 1), nearly all SNPs affecting both chronotype and sleep duration also influence DEP. Similar patterns were observed between SCZ and chronotype, SCZ and sleep duration, and BIP and sleep duration. The lowest proportion for any sleep-related phenotype shared with a psychiatric disorder was observed for BIP and chronotype. In contrast, the highest proportion of SNPs affecting psychiatric disorders that also influence sleep-related phenotypes was identified for BIP and insomnia.

Shared and Novel Loci for Psychiatric Disorders and Sleep-Related Phenotypes

For the conjFDR analyses of BIP and the sleep-related phenotypes, 9, 1, and 6 LD-independent loci were significantly (conjFDR $< .01$) associated with, and shared between, BIP and chronotype, insomnia, and sleep duration, respectively (Tables S2 and S3 in Supplement 2). Evaluation of these loci revealed that none were novel for BIP (Table S2 in Supplement 2). A Manhattan plot from these conjFDR analyses is presented in Figure 2A. Twenty-two credible genes were mapped to these loci using all three mapping strategies (Table S4 in Supplement 2).

A total of 22, 12, and 21 LD-independent loci were significantly (conjFDR $< .01$) associated with, and shared between, DEP and chronotype, insomnia, and sleep duration, respectively (Tables S6 and S7 in Supplement 2). Of these, 4 shared loci between DEP and chronotype and 4 shared loci between

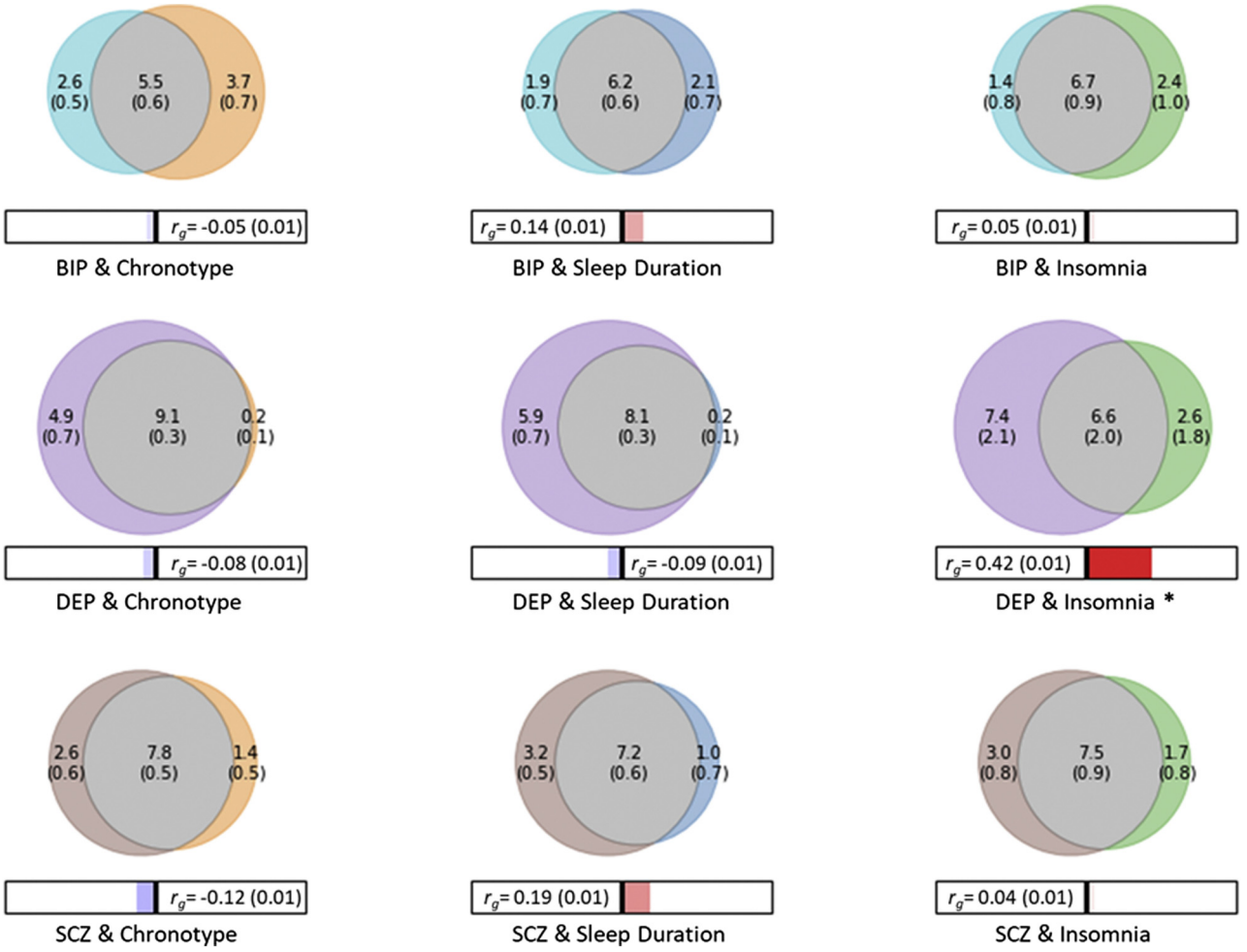

Figure 1. Venn diagrams depicting the estimated number of trait-influencing variants shared (gray) between psychiatric disorders (left circle; BIP, DEP, and SCZ) and sleep-related phenotypes (right circle; chronotype, insomnia, and sleep duration) and unique (colors) to either of them. The number of trait-influencing variants in thousands is shown, with the standard error in thousands provided in parentheses. The size of the circles reflects the polygenicity of each phenotype, with larger circles corresponding to greater polygenicity and vice versa. The estimated genetic correlation for each pair is also shown below the corresponding Venn diagram, with an accompanying directional scale (negative, blue shades; positive, red shades). *MiXeR was unable to accurately quantify the genetic overlap between DEP and insomnia because of their low heritability and high polygenicity (see Table S1 in Supplement 2 and Figure S2 in Supplement 1 for further details). BIP, bipolar disorder; DEP, depression; SCZ, schizophrenia.

