Neurosci Bull February 1, 2015, 31(1): 141–159. http://www.neurosci.cn
DOI: 10.1007/s12264-014-1495-3

·Review·

Genetics and epigenetics of circadian rhythms and their potential roles in neuropsychiatric disorders

Chunyu Liu[1,2], Michael Chung[2]

[1]*State Key Laboratory of Medical Genetics of China, Changsha 410078, China*

[2]*Department of Psychiatry, University of Illinois at Chicago, Chicago, Illinois, USA*

Corresponding author: Chunyu Liu. E-mail: liucy@uic.edu

Circadian rhythm alterations have been implicated in multiple neuropsychiatric disorders, particularly those of sleep, addiction, anxiety, and mood. Circadian rhythms are known to be maintained by a set of classic clock genes that form complex mutual and self-regulatory loops. While many other genes showing rhythmic expression have been identified by genome-wide studies, their roles in circadian regulation remain largely unknown. In attempts to directly connect circadian rhythms with neuropsychiatric disorders, genetic studies have identified gene mutations associated with several rare sleep disorders or sleep-related traits. Other than that, genetic studies of circadian genes in psychiatric disorders have had limited success. As an important mediator of environmental factors and regulators of circadian rhythms, the epigenetic system may hold the key to the etiology or pathology of psychiatric disorders, their subtypes or endophenotypes. Epigenomic regulation of the circadian system and the related changes have not been thoroughly explored in the context of neuropsychiatric disorders. We argue for systematic investigation of the circadian system, particularly epigenetic regulation, and its involvement in neuropsychiatric disorders to improve our understanding of human behavior and disease etiology.

Keywords: epigenetics; circadian rhythms; neuropsychiatry

Introduction

Circadian rhythms are endogenous biological cycles ~24 h in length. They are found in most living organisms, and can be adjusted by factors called *zeitgebers,* or "time-givers", including light[1], temperature[2], diet[3], odor[4], and gravity[5], light being the dominant cue. Maintaining a rhythmic daily life is critical for surviving the recurrent environmental changes. These rhythms can be easily observed in behaviors such as sleeping and eating, but also, less visibly, affect crucial biological systems such as metabolism[6,7] and the cardiovascular system[7].

Multiple lines of evidence have suggested the potential roles of circadian rhythms in neuropsychiatric disorders such as sleep disorders, anxiety, mood disorders and addiction. Meanwhile, studies in animal models have identified several regulators and effectors of the endogenous clock. These core clock genes are known to comprise transcriptional-translational auto-regulatory complexes. However, these remain insufficient to explain all observations, especially the contribution to human behavioral traits and disorders. Further identification of the molecular components of circadian systems and their regulatory relationships is an important step for understanding neuropsychiatric disorders and for developing better diagnostics and treatment.

This review describes current findings on the genetic and epigenetic determinants of the circadian system in the context of neuropsychiatric disorders. By reviewing the literature, we highlight the complexity of circadian regulation beyond the classic core clock genes. Such complexity involves many genetic and epigenetic factors.

Since epigenetic mechanisms are important mediators of environmental factors and regulators of rhythmic gene expression, we therefore propose that developing comprehensive genome-wide and epigenome-wide data from multiple sample sources will improve our understanding of the circadian regulatory system and its role in neuropsychiatric disorders.

Clock Genes, Rhythmic Expression, and Regulatory Networks

Circadian rhythms in vertebrates are controlled by a conserved brain region in the anterior hypothalamus called the suprachiasmatic nucleus (SCN), made up of about 20 000 neurons. The SCN serves as a central regulator of circadian rhythms throughout the rest of the brain[8] and the body[9]. At the same time, peripheral tissues, even cultured cells[10;11] have their own local, autonomous clocks that can be self-sustaining, but they may be synchronized by signals from the SCN[12].

Clock genes underlying circadian rhythms can be broadly defined as genes that show diurnal variation of activity or function, typically showing rhythmic changes of transcript abundance, as such measures are more accessible than other molecular phenotypes, such as protein levels and activity. Although an increasing number of genes have been found to demonstrate the circadian characteristics of clock-controlled genes (CCGs), a small set of genes is denoted here as core “classic clock genes (CGs)”. The CGs include Period (*PER*), Timeless (*TIM*), Clock (*CLK*), Cycle (*CYC*, a *Drosophila* gene, with the mammalian homolog *ARNTL* or *BMAL1*), Cryptochrome (*CRY*), *REV-ERBalpha,* retinoic acid related-orphan receptor alpha (*RORalpha*), D-box-binding protein (*DBP*), thyrotrophic embryonic factor (*TEF*), hepatic leukemia factor (*HLF*), *E4BP4* (*also known as NFIL3*), deleted in esophageal cancer 1 (*DEC1*), *DEC2,* Neuronal PAS domain-containing protein 2 (*NPAS2*), and Double Time (*DBT, a Drosophila* gene, with the mammalian homolog casein kinase 1e, *CSNK1E*). These genes were mainly identified by the screening of mutants of fruit flies, mice, and hamsters[13]. These few CGs make up a group of auto-regulatory loops and present rhythmic expression of their own and their regulatory target transcripts. The CGs have been frequently called clock genes in the literature but as will be discussed in this review, these CGs only represent a small set of a much broader network of clock genes.

Most of the CGs encode proteins that function as transcription factors to drive the rhythmic expression of their target genes. Some of the CG proteins form heterodimer complexes, such as PER-CRY, CLK-BMAL1, and TIM-PER. They not only regulate the expression of many other genes that carry E-box promoters, but also their own expression. In contrast, *DBP, HLF, TEF*, and *E4BP4* regulate through D-box promoters[14,15]; while the REV-ERB alpha and ROR family members bind to the REV-ERB/ROR response element (RRE)[16]. cAMP response elements (CREs) are also central regulatory motifs that mediate rhythmic expression[17]. These regulatory systems have been thoroughly reviewed[13,18-20].

In addition to CGs, hundreds of non-CG genes are transcribed rhythmically. They are part of the broadly-defined clock genes. In fact, one would expect that genes carrying E-box, D-box, RRE, and CRE promoters could be potential clock genes[21,22]. Certainly, these genes could include both the drivers and passengers of a large circadian regulatory system, though most of the cause-effect relationships remain to be discovered. Increasing numbers of CGs have been identified through genome-wide expression profiling studies, mostly in mice, as summarized in Table 1. Just to name a few, 2%–10% of genes are expressed in a circadian manner in various mouse tissues[23-28]; in the mouse SCN, 337 genes were found to be expressed cyclically, and 335 were in the liver[26]. Another mouse study detected 575 genes in the liver and 462 in the heart with circadian expression[27].

