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The relationship between circadian gene single nucleotide polymorphisms and clinical and behavioral assessments of sleep and rhythms and course of illness characteristics in subjects with bipolar type I disorder

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1. Introduction

Rhythm disruptions are core clinical features of bipolar disorder [1] and have been hypothesized as underlying pathophysiological mechanisms of the illness [2]. The disorder is often times marked by chronobiological fluctuations and disturbances. Certain course of illness characteristics, such as rapid cycling and seasonality, also suggest rhythm disturbances to be a component of the disorder.

All organisms exhibit rhythmic oscillations in a variety of physiological processes [3]. These rhythms are largely regulated by the biological timing system [4]. While the master timekeeping mechanism is the suprachiasmatic nucleus (SCN) of the hypothalamus [5], at the core of the circadian timing system are endogenous molecular clocks comprised of “clock genes” [3,4]. Endogenous molecular clocks function as interconnected transcriptional and translational feedback loops [3,4]. It is the rhythmic expression of circadian genes that result in the rhythmic properties (i.e., phase, period, amplitude) of endogenous clocks. The core molecular clock is structured as follows: clock circadian regulator (CLOCK) and aryl hydrocarbon receptor nuclear translocator like (ARNTL) form a heterodimer that act as positive regulators activating the transcription of period circadian regulator (PER) and cryptochrome circadian regulator (CRY) genes. PER and CRY proteins form a heterodimer which, in turn, inhibit the transcriptional activity of the CLOCK:ARNTL heterodimer. The resulting decrease in PER and CRY concentrations resets the cycle. The pushes and pulls of these transcriptional/translational feedback loops sustain the period of the circadian oscillator at a near 24-h period. This process is modulated by several factors like kinases such as glycogen synthase kinase 3 beta (GSK3B) and casein kinase 1 epsilon (CSNK1E). In addition to their central role as timekeepers, endogenous molecular clocks regulate the expression of clock-controlled output genes whose products are responsible for the temporal organization of physiological processes many of which are implicated in mood regulation [6,7]. It is now accepted that virtually every cell contains an autonomous circadian clock [8] and that the circadian timing system is comprised not of one central loop but rather multiple interconnected loops [9].

In their preeminent textbook, Manic-Depressive Illness, Goodwin and Jamison postulated that “the genetic defect in manic depressive illness involves the circadian pacemaker or systems that modulate it” [10]. As a complex trait disorder [11], multiple genetic risk factors are likely associated with the development of bipolar disorder. Circadian genes are plausible candidate genes for bipolar disorder [10]. It has been proposed that the phenotypic expression of certain diseases may be related to the functioning of molecular clocks [12]. From a phenotypic standpoint, circadian gene variants may impact the expression of bipolar disorder. Circadian gene polymorphisms have been associated with recurrence rates and cycling patterns [13,14], insomnia [13,15], age at illness onset [16], diurnal patterns of mood expression [13], and response to treatments such as sleep deprivation [16] and lithium [17].

We, therefore, designed a proof-of-concept study to assess the relationship between circadian gene single nucleotide polymorphisms (SNPs) and clinical and behavioral assessments of sleep and rhythms and course of illness characteristics in subjects with bipolar type I disorder (BDI).

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2. Material and methods

2.1. Subjects

Sixty six (66) BDI subjects were included for evaluation. Subjects were assessed at the University of Texas Southwestern Medical Center at Dallas (UTSW) and the University of Texas Health Science Center San Antonio (UTHSCSA) between the dates of February 25, 2009 to October 30, 2009. Patients were recruited from county and community hospitals, the university medical center, community mental health clinics, and psychiatric and clinical research groups at UTSW and UTHSCSA. The study was approved by the UTSW and UTHSCSA institutional review boards and was consistent with standard for the ethical conduct of human research. Written informed consent was obtained for all subjects.

Subjects with a history of neurological impairment or uncontrolled medical conditions with the potential to disrupt sleep-wake cycle and rhythms, shift work or diurnal changes in work schedule four weeks prior to or during the course of the study, travel involving three or more time zones occurring four weeks prior to or during the course of the study, current use of hypnotic agents for sleep, and a history of substance abuse or dependence one month prior to study participation were excluded from the study. DSM-IV Axis I diagnosis of BDI was confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) [18] or Mini International Neuropsychiatric Interview (MINI) [19]. All cases were then subject to a best estimate diagnostic consensus including a minimum of three experienced clinicians in order to confirm the diagnosis.

2.2. Subject clinical and demographic information

The demographic variables collected included age, gender, and race. Young Mania Rating Scale (YMRS) [20] was used to determine the degree of manic symptoms while the clinician-rated 30-item Inventory of Depressive Symptoms rating scale (IDS-30-C) [21] was used to determine the degree of depressive symptoms. Information regarding course of illness was gathered using both structured clinical interviews (SCID-I/P or MINI) and detailed psychiatric histories. Course of illness characteristics gathered included: age at onset of psychiatric symptoms (age at first recognized psychiatric symptoms), age at onset of mania (age at first manic or hypomanic episode), age at onset of depression (age at first depressive episode), polarity of first episode (depressed or manic), rapid cycling (DSM-IV-TR definition), degree of inter-episode recovery (with or without good inter-episode recovery), history of psychosis, and history of suicide attempts. A history of current medication use was also obtained.

2.3. Chronobiological and sleep rating scale assessments

The Pittsburgh Sleep Quality Inventory (PSQI) [22] was used to characterize sleep quality and the history and course of sleep wake patterns. The Composite Scale for Morningness (CSM) [23] assessed participant's chronotype or diurnal preference for daily activities. The Seasonal Pattern Assessment Questionnaire (SPAQ) [24] was used to assess whether personal activity and behaviors were related to changes in seasons. Sleep diaries were used to help record participant's sleeping and waking patterns.

Actigraphy. Basic Motionlogger actigraph units (Ambulatory Monitoring, Inc., Ardsley, NY) were used to collect data regarding locomotor activity. Data was sampled in 60-second epochs. Subjects wore the apparatus continuously on the non-dominant wrist for 7 days. Summary statistics characterizing circadian rhythms and sleep-wake cycles were calculated using Action 4 circadian rhythm analysis software (Ambulatory Monitoring, Inc., Ardsley, NY) and Action W-2 Software (Ambulatory Monitoring, Inc., Ardsley, NY).

The 24-h autocorrelation coefficient [25] was used as an indicator of the degree of rhythmicity. This value represents the correlation of a time series with its own past and future values and may be taken as an indicator of the degree of rhythmicity. Higher 24-h autocorrelation scores indicate a higher degree of rhythmicity. Lower scores indicate a lower degree of rhythmicity. Cosinor analysis [26,27] was used to calculate the amplitude, the difference between the peak and mean value of the cosine wave, and the mesor, the mean value of the cosine curve best fitting the data. The circadian quotient [25], or amplitude to mesor ratio, was then calculated and used as a proxy for the robustness of rhythms. Goodness-of-fit omega was used to calculate how well the cosinor model fit the actigraph data [28]. The UCSD Sleep Algorithm was used to calculate the following sleep-wake variables: sleep minutes (average daily minutes scored as sleep), wake minutes (average daily minutes scored as wake), percent sleep (percentage of minutes scored as sleep), and sleep efficiency (actual time spent asleep to the total sleep episode time) and wake after sleep onset (WASO) (minutes scored as wake during the sleep period).