Table 1. Number of Overlapping Single Nucleotide Polymorphisms as a Proportion of the Total Polygenicity of Each Trait, Dice Coefficient, and Mean Variant Effect Concordance Within the Shared Component for Each Pairwise Analysis

Psychiatric Disorder	% Proportion of Psych Disorder Shared With Sleep-Related Phenotype	Sleep-Related Phenotype	% Proportion of Sleep-Related Phenotype Shared With Psych Disorder	Dice Coefficient, Mean % (SD)	Concordance, Mean (SD)
BIP	68%	Chronotype	60%	64% (6)	0.48 (0.01)
	83%	Insomnia	74%	78% (10)	0.52 (0.01)
	76%	Sleep duration	75%	76% (8)	0.56 (0.01)
DEP	65%	Chronotype	98%	78% (3)	0.47 (0.01)
	nd	Insomnia	nd	nd	0.82 (0.12)
	58%	Sleep duration	98%	73% (3)	0.46 (0.01)
SCZ	75%	Chronotype	85%	80% (5)	0.45 (0.01)
	71%	Insomnia	82%	76% (8)	0.52 (0.01)
	69%	Sleep duration	88%	78% (6)	0.58 (0.01)

The number of overlapping single nucleotide polymorphisms in each bivariate analysis are presented as a proportion of the total polygenicity of each trait. MiXeR could not accurately quantify the polygenic overlap between depression and insomnia, and as a result, these values were nd.

BIP, bipolar disorder; DEP, depression; nd, not determined; Psych, psychiatric; SCZ, schizophrenia.

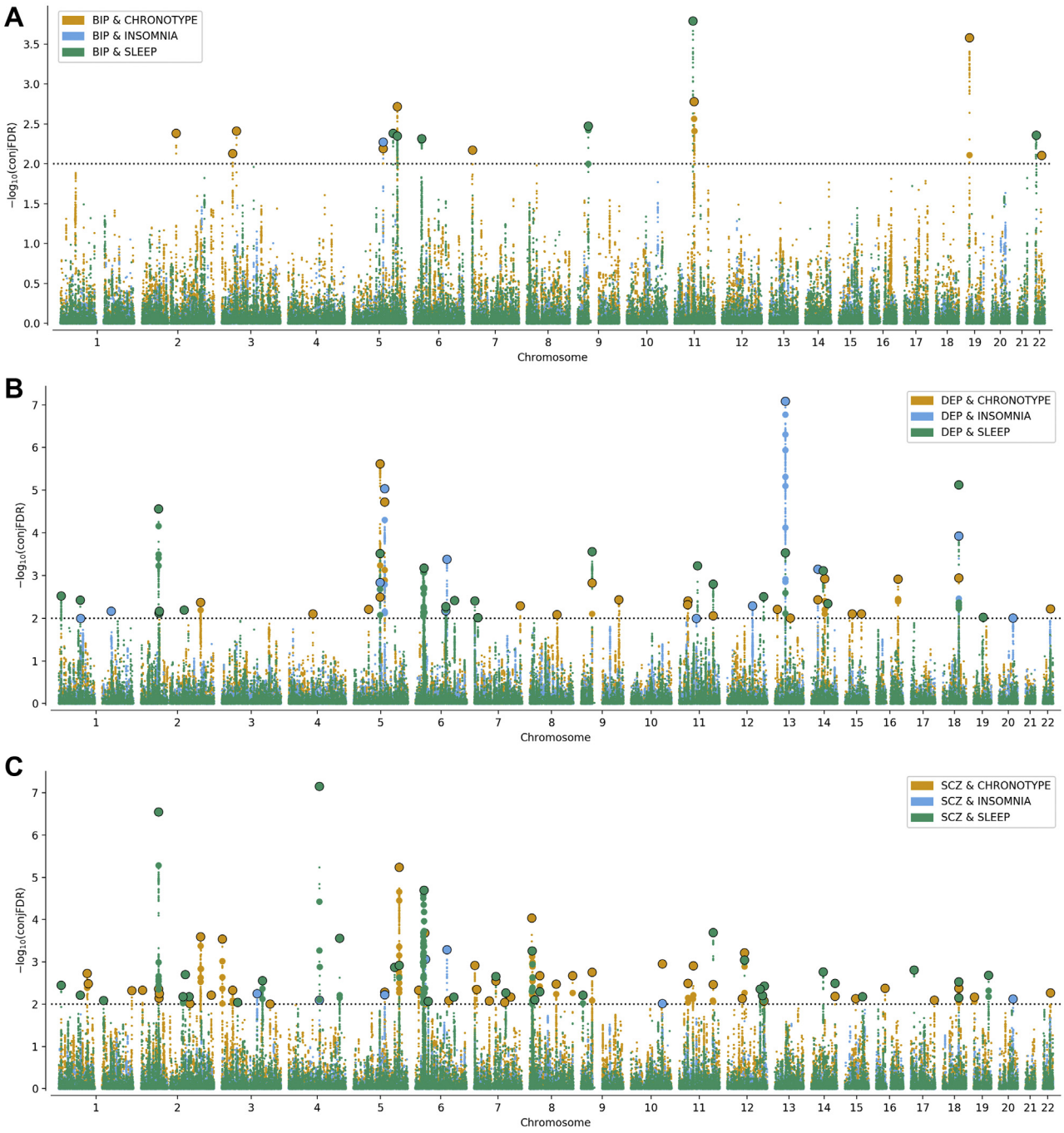

Figure 2. Common genetic variants jointly associated with sleep-related phenotypes (chronotype, insomnia, and sleep duration) and **(A)** BIP, **(B)** DEP, and **(C)** SCZ at conjFDR $< .01$. Manhattan plots show the $-\log_{10}$ transformed conjFDR values for each SNP on the y-axis and chromosomal positions along the x-axis. The dotted horizontal line represents the threshold for significant shared associations (conjFDR $< .01$, i.e., $-\log_{10}$(conjFDR) > 2). Independent lead SNPs are encircled in black. The significant shared signals in the major histocompatibility complex region (chr6:25119106–33854733) and region 8p23.1 (chr8:8091701–11835712) are represented by one lead SNP only. Further details are provided in Tables 1 and 2, and Tables S3, S7, and S11 in Supplement 2. BIP, bipolar disorder; conjFDR, conjunctional false discovery rate; DEP, depression; SCZ, schizophrenia; SLEEP, sleep duration; SNP, single nucleotide polymorphism.