Human studies have also revealed time-dependent expression in blood and brain. A 2010 study on gene expression induced by food-intake identified expression changes associated with biopsy time for 8 197 genes in blood (false discovery rate (FDR) 2.6%)[29]. This is the largest human circadian study thus far, with 40 individuals sampled at 14 time-points each, for a total of 560 blood samples. In this study, Li *et al.* (2013) reported circadian expression in human postmortem brain. They used time of death to represent time-points in the 24-h cycle, turning individual differences into differences of expression at different time-points. They analyzed 12 000 transcripts in six brain areas (dorsolateral prefrontal cortex, anterior cingulate cortex, hippocampus, amygdala, nucleus

Table 1. Genome-wide studies of the genetics and epigenetics of circadian rhythms

Author, Year	Species	Tissues	Measure	Strains	Microarray/Methods
McDonald *et al.* 2001[153]	*Drosophila*	Head	Expression	clock mutant (Clk) flies	Affymetrix array
Hughes *et al.* 2012[135]	*Drosophila*	Brain	Expression	Wild-type Canton-S flies, y w, per0, and per0 in a Canton-S background	RNA-Seq, 100-bp paired-end reads. On average, each sample >40 million readsa
Kornmann *et al.* 2001[24]	Mouse	Liver	Expression	C57BL/6 X 129/SV	ADDER (Amplification of Double-stranded cDNA End Restriction fragments) differential display
Ueda *et al.* 2002[154]	Mouse	SCN and liver	Expression	Balb/c	Affymetrix U74Av2 and U74A oligonucleotide array
Akhtar *et al.* 2002[23]	Mouse	Liver	Expression		Custom-made cDNA microarray
Panda *et al.* 2002[26]	Mouse	SCN and liver	Expression	Male C57BL/6J and clock mutant	Affymetrix mouse (U74A) high-density arrays
Storch *et al.* 2002[27]	Mouse	Liver and heart	Expression	C57/Bl6	Affymetrix U74Av2 oligonucleotide array
Zvonic *et al.* 2006[155]	Mouse	Liver, brown and white adipose tissue	Expression	AKR/J	Mouse430a2
Oster *et al.* 2006[156]	Mouse	Adrenal gland	Expression	C57BL/6J	Mouse4302
Lemos *et al.* 2006[157]	Monkey (*Macaca mulatta*)	Adrenal gland	Expression		Affymetrix U133-A GeneChips.
Zvonic *et al.* 2007[158]	Mouse	Calvarial bone	Expression	AKR/J	Mouse430a2
Yang *et al.* 2007[159]	Mouse	Prefrontal Cortex	Expression	C57BL/6J	Mouse4302
Maret *et al.* 2007[160]	Mouse	Whole brain	Expression	C57BL/6J, AKR/J, DBA/2J	Mouse4302
Bray *et al.* 2007[161]	Mouse	Atrium and ventricle	Expression	Cardiomyocyte-specific circadian clock mutant	illuminaMousev1
Miller *et al.* 2007[25]	Mouse	Liver, skeletal muscle, gastrocnemius	Expression clock mutant	Male C57BL/6J and	custom-made genome arrays
Storch *et al.* 2007[28]	Mouse	Retina	Expression	Male CBA/CaJ	Affymetrix mouse 430.2 arrays
Yan *et al.* 2008[32]	Mouse, human, and monkey	14 tissue	Expression	22 datasets	
Hughes *et al.* 2012[12]	Mouse	Liver	Expression	ClockΔ19 mouse Arrays	Affymetrix Mouse Exon 1.0 ST
Zambon *et al.* 2003[208]	Human	Skeletal muscle	Expression		Affymetrix U95a
Leonardson *et al.* 2010[29]	Human	Blood	Expression		Custom array
Li *et al.* 2013[30]	Human	6 brain areas	Expression		Affymetrix U133-A or U133Plus-v2 GeneChips
Lim *et al.* 2014[31]	Human	Dorsolateral	Gene Expression and DNA methylation		Illumina Infinium HumanMethylation450k Bead Chip; Illumina HiSeq prefrontal cortex with 101 bp pairedend reads and 150-M reads for the first 12 samples. Remaining samples, 50-M reads

accumbens, and cerebellum) from 55 controls and 34 major depressive disorder (MDD) patients[30]. Among the healthy controls, >417 transcripts in each region showed 24-h oscillation (nominal P <0.05), while 169 genes had an FDR of <0.5 for combined P values across regions. These 169 genes are considered to be common circadian genes in the brain[30]. Another study on human postmortem dorsolateral prefrontal cortex samples from 536 individuals used RNA-Seq and global statistics to show rhythmic expression without naming specific clock genes[31].

Most of these cases of rhythmic expression are tissue-specific, suggesting tissue-specific regulatory network. Only 28 cycling genes are shared between mouse SCN and liver[26], while 37 are shared between mouse liver and heart[27]. Another analysis of 21 microarray data sets from 14 mouse tissues found that the expression of 41 out of 19 168 genes showed consistent circadian oscillation across multiple tissues[32]. This alerts us to the fact that studies of the circadian regulatory system should take tissue-specificity into account.

It should be noted that the number of cyclically-expressed genes reported is related to the experimental design, statistical method, and significance cutoff. With the liberal significance criteria (P <0.05) used in the human brain study by Li *et al.*, some of the CGs still did not show rhythmicity[30]. However, these findings are not definitive, since many pre- and post-mortem factors could have destroyed rhythmic expression patterns and produced false-negatives. Moreover, as transcription factors are typically expressed at low levels, major circadian regulators, which are often transcription factors, could be missed by some of the techniques used in genome-wide studies when sensitivity is not sufficient.

After considering experimental artifacts, the fact that many genes other than CGs are rhythmically expressed and that some CGs do not show cycling expression in genome-wide studies could have many implications, including the possibility that our current list of clock genes may not be exhaustive. Given the complexity of the system, it is likely that we have not yet identified the complete set of genes regulating and responding to circadian rhythms. Several studies have proposed novel genes as important central regulator genes. For example, a 2008 study of mutant mice proposed that the *NR3C1* and *FKBP/HSP90* complexes are central to the control of circadian gene expression by environmental cues[32]. *CHRONO*[33,34] and *UBE3A*[35] were found to be essential in regulating circadian rhythms in mice in three 2014 studies. Genes involving protein translation, including rRNA, also showed rhythmic expression[36]. Furthermore, an siRNA screen of a human osteosarcoma cell line, targeting 17 631 known and 4 837 predicted human genes, discovered ~343 clock genes or modulators[37]. These data suggest that the underlying organization of circadian rhythms has not yet been completely described.

Rhythmic expression is certainly not the only aspect of circadian rhythms. Protein abundance and post-translational modifications, such as phosphorylation and ubiquitination, have also been shown to have daily oscillations in *Neurospora crassa*, the fruit fly, and multiple tissues in mouse, rat, and hamster, as reviewed by others[38-41]. Similar circadian molecular mechanisms may exist in humans, but remain to be explored. From chromatin to transcripts, mRNA to proteins and to protein modifications, circadian rhythms encompass a complex regulatory system, including the epigenomic components discussed below.

Genetics of Sleep-Related Traits

While circadian patterns can be observed from the molecular level all the way up to the organismal behavior level, the sleep-wake cycle and other sleep-related traits are probably the most salient outputs of the circadian clocks. These traits are known to be heritable[44], and the underlying genes can be identified directly by genetic methods using human population data, without relying on knowledge of specific clock genes. The heritability of sleep measures, including timing, duration, and quality, varies between 12.4% and 29.4%[42]. A study of 410 normal adults has identified a polymorphism in *CLK* associated with morningness-eveningness preferences[43]. Furthermore, in a GWAS of 4 251 individuals, Allebrandt *et al.* (2013) identified an intronic variant (rs11046205) in the *ABCC9* gene associated with sleep duration (P = 3.99e-8)[44].

On the other hand, the circadian system is not the only regulator of sleep. Energy homeostasis and its interactions with circadian rhythms also contribute to maintenance of the sleep-wake cycle[45,46]. While homeostasis and other factors play significant roles in sleep regulation, sleep has

been used as the major model to study the genetics and regulation of circadian rhythms, although it should be noted that the genetics of the sleep-wake cycle is not necessarily all about circadian rhythms.

Healthy people vary in their preferences for sleep timing and length; some are often classified as morning "lark" or evening "owl" chronotypes. If these variations do not impair the quality of life, they are considered normal. Sleep-wake behaviors in humans and animal models offer opportunities to understand circadian regulation. In humans, variable sleep traits or disorders provide avenues for studying the molecular bases of sleep regulation, and, by extension, circadian rhythms. In animal models, one can take advantage of better-controlled environmental factors to study their contribution to circadian regulation. For example, manipulating the lighting environment and feeding pattern have been shown to induce circadian and related genomic and epigenomic changes[47].