2.4. DNA isolation and genotyping

DNA was isolated from whole blood. SNPs were genotyped using GoldenGate Custom Genotyping Assay and run on the BeadExpress System (Illumina Inc., San Diego, CA). Genotyping was blinded to subject diagnosis and characteristics. The SNP panel consisted of variants from circadian genes selected from the literature and based on previous suggestive association with bipolar disorder [13,14,16,29–36] (Table 1). SNPs located on the following genes were included for

Table 1
Circadian Gene Variants. Table 1 presents the circadian single nucleotide polymorphisms (SNP) selected for inclusion in the study. Information regarding SNP, gene, chromosome (CHR), base pair positions (GRCh38.p12). Associated literature references are also included.

SNP	Gene	CHR	Position	Citations
rs228642	PER3	1	7803233	[30,76,97]
rs10462020	PER3	1	7820623	[30,76,97]
rs2640909	PER3	1	7830057	[30,76,97]
rs934945	PER2	2	238246412	[30,97]
rs2304674	PER2	2	238273263	[30,97]
rs2304672	PER2	2	238277948	[30,97]
rs334555	GSK3B	3	120085289	[16,32,36,97]
rs3755557	GSK3B	3	120096110	[52]
rs11927974	near GSK3B	3	120105190	[40]
rs10462028	CLOCK	4	55432133	[35]
rs1801260	CLOCK	4	55435202	[13,14,30,35,97]
rs3736544	CLOCK	4	55443825	[13,14,30,35,97]
rs17777927	CLOCK	4	55446466	[13,14,30,35,97]
rs11932595	CLOCK	4	55457430	[13,14,30,35,97]
rs4340844	CLOCK	4	55462689	[13,14,30,35,97]
rs6850524	CLOCK	4	55515830	[13,14,30,35,97]
rs7732671	PPARGC1B	5	149832680	[98]
rs7022435	RORB	9	74629537	[30,34]
rs3750420	RORB	9	74634466	[30,34]
rs3903529	RORB	9	74649312	[30,34]
rs6486122	ARNTL	11	13339977	[13,29,30,35,97]
rs3816360	ARNTL	11	13346203	[13,29,30,35,97]
rs1868049	ARNTL	11	13362135	[13,29,30,35,97]
rs3789327	ARNTL	11	13363769	[13,29,30,35,97]
rs11022778	ARNTL	11	13369313	[13,29,30,35,97]
rs969485	ARNTL	11	13381496	[13,29,30,35,97]
rs10838524	CRY2	11	45848626	[13,30,35,97]
rs10838527	CRY2	11	45881643	[13,30,35,97]
rs2291738	TIMELESS	12	56421497	[13,29,30]
rs11113179	CRY1	12	107059007	[30,35]
rs2289591	PER1	17	8144692	[13,30,35,97]
rs2735611	PER1	17	8144965	[13,30,35,97]
rs885747	PER1	17	8147419	[13,30,35,97]
rs2314339	NR1D1	17	40096959	[13,30,33,35,98]
rs4510078	CSNK1D	17	82247837	[30]
rs2075983	CSNK1E	22	38294692	[13,30,35,97]
rs1534891	CSNK1E	22	38299094	[13,30,35,97]

assessment: ARNTL, CLOCK, casein kinase 1 delta (CSNK1D), CSNK1E, cryptochrome circadian regulator 1 (CRY1), cryptochrome circadian regulator 2 (CRY2), GSK3B, nuclear receptor subfamily 1 group D member 1 (NR1D1), period circadian regulator 1 (PER1), period circadian regulator 2 (PER2), period circadian regulator 3 (PER3), PPARG coactivator 1 beta (PPARGC1B), RAR related orphan receptor B (RORB), and timeless circadian regulator (TIMELESS).

2.5. Quality control

A total of 66 subjects with bipolar disorder were genotyped for 39 SNPs. All samples and SNPs had a call rate (non-missing information) greater than 95%. Two of the SNPs (rs3750420 and rs2314339) had a minor allele frequency (MAF) less than 0.05 and were excluded from further analysis. Hardy-Weinberg Equilibrium (HWE) was tested using the chi-square test as implemented in the software PLINK. No SNP failed the HWE p-value cut-off of 0.005.

2.6. Statistical analysis

Continuous variables were described using mean and standard deviation. Categorical variables were summarized using frequency and percentages. With respect to genetic analysis, SNPs were tested for association with the actigraphy- and clinically-based variables after adjustment for age, gender, race, mood state, and medication use. Associations for course of illness characteristics were adjusted for race and gender. Since the inheritance pattern for the genes studied are not known, the additive model was initially used for testing all SNP associations. SNP associations that were significant in the additive model were further tested using the dominant and recessive models. The commands –linear and –logistic were used for continuous and binary outcomes, respectively. The level for statistical significance was set at a p-value of less than 1.35e−3, which was obtained by the Bonferroni method (0.05/37). The PLINK software [37] was used for all analyses.

3. Results

3.1. Sample characteristics

Table 2 summarizes the demographic, clinical, and course of illness characteristics of our study cohort. The mean age of the sample was 42.41 ± 11.65 years and female predominant (65.15%). The majority (60.6%) of the subjects were self-reported Caucasians followed by Hispanics (19.70%) and African Americans (19.70%). The majority (82.54%) of subjects were taking psychotropic medications. The mood symptomatology was in the mild to moderate range with mean YMRS and IDS-30-C scores of 14.7 ± 7.34 and 21.84 ± 10.91, respectively. The mean ages of onset of psychiatric symptoms, depression, and mania were 18.16 ± 9.18, 18.58 ± 8.34, and 21.75 ± 10.03, respectively. Within the sample, 60.66% met criteria for rapid cycling, 71.43% had poor inter-episode recovery, 68.25% had experienced psychosis, and 56.25% reported a history of suicide attempt. 79.03% reported their first episode as depressive. PSQI score (9.8 ± 4.26) was indicative of moderate sleep disturbance, CSM score of intermediate chronotype (32.76 ± 8.39), and SPAQ scores of moderate seasonality (9.23 ± 6.63).

Table 3 summarizes actigraphic variables calculated for the sample. Cosinor-based variables for the sample were as follows. Amplitude, mesor, circadian quotient demonstrated means and standard deviations of 2654.21 ± 1132.18, 3496.4 ± 1514.83, and 0.78 ± 0.16, respectively. Goodness-of-fit omega scored as 0.47 ± 0.14 demonstrating a moderate fit of the data with the cosine model. The 24-h autocorrelation coefficient was 0.34 ± 0.13 suggesting a low level of correlation between activity at the same time point on each observational day. Over the observational period an average of 393.66 ± 95.71 min were scored as sleep, 900.96 ± 122.34 min were scored as wake, with the percentage of sleep scored as 28.14 ± 7.21%. Sleep efficiency was 66.6 ± 12.98 and wake after sleep onset was 260.52 ± 136.29 min.