DEP and sleep duration are novel risk loci for DEP (Table 2; Table S6 in Supplement 2). A Manhattan plot from these conjFDR analyses is presented in Figure 2B. When considering all DEP-associated loci, 29 credible genes were identified using all three mapping strategies (Table S8 in Supplement 2).

Table 2. Novel Loci for Psychiatric Disorders, Jointly Associated With Sleep-Related Phenotypes, at conjFDR $< .01$

Psychiatric Disorder	Sleep-Related Phenotype	Lead SNP	A1/A2	Chr	Credible Mapped Gene	Nearest Gene	Psych *p*	Psych *z*	Sleep-Related *p*	Sleep-Related *z*	conjFDR
DEP	Sleep duration[a]	rs2110399	A/G	2	–	*AC007381.3*	2.138×10^{-5}	−4.250	1.100×10^{-5}	4.397	6.780×10^{-3}
	Sleep duration[a]	rs12477455	C/T	2	–	*ARHGAP15*	1.693×10^{-5}	−4.302	3.200×10^{-5}	−4.159	6.353×10^{-3}
	Sleep duration[a]	rs12194348	G/T	6	*SAMD3*	*SAMD3*	9.340×10^{-6}	−4.432	6.800×10^{-7}	4.967	3.803×10^{-3}
	Chronotype[a]	rs2622237	A/G	7	–	*DPP6*	3.066×10^{-6}	4.666	6.900×10^{-6}	4.497	5.085×10^{-3}
	Chronotype	rs3950221	G/A	8	*AB015752.3*	*LINC00534*	9.788×10^{-6}	−4.422	1.600×10^{-5}	−4.314	8.160×10^{-3}
	Chronotype	rs326779	A/G	11	–	*RP5-1027O15.1*	4.930×10^{-6}	−4.568	2.100×10^{-6}	−4.744	3.936×10^{-3}
	Chronotype[a]	rs17543181	G/A	13	–	*WASF3*	3.429×10^{-6}	−4.643	9.400×10^{-6}	4.431	6.074×10^{-3}
	Sleep duration[a]	rs34851357	T/G	19	–	*C7C-360P9.2*	2.836×10^{-5}	−4.186	5.700×10^{-5}	−4.025	9.546×10^{-3}
SCZ	Chronotype	rs113395535	C/T	2	–	*AC022311.1*	8.933×10^{-6}	4.442	4.000×10^{-12}	6.937	4.636×10^{-3}
	Sleep duration	rs12611523	A/G	2	–	*AC097721.2*	2.538×10^{-5}	−4.211	3.100×10^{-8}	5.536	6.620×10^{-3}
	Sleep duration[a]	rs12467561	A/G	2	*AC009506.1*	*AC009961.3*	1.699×10^{-5}	4.301	2.700×10^{-5}	4.197	6.557×10^{-3}
	Chronotype[a]	rs10255350	C/T	7	–	*NXPH1*	8.373×10^{-6}	4.455	4.300×10^{-7}	5.055	4.459×10^{-3}
	Chronotype	rs6943153	T/C	7	–	*GRB10*	2.320×10^{-5}	−4.232	6.100×10^{-9}	−5.814	8.226×10^{-3}
	Sleep duration	rs17512210	T/G	17	–	*SHISA6*	2.749×10^{-6}	4.689	7.600×10^{-9}	−5.777	1.529×10^{-3}

The most strongly associated SNPs in independent genomic loci shared between indicated psychiatric disorders and sleep-related phenotypes at conjFDR $< .01$ after merging regions <250 kb apart into a single locus. The table presents Chr, credible mapped gene, and nearest gene, as well as *p* values and *z* scores from the original genome-wide association study summary statistics. A1, allele 1; A2, allele 2; Chr, chromosomal position; conjFDR, conjunctional false discovery rate; DEP, depression; SCZ, schizophrenia; SNP, single nucleotide polymorphism.
[a]Novel for the indicated sleep-related phenotype as well. For more details and a list of all candidate variants in these loci, see Tables S6, S7, S10, and S11 in Supplement 2.

Finally, conjFDR analyses revealed 43, 7, and 34 LD-independent loci significantly (conjFDR $< .01$) associated with, and shared between, SCZ and chronotype, insomnia, and sleep duration, respectively (Tables S10 and S11 in Supplement 2). Three loci shared between SCZ and chronotype and 3 loci shared between SCZ and sleep duration are novel risk loci for SCZ (Table 2; Table S10 in Supplement 2). A Manhattan plot from these conjFDR analyses is presented in Figure 2C. Gene mapping analysis using lead SNPs within the SCZ-associated loci implicated 32 credible genes.

When considering the sleep-related phenotypes, 12, 3, and 31 novel loci were identified for chronotype, insomnia, and sleep duration, respectively (Table 3).

Of the genes mapped to each of the shared loci described above, 70 unique credible genes were mapped by all three gene-mapping strategies (Table 4; Tables S4, S8, and S13 in Supplement 2). The *LOC100127955* gene was mapped to lead SNPs of shared loci for all three psychiatric disorders, as well as chronotype and sleep duration (Table 4). A further 19 credible genes were mapped to loci for at least three of the investigated phenotypes (Table 4). The remaining 50 credible genes were unique to specific bivariate analyses (Table 4). Results from network analysis identified multiple relationships between these credible genes, including physical interactions, gene coexpression, genetic interactions, and predicted and shared protein domains (Figure S3 in Supplement 1 and Table S15 in Supplement 2).