Circadian Disruptions Are Implicated in Neuropsychiatric Disorders

Disruption of circadian rhythms is associated with or implicated in many traits or diseases, including metabolic syndrome[48], obesity[49], diabetes[50], inflammatory diseases and autoimmune disorders[51], cancer[52], drug efficacy and toxicity[53], cardiovascular disorders[54], and mental disorders[55,56].

Among neuropsychiatric disorders, sleep-wake disorders, anxiety, mood disorders, and addiction have the strongest connections to altered circadian rhythms. While the connection between circadian rhythms and sleep-wake disorder is self-evident, circadian rhythms have been implicated in other psychiatric disorders based on biological and clinical observations. Specifically, many of these disorders exhibit co-morbidity with sleep disturbance and their treatments often elicit responses that are related to candidate clock genes and behavioral or clock gene expression changes in animal models. Additional links between circadian rhythms and neuropsychiatric disorders can be found in several candidate gene association studies. Major evidence is summarized in Table 2. A few examples of ***indirect evidence*** linking circadian rhythms to non-sleep-related neuropsychiatric disorders are as follows: abnormal sleep is co-morbid with many disorders[57]. Persistent sleep disturbances have been found to increase the risk of developing anxiety[58] and depression[59;60]. Insomnia and substance abuse disorders promote the risk of each other[60,61]. Melatonin is important in synchronizing circadian rhythms[62], and agomelatine that targets the melatonergic system is an antidepressant[63]; agomelatine has been shown to increase the relative amplitude of an individual's rest-activity cycles[64]. Ketamine, a drug with rapid-acting antidepressive effects, influences the recruitment of the CLK-BMAL1 complex to E-box promoters and alters the expression of CGs[65]. Another antidepressant, escitalopram, has been reported to restore the disrupted rhythmic expression of several CGs in a study of blood samples from 12 MDD patients and 12 controls[66]. Animal models with disrupted clock genes show behavioral changes similar to mood disorders[67] or schizophrenia[68]. Therefore, circadian rhythms have been of interest in the study of these disorders. However, the question of causation largely remains to be addressed.

A multi-system hypothesis has been formulated to explain the connections between circadian rhythm disturbance and addiction, as well as anxiety. Based on a literature review, Gorwood highlighted the cortisol-melatonin-vasopressin interaction for anxiety, as this interaction nicely bridges stress-response and circadian systems[69]. Drugs of abuse may influence the interwoven molecular networks of circadian rhythms, stress-response, reward circuitry, neuroplasticity and memory, and ultimately lead to the development of addiction, as well as withdrawal symptoms. The paraventricular nucleus in the hypothalamus has been proposed to be the location where circadian and stress signals converge, and where multiple clock genes, neuropeptides, and stress-response genes interact[70]. Such interactions between circadian systems and stress-response systems may play an important role in many psychiatric disorders, including but not limited to addiction[71].

The dopamine D2 receptor (*DRD2*) is another interesting candidate linking the circadian system and the reward pathway, as it mediates the photic response to regulate circadian rhythms, and the most important reward pathway is dopaminergic[72]. Several candidate gene studies have found significant associations between *DRD2* variants and different kinds of addiction (alcohol, cocaine, heroin, and nicotine)[73,74]. However, a meta-analysis[75] and

Table 2. Studies that implicate circadian rhythms in psychiatric disorders

	Mood disorder (MDD and bipolar disorder)	Anxiety	Addiction
Sleep disturbance comorbidity, or as a risk factor	Risk factor for developing MDD[59,60]. Abnormal circadian rhythms in hormone levels, body temperature, sleep, and behavioral patterns reported in patients with MDD[162-164]; degree of circadian misalignment correlated with severity of depression[165]; sleep disturbance in manic and depressive phases, even possibly euthymic phases[166,167].	Risk factor for developing anxiety[58]; children daily regularity predicts anxiety levels >10 years later[168]	Bi-directional relationship: addiction disrupts circadian rhythms; sleep and mood problems increase chance of addiction[60;169]
Therapy	Seasonal affective disorder (SAD) patients respond to light therapy[170]; sleep deprivation treats depression[171]; sleep deprivation may switch a depressed patient into hypomania or mania[172]; agomelatine increases relative amplitude rest-activity cycles[64]; lithium lengthens circadian period in hamsters[173].	Agomelatine affects circadian rhythms[64], also effective in treating anxiety disorders[176,177].	
Chronotype	Mood disorders associated with chronotype[178,179]		Evening chronotype associated with substance abuse[180;181]
Social rhythms	Disrupted social rhythms[182-184]	Lower daily regularity in anxiety patients[185]	
Seasonal pattern	Seasonal changes in bipolar disorder[186,187]		Case report of SAD with cyclical cocaine craving[188]
Hormone	Rhythmic melatonin level[189,190]	Cortisol level is rhythmic[191]	Cortisol secretion patterns linked to addiction[192]
Clock gene genetic association	17 studies of candidate genes[193]	One candidate gene study[194]	Six genetic studies[195-200]
Clock genes in animal models	Knockout of REV-ERB alpha increases midbrain dopamine production and induces mania-like behavior by regulating tyrosine hydroxylase gene expression in a mouse study[201]. Clk mutant shows mania[67]	Per1 and Per2 expression levels in nucleus accumbens regulate anxiety levels in knockout mouse models and mice experiencing chronic social defeat stress[202]. Clk mutant less anxious[67]	14 studies of Clock, per1, and per2 mutant mice showed behavior changes in response to drug[203]
Clock gene expression in response to drug treatment	Ketamine influences expression of clock genes[65]; escitalopram restores disrupted rhythmic expression of several clock genes[66]; lithium affects expression of multiple clock genes[174,175,204]; valproic acid changes phase and amplitude of *PER2* expression in cultured cells[117].	Anxiolytic medications reduce mPer1 expression in mice[205]	Chronic methamphetamine treatment desynchronizes clock gene expression between striatum and SCN[206]; ethanol and drugs of abuse alter clock gene expression in SCN and other brain regions[203]
Clock gene expression changes in patients	Expression changes of clock genes in MDD brain[30] and blood[207].		
Review	Gonzalez 2014[193]	Philip Gorwood, 2012[69]	Logan RW *et al*. 2014[203]

a GWAS[76] of alcoholism reported inconsistent results, suggesting that the *DRD2* contribution may be small, if at all. A *DRD2* variant has also been reported to be associated with anxiety disorders with co-morbid alcohol-use disorder[77]. But the finding is also weak and requires replication.

Circadian Genetics of Neuropsychiatric Disorders

Genetic studies may capture direct evidence that specific clock genes are involved in neuropsychiatric disorders if mutations or variants of clock genes are associated with the risk of disorders. Genetic association is an important venue leading to the translation of clues from animal models to clinical relevance.

Sleep-Wake Disorders

Sleep-wake disorders impair the quality of life, affect learning, memory, and mood. These disorders have a clear genetic basis. Family and twin studies of insomnia report heritability ranging between 21% and 58%[78-80] [see Palagini *et al.* (2014) for a thorough review[81]]. Travel across time zones, sleep deprivation, and shiftwork all disturb sleep patterns. Insomnia, hypersomnia, and narcolepsy are major sleep-wake disorders[82]. Some of these are common, like insomnia (~10% of adults have severe insomnia that cause daytime consequences[83]), and some are rare, like narcolepsy (affecting ~1 in 3 000)[84]. Jet-lag and shiftwork-related sleep problems are common in specific occupations, like flight attendants, nurses, and soldiers.

Mutations in genes responsible for some specific, mostly rare forms of sleep disorders have been discovered. A mutation (R192H) in *GABRB3* has been found in patients with chronic insomnia. Since *GABRB3* encodes a subunit of a chloride channel that serves as the receptor for gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter of the mammalian nervous system, a decrease in GABAergic inhibition may contribute to insomnia[85]. Interestingly, hypersomnia was also recently linked to GABA(A) receptor regulation[86]. Another excessive sleeping disorder, narcolepsy, is mostly caused by a deficiency in hypocretin (*HCRT*), an excitatory neuropeptide[87].