Table 2
Demographic, Clinical, and Course of Illness Characteristics. Table 2 presents the demographic, clinical, and course of illness characteristics of the study sample. Categorical variables are reported as numbers (percentages). Continuous variables are reported as means ± standard deviations. Young Mania Rating Scale (YMRS). 30-Item Inventory of Depressive Symptoms scale (IDS-30-C), Pittsburgh Sleep Quality Index (PSQI), Composite Scale for Morningness (CSM), Seasonal Pattern Assessment Questionnaire (SPAQ).

Demographic, Clinical, and Course of Illness Characteristics	
Demographic Characteristics	
Age	42.41 ± 11.65
Gender	
Male	23 (34.85%)
Female	43 (65.15%)
Race	
Caucasian	40 (60.61%)
African American	13 (19.70%)
Hispanic	13 (19.70%)
Clinical Characteristics	
YMRS Score	14.7 ± 7.34
IDS-30-C Score	21.84 ± 10.91
Medications	
Unmedicated	11 (17.46%)
Medicated	55 (82.54%)
Lithium	14 (22.58%)
Anticonvulsant	33 (53.23%)
Antipsychotic	25 (40.32%)
Antidepressant	23 (37.10%)
Benzodiazepine	18 (29.03%)
Course of Illness Characteristics	
Age at onset psychiatric symptoms (in years)	18.16 ± 9.18
Age at onset of mania (in years)	21.75 ± 10.03
Age at onset of depression (in years)	18.58 ± 8.34
Polarity of first episode	
Depression	49 (79.03%)
Mania	13 (20.97%)
Rapid Cycling	37 (60.66%)
Poor Inter-Episode Recovery	48 (71.43%)
History of Psychosis	43 (68.25%)
History of Suicide Attempt	36 (56.25%)
Sleep, Chronotype, and Seasonality Rating Scales	
PSQI	9.8 ± 4.26
CSM	32.76 ± 8.39
SPAQ	9.23 ± 6.63

3.2. Relationships between circadian gene SNPs and actigraphy, clinical, and course of illness characteristics

Table 4 presents nominally and statistically significant associations after adjustment for age, gender, race, and medication use. Multiple SNPs demonstrated suggestive associations with two associations remaining significant after correction for multiple testing (Table 5). The GSK3B variant rs334555 (C > G), which had a MAF of 9.1%, was significantly associated with lower CSM scores (regression coefficient = −7.34, p-value = 1.04e−3, additive genetic model; regression coefficient = −9.15, p-value = 2.90e−4, dominant genetic model). The RORB variant rs7022435 (G > A), which had a MAF of 23.5%, was significantly associated with higher PSQI scores (regression coefficient = 2.68; p-value = 1.04e−3, additive genetic model; regression coefficient = 2.85, p-value = 3.67e−3, dominant genetic model; regression coefficient = 5.15, p-value = 2.74e−2, recessive genetic model).

Table 3
Actigraphy Statistics. Table 3 presents the actigraphy statistics of the study sample. Rhythm related actigraphy variables include: *Amplitude* (the difference between the peak and mean value of the cosine wave), *Mesor* (the mean value of the cosine curve best fitting the data), *Circadian Quotient* (amplitude to mesor ratio; used as a proxy for the robustness of rhythms), *24-h Autocorrelation Coefficient* (the similarity between observations as a function of the time lag between them with a value of 1 indicating perfect correlation and a value of −1 indicating a perfect negative correlation; taken as an indicator of the strength of the rhythm), and *Goodness-of-Fit Omega* (statistical test used to calculate how well the cosinor model fits the actigraphy data). Sleep related actigraphy variables include: *Sleep Minutes* (average minutes scored as sleep), *Wake Minutes* (total minutes scored as wake), *Percent Sleep* (percentage of minutes scored as sleep), and *Sleep Efficiency* (actual time spent asleep to the total sleep episode time) and *Wake After Sleep Onset* (average minutes scored as wake during the sleep period).

Actigraphy Statistics	
Actigraphy Rhythm Measures	Mean ± SD
Amplitude	2654.21 ± 1132.18
Mesor	3496.4 ± 1514.83
Circadian Quotient	0.78 ± 0.16
24-h Autocorrelation Coefficient	0.34 ± 0.13
Goodness-of-Fit Omega	0.47 ± 0.14
Actigraphy Sleep-Wake Measures	Mean ± SD
Sleep Minutes	393.66 ± 95.71
Wake Minutes	900.96 ± 122.34
Percent Sleep	28.14 ± 7.21
Sleep Efficiency	66.6 ± 12.98
Wake After Sleep Onset	260.52 ± 136.29

4. Discussion

In this manuscript we present the findings of a proof-of-concept study designed to assess the relationship between circadian gene variants and sleep, rhythm, and course of illness characteristics in subjects with BDI. Several nominally significant associations were noted. After correction for multiple testing, 2 associations remained statistically significant.

The rs334555 polymorphism on GSK3B was significantly associated with lower CSM scores under additive ($p = 1.04e-3$) and dominant ($p = 2.90e-4$) models, indicating an association with an evening chronotype. This SNP was also nominally associated with a lower degree of wake after sleep onset, greater degree of sleep efficiency, higher 24-h autocorrelation coefficient scores, and rapid cycling phenotype. The variant rs334555 has previously been associated with impulsivity [38] and white matter abnormalities [39] in bipolar disorder and has been reported as a component of a haplotype associated with early age at onset of major depressive disorder [40]. GSK3B is a kinase that modulates the circadian timing system by phosphorylating molecular clock proteins [41]. A growing body of literature suggests that this gene may be an important factor in understanding the pathophysiology of bipolar disorder. Variants in GSK3B have been associated with the disorder [42,43] and with clinical characteristics of the illness such as an increased risk for suicidal behavior [44], later age at onset [16,32], manic and depressive dimensions [45] and delusional thoughts [46]. GSK3B may also play an important role in the treatment of bipolar disorder. Mood stabilizers have been shown to directly affect the functioning of GSK3B [47–51] and may do so by modify the functioning of molecular clocks [47,50]. Studies have also reported that GSK3B variants may be associated with variations in treatment responses in bipolar disorder [16,17,52,53].

RORB is a transcription factor that demonstrates circadian expression and regulates the expression of various core circadian genes [9,54]. In our sample, the RORB rs7022435 SNP was significantly associated with higher PSQI scores indicative of a greater degree of sleep disturbance. This SNP also demonstrated a nominal association with a lower age at onset of psychiatric symptoms. RORB rs7022435 has previously been established to associate with BD compared to controls by McGrath et al. (Case-Control OR = 2.881, Case-Control P-value = 1.10E−06), as was a haplotype (A-A-A) consisting of RORB variants rs7022435 – rs17691614 – rs7032677 (P-value = 8.17E−07, Permuted P-value less than 0.001) [34]. Other RORB SNPs have been reported that associate with BD risk compared to healthy controls [30,55]. Convergent functional genomics studies have also identified RORB as a potential risk gene for BD [56,57]. Relationships between RORB markers and verbal intelligence [58] as well as seasonality [59] have also been reported in BD. Our findings along with prior research suggest that, by influencing the core molecular clock, genetic variants in RORB can have an effect on the risk for developing BD as well as the expression of the illness.