In total, all the shared loci identified using the conjFDR methodology are represented by 146 unique lead SNPs, of which 49 were identified as eQTLs for 115 unique genes within 12 different brain tissues in the GTEx database (Table S12 in Supplement 2). Implicated brain regions include the basal ganglia and related structures, as well as the cortex, hippocampus, and cerebellum. These brain tissues were identified by lead SNPs within shared loci between chronotype and sleep duration and all investigated psychiatric disorders. Moreover, 76 lead SNPs were identified as QTLs in the PsychEncode database (Table S16 in Supplement 2). No significant eQTLs were identified for lead SNPs shared between psychiatric disorders and insomnia. Further information related to the functional annotation and gene-mapping results of the specific identified loci is available in Supplement 1.

DISCUSSION

The current study employed GWAS summary statistics from sleep-related phenotypes and psychiatric disorders to better understand the shared underlying genetic architecture. Using the novel MiXeR tool (25), our results provide further evidence of extensive genetic overlap between sleep-related phenotypes and psychiatric disorders, which is consistent with the strong phenotypic correlations and comorbidity observed in the clinic, as well as previous genetic findings. We identified substantial genetic overlap between major psychiatric disorders (BIP, DEP, and SCZ) and sleep-related phenotypes (chronotype, insomnia, and sleep duration), beyond genetic correlation. Further, we identified 146 specific shared loci between pairs of sleep-related phenotypes and psychiatric disorders, of which 42 were novel for at least one of the investigated phenotypes. Finally, we annotated these specific

Table 3. Novel Loci for Sleep-Related Phenotypes, Jointly Associated With Psychiatric Disorders, at conjFDR < .01

Sleep-Related Phenotype	Psychiatric Disorder	Lead SNP	A1/A2	Chr	Credible Mapped Gene	Nearest Gene	Sleep-Related *p*	Sleep-Related *z*	Psych *p*	Psych *z*	conjFDR
Chronotype	BIP	rs11123241	A/G	2	–	*RNU2-41P*	2.500×10^{-6}	−4.708	5.012×10^{-6}	−4.564	4.141×10^{-3}
	SCZ	rs938575	G/A	2	*NGEF*	*NGEF*	1.500×10^{-5}	4.329	1.854×10^{-10}	6.373	6.067×10^{-3}
	DEP	rs80315381	T/C	5	–	*RNU6-1296P*	9.700×10^{-6}	−4.424	8.879×10^{-7}	4.915	6.187×10^{-3}
	BIP SCZ	rs12154473 rs13244345	A/G	7	*LOC100127955*	*MAD1L1*	7.600×10^{-6}	4.476	2.694×10^{-6}	−4.693	6.702×10^{-3}
	SCZ[a]	rs10255350	C/T	7	–	*NXPH1*	4.300×10^{-7}	5.055	8.373×10^{-6}	4.455	4.459×10^{-3}
	DEP[a]	rs2622237	A/G	7	–	*DPP6*	6.900×10^{-6}	4.497	3.066×10^{-6}	4.666	5.085×10^{-3}
	SCZ	rs13250349	C/T	8	–	*RP11-586K2.1*	4.800×10^{-6}	4.573	2.564×10^{-6}	−4.703	3.329×10^{-3}
	SCZ	rs11777164	C/T	8	–	*TSNARE1*	2.000×10^{-6}	−4.753	2.177×10^{-9}	5.984	2.122×10^{-3}
	DEP[a]	rs17543181	G/A	13	–	*WASF3*	9.400×10^{-6}	4.431	3.429×10^{-6}	−4.643	6.074×10^{-3}
	DEP	rs4595767	A/G	15	–	*LINGO1*	1.500×10^{-5}	4.329	5.974×10^{-6}	−4.527	7.888×10^{-3}
	SCZ	rs62057756	G/A	16	*INO80E*	*GDPD3*	7.400×10^{-6}	−4.482	1.455×10^{-6}	−4.817	4.174×10^{-3}
	SCZ	rs12936687	G/A	17	–	*RPTOR*	2.500×10^{-5}	4.215	8.809×10^{-6}	4.445	8.035×10^{-3}
Insomnia	DEP	rs6693299	A/G	1	–	*RFWD2*	3.280×10^{-5}	4.153	1.622×10^{-7}	5.238	6.850×10^{-3}
	SCZ	rs77335224	C/T	10	*CNNM2*	*AS3MT*	1.938×10^{-5}	−4.272	5.375×10^{-14}	−7.522	9.602×10^{-3}
	DEP	rs10132715	A/G	14	–	*LRFN5*	1.707×10^{-6}	4.785	3.219×10^{-8}	−5.529	7.093×10^{-4}
Sleep Duration	DEP SCZ	rs301819	A/G	1	*RERE*	*RERE*	1.100×10^{-5}	−4.397	1.036×10^{-8}	5.725	2.972×10^{-3}
	DEP SCZ	rs34305371 rs72677193	G/A	1	–	*NEGR1*	8.200×10^{-7}	4.931	9.207×10^{-6}	4.435	3.762×10^{-3}
	SCZ	rs1050818	A/C	1	*TARS2*	*MRPS21*	3.700×10^{-5}	4.125	2.498×10^{-6}	4.708	8.133×10^{-3}
	DEP[a]	rs2110399	A/G	2	–	*AC007381.3*	1.100×10^{-5}	4.397	2.138×10^{-5}	−4.250	6.780×10^{-3}
	DEP[a]	rs12477455	C/T	2	–	*ARHGAP15*	3.200×10^{-5}	−4.159	1.693×10^{-5}	−4.302	6.353×10^{-3}
	SCZ[a]	rs12467561	A/G	2	*AC009506.1*	*AC009961.3*	2.700×10^{-5}	4.197	1.699×10^{-5}	4.301	6.557×10^{-3}
	SCZ	rs36029422	C/T	3	–	*CACNA1D*	3.600×10^{-5}	4.132	4.152×10^{-5}	−4.099	9.001×10^{-3}
	SCZ	rs7653924	C/T	4	–	*SH3RF1*	2.900×10^{-7}	−5.130	5.767×10^{-8}	5.426	2.761×10^{-4}
	DEP	rs895295	G/A	5	–	*TMEM161B-AS1*	4.300×10^{-7}	5.055	4.180×10^{-10}	6.247	3.015×10^{-4}
	BIP SCZ	rs4246036 rs4958318	C/T	5	–	*AC091969.1*	3.300×10^{-6}	−4.651	7.464×10^{-6}	4.480	4.464×10^{-3}
	DEP	rs12215909	T/C	6	–	*ASCC3*	1.600×10^{-5}	4.314	1.515×10^{-5}	−4.326	5.322×10^{-3}
	SCZ	rs13219424	C/T	6	–	*PTPRK*	1.100×10^{-5}	4.397	2.653×10^{-5}	−4.201	6.797×10^{-3}
	DEP[a]	rs12194348	G/T	6	*TMEM200A*	*SAMD3*	6.800×10^{-7}	4.967	9.340×10^{-6}	−4.432	3.803×10^{-3}
	DEP	rs6460896	G/A	7	–	*TMEM106B*	5.800×10^{-5}	−4.021	1.021×10^{-5}	4.413	9.659×10^{-3}
	SCZ	rs2867673	C/T	7	–	*CALN1*	3.200×10^{-6}	−4.658	1.250×10^{-5}	4.369	8.664×10^{-3}
	SCZ	rs10241415	A/G	7	*KMT2E*	*SRPK2*	2.000×10^{-5}	4.265	4.502×10^{-9}	5.865	5.335×10^{-3}