Mutations in *PER2* and *CSNK1D* have been reported in Advanced Sleep Phase Syndrome (ASPS) patients. A rare autosomal dominant mutation of *PER2* has been found to be responsible for ASPS in members of a Utah family[88]. CKIdelta (*CSNK1D*) was found to have a missense mutation responsible for ASPS[89].

Knockout or mutation of many other genes, including *IA2*[90], has been found to change sleep-related behaviors in mice, and has been reviewed elsewhere[91]. These genes could be candidates for human sleep disorders, but mutations have not been detected in humans so far.

The search for genes of the common forms of sleep disorders has produced positive and negative results. A GWAS of insomnia with 2 267 samples did not detect any significant genome-wide association[92]. However, several other sleep disorders have yielded significant genome-wide signals in GWASs with hundreds of cases, including restless legs syndrome (*MEIS1*, *BTBD9*, *PTPRD*, *MAP2K5*, *SKOR1*, *TOX3*, *BC034767*, *MAP2K5*, and *LBXCOR1*)[93-96] and narcolepsy (*TRA-alpha* and *TRAJ10*)[97].

It should be noted that a circadian defect is not the only cause of sleep-wake disorders. Cardiovascular, neurological, and pulmonary diseases, substance use and medication, irregular metabolism, and bad habits can all disturb sleep. One can certainly argue that some of the genes associated with sleep disorders may not be involved in circadian regulation at all. In fact, among the classic clock genes, CGs, only *PER2* has been found to carry a mutation [c.1984A>G (p.Ser662Gly)] responsible for a sleep disorder[88]; all the other associated genes are outside of the CGs. Most of them do not have any known connection with circadian regulation, or have not been studied for rhythmic expression. How sleep disorder-associated genes are related to circadian rhythms remains to be investigated. It may turn out that some of these non-CG genes are also actual clock genes, participating in circadian regulation.

Non-Sleep-Related Neuropsychiatric Disorders

Genetic variants of candidate genes of CGs have been tested for association with bipolar disorder[98,99], depression[100], seasonal affective disorder[101,102], or anxiety disorders[77], alcohol use[103], heroin addiction[104], bipolar disorder and schizophrenia[105], major depression and bipolar disorder[106], and depression and sleep disorder[107]. Though some positive associations were reported, most findings were weak and not replicated.

Genetic associations of ~360 selected clock genes

were systematically assessed in 14 psychiatric GWAS data sets based on relaxed thresholds for significance by McCarthy *et al.* (2013)[108]. Bipolar disorder, schizophrenia, attention deficit hyperactivity disorder, and MDD as a group of disorders and lithium-responsiveness have been shown to have association signals enriched in 18 core clock genes and genes reported to be rhythmically expressed in more than six mouse tissues. This is the first GWAS evidence supporting potential genetic contributions of the circadian system to neuropsychiatric disorders, although the selection of clock genes in this study may be debatable and replication is warranted.

It is important to note that the CGs did not appear as any of the top GWAS signals of these psychiatric disorders, despite the fact that circadian disruption has been strongly implicated in such disorders. Genetic studies of depression, anxiety, and addiction have yielded largely negative results[109-113]. The study by McCarthy *et al.* suggested collective weak contributions from clock genes to the susceptibility of various disorders. This has several implications. First, it is possible that other non-CG genes associated with disease are also part of the circadian system, but have not yet been identified as such. Second, clock genes may be more relevant to specific subtypes or endophenotypes of those diseases; therefore, subgroups of those disorders may provide better association with clock genes. Last, the circadian system may contribute more to disease risk through a non-genetic route, such as epigenetics.

Epigenetic Factors Regulate Circadian Rhythms

When genetics has had limited success in providing direct evidence to link circadian rhythms to neuropsychiatric disorders, epigenetics naturally attracted attention as the critical regulator (for gene expression) and mediator (for environmental factors). Then the first questions are whether epigenetic factors regulate circadian rhythms as they should in theory, and what these circadian epigenetic factors are.

The circadian system is dynamic and flexible, and is tightly regulated by the interactions between internal molecular systems and environmental cues. The environmental factors, including light, food, temperature, stress, hormones, drugs, and age, act through epigenetic factors to shape the phenotypes. Gene expression, as the molecular representative of circadian rhythms, is known to be regulated by genetic variants and epigenetic factors. Epigenetic factors include DNA methylation, histone modification (e.g., methylation, acetylation, phosphorylation, and citrullination, biotinylation, ribosylation, ubiquitination, and palmitoylation), and non-coding RNAs. Studies on histone acetylation, DNA methylation, non-coding RNA, and RNA modification have shed light on their roles in regulating the expression of clock genes, and ultimately, circadian phenotypes. With such studies, we could look for circadian epigenetic factors, and further study their contribution to neuropsychiatric disorders.

Acetylation and Deacetylation

The epigenetic mechanism that *CLK* uses to regulate circadian rhythms is histone acetylation and deacetylation. Etchegaray *et al.* (2003) showed in a mouse liver study that histone acetyltransferase (HAT) p300 works with the Clock/Bmal1 complex to regulate histone H3 acetylation at the promoters of the Cry and Per genes to influence their expression[114]. Doi *et al.* (2006) further showed that CLK itself possesses HAT activity, which can be enhanced by its partner BMAL1, when bound to E-box[115]. CLK is also involved in acetylating other non-histone substrates including BMAL1. Acetylated BMAL1 recruits CRY1 to the CLK-BMAL1 complex and represses transcription[116].

Histone deacetylase (HDAC) has a function opposite to that of HAT, and is also an important regulator of circadian rhythms and memory formation, as well as metabolism. It removes acetyl groups from ε-N-acetyl lysine on histones, allowing the histones to wrap the DNA more tightly. The HDAC inhibitor valproic acid and trichostatin A were found to increase H3 acetylation and affect *Per2* expression in an *in vitro* study[117].

A mouse model has shown that Hdac3, one of the Hdac subtypes, is recruited by nuclear receptor corepressor 1 (Ncor1) and is involved in repressing *Bmal1* expression, thus affecting circadian rhythms and metabolism[118]. Hdac3 recruitment also fluctuates rhythmically in the mouse liver, in conjunction with Rev-erb-alpha and Ncor, to form a Hdac3/Rev-erb-alpha/Ncor complex[119]. It is to be expected that the transcription of many genes oscillate with the fluctuation of HDAC3-related histone modification, or Rev-Erb-alpha/NCoR1-related signaling pathways.

Another member of the HDAC family, an NAD(+)-dependent protein deacetylase, SIRT1, also works directly with clock genes. SIRT1 binds CLK-BMAL1 and promotes deacetylation and degradation of the PER2 protein in mice[120]. SIRT1 is also a metabolic sensor, as it requires binding of its coenzyme NAD+ for its HDAC enzymatic activity. Thus, through SIRT1, metabolic states are linked to the circadian system. In addition, *SIRT1* has been implicated in aging and neurodegeneration[121,122], synaptic plasticity, and memory formation in mouse studies[123,124].

The lysine-specific demethylase JumonjiC and ARID domain-containing histone lysine demethylase 1a are also major binding partners of CLK-BMAL1. This can inhibit HDAC1 function and enhance transcription by CLK-BMAL1 in a demethylase-independent manner. The CLK-BMAL1 complex plays a conserved circadian regulatory role across insect and mammalian species[125].