In toto, the findings of this study are in line with previous literature that supports the possible impact that circadian gene variants may have on the phenotypic expression of bipolar disorder and may highlight important areas for future research. For example, circadian gene variants have been associated with chronotype in bipolar disorder [60,61]. In addition to the relationship noted between the rs334555 GSK3B 3 SNP and chronotype, we report 2 additional SNPs demonstrating suggestive associations with CSM scores. This line of investigation may be of importance given that an evening chronotype has been associated with the illness [62–64] and clinical correlates such as rapid mood swings [65,66], greater recurrence rates [65], and an earlier age of illness onset [65]. Additionally, Hasler et al. reported that evening chronotypes with insomnia displayed diurnal patterns of positive affect characterized by phase delay and smaller amplitude, reduced degree of diurnal variation in the metabolism of the medial prefrontal cortex and the striatum [67].

Our study findings also support previous literature that suggests relationships between circadian gene variants and sleep characteristics in bipolar disorder [13,15,68]. In addition to the associations between the RORB rs7022435 SNP and PSQI scores, two additional variants located in RORB were associated with higher PSQI scores. The PER2 SNP rs2304674 also showed several nominal associations with sleep variables. This would indicate an important area for future research as sleep disturbances are a hallmark of bipolar disorder [69–72] and may represent a heritable phenomenon [73].

Some of the findings also suggest that circadian gene variants may be important factors in determining course of illness characteristics in bipolar disorder. As in other studies [13,14,74], we report three associations that suggest the relationship between circadian gene polymorphisms and a rapid cycling phenotype. These findings are also in line with some reports suggesting that rapid cycling may be associated with underlying circadian disruption [75]. As in prior studies [16,33,76], we also noted nominal associations between circadian gene variants and an earlier age at illness onset. In keeping with other reports [77,78], we report 6 circadian gene polymorphisms, 3 on ARNTL and 3 on CSNK1E, which demonstrated a suggestive association with suicidality. This may be a particularly important area of interest as suicidal ideation has been related to circadian disruption [53,79–84], an evening chronotype [79,85–87], and with greater incidence frequency in the evening hours [88,89]. Variants in ARNTL have reached genome-wide significant levels of association in genome-wide association studies (GWAS) of schizophrenia [90], chronotype [91], and cognitive function [92]. In addition, we have previously reported that ARNTL and CSNK1E haplotypes are associated with bipolar disorder in Hispanic pedigrees [93].

A strength of this study includes examining the relationships between circadian gene variants and chronobiological and course of illness characteristics in the disorder. Another strength is that our study is one of few that sought to examine the relationships between circadian gene variants and actigraphically-based measurements of sleep and activity rhythms. Previous studies have reported associations between CLOCK 31111 T/C SNP and variations in diurnal activity [68,94], delayed sleep onset [68], and reduced amount of nighttime sleep [68].

Table 4
Associations between circadian gene single nucleotide polymorphisms (SNPs) and clinical and behavioral assessments of sleep and rhythms and course of illness characteristics. The significant and nominally significant single nucleotide circadian gene polymorphisms and clinical and behavioral assessments of sleep and rhythms and course of illness characteristics are summarized. † denotes adjustments. Associations for actigraphy- and clinically-based were adjusted for age, gender, race, mood state, and medication use. Associations for course of illness characteristics were adjusted for race and gender. Bolded font and * denote statistical significance after Bonferroni correction. Pittsburgh Sleep Quality Index (PSQI), Composite Scale for Morningness (CSM).

Circadian Gene	SNP	Associated Variable	Regression Coefficient†	p-Value†	Bonferroni Adjusted p-Value
ARNTL	rs6486122	History of Suicide	2.411	0.0159	0.5883
	rs3816360	Goodness-of-Fit Omega	2.032	0.0473	1.0000
	rs1868049	History of Suicide	−2.380	0.0173	0.6401
	rs3789327	History of Suicide	−2.800	0.0051	0.1887
		Mesor	−2.310	0.0249	0.9213
	rs11022778	CSM	−2.082	0.0420	1.0000
	rs969485	Rapid Cycling	2.238	0.0252	0.9324
CLOCK	rs1801260	Circadian Quotient	2.052	0.0452	1.0000
	rs3736544	Age at Onset Psychiatric Symptoms	−2.552	0.0133	0.4921
		Goodness-of-Fit Omega	−2.240	0.0294	1.0000
	rs6850524	Goodness-of-Fit Omega	2.097	0.0409	1.0000
CRY1	rs11113179	Week After Sleep Onset	2.349	0.0227	0.8399
		PSQI	2.034	0.0468	1.0000
CSNK1D	rs4510078	24-Hr Autocorrelation	2.244	0.0291	1.0000
		CSM	−2.208	0.0315	1.0000
		Goodness-of-Fit Omega	−2.041	0.0464	1.0000
CSNK1E	rs2075983	History of Suicide	−2.222	0.0263	0.9731
	rs6001093	History of Suicide	−2.941	0.0033	0.1221
	rs135757	History of Suicide	−2.533	0.0113	0.4181
		Rapid Cycling	−2.286	0.0223	0.8251
GSK3B	**rs334555**	**CSM**	**−3.434**	**0.0011***	**0.0407***
		Week After Sleep Onset	−2.576	0.0129	0.4773
		Sleep Efficiency	2.313	0.0247	0.9139
		24-Hr Autocorrelation	2.290	0.0261	0.9657
		Rapid Cycling	−2.139	0.0324	1.0000
	rs3755557	24-Hr Autocorrelation	−2.146	0.0365	1.0000
	rs11927974	Mesor	2.750	0.0082	0.3034
		Amplitude	2.101	0.0405	1.0000
PER2	rs2304674	Sleep Efficiency	−2.876	0.0058	0.2146
		Mesor	2.802	0.0071	0.2627
		Sleep Minutes	−2.446	0.0179	0.6623
		Percent Sleep	−2.381	0.0210	0.7770
		Wake Minutes	2.328	0.0238	0.8806
RORB	rs7022435	**PSQI**	**3.463**	**0.0010***	**0.0370***
		Age at Onset Psychiatric Symptoms	−3.024	0.0037	0.1369
	rs3903529	Age at Onset Psychiatric Symptoms	−2.760	0.0077	0.2849
		PSQI	2.614	0.0115	0.4255
TIMELESS	rs2291738	Goodness-of-Fit Omega	−2.462	0.0172	0.6364

Table 5
Association of circadian gene variants with chronotypic profiles. Circadian Gene polymorphism, MAF, associated outcome variables, and adjusted coefficients and respective p-values are presented for additive, dominant, and recessive models. The RORB variant rs7022435 was significantly associated with PSQI (regression coefficient = 2.68; p-value = 1.04e−3, additive genetic model; regression coefficient = 2.85, p-value = 3.67e−3, dominant genetic model; regression coefficient = 5.15, p-value = 2.74e−2, recessive genetic model). The GSK3B variant rs334555 was significantly associated with CSM (regression coefficient = −7.34, p-value = 1.04e−3, additive genetic model; regression coefficient = −9.15, p-value = 2.90e−4, dominant genetic model). Pittsburgh Sleep Quality Index (PSQI), Composite Scale for Morningness (CSM).