Table 3. Continued

Sleep-Related Phenotype	Psychiatric Disorder	Lead SNP	A1/A2	Chr	Credible Mapped Gene	Nearest Gene	Sleep-Related *p*	Sleep-Related *z*	Psych *p*	Psych *z*	conjFDR
	SCZ	rs2959623	G/T	8	–	*ZDHHC2*	3.500×10^{-5}	4.138	1.252×10^{-6}	−4.847	7.836×10^{-3}
	SCZ	rs139253412	T/G	8	–	*RP11-317N12.1*	1.200×10^{-5}	−4.378	1.638×10^{-5}	−4.309	5.005×10^{-3}
	SCZ	rs2770734	C/A	9	–	*KDM4C*	2.400×10^{-5}	4.224	6.534×10^{-6}	4.508	6.060×10^{-3}
	BIP	rs62535709	C/T	9	–	*ZCCHC7*	7.000×10^{-7}	−4.961	5.234×10^{-6}	4.555	3.356×10^{-3}
	SCZ	rs61937595	C/T	12	–	*R3HDM2*	1.600×10^{-6}	4.798	4.391×10^{-11}	−6.590	8.999×10^{-4}
	SCZ	rs1790099	C/T	12	–	*MPHOSPH9*	1.200×10^{-5}	4.378	2.946×10^{-6}	−4.675	3.730×10^{-3}
	DEP	rs1885767	A/G	13	–	*LINC01065*	4.100×10^{-7}	−5.064	3.731×10^{-11}	6.614	2.909×10^{-4}
	DEP	rs3742790	T/C	14	*AREL1*	*YLPM1*	2.000×10^{-5}	−4.265	7.853×10^{-6}	−4.469	4.542×10^{-3}
	SCZ	rs1405238	C/T	14	–	*BCL11B*	2.900×10^{-6}	−4.678	8.254×10^{-6}	4.458	3.205×10^{-3}
	SCZ	rs62012044	G/A	15	–	*EFTUD1*	1.300×10^{-5}	4.360	2.490×10^{-5}	−4.216	6.544×10^{-3}
	DEP[a]	rs34851357	T/G	19	–	*CTC-360P9.2*	5.700×10^{-5}	−4.025	2.836×10^{-5}	−4.186	9.546×10^{-3}
	SCZ	rs73057994	C/A	19	–	*NOSIP:PRRG2*	1.300×10^{-6}	4.840	4.253×10^{-6}	−4.599	2.051×10^{-3}
	BIP	rs4821402	G/A	22	*MAPK1*	*MAPK1*	4.700×10^{-6}	−4.578	9.811×10^{-7}	−4.895	4.381×10^{-3}

The most strongly associated SNPs in independent genomic loci shared between indicated psychiatric disorders and sleep-related phenotypes at conjFDR $< .01$ after merging regions <250 kb apart into a single locus. The table presents Chr, credible mapped gene, and nearest gene, as well as *p* values and *z* scores from the original genome-wide association study summary statistics.

A1, allele 1; A2, allele 2; BIP, bipolar disorder; Chr, chromosomal position; conjFDR, conjunctional false discovery rate; DEP, depression; SCZ, schizophrenia; SNP, single nucleotide polymorphism.

[a]Novel for the indicated psychiatric disorder as well. For more details and a list of all candidate variants in these loci, see Tables S2, S3, S6, S7, S10, and S11 in Supplement 2.

shared loci and identified a subset of 70 credible genes and numerous eQTLs for multiple brain tissues, including the basal ganglia and related structures, as well as the cortex, hippocampus, and cerebellum.

The MiXeR results showed similar polygenicity for the majority of traits investigated (~8000–10,000 trait-influencing variants), except for depression, which had a much greater polygenicity (~14,000 trait-influencing variants), highlighting the genetic complexity of all of these traits. Moreover, the results identified extensive genetic overlap between sleep-related phenotypes and psychiatric disorders, consistent with previous literature. In a scenario with a substantial overlap of genetic loci and moderate genetic correlation, there is likely a mix of agonistic and antagonistic effect directions among the shared variants, consistent with the concordance rates of approximately 50% observed between traits. This implicates shared molecular biological processes between sleep-related phenotypes and psychiatric disorders, which have mixed effect directions within and between phenotypes. These results are in line with the growing evidence for shared genetic architecture between related phenotypes (38–40) indicating mixed effect directions. These results suggest that the genetic architecture and biological processes shared by sleep phenotypes and psychiatric disorders are present in one type of trait (e.g., sleep phenotype) even in the absence of the other type (e.g., psychiatric disorder). The current findings may indicate that the clinical observations of sleep problems increasing risk for psychiatric disorders and vice versa (15) may still have a genetic influence even in the absence of genetic correlation. Heterogeneity among individuals affected by the same psychiatric disorder is observed through wide distributions of polygenic risk scores (that overlap largely with unaffected control individuals) (41) as well as in brain morphology (42) and is masked at the group level. Thus, patterns of concordance and discordance, within specific biological processes and pathways, may interplay with the environment to drive the phenotypic comorbidities within particular disorder subgroups. For example, we may speculate that altered brain morphology and neurotransmitter signaling are both biological processes that might influence phenotypic comorbidity between psychiatric disorders and sleep-related phenotypes. Moreover, the interplay of these and other biological processes are also likely to modulate effects at the phenotypic level. Specific subgroups of individuals may have high concordance/discordance within genes implicated in one or both of these biological processes, resulting in variance in related traits and comorbidities. These complex relationships are not detected at the group level, as is the case for the participants included in the GWAS summary statistics used in this study. As GWAS sample sizes increase, deep phenotyping of included participants for known comorbidities will be essential to investigate potential subgroups.