DNA Methylation

The role of DNA methylation in circadian regulation is supported by a human study in which plasma homocysteine levels and the global DNA methylation level showed 24-h variation in the blood of 15 males and 15 females[126]. Homocysteine level has been linked to DNA methylation in many studies[127]. An epigenome-wide study using methyl-DNA immunoprecipitation (MeDIP-chip) in mice showed that altered day-length changed gene expression profiles and promoter DNA methylation in the SCN, suggesting that DNA methylation regulates the circadian clock in the SCN[128]. Moreover, a study in mice showed that sleep deprivation can change the DNA methylation and hydroxymethylation of hundreds to thousands of CpG sites near genes involved in neuritogenesis and synaptic plasticity, the cytoskeleton, signaling, and neurotransmission[129]. Direct evidence supporting the roles of DNA methylation in regulating circadian rhythms came from a human study, which used global statistics to show evidence of significant 24-h rhythmicity of DNA methylation, as well as its correlation with rhythmic gene expression in human dorsolateral prefrontal cortex[31].

Non-coding RNA

MicroRNAs (miRNAs), probably the most intensively studied class of non-coding RNAs (ncRNAs) so far, may contribute to the regulation of circadian rhythms. Dicer is the major enzyme in miRNA biogenesis, and Dicer-deficient mice and cells show shorter circadian cycles due to faster translation of *PER1* and *PER2* proteins. It has been proposed that microRNAs miR-24, miR-29a, and miR-30a specifically target *PER1* and *PER2,* thus determining the period of the cycle[130].

Studies in mice have also implicated two other miRNAs, miR-134 and miR-132, in circadian regulation. miR-134 is brain-specific, and regulated by *SIRT1*[124]. It is involved in the regulation of CREB and BDNF levels, proteins that are important in many neuronal functions and activities[124]. miR-132 is a direct link between light and chromatin remodeling: it is induced by photic entrainment cues *via* the mitogen-activated protein kinase (MAPK)–*CREB* signaling pathway[131] and regulates chromatin remodeling and translation[132].

Other ncRNAs have strong potential in regulating circadian rhythms too. Rhythmic expression has been reported for 112 long non-coding RNAs (lncRNAs) in the rat pineal gland, which is the source of melatonin[133], while melatonin is an important hormone timing circadian rhythms. A study of *Neurospora* gene frequency (frq) demonstrated that lncRNAs regulate circadian rhythms through anti-sense expression[134]. RNA-Seq of *period*-null *Drosophila* has identified several ncRNAs with diurnal expression, including a family of small nucleolar RNAs (snoRNAs)[135]. It should be noted that some ncRNAs, particularly lncRNAs, evolved fast and are species-specific[136,137]. These findings in non-humans only suggest possible epigenetic mechanisms that may occur in humans. The actual genes in humans remain to be discovered.

RNA Modification

Post-transcriptional RNA processing and modification may be relevant to clock function. A recent study in mice and cultured human cells showed that n^6-methyladenosine RNA-methylation, one of the most common RNA modifications, is involved in circadian clock regulation[138].

Studies have also shown that diet affects the epigenetic regulation of circadian function. In a study of Japanese macaques, a maternal high-fat diet *in utero* disrupted the regulation of expression, and increased individual variations in fetal hepatic *Npas2*, one of the CGs. Such disruption was associated with altered histone acetylation (H3K14ac) but not DNA methylation at the *Npas2* promoter region. These changes of gene expression and histone modification were

reversed by postnatal diet[139]. Exposure to different lengths of light per day changes the SCN and neuronal *Per1* gene expression and behavior after birth in mice[140], suggesting possible epigenetic modification induced by early-life environmental effects, although epigenetics was not part of the study.

The epigenetics of circadian systems is a new, emerging research field, leaving a lot to be investigated. Most studies have been performed in mouse models, and only a few in humans. Since differences in epigenetic regulation between mice and humans during preimplantation development have been reported[141], findings from mice and other species may not translate to humans directly. Moreover, many epigenetic factors, such as hydroxymethylation, lncRNAs, and most of the histone modifications other than acetylation, have not been studied in the context of circadian regulation in humans. Even for those factors studied, the findings are still fragmentary, and do not form one coherent picture of the regulatory system. It is not known whether these factors work independently or interactively to regulate each of the clock genes, or the circadian system as a whole, and how. For these reasons, we advocate a more comprehensive epigenomic study of the circadian system in humans.

Circadian Epigenetics in Neuropsychiatric Disorders

Although plenty of data have implicated circadian rhythms in the risk of neuropsychiatric disorders, and that epigenetic factors are important regulators of these rhythms, only very limited studies have been performed to explore the epigenetics changes in neuropsychiatric disorders.

Sleep-Related Disorders

A few studies have been published on gene expression changes in disturbed sleep. The epigenetic regulation of those changes remains largely unknown as only one candidate gene study exists for DNA methylation.

Möller-Levet *et al.* studied gene expression profiles and reported that 711 genes were up- or down-regulated in the blood of people suffering from insufficient sleep. The number of genes with a circadian expression profile was also reduced from 1 855 to 1 481[142]. This same research group also studied the blood transcriptome in desynchrony of sleep-wake timing and circadian rhythms, and identified a dramatic reduction of rhythmic transcripts (6.4% to 1.0%) caused by desynchrony[143]. The chromatin modification and expression regulation pathways were consistently implicated by the differentially-expressed genes in these two sleep studies.

Bollati *et al.* (2010) studied the effects of daytime and nighttime shiftwork on global DNA methylation and the methylation of the promoters of three candidate genes (glucocorticoid receptor, tumor necrosis factor alpha (TNF-α), and interferon-gamma) using peripheral blood DNA from 100 shift-workers and 50 day-workers in Northern Italy. A small but significant difference in methylation was detected between morning and evening type shift-workers in the TNF-α promoter. However, no significant methylation difference was detected when comparing shift-workers to day-workers[144]. It is notable that all the reported associations or correlations were weak.

Non-Sleep-Related Neuropsychiatric Disorders

Prader-Willi syndrome (PWS) is the first neuropsychiatry disorder with evidence of disrupted circadian epigenomics. PWS is a genetic disorder featuring obesity, intellectual disability, and sleep abnormalities. This disorder is frequently co-morbid with psychiatric problems[145]. It is caused by a deletion on the paternal chromosome 15q11-q13, considered to be caused by loss of snoRNAs[146], which are processed products of a lncRNA gene, 116HG. A study of mice lacking 116HG showed altered expression of several clock genes and energy use in the brain[147].

Another pilot study connecting the genetics and epigenetics of clock genes to psychiatric disorders is on miRNA. The precursor of miR-182 was found to carry an SNP rs76481776 that is associated with late insomnia in MDD patients (corrected P <0.00625), in a study of 359 MDD patients and 341 control individuals. *CLK* is one predicted target of miR-182 and the regulatory relationship was validated by *in vitro* assays[148]. This relationship between an SNP, the expression of an miRNA, and its targets warrants further investigation. However, it does suggest that we should pay more attention to subtypes or endophenotypes rather than diagnostic classification, when studying the genetics and epigenetics of those disorders.

Clearly, circadian epigenomics has not received sufficient attention in the study of neuropsychiatric disorders although the circadian rhythms have been one of the major phenotypes to study in these disorders.

Future Perspectives

Based on the studies reviewed above, we see that knowledge of the regulatory systems of circadian rhythms may provide an opportunity to understand psychiatric disorders. However, we still have limited understanding of the broader network context of such circadian regulatory systems, particularly the epigenetic aspects of such regulation. Genes involved in circadian rhythms remain to be discovered and organized into network systems. Epigenomics need to be integrated in order to complete the circuitry regulating expression, and connected with environmental factors. More importantly, considering such regulation and networks in the context of neuropsychiatric disorders would provide new perspectives on the link between circadian and human behaviors, therefore allowing better understanding of the disorders.