SNP	MAF	Outcome Variable	Adjusted* Coefficient (p-value)		
			Additive	Dominant	Recessive
rs7022435	0.23	PSQI	2.68 (0.00104)	2.85 (0.00367)	5.15 (0.02736)
rs334555	0.09	CSM	−7.34 (0.00114)	−9.15 (0.00029)	−1.65 (0.83730)

Another study reported a polymorphism in the acetyl O-methyltransferase gene to be associated with longer sleep duration, greater activity levels during sleep periods, and greater inter-daily stability of activity rhythms [95]. Collectively, these studies demonstrate the utility of using chronobiological markers and course of illness characteristics to help discover phenotypic variants associated with the illness.

Limitations of our study should also be noted. Our small sample size may leave room for false positive findings and might result in a lack of power for some analyses. The results will, therefore, need to be replicated in larger samples. While we attempted to account for variables (i.e., age, gender, race, medication use) that may be impacting the relationships between circadian genes and outcome variables of interest, larger sample sizes will allow for the assessment of the relative impacts of these variables in establishing these relationships. For example, the sample was multi-racial. Although we adjusted for race, confounding due to population structure cannot be eliminated.

In addition to increasing the sample size, other methodological approaches to assessing the relationship between circadian genes and chronobiological phenotypes are necessary. Since our study focused only on SNPs, there is an inherent limitation to the number of markers representing the circadian genes. Sequencing of the circadian genes will, therefore, be necessary to characterize the associations between

circadian genes and chronobiological characteristics of the disorder. As has been recently shown [96], linkage analysis may be an important methodological approach to determine the heritability of chronotype in relation to circadian gene variants in BD.

The current study protocol allowed the comparison of groups of patients that share common clinical features and course of illness characteristics investigated that are not relevant to healthy controls (e.g. age at onset of psychiatric symptoms, polarity of first episode, rapid cycling, poor inter-episode recovery, history of psychosis), thereby preventing any conclusions pertaining to associations specific to BDI. Future research including healthy controls, particularly as they relate to chronobiological characteristics, would strengthen the results of this study by determining if these findings are disease specific or are noted in other psychiatric illnesses or in subjects not suffering from a psychiatric disorder. Subsequent studies should address this methodological limitation.

A further limitation of this study is the cross-sectional design. Future studies will benefit from longer observational periods in order to fully capture circadian phenotypes particularly when utilizing tools such as actigraphy. In addition, longer observational periods may help to further account for the effects of mood state and medications. Longitudinal studies specifically focusing on characterizing biological rhythms may help to define specific phenotypes of the disorder and therefore increase the power of future genetic association studies.

5. Conclusions

Biological rhythm disturbances have been suggested to play a key role in the pathophysiology of bipolar disorder. In this manuscript, we present the findings of a proof-of-concept study designed to assess the relationships between circadian gene variants and clinical and behavioral assessments of sleep and rhythms and course of illness characteristics in subjects with BDI. In this study, we found 2 statistically significant associations (GSK3B SNP, rs334555, with evening chronotype and RORB SNP, rs7022435, with higher PSQI scores). In addition, several other suggestive associations were noted. Further research in larger sample sizes is required to more definitively explore the relationships between circadian gene variants and characteristics of BDI.

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmip.2019.01.001.

References

[1] American Psychiatric Association. and American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders : DSM-5. 5th ed. 2013, Arlington, VA: American Psychiatric Association. xliv, p. 947.
[2] Gonzalez R. The relationship between bipolar disorder and biological rhythms. J Clin Psychiatry 2014;75(4):e323–31. https://doi.org/10.4088/JCP.13r08507.
[3] Edery I. Circadian rhythms in a nutshell. Physiol Genomics 2000;3(2):59–74.
[4] Reppert SM, Weaver DR. Coordination of circadian timing in mammals. Nature 2002;418(6901):935–41. https://doi.org/10.1038/nature00965 nature00965 [pii].
[5] Schmidt TM, Chen SK, Hattar S. Intrinsically photosensitive retinal ganglion cells: many subtypes, diverse functions. Trends Neurosci 2011;34(11):572–80. https://doi.org/10.1016/j.tins.2011.07.001.
[6] Ketchesin KD, Becker-Krail D, McClung CA. Mood-Related Central and Peripheral Clocks. Eur J Neurosci 2018. https://doi.org/10.1111/ejn.14253.
[7] Huhne A, Welsh DK, Landgraf D. Prospects for circadian treatment of mood disorders. Ann Med 2018:1–18. https://doi.org/10.1080/07853890.2018.1530449.
[8] Liu AC, Welsh DK, Ko CH, Tran HG, Zhang EE, Priest AA, et al. Intercellular coupling confers robustness against mutations in the SCN circadian clock network. Cell 2007;129(3):605–16. https://doi.org/10.1016/j.cell.2007.02.047.
[9] Ueda HR, Hayashi S, Chen W, Sano M, Machida M, Shigeyoshi Y, et al. System-level identification of transcriptional circuits underlying mammalian circadian clocks. Nat Genet 2005;37(2):187–92.
[10] Goodwin FK, Jamison KR. Manic-depressive illness. 1990, New York: Oxford University Press. xxi, 938 , [2] of plates.
[11] Craddock N, Sklar P. Genetics of bipolar disorder. Lancet 2013;381(9878):1654–62. https://doi.org/10.1016/S0140-6736(13)60855-7.
[12] Saini C, Brown SA, Dibner C. Human peripheral clocks: applications for studying circadian phenotypes in physiology and pathophysiology. Front Neurol 2015;6:95. https://doi.org/10.3389/fneur.2015.00095.
[13] Shi J, Wittke-Thompson JK, Badner JA, Hattori E, Potash JB, Willour VL, et al. Clock genes may influence bipolar disorder susceptibility and dysfunctional circadian rhythm. Am J Med Genet B Neuropsychiatr Genet 2008.
[14] Benedetti F, Serretti A, Colombo C, Barbini B, Lorenzi C, Campori E, et al. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. Am J Med Genet B Neuropsychiatr Genet 2003;123(1):23–6.
[15] Serretti A, Benedetti F, Mandelli L, Lorenzi C, Pirovano A, Colombo C, et al. Genetic dissection of psychopathological symptoms: insomnia in mood disorders and CLOCK gene polymorphism. Am J Med Genet B Neuropsychiatr Genet 2003;121(1):35–8.
[16] Benedetti F, Serretti A, Colombo C, Lorenzi C, Tubazio V, Smeraldi E. A glycogen synthase kinase 3-beta promoter gene single nucleotide polymorphism is associated with age at onset and response to total sleep deprivation in bipolar depression. Neurosci Lett 2004;368(2):123–6.
[17] Benedetti F, Serretti A, Pontiggia A, Bernasconi A, Lorenzi C, Colombo C, et al. Long-term response to lithium salts in bipolar illness is influenced by the glycogen synthase kinase 3-beta -50 T/C SNP. Neurosci Lett 2005;376(1):51–5.
[18] Ventura J, Liberman RP, Green MF, Shaner A, Mintz J. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). Psychiatry Res 1998;79(2):163–73.
[19] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl 20):22–33. quiz 34–57.
[20] Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–35.
[21] Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996;26(3):477–86.
[22] Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193–213.
[23] Smith CS, Reilly C, Midkiff K. Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. J Appl Psychol 1989;74(5):728–38.
[24] Rosenthal NE, Bradt, G.H., Wehr, T.A. Seasonal pattern assessment questionnaire, in National Institute of Mental Health, Washington, DC. 1987.
[25] Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003;26(3):342–92.
[26] Salvatore P, Ghidini S, Zita G, De Panfilis C, Lambertino S, Maggini C, et al. Circadian activity rhythm abnormalities in ill and recovered bipolar I disorder patients. Bipolar Disord 2008;10(2):256–65.
[27] Erbel-Sieler C, Dudley C, Zhou Y, Wu X, Estill SJ, Han T, et al. Behavioral and regulatory abnormalities in mice deficient in the NPAS1 and NPAS3 transcription factors. Proc Natl Acad Sci U S A 2004;101(37):13648–53. https://doi.org/10.1073/pnas.0405310101 [pii].
[28] Cornelissen G. Cosinor-based rhythmometry. Theor Biol Med Model 2014;11:16. https://doi.org/10.1186/1742-4682-11-16.
[29] Mansour HA, Wood J, Logue T, Chowdari KV, Dayal M, Kupfer DJ, et al. Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. Genes Brain Behav 2006;5(2):150–7. https://doi.org/10.1111/j.1601-183X.2005.00147.x.
[30] Mansour HA, Talkowski ME, Wood J, Chowdari KV, McClain L, Prasad K, et al. Association study of 21 circadian genes with bipolar I disorder, schizoaffective disorder, and schizophrenia. Bipolar Disord 2009;11(7):701–10. https://doi.org/