Leveraging the extensive polygenic overlap between sleep-related phenotypes and psychiatric disorders, we used the condFDR/conjFDR method to identify the specific genetic loci involved. Numerous shared loci were identified between each pair of investigated phenotypes. Among these, novel loci were identified for DEP (n = 8), SCZ (n = 6), chronotype (n = 12), insomnia (n = 3), and sleep duration (n = 29), demonstrating the utility of this statistical framework to increase discovery and

Table 4. Credible Genes Mapped to Lead SNPs of Shared Loci Between Psychiatric Disorders and Sleep-Related Phenotypes

Lead SNP-Associated Phenotypes	No.	Credible Mapped Gene(s)
BIP, Chronotype, DEP, SCZ, Sleep Duration	1	*LOC100127955*[a]
Chronotype, Insomnia, DEP, Sleep Duration	2	*CTC-498M16.4, LINC00461*
Chronotype, DEP, SCZ, Sleep Duration	1	*ZCCHC7*
Chronotype, Insomnia, SCZ	4	*AS3MT, C10orf32-ASMT, CNNM2*[b], *NT5C2*
Chronotype, DEP, SCZ	1	*PLCL1*
Insomnia, DEP, Sleep Duration	2	*TMEM161B, TMEM161B-AS1*
Insomnia, DEP, SCZ	4	*CSE1L, DDX27, RP1-155G6.4, ZNFX1*
BIP, DEP, Sleep Duration	5	*FADS2, FEN1, TMEM258, ZKSCAN8, ZNF192P1*
BIP, Chronotype	8	*CNIH2, GAL3ST3, ILF3-AS1, RAB1B, SF3B2, SLC44A2, TMEM151A, YIF1A*
Chronotype, DEP	4	*AB015752.3, DENND1A, LRFN5, SF3B1*
Chronotype, SCZ	14	*C6orf3, CERS5, COX14, DIP2B, DOC2A, GIGYF2, GPD1, INO80E*[a], *NGEF*[a], *PACSIN3, PPM1L, RP4-605O3.4, TAOK2, TRAF3IP2*
Insomnia, SCZ	1	*IP6K3*
BIP, Sleep Duration	8	*HIST1H2BL, HIST1H4L, MAPK1*[c], *PGBD1, RP1-97D16.1, ZKSCAN3, ZNF204P, ZSCAN31*
DEP, Sleep Duration	9	*AREL1*[c], *DLST, RERE*[c], *RP11-220I1.1, RP5-1115A15.1, RPS6KL1, SAMD3*[d], *SPPL3, TMEM200A*[c]
SCZ, Sleep Duration	6	*AC009506.1*[c,e], *BAZ2B, CUL9, DNPH1, KMT2E*[c], *TARS2*[c]

Unique genes mapped to lead SNPs, of shared loci between psychiatric disorders and sleep-related phenotypes, by the three employed mapping strategies: 1) positional mapping, 2) expression quantitative trait locus mapping, and 3) chromatin interaction mapping. Additional details are provided in Tables S2, S6, and S10 in Supplement 2.

BIP, bipolar disorder; DEP, depression; SCZ, schizophrenia; SNP, single nucleotide polymorphism.

[a]Genes mapped to the novel loci chronotype.

[b]Genes mapped to the novel loci insomnia.

[c]Genes mapped to the novel loci sleep duration.

[d]Genes mapped to the novel loci depression.

[e]Genes mapped to the novel loci schizophrenia.

uncover polygenic overlap between complex phenotypes (28). In-silico analyses of these novel loci indicate potential regulatory functionality and deleterious effects on protein structure and function, as well as QTL effects in a number of brain tissues for identified lead SNPs.

Moreover, we determined a subset of 70 unique credible genes that map to specific identified shared loci based on three independent gene-mapping strategies. Network analysis highlights that this subset of genes are predominantly linked by physical interactions and gene coexpression. One gene, the noncoding RNA *LOC100127955*, was mapped to lead SNPs associated with BIP, DEP, SCZ, chronotype, and sleep duration. Variants within this gene have also been implicated in other behavioral phenotypes, including autism spectrum disorder (43), risk-taking behavior (44), and age of smoking initiation (45). The function of this gene is currently unknown, and gene coexpression results indicate that it is most likely coexpressed with other noncoding RNA genes (46). However, *LOC100127955* shows higher expression in brain tissue when compared with other tissues, specifically within regions of the cortex, the amygdala, and the hippocampus (Figure S4 in Supplement 1). It is tempting to speculate that the expression of *LOC100127955* in these brain regions provides some clue as to the possible mechanisms through which it may modulate sleep-related phenotypes and development of psychiatric disorders; however, functional studies are required to better understand the role of this gene and the possible biological processes that it may contribute to.

Another 19 genes were mapped to lead SNPs for at least three phenotypes. Interestingly, however, the majority of credible mapped genes were specific to particular bivariate analyses of sleep-related phenotypes and psychiatric disorders. These results further emphasize the complex underlying genetic architecture and biology of these phenotypes, suggesting the involvement of common shared processes, mechanisms, and pathways, as well as phenotype-specific aspects. Although further research is required to validate these results, future studies should interrogate the genes identified here and their associated mechanisms and pathways to improve our understanding of the shared genetic etiology of sleep-related phenotypes and psychiatric disorders. Moreover, it should be noted that the gene mapping performed in this study, based on identified specific loci, represents only a small fraction of the genetic architecture of the traits investigated. At any rate, while these findings may not be representative of the complete genetic etiology of these traits, they are informative and provide some basis to further explore the underlying shared genetic architecture of sleep-related phenotypes and psychiatric disorders.