Understanding the complex biological systems that produce them is necessary to decipher complex traits such as neuropsychiatric disorders[149]. Circadian regulation is a complex biological system. Environmental factors and internal biological infrastructure work together: light acting through photoreceptors, food working through SIRT1-related pathways, and psychological stress through the hypothalamo-pituitary-adrenal neuroendocrine system, all of which regulate an organism's internal clock. Serotonergic, dopaminergic, and maybe other neurotransmitter systems interact with circadian regulatory networks to influence human behavior and disorders.

Our current knowledge about circadian rhythms is largely derived from studies of candidate genes, their biochemistry, genomics, and epigenomic regulation. There are very limited genome-wide, systematic studies in humans (Table 1). Genome-wide studies are critical for obtaining an unbiased understanding of biological systems. It is important to put existing knowledge into a biological network, to re-assess all the interactions and signaling connections. Novel components of circadian controls, from environmental cues to the downstream effectors, will be discovered. Several papers have advocated the use of systems biology to study circadian rhythms, and to construct the regulatory system of circadian rhythms through integration of multiple -omics[150-152].

A complete circadian regulation system should contain every member of the circadian regulation cascades, from the core clock modulators to the downstream effector genes. It should also represent regulators at different levels, from environmental cues to epigenetic factors, RNA and protein modifications. Relationships among these nodes, genes, and their interactions are critical parts of the system. The use of such systems holds the key to understanding circadian rhythms and their role in neuropsychiatric disorders.

Regulatory systems are spatiotemporally-specific. This suggests that tissue selection is important for the study of circadian rhythms and psychiatric disorders. The brain is the critical organ/tissue for understanding neuropsychiatric traits or disorders, including those that are circadian-related, particularly as circadian regulation is tissue-specific. However, other than imaging studies, it is almost impossible to study circadian dynamics in the live human brain. Excessive assumptions have to be made in the analyses of human postmortem data. Different individuals could differ by variables other than the time of death. Model animal brains, cultured or induced neuronal cells derived from stem cells, and human blood are a few alternatives that could provide multiple time-point data around the clock. However, each model system has its own limitations. Complementary use of these different models may help us build a comprehensive understanding of the regulatory network and its relevance to human circadian-related traits and disorders.

Genomic and epigenomic studies of patient and control samples should also take diurnal variations into account. Hundreds or even more genes have variable gene expression or epigenetic markers within 24-h. In the past, the time when data or material was collected has rarely been recorded and incorporated into analyses. As a result, artifacts may have been introduced into some published data unless the sample collection was done at a similar time of day. Circadian studies in healthy humans will provide critical baseline information for other studies when time of day data are not available.

The findings from genetic and epigenetic studies could lead to novel drug targets. Belsomra, a hypocretin receptor antagonist, was recently approved by the Food and Drug Administration (USA) as a new drug to treat insomnia. Hypocretin has been connected to the sleep-wake cycle since the discovery of a mutation responsible

for narcolepsy, though it is not considered one of the CGs. We may have many other drug targets buried in the list of components with rhythmic expression or epigenetic regulation of circadian rhythms, the complete circadian regulation systems. Epigenetic drugs have great potential in treating neuropsychiatric disorders. Theoretically, it will be much easier to use drugs to modify the epigenome than to correct mutated genes.

Understanding the genetics and epigenetics of circadian-related traits and diseases will lead to better and more precise diagnosis of circadian-related disorders. Ultimately, this will improve the quality of life for people suffering from disorders due to jet-lag or shift-work, when we are able to develop epigenetic interventions to ease the pains and discomfort.

Through our review, it is clear that epigenetics may play important roles in regulating circadian rhythms and associated neuropsychiatric disorders, but related studies are lacking today. The circadian cycle is a highly environment-dependent biological process. The circadian cycle is one of the best models to study environmental impact and gene-environment interactions. Much effort should be placed on this interesting research field. Using circadian-related phenotypes and biomarkers, we may have an exceptional opportunity to access the dark kernel of psychiatric disorders.

ACKNOWLEDGEMENTS

We thank Ms. Kay Grennan and Dr. Annie Shieh for critical and thoughtful reading of this manuscript. We also thank Dr. Minhan Yi and Ms. Haiyan Tang for helping proofreading. This review was supported by grants to CL from the NIH, USA (R01-ES024988 and U01-MH103340) and the Central South University of China.

Received date: 2014-09-22; Accepted date: 2015-01-19

REFERENCES

[1] Honma K, Honma S, Wada T. Entrainment of human circadian rhythms by artificial bright light cycles. Experientia 1987, 43: 572–574.

[2] Buhr ED, Yoo SH, Takahashi JS. Temperature as a universal resetting cue for mammalian circadian oscillators. Science 2010, 330: 379–385.

[3] Sherman H, Genzer Y, Cohen R, Chapnik N, Madar Z, Froy O. Timed high-fat diet resets circadian metabolism and prevents obesity. FASEB J 2012, 26: 3493–3502.

[4] Abraham U, Saleh M, Kramer A. Odor is a time cue for circadian behavior. J Biol Rhythms 2013, 28: 26–37.

[5] Fuller CA, Hoban-Higgins TM, Griffin DW, Murakami DM. Influence of gravity on the circadian timing system. Adv Space Res 1994, 14: 399–408.

[6] Bailey SM, Udoh US, Young ME. Circadian regulation of metabolism. J Endocrinol 2014, 222: R75–R96.

[7] Morris CJ, Yang JN, Scheer FA. The impact of the circadian timing system on cardiovascular and metabolic function. Prog Brain Res 2012, 199: 337–358.

[8] Abe M, Herzog ED, Yamazaki S, Straume M, Tei H, Sakaki Y, *et al.* Circadian rhythms in isolated brain regions. J Neurosci 2002, 22: 350–356.

[9] Balsalobre A. Clock genes in mammalian peripheral tissues. Cell Tissue Res 2002, 309: 193–199.

[10] Leise TL, Wang CW, Gitis PJ, Welsh DK. Persistent cell-autonomous circadian oscillations in fibroblasts revealed by six-week single-cell imaging of PER2::LUC bioluminescence. PLoS One 2012, 7: e33334.

[11] Ruan GX, Allen GC, Yamazaki S, McMahon DG. An autonomous circadian clock in the inner mouse retina regulated by dopamine and GABA. PLoS Biol 2008, 6: e249.

[12] Hughes ME, Hong HK, Chong JL, Indacochea AA, Lee SS, Han M, *et al.* Brain-specific rescue of Clock reveals system-driven transcriptional rhythms in peripheral tissue. PLoS Genet 2012, 8: e1002835.

[13] Wager-Smith K, Kay SA. Circadian rhythm genetics: from flies to mice to humans. Nat Genet 2000, 26: 23–27.

[14] Gachon F, Olela FF, Schaad O, Descombes P, Schibler U. The circadian PAR-domain basic leucine zipper transcription factors DBP, TEF, and HLF modulate basal and inducible xenobiotic detoxification. Cell Metab 2006, 4: 25–36.

[15] Mitsui S, Yamaguchi S, Matsuo T, Ishida Y, Okamura H. Antagonistic role of E4BP4 and PAR proteins in the circadian oscillatory mechanism. Genes Dev 2001, 15: 995–1006.

[16] Jetten AM, Kurebayashi S, Ueda E. The ROR nuclear orphan receptor subfamily: critical regulators of multiple biological processes. Prog Nucleic Acid Res Mol Biol 2001, 69: 205–247.

[17] Obrietan K, Impey S, Smith D, Athos J, Storm DR. Circadian regulation of cAMP response element-mediated gene expression in the suprachiasmatic nuclei. J Biol Chem 1999, 274: 17748–17756.

[18] Buhr ED, Takahashi JS. Molecular components of the Mammalian circadian clock. Handb Exp Pharmacol 2013, (217): 3–27.

[19] Brown SA, Azzi A. Peripheral circadian oscillators in mammals. Handb Exp Pharmacol 2013, (217): 45–66.