10.1111/j.1399-5618.2009.00756.x.
[31] Nievergelt CM, Kripke DF, Barrett TB, Burg E, Remick RA, Sadovnick AD, et al. Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 2006;141(3):234–41.
[32] Benedetti F, Bernasconi A, Lorenzi C, Pontiggia A, Serretti A, Colombo C, et al. A single nucleotide polymorphism in glycogen synthase kinase 3-beta promoter gene influences onset of illness in patients affected by bipolar disorder. Neurosci Lett 2004;355(1–2):37–40.
[33] Severino G, Manchia M, Contu P, Squassina A, Lampus S, Ardau R, et al. Association study in a Sardinian sample between bipolar disorder and the nuclear receptor REV-ERBalpha gene, a critical component of the circadian clock system. Bipolar Disord 2009;11(2):215–20. https://doi.org/10.1111/j.1399-5618.2009.00667.x.
[34] McGrath CL, Glatt SJ, Sklar P, Le-Niculescu H, Kuczenski R, Doyle AE, et al. Evidence for genetic association of RORB with bipolar disorder. BMC Psychiatry 2009;9:70. https://doi.org/10.1186/1471-244X-9-70.
[35] Soria V, Martinez-Amoros E, Escaramis G, Valero J, Perez-Egea R, Garcia C, et al. 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 2010;35(6):1279–89. https://doi.org/10.1038/npp.2009.230.
[36] Szczepankiewicz A, Skibinska M, Hauser J, Slopien A, Leszczynska-Rodziewicz A, Kapelski P, et al. Association analysis of the GSK-3beta T-50C gene polymorphism with schizophrenia and bipolar disorder. Neuropsychobiology 2006;53(1):51–6. https://doi.org/10.1159/000090704.
[37] Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81(3):559–75. https://doi.org/10.1086/519795.
[38] Jimenez E, Arias B, Mitjans M, Goikolea JM, Roda E, Ruiz V, et al. Association between GSK3beta gene and increased impulsivity in bipolar disorder. Eur Neuropsychopharmacol 2014;24(4):510–8. https://doi.org/10.1016/j.euroneuro.2014.01.005.
[39] Benedetti F, Bollettini I, Barberi I, Radaelli D, Poletti S, Locatelli C, et al. Lithium and GSK3-beta promoter gene variants influence white matter microstructure in bipolar disorder. Neuropsychopharmacology 2013;38(2):313–27. https://doi.org/10.1038/npp.2012.172.
[40] Saus E, Soria V, Escaramis G, Crespo JM, Valero J, Gutierrez-Zotes A, et al. A haplotype of glycogen synthase kinase 3beta is associated with early onset of unipolar major depression. Genes Brain Behav 2010;9(7):799–807. https://doi.org/10.1111/j.1601-183X.2010.00617.x.
[41] Besing RC, Paul JR, Hablitz LM, Rogers CO, Johnson RL, Young ME, et al. Circadian rhythmicity of active GSK3 isoforms modulates molecular clock gene rhythms in the suprachiasmatic nucleus. J Biol Rhythms 2015;30(2):155–60. https://doi.org/10.1177/0748730415573167.
[42] Ronai Z, Kovacs-Nagy R, Szantai E, Elek Z, Sasvari-Szekely M, Faludi G, et al. Glycogen synthase kinase 3 beta gene structural variants as possible risk factors of bipolar depression. Am J Med Genet B Neuropsychiatr Genet 2014;165B(3):217–22. https://doi.org/10.1002/ajmg.b.32223.
[43] Lachman HM, Pedrosa E, Petruolo OA, Cockerham M, Papolos A, Novak T, et al. Increase in GSK3beta gene copy number variation in bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 2007;144B(3):259–65. https://doi.org/10.1002/ajmg.b.30498.
[44] Jimenez E, Arias B, Mitjans M, Goikolea JM, Roda E, Saiz PA, et al. Genetic variability at IMPA2, INPP1 and GSK3beta increases the risk of suicidal behavior in bipolar patients. Eur Neuropsychopharmacol 2013;23(11):1452–62. https://doi.org/10.1016/j.euroneuro.2013.01.007.
[45] Bureau A, Beaulieu JM, Paccalet T, Chagnon YC, Maziade M. The interaction of GSK3B and FXR1 genotypes may influence the mania and depression dimensions in mood disorders. J Affect Disord 2017;213:172–7. https://doi.org/10.1016/j.jad.2017.02.023.
[46] Serretti A, Benedetti F, Mandelli L, Calati R, Caneva B, Lorenzi C, et al. Association between GSK-3beta -50T/C polymorphism and personality and psychotic symptoms in mood disorders. Psychiatry Res 2008;158(2):132–40. https://doi.org/10.1016/j.psychres.2007.06.017.
[47] Li X, Bijur GN, Jope RS. Glycogen synthase kinase-3beta, mood stabilizers, and neuroprotection. Bipolar Disord 2002;4(2):137–44.
[48] De Sarno P, Li X, Jope RS. Regulation of Akt and glycogen synthase kinase-3 beta phosphorylation by sodium valproate and lithium. Neuropharmacology 2002;43(7):1158–64.
[49] Gould TD, Chen G, Manji HK. In vivo evidence in the brain for lithium inhibition of glycogen synthase kinase-3. Neuropsychopharmacology 2004;29(1):32–8. https://doi.org/10.1038/sj.npp.1300283.
[50] Padiath QS, Paranjpe D, Jain S, Sharma VK. Glycogen synthase kinase 3beta as a likely target for the action of lithium on circadian clocks. Chronobiol Int 2004;21(1):43–55.
[51] O'Brien WT, Klein PS. Validating GSK3 as an in vivo target of lithium action. Biochem Soc Trans 2009;37(Pt 5):1133–8. https://doi.org/10.1042/BST0371133.
[52] Iwahashi K, Nishizawa D, Narita S, Numajiri M, Murayama O, Yoshihara E, et al. Haplotype analysis of GSK-3beta gene polymorphisms in bipolar disorder lithium responders and nonresponders. Clin Neuropharmacol 2014;37(4):108–10. https://doi.org/10.1097/WNF.0000000000000039.
[53] McCarthy MJ, Wei H, Marnoy Z, Darvish RM, McPhie DL, Cohen BM, et al. Genetic and clinical factors predict lithium's effects on PER2 gene expression rhythms in cells from bipolar disorder patients. Transl Psychiatry 2013;3:e318https://doi.org/10.1038/tp.2013.90.
[54] Ueda HR, Chen W, Adachi A, Wakamatsu H, Hayashi S, Takasugi T, et al. A transcription factor response element for gene expression during circadian night. Nature 2002;418(6897):534–9. https://doi.org/10.1038/nature00906.