This study applied MiXeR to quantify the number of unique and shared genetic variants between psychiatric disorders and sleep-related traits and the congruency of variants within the shared component. Following this, a subset of specific variants within this shared component were identified and annotated. Despite this, the exact role of variants within this shared component, their interplay with environmental and lifestyle factors, and how this may modulate phenotypic comorbidities require further investigation. Furthermore, it is also possible that common variants cannot fully explain the overall comorbidity, but that it is the psychiatric disorder itself that is causative or that other environmental and lifestyle factors or rare

variants contribute to the phenotypic comorbidities observed. The main limitation to the condFDR/conjFDR method, which it inherits from the GWAS it draws upon, is that it is agnostic to specific causal variants underlying the shared loci. These shared loci could arise because of both shared or separate causal variants, or mediated pleiotropy, where one phenotype is causative for the other (28,47). Whenever separate causal variants underlie a specific shared locus, this has implications for the functionality of that locus in each of the associated traits because separate variants may influence different genes or other biological processes. Mediated pleiotropy may result in identification of a false positive shared locus where the causal variant is only truly associated with one of the traits (28). Moreover, both condFDR/conjFDR and MiXeR are limited to bivariate analyses, so it is not possible to determine whether the identified genetic overlap is influenced by additional factors, such as social stratification and socioeconomic status, as has recently been shown (48–50). A final limitation is that patients with self-reported psychiatric disorders were not excluded from the sleep phenotype GWAS samples (20–22). Although the number of individuals with BIP and SCZ is low in the UK Biobank (n ~ 1000), there are a large number of individuals with self-reported or diagnosed depression, which may result in inflated MiXeR shared components and/or false positive shared loci between sleep phenotypes and DEP.

In conclusion, we have demonstrated novel and substantial polygenic overlap between psychiatric disorders (BIP, DEP, and SCZ) and sleep-related phenotypes (chronotype, insomnia, and sleep duration). These findings highlight a greater quantity of genetic overlap than that indicated by genetic correlation. Interestingly, the majority of bivariate analyses showed only moderate congruency of effect direction for genetic variants within the shared component, suggestive of a complex genetic relationship and potential subgroups with higher or lower genetic concordance. Future studies and deep phenotyping may allow for analysis of these subgroups to improve risk stratification of individuals with comorbid sleep disturbances and psychiatric disorders. Moreover, we have identified numerous shared loci and a subset of credible genes likely to play a role in the underlying genetic etiology of these phenotypes, which may represent novel drug targets and thus opportunities for personalized approaches to treatment.

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REFERENCES

1. Laskemoen JF, Simonsen C, Büchmann C, Barrett EA, Bjella T, Lagerberg TV, *et al.* (2019): Sleep disturbances in schizophrenia spectrum and bipolar disorders - A transdiagnostic perspective. Compr Psychiatry 91:6–12.
2. Harvey AG, Murray G, Chandler RA, Soehner A (2011): Sleep disturbance as transdiagnostic: Consideration of neurobiological mechanisms. Clin Psychol Rev 31:225–235.
3. Freeman D, Sheaves B, Waite F, Harvey AG, Harrison PJ (2020): Sleep disturbance and psychiatric disorders. Lancet Psychiatry 7:628–637.
4. Waite F, Sheaves B, Isham L, Reeve S, Freeman D (2020): Sleep and schizophrenia: From epiphenomenon to treatable causal target. Schizophr Res 221:44–56.
5. Steardo LJ, de Filippis R, Carbone EA, Segura-Garcia C, Verkhratsky A, De Fazio P (2019): Sleep disturbance in bipolar disorder: Neuroglia and circadian rhythms. Front Psychiatry 10:501.
6. Riemann D, Krone LB, Wulff K, Nissen C (2020): Sleep, insomnia, and depression. Neuropsychopharmacology 45:74–89.
7. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 5th ed. Washington, DC: American Psychiatric Association.
8. Reeve S, Nickless A, Sheaves B, Hodgekins J, Stewart SLK, Gumley A, *et al.* (2019): Sleep duration and psychotic experiences in patients at risk of psychosis: A secondary analysis of the EDIE-2 trial. Schizophr Res 204:326–333.
9. Davies G, Haddock G, Yung AR, Mulligan LD, Kyle SD (2017): A systematic review of the nature and correlates of sleep disturbance in early psychosis. Sleep Med Rev 31:25–38.