[20] Bozek K, Relogio A, Kielbasa SM, Heine M, Dame C, Kramer

A, *et al.* Regulation of clock-controlled genes in mammals. PLoS One 2009, 4: e4882.

[21] Kumaki Y, Ukai-Tadenuma M, Uno KD, Nishio J, Masumoto KH, Nagano M, *et al.* Analysis and synthesis of high-amplitude Cis-elements in the mammalian circadian clock. Proc Natl Acad Sci U S A 2008, 105: 14946–14951.

[22] Bozek K, Kielbasa SM, Kramer A, Herzel H. Promoter analysis of Mammalian clock controlled genes. Genome Inform 2007, 18: 65–74.

[23] Akhtar RA, Reddy AB, Maywood ES, Clayton JD, King VM, Smith AG, *et al.* Circadian cycling of the mouse liver transcriptome, as revealed by cDNA microarray, is driven by the suprachiasmatic nucleus. Curr Biol 2002, 12: 540–550.

[24] Kornmann B, Preitner N, Rifat D, Fleury-Olela F, Schibler U. Analysis of circadian liver gene expression by ADDER, a highly sensitive method for the display of differentially expressed mRNAs. Nucleic Acids Res 2001, 29: E51.

[25] Miller BH, McDearmon EL, Panda S, Hayes KR, Zhang J, Andrews JL, *et al.* Circadian and CLOCK-controlled regulation of the mouse transcriptome and cell proliferation. Proc Natl Acad Sci U S A 2007, 104: 3342–3347.

[26] Panda S, Antoch MP, Miller BH, Su AI, Schook AB, Straume M, *et al.* Coordinated transcription of key pathways in the mouse by the circadian clock. Cell 2002, 109: 307–320.

[27] Storch KF, Lipan O, Leykin I, Viswanathan N, Davis FC, Wong WH, *et al.* Extensive and divergent circadian gene expression in liver and heart. Nature 2002, 417: 78–83.

[28] Storch KF, Paz C, Signorovitch J, Raviola E, Pawlyk B, Li T, *et al.* Intrinsic circadian clock of the mammalian retina: importance for retinal processing of visual information. Cell 2007, 130: 730–741.

[29] Leonardson AS, Zhu J, Chen Y, Wang K, Lamb JR, Reitman M, *et al.* The effect of food intake on gene expression in human peripheral blood. Hum Mol Genet 2010, 19: 159–169.

[30] Li JZ, Bunney BG, Meng F, Hagenauer MH, Walsh DM, Vawter MP, *et al.* Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. Proc Natl Acad Sci U S A 2013, 110: 9950–9955.

[31] Lim AS, Srivastava GP, Yu L, Chibnik LB, Xu J, Buchman AS, *et al.* 24-hour rhythms of DNA methylation and their relation with rhythms of RNA expression in the human dorsolateral prefrontal cortex. PLoS Genet 2014, 10: e1004792.

[32] Yan J, Wang H, Liu Y, Shao C. Analysis of gene regulatory networks in the mammalian circadian rhythm. PLoS Comput Biol 2008, 4: e1000193.

[33] Goriki A, Hatanaka F, Myung J, Kim JK, Yoritaka T, Tanoue S, *et al.* A novel protein, CHRONO, functions as a core component of the mammalian circadian clock. PLoS Biol 2014, 12: e1001839

[34] Anafi RC, Lee Y, Sato TK, Venkataraman A, Ramanathan C, Kavakli IH, Hughes ME, Baggs JE, Growe J, Liu AC, *et al.* Machine learning helps identify CHRONO as a circadian clock component. PLoS Biol 2014, 12: e1001840.

[35] Gossan NC, Zhang F, Guo B, Jin D, Yoshitane H, Yao A, *et al.* The E3 ubiquitin ligase UBE3A is an integral component of the molecular circadian clock through regulating the BMAL1 transcription factor. Nucleic Acids Res 2014, 42: 5765–5775.

[36] Jouffe C, Cretenet G, Symul L, Martin E, Atger F, Naef F, *et al.* The circadian clock coordinates ribosome biogenesis. PLoS Biol 2013, 11: e1001455.

[37] Zhang EE, Liu AC, Hirota T, Miraglia LJ, Welch G, Pongsawakul PY, *et al.* A genome-wide RNAi screen for modifiers of the circadian clock in human cells. Cell 2009, 139: 199–210.

[38] Podobed PS, Kirby GM, Martino TA. Circadian Proteomics and Its Unique Advantage for Discovery of Biomarkers of Heart Disease. In: Tsz Kwong Man, editor. Proteomics - Human Diseases and Protein Functions. InTech, 2012.

[39] Mehra A, Baker CL, Loros JJ, Dunlap JC. Post-translational modifications in circadian rhythms. Trends Biochem Sci 2009, 34: 483–490.

[40] Moller M, Lund-Andersen C, Rovsing L, Sparre T, Bache N, Roepstorff P, *et al.* Proteomics of the photoneuroendocrine circadian system of the brain. Mass Spectrom Rev 2010, 29: 313–325.

[41] Mauvoisin D, Dayon L, Gachon F, Kussmann M. Proteomics and circadian rhythms: It's all about signaling! Proteomics. 2014,

[42] Klei L, Reitz P, Miller M, Wood J, Maendel S, Gross D, *et al.* Heritability of morningness-eveningness and self-report sleep measures in a family-based sample of 521 hutterites. Chronobiol Int 2005, 22: 1041–1054.

[43] Katzenberg D, Young T, Finn L, Lin L, King DP, Takahashi JS, *et al.* A CLOCK polymorphism associated with human diurnal preference. Sleep 1998, 21: 569–576.

[44] Allebrandt KV, Amin N, Muller-Myhsok B, Esko T, Teder-Laving M, Azevedo RV, *et al.* A K(ATP) channel gene effect on sleep duration: from genome-wide association studies to function in Drosophila. Mol Psychiatry 2013, 18: 122–132.

[45] Silver R, Kriegsfeld LJ. Circadian rhythms have broad implications for understanding brain and behavior. Eur J Neurosci 2014, 39: 1866–1880.

[46] Huang W, Ramsey KM, Marcheva B, Bass J. Circadian rhythms, sleep, and metabolism. J Clin Invest 2011, 121: 2133–2141.

[47] Barclay JL, Husse J, Bode B, Naujokat N, Meyer-Kovac J, Schmid SM, *et al.* Circadian desynchrony promotes metabolic disruption in a mouse model of shiftwork. PLoS One 2012, 7: e37150.

[48] Maury E, Ramsey KM, Bass J. Circadian rhythms and

metabolic syndrome: from experimental genetics to human disease. Circ Res 2010, 106: 447–462.

[49] Froy O. Metabolism and circadian rhythms--implications for obesity. Endocr Rev 2010, 31: 1–24.

[50] Nagorny C, Lyssenko V. Tired of diabetes genetics? Circadian rhythms and diabetes: the MTNR1B story? Curr Diab Rep 2012, 12: 667–672.

[51] Swanson GR, Burgess HJ, Keshavarzian A. Sleep disturbances and inflammatory bowel disease: a potential trigger for disease flare? Expert Rev Clin Immunol 2011, 7: 29–36.

[52] Savvidis C, Koutsilieris M. Circadian rhythm disruption in cancer biology. Mol Med 2012, 18: 1249–1260.

[53] Levi F, Schibler U. Circadian rhythms: mechanisms and therapeutic implications. Annu Rev Pharmacol Toxicol 2007, 47: 593–628.

[54] Takeda N, Maemura K. Circadian clock and cardiovascular disease. J Cardiol 2011, 57: 249–256.

[55] Lamont EW, Coutu DL, Cermakian N, Boivin DB. Circadian rhythms and clock genes in psychotic disorders. Isr J Psychiatry Relat Sci 2010, 47: 27–35.