[55] Lai YC, Kao CF, Lu ML, Chen HC, Chen PY, Chen CH, et al. Investigation of associations between NR1D1, RORA and RORB genes and bipolar disorder. PLoS ONE 2015;10(3):e0121245https://doi.org/10.1371/journal.pone.0121245.
[56] Le-Niculescu H, Patel SD, Bhat M, Kuczenski R, Faraone SV, Tsuang MT, et al. Convergent functional genomics of genome-wide association data for bipolar disorder: comprehensive identification of candidate genes, pathways and mechanisms. Am J Med Genet B Neuropsychiatr Genet 2009;150B(2):155–81. https://doi.org/10.1002/ajmg.b.30887.
[57] Patel SD, Le-Niculescu H, Koller DL, Green SD, Lahiri DK, McMahon FJ, et al. Coming to grips with complex disorders: genetic risk prediction in bipolar disorder using panels of genes identified through convergent functional genomics. Am J Med Genet B Neuropsychiatr Genet 2010;153B(4):850–77. https://doi.org/10.1002/ajmg.b.31087.
[58] Ersland KM, Christoforou A, Stansberg C, Espeseth T, Mattheisen M, Mattingsdal M, et al. Gene-based analysis of regionally enriched cortical genes in GWAS data sets of cognitive traits and psychiatric disorders. PLoS ONE 2012;7(2):e31687https://doi.org/10.1371/journal.pone.0031687.
[59] Geoffroy PA, Lajnef M, Bellivier F, Jamain S, Gard S, Kahn JP, et al. Genetic association study of circadian genes with seasonal pattern in bipolar disorders. Sci Rep 2015;5:10232. https://doi.org/10.1038/srep10232.
[60] Etain B, Jamain S, Milhiet V, Lajnef M, Boudebesse C, Dumaine A, et al. Association between circadian genes, bipolar disorders and chronotypes. Chronobiol Int 2014;31(7):807–14. https://doi.org/10.3109/07420528.2014.906445.
[61] Melroy-Greif WE, Gizer IR, Wilhelmsen KC, Ehlers CL. Genetic influences on evening preference overlap with those for bipolar disorder in a sample of mexican Americans and american Indians. Twin Res Hum Genet 2017;20(6):499–510. https://doi.org/10.1017/thg.2017.62.
[62] Wood J, Birmaher B, Axelson D, Ehmann M, Kalas C, Monk K, et al. Replicable differences in preferred circadian phase between bipolar disorder patients and control individuals. Psychiatry Res 2009;166(2–3):201–9. S0165-1781(08)00064-4 [pii] 10.1016/j.psychres.2008.03.003.
[63] Ahn YM, Chang J, Joo YH, Kim SC, Lee KY, Kim YS. Chronotype distribution in bipolar I disorder and schizophrenia in a Korean sample. Bipolar Disord 2008;10(2):271–5. https://doi.org/10.1111/j.1399-5618.2007.00573.x.
[64] Gershon A, Kaufmann CN, Depp CA, Miller S, Do D, Zeitzer JM, et al. Subjective versus objective evening chronotypes in bipolar disorder. J Affect Disord 2018;225:342–9. https://doi.org/10.1016/j.jad.2017.08.055.
[65] Mansour HA, Wood J, Chowdari KV, Dayal M, Thase ME, Kupfer DJ, et al. Circadian phase variation in bipolar I disorder. Chronobiol Int 2005;22(3):571–84. https://doi.org/10.1081/CBI-200062413.
[66] Oginska H, Mojsa-Kaja J, Mairesse O. Chronotype description: In search of a solid subjective amplitude scale. Chronobiol Int 2017;34(10):1388–400. https://doi.org/10.1080/07420528.2017.1372469.
[67] Hasler BP, Germain A, Nofzinger EA, Kupfer DJ, Krafty RT, Rothenberger SD, et al. Chronotype and diurnal patterns of positive affect and affective neural circuitry in primary insomnia. J Sleep Res 2012;21(5):515–26. https://doi.org/10.1111/j.1365-2869.2012.01002.x.
[68] Benedetti F, Dallaspezia S, Fulgosi MC, Lorenzi C, Serretti A, Barbini B, et al. Actimetric evidence that CLOCK 3111 T/C SNP influences sleep and activity patterns in patients affected by bipolar depression. Am J Med Genet B Neuropsychiatr Genet 2007;144B(5):631–5. https://doi.org/10.1002/ajmg.b.30475.
[69] Hudson JI, Lipinski JF, Keck Jr. PE, Aizley HG, Lukas SE, Rothschild AJ, et al. Polysomnographic characteristics of young manic patients. Comparison with unipolar depressed patients and normal control subjects. Arch Gen Psychiatry 1992;49(5):378–83.
[70] Eidelman P, Talbot LS, Gruber J, Harvey AG. Sleep, illness course, and concurrent symptoms in inter-episode bipolar disorder. J Behav Ther Exp Psychiatry 2010;41(2):145–9. S0005-7916(09)00098-6 [pii] 10.1016/j.jbtep.2009.11.007.
[71] Eidelman P, Talbot LS, Gruber J, Hairston I, Harvey AG. Sleep architecture as correlate and predictor of symptoms and impairment in inter-episode bipolar disorder: taking on the challenge of medication effects. J Sleep Res 2010;19(4):516–24. https://doi.org/10.1111/j.1365-2869.2010.00826.x JSR826 [pii].
[72] Gruber J, Harvey AG, Wang PW, Brooks 3rd JO, Thase ME, Sachs GS, et al. Sleep functioning in relation to mood, function, and quality of life at entry to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Affect Disord 2009;114(1–3):41–9. S0165-0327(08)00266-8 [pii] 10.1016/j.jad.2008.06.028.
[73] Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar disorder. J Affect Disord 2010;121(1–2):127–35. https://doi.org/10.1016/j.jad.2009.05.022 S0165-0327(09)00227-4 [pii].
[74] Sjoholm LK, Backlund L, Cheteh EH, Ek IR, Frisen L, Schalling M, et al. CRY2 is associated with rapid cycling in bipolar disorder patients. PLoS One 2010;5(9):e12632https://doi.org/10.1371/journal.pone.0012632.
[75] Wilk K, Hegerl U. Time of mood switches in ultra-rapid cycling disorder: a brief review. Psychiatry Res 2010;180(1):1–4. https://doi.org/10.1016/j.psychres.2009.08.011.
[76] Benedetti F, Dallaspezia S, Colombo C, Pirovano A, Marino E, Smeraldi E. A length polymorphism in the circadian clock gene Per3 influences age at onset of bipolar disorder. Neurosci Lett 2008;445(2):184–7. https://doi.org/10.1016/j.neulet.2008.09.002.
[77] Benedetti F, Riccaboni R, Dallaspezia S, Locatelli C, Smeraldi E, Colombo C. Effects of CLOCK gene variants and early stress on hopelessness and suicide in bipolar depression. Chronobiol Int 2015;32(8):1156–61. https://doi.org/10.3109/