10. Harvey AG (2009): A transdiagnostic approach to treating sleep disturbance in psychiatric disorders. Cogn Behav Ther 38(suppl 1): 35–42.
11. Reid KJ, Jaksa AA, Eisengart JB, Baron KG, Lu B, Kane P, *et al.* (2012): Systematic evaluation of Axis-I DSM diagnoses in delayed sleep phase disorder and evening-type circadian preference. Sleep Med 13:1171–1177.
12. Merikanto I, Kronholm E, Peltonen M, Laatikainen T, Vartiainen E, Partonen T (2015): Circadian preference links to depression in general adult population. J Affect Disord 188:143–148.
13. Walker WH, Walton JC, DeVries AC, Nelson RJ (2020): Circadian rhythm disruption and mental health. Transl Psychiatry 10:28.
14. Krystal AD (2020): Sleep therapeutics and neuropsychiatric illness. Neuropsychopharmacology 45:166–175.
15. Harvey AG (2008): Sleep and circadian rhythms in bipolar disorder: Seeking synchrony, harmony, and regulation. Am J Psychiatry 165:820–829.
16. Wulff K, Porcheret K, Cussans E, Foster RG (2009): Sleep and circadian rhythm disturbances: Multiple genes and multiple phenotypes. Curr Opin Genet Dev 19:237–246.
17. Shi J, Wittke-Thompson JK, Badner JA, Hattori E, Potash JB, Willour VL, *et al.* (2008): Clock genes may influence bipolar disorder susceptibility and dysfunctional circadian rhythm. Am J Med Genet B Neuropsychiatr Genet 147B:1047–1055.
18. Soria V, Martínez-Amorós E, Escaramís G, Valero J, Pérez-Egea R, García C, *et al.* (2010): Differential association of circadian genes with mood disorders: CRY1 and NPAS2 are associated with unipolar major depression and CLOCK and VIP with bipolar disorder. Neuropsychopharmacology 35:1279–1289.
19. Johansson AS, Owe-Larsson B, Hetta J, Lundkvist GB (2016): Altered circadian clock gene expression in patients with schizophrenia. Schizophr Res 174:17–23.
20. Jones SE, Lane JM, Wood AR, van Hees VT, Tyrrell J, Beaumont RN, *et al.* (2019): Genome-wide association analyses of chronotype in 697, 828 individuals provides insights into circadian rhythms. Nat Commun 10:343.
21. Jansen PR, Watanabe K, Stringer S, Skene N, Bryois J, Hammerschlag AR, *et al.* (2019): Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. Nat Genet 51:394–403.
22. Dashti HS, Jones SE, Wood AR, Lane JM, van Hees VT, Wang H, *et al.* (2019): Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. Nat Commun 10:1100.
23. Gratten J, Wray NR, Keller MC, Visscher PM (2014): Large-scale genomics unveils the genetic architecture of psychiatric disorders. Nat Neurosci 17:782–790.
24. Timpson NJ, Greenwood CMT, Soranzo N, Lawson DJ, Richards JB (2018): Genetic architecture: The shape of the genetic contribution to human traits and disease. Nat Rev Genet 19:110–124.
25. Frei O, Holland D, Smeland OB, Shadrin AA, Fan CC, Maeland S, *et al.* (2019): Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation. Nat Commun 10:2417.
26. Andreassen OA, Djurovic S, Thompson WK, Schork AJ, Kendler KS, O'Donovan MC, *et al.* (2013): Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. Am J Hum Genet 92:197–209.
27. Andreassen OA, Thompson WK, Dale AM (2014): Boosting the power of schizophrenia genetics by leveraging new statistical tools. Schizophr Bull 40:13–17.
28. Smeland OB, Frei O, Shadrin A, O'Connell K, Fan CC, Bahrami S, *et al.* (2020): Discovery of shared genomic loci using the conditional false discovery rate approach. Hum Genet 139:85–94.
29. Smeland OB, Frei O, Dale AM, Andreassen OA (2020): The polygenic architecture of schizophrenia - Rethinking pathogenesis and nosology. Nat Rev Neurol 16:366–379.
30. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, *et al.* (2019): Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat Genet 51:793–803.
31. Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014): Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421–427.
32. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, *et al.* (2018): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet 50:668–681.
33. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, *et al.* (2018): Meta-analysis of genome-wide association studies for height and body mass index in ~700000 individuals of European ancestry. Hum Mol Genet 27:3641–3649.
34. Schwartzman A, Lin X (2011): The effect of correlation in false discovery rate estimation. Biometrika 98:199–214.
35. Watanabe K, Taskesen E, van Bochoven A, Posthuma D (2017): Functional mapping and annotation of genetic associations with FUMA. Nat Commun 8:1826.
36. GTEx Consortium (2015): Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. Science 348:648–660.
37. Wang D, Liu S, Warrell J, Won H, Shi X, Navarro FCP, *et al.* (2018): Comprehensive functional genomic resource and integrative model for the human brain. Science 362:eaat8464.
38. Bahrami S, Steen NE, Shadrin A, O'Connell K, Frei O, Bettella F, *et al.* (2020): Shared genetic loci between body mass index and major psychiatric disorders: A genome-wide association study. JAMA Psychiatry 77:503–512.
39. Smeland OB, Bahrami S, Frei O, Shadrin A, O'Connell K, Savage J, *et al.* (2020): Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. Mol Psychiatry 25:844–853.
40. O'Connell KS, Shadrin A, Smeland OB, Bahrami S, Frei O, Bettella F, *et al.* (2020): Identification of genetic loci shared between attention-deficit/hyperactivity disorder, intelligence, and educational attainment. Biol Psychiatry 87:1052–1062.
41. Murray GK, Lin T, Austin J, McGrath JJ, Hickie IB, Wray NR (2021): Could polygenic risk scores be useful in psychiatry?: A review. JAMA Psychiatry 78:210–219.
42. Wolfers T, Doan NT, Kaufmann T, Alnæs D, Moberget T, Agartz I, *et al.* (2018): Mapping the heterogeneous phenotype of schizophrenia and bipolar disorder using normative models. JAMA Psychiatry 75:1146–1155.
43. Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium (2017): Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. Mol Autism 8:21.
44. Karlsson Linnér R, Biroli P, Kong E, Meddens SFW, Wedow R, Fontana MA, *et al.* (2019): Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. Nat Genet 51:245–257.
45. Liu M, Jiang Y, Wedow R, Li Y, Brazel DM, Chen F, *et al.* (2019): Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nat Genet 51:237–244.
46. Obayashi T, Kagaya Y, Aoki Y, Tadaka S, Kinoshita K (2019): COXPRESdb v7: A gene coexpression database for 11 animal species supported by 23 coexpression platforms for technical evaluation and evolutionary inference. Nucleic Acids Res 47:D55–D62.
47. Solovieff N, Cotsapas C, Lee PH, Purcell SM, Smoller JW (2013): Pleiotropy in complex traits: Challenges and strategies. Nat Rev Genet 14:483–495.
48. Abdellaoui A, Hugh-Jones D, Yengo L, Kemper KE, Nivard MG, Veul L, *et al.* (2019): Genetic correlates of social stratification in Great Britain. Nat Hum Behav 3:1332–1342.
49. Belsky DW, Caspi A, Arseneault L, Corcoran DL, Domingue BW, Harris KM, *et al.* (2019): Genetics and the geography of health, behaviour and attainment. Nat Hum Behav 3:576–586.
50. Muniz Carvalho C, Wendt FR, Maihofer AX, Stein DJ, Stein MB, Sumner JA, *et al.* (2021): Dissecting the genetic association of C-reactive protein with PTSD, traumatic events, and social support. Neuropsychopharmacology 46:1071–1077.