[56] Lamont EW, Legault-Coutu D, Cermakian N, Boivin DB. The role of circadian clock genes in mental disorders. Dialogues Clin Neurosci 2007, 9: 333–342.

[57] Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat Rev Neurosci 2010, 11: 589–599.

[58] Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. Sleep 2007, 30: 873–880.

[59] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA 1989, 262: 1479–1484.

[60] Roane BM, Taylor DJ. Adolescent insomnia as a risk factor for early adult depression and substance abuse. Sleep 2008, 31: 1351–1356.

[61] Shibley HL, Malcolm RJ, Veatch LM. Adolescents with insomnia and substance abuse: consequences and comorbidities SHIBLEY2008. J Psychiatr Pract 2008, 14: 146–153.

[62] Armstrong SM, Cassone VM, Chesworth MJ, Redman JR, Short RV. Synchronization of mammalian circadian rhythms by melatonin. J.Neural Transm.Suppl 1986, 21: 375–394.

[63] de BC, Guardiola-Lemaitre B, Mocaer E, Renard P, Munoz C, Millan MJ. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. Nat Rev Drug Discov 2010, 9: 628–642.

[64] Kasper S, Hajak G, Wulff K, Hoogendijk WJ, Montejo AL, Smeraldi E, *et al.* Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. J Clin Psychiatry 2010, 71: 109–120.

[65] Bellet MM, Vawter MP, Bunney BG, Bunney WE, Sassone-Corsi P. Ketamine influences CLOCK:BMAL1 function leading to altered circadian gene expression. PLoS One 2011, 6: e23982.

[66] Li SX, Liu LJ, Xu LZ, Gao L, Wang XF, Zhang JT, *et al.* Diurnal alterations in circadian genes and peptides in major depressive disorder before and after escitalopram treatment. Psychoneuroendocrinology 2013, 38: 2789–2799.

[67] Roybal K, Theobold D, Graham A, DiNieri JA, Russo SJ, Krishnan V, *et al.* Mania-like behavior induced by disruption of CLOCK. Proc Natl Acad Sci U S A 2007, 104: 6406–6411.

[68] Oliver PL, Sobczyk MV, Maywood ES, Edwards B, Lee S, Livieratos A, *et al.* Disrupted circadian rhythms in a mouse model of schizophrenia. Curr Biol 2012, 22: 314–319.

[69] Gorwood P. Anxiety disorders and circadian rhythms. Medicographia 2012, 34: 289–294.

[70] Wong CC, Schumann G. Integration of the circadian and stress systems: influence of neuropeptides and implications for alcohol consumption. J Neural Transm 2012, 119: 1111–1120.

[71] Landgraf D, McCarthy MJ, Welsh DK. Circadian clock and stress interactions in the molecular biology of psychiatric disorders. Curr Psychiatry Rep 2014, 16: 483.

[72] Doi M, Yujnovsky I, Hirayama J, Malerba M, Tirotta E, Sassone-Corsi P, *et al.* Impaired light masking in dopamine D2 receptor-null mice DOI2006. Nat Neurosci 2006, 9: 732–734.

[73] Clarke TK, Weiss AR, Ferarro TN, Kampman KM, Dackis CA, *et al.* The dopamine receptor D2 (DRD2) SNP rs1076560 is associated with opioid addiction. Ann Hum Genet 2014, 78: 33–39.

[74] Li MD, Burmeister M. New insights into the genetics of addiction. Nat Rev Genet 2009, 10: 225–231.

[75] Wang F, Simen A, Arias A, Lu QW, Zhang H. A large-scale meta-analysis of the association between the ANKK1/DRD2 Taq1A polymorphism and alcohol dependence. Hum Genet 2013, 132: 347–358.

[76] Olfson E, Bierut LJ. Convergence of genome-wide association and candidate gene studies for alcoholism. Alcohol Clin Exp Res 2012, 36: 2086–2094.

[77] Sipila T, Kananen L, Greco D, Donner J, Silander K, Terwilliger JD, *et al.* An association analysis of circadian genes in anxiety disorders. Biol Psychiatry 2010, 67: 1163–1170.

[78] Wing YK, Zhang J, Lam SP, Li SX, Tang NL, Lai KY, *et al.* Familial aggregation and heritability of insomnia in a

community-based study. Sleep Med 2012, 13: 985–990.

[79] McCarren M, Goldberg J, Ramakrishnan V, Fabsitz R. Insomnia in Vietnam era veteran twins: influence of genes and combat experience. Sleep 1994, 17: 456–461.

[80] Watson NF, Goldberg J, Arguelles L, Buchwald D. Genetic and environmental influences on insomnia, daytime sleepiness, and obesity in twins. Sleep 2006, 29: 645–649.

[81] Palagini L, Biber K, Riemann D. The genetics of insomnia--evidence for epigenetic mechanisms? Sleep Med Rev 2014, 18: 225–235.

[82] Manfredi RL, Brennan RW, Cadieux RJ. Disorders of excessive sleepiness: narcolepsy and hypersomnia. Semin Neurol 1987, 7: 250–258.

[83] Buysse DJ. Insomnia. JAMA 2013, 309: 706–716.

[84] Longstreth WT, Jr., Koepsell TD, Ton TG, Hendrickson AF, van BG. The epidemiology of narcolepsy. Sleep 2007, 30: 13–26.

[85] Buhr A, Bianchi MT, Baur R, Courtet P, Pignay V, Boulenger JP, *et al*. Functional characterization of the new human GABA(A) receptor mutation beta3(R192H). Hum Genet 2002, 111: 154–160.

[86] Rye DB, Bliwise DL, Parker K, Trotti LM, Saini P, Fairley J, *et al.* Modulation of vigilance in the primary hypersomnias by endogenous enhancement of GABAA receptors. Sci.Transl. Med. 2012, 4: 161ra151.

[87] Wurtman RJ. Narcolepsy and the hypocretins. Metabolism 2006, 55 (10 Suppl 2): S36–S39.

[88] Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, *et al.* An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. Science 2001, 291: 1040–1043.

[89] Xu Y, Padiath QS, Shapiro RE, Jones CR, Wu SC, Saigoh N, *et al.* Functional consequences of a CKIdelta mutation causing familial advanced sleep phase syndrome. Nature 2005, 434: 640–644.

[90] Punia S, Rumery KK, Yu EA, Lambert CM, Notkins AL, Weaver DR. Disruption of gene expression rhythms in mice lacking secretory vesicle proteins IA-2 and IA-2beta. Am J Physiol Endocrinol Metab 2012, 303: E762–E776.

[91] Zhang EE, Kay SA. Clocks not winding down: unravelling circadian networks. Nat Rev Mol Cell Biol 2010, 11: 764–776.

[92] Byrne EM, Gehrman PR, Medland SE, Nyholt DR, Heath AC, Madden PA, *et al.* A genome-wide association study of sleep habits and insomnia. Am J Med Genet B Neuropsychiatr Genet 2013, 162B: 439–451.

[93] Winkelmann J, Czamara D, Schormair B, Knauf F, Schulte EC, Trenkwalder C, *et al.* Genome-wide association study identifies novel restless legs syndrome susceptibility loci on 2p14 and 16q12.1. PLoS Genet 2011, 7: e1002171.

[94] Schormair B, Kemlink D, Roeske D, Eckstein G, Xiong L, Lichtner P, *et al.* PTPRD (protein tyrosine phosphatase receptor type delta) is associated with restless legs syndrome. Nat Genet 2008, 40: 946–948.

[95] Winkelmann J, Schormair B, Lichtner P, Ripke S, Xiong L, Jalilzadeh S, *et al.* Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet 2007, 39: 1000–1006.

[96] Stefansson H, Rye DB, Hicks A, Petursson H, Ingason A, Thorgeirsson TE, *et al.* A genetic risk factor for periodic limb movements in sleep