07420528.2015.1060603.
[78] Pawlak J, Dmitrzak-Weglarz M, Maciukiewicz M, Wilkosc M, Leszczynska-Rodziewicz A, Zaremba D, et al. Suicidal behavior in the context of disrupted rhythmicity in bipolar disorder–data from an association study of suicide attempts with clock genes. Psychiatry Res 2015;226(2–3):517–20. https://doi.org/10.1016/j.psychres.2015.01.010.
[79] Bahk YC, Han E, Lee SH. Biological rhythm differences and suicidal ideation in patients with major depressive disorder. J Affect Disord 2014;168:294–7. https://doi.org/10.1016/j.jad.2014.07.001.
[80] Verkes RJ, Kerkhof GA, Beld E, Hengeveld MW, van Kempen GM. Suicidality, circadian activity rhythms and platelet serotonergic measures in patients with recurrent suicidal behaviour. Acta Psychiatr Scand 1996;93(1):27–34.
[81] Rockwell DA, Winget CM, Rosenblatt LS, Higgins EA, Hetherington NW. Biological aspects of suicide: circadian disorganization. J Nerv Ment Dis 1978;166(12):851–8.
[82] Chakravorty S, Smith RV, Perlis ML, Grandner MA, Kranzler HR. Circadian pattern of deaths due to suicide in intoxicated alcohol-dependent individuals. J Clin Psychiatry 2018;79(6). https://doi.org/10.4088/JCP.17m11800.
[83] Benard V, Etain B, Vaiva G, Boudebesse C, Yeim S, Benizri C, et al. Sleep and circadian rhythms as possible trait markers of suicide attempt in bipolar disorders: an actigraphy study. J Affect Disord 2019;244:1–8. https://doi.org/10.1016/j.jad.2018.09.054.
[84] Akkaya-Kalayci T, Kapusta ND, Waldhor T, Bluml V, Poustka L, Ozlu-Erkilic Z. The association of monthly, diurnal and circadian variations with suicide attempts by young people. Child Adolesc Psychiatry Ment Health 2017;11:35. https://doi.org/10.1186/s13034-017-0171-6.
[85] Chan JW, Lam SP, Li SX, Yu MW, Chan NY, Zhang J, et al. Eveningness and insomnia: independent risk factors of nonremission in major depressive disorder. Sleep 2014;37(5):911–7. https://doi.org/10.5665/sleep.3658.
[86] Gau SS, Shang CY, Merikangas KR, Chiu YN, Soong WT, Cheng AT. Association between morningness-eveningness and behavioral/emotional problems among adolescents. J Biol Rhythms 2007;22(3):268–74. https://doi.org/10.1177/0748730406298447.
[87] Park H, Lee HK, Lee K. Chronotype and suicide: The mediating effect of depressive symptoms. Psychiatry Res 2018;269:316–20. https://doi.org/10.1016/j.psychres.2018.08.046.
[88] Caracciolo S, Manfredini R, Gallerani M, Tugnoli S. Circadian rhythm of parasuicide in relation to violence of method and concomitant mental disorder. Acta Psychiatr Scand 1996;93(4):252–6.
[89] Motohashi Y. Circadian variation in suicide attempts in Tokyo from 1978 to 1985. Suicide Life Threat Behav 1990;20(4):352–61.
[90] Borglum AD, Demontis D, Grove J, Pallesen J, Hollegaard MV, Pedersen CB, et al. Genome-wide study of association and interaction with maternal cytomegalovirus infection suggests new schizophrenia loci. Mol Psychiatry 2014;19(3):325–33. https://doi.org/10.1038/mp.2013.2.
[91] Hu Y, Shmygelska A, Tran D, Eriksson N, Tung JY, Hinds DA. GWAS of 89,283 individuals identifies genetic variants associated with self-reporting of being a morning person. Nat Commun 2016;7:10448. https://doi.org/10.1038/ncomms10448.
[92] Davies G, Lam M, Harris SE, Trampush JW, Luciano M, Hill WD, et al. Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. Nat Commun 2018;9(1):2098. https://doi.org/10.1038/s41467-018-04362-x.
[93] Gonzalez R, Gonzalez S, Villa E, Ramirez M, Zavala J, Armas R, et al. Identification of circadian gene variants in bipolar disorder in Latino populations. J Affect Disord 2015;186:367–75. https://doi.org/10.1016/j.jad.2015.07.014.
[94] Benedetti F, Radaelli D, Bernasconi A, Dallaspezia S, Falini A, Scotti G, et al. Clock genes beyond the clock: CLOCK genotype biases neural correlates of moral valence decision in depressed patients. Genes Brain Behav 2008;7(1):20–5. https://doi.org/10.1111/j.1601-183X.2007.00312.x.
[95] Geoffroy PA, Boudebesse C, Henrion A, Jamain S, Henry C, Leboyer M, et al. An ASMT variant associated with bipolar disorder influences sleep and circadian rhythms: a pilot study. Genes Brain Behav 2014;13(3):299–304. https://doi.org/10.1111/gbb.12103.
[96] Pagani L, St-Clair PA, Teshiba TM, Service SK, Fears SC, Araya C. Genetic contributions to circadian activity rhythm and sleep pattern phenotypes in pedigrees segregating for severe bipolar disorder. Proc Natl Acad Sci USA 2016;113(6):E754–61. https://doi.org/10.1073/pnas.1513525113.
[97] Nievergelt CM, Kripke DF, Barrett TB, Burg E, Remick RA, Sadovnick AD, et al. Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 2006;141B(3):234–41. https://doi.org/10.1002/ajmg.b.30252.
[98] Kripke DF, Nievergelt CM, Joo E, Shekhtman T, Kelsoe JR. Circadian polymorphisms associated with affective disorders. J Circadian Rhythms 2009;7:2. https://doi.org/10.1186/1740-3391-7-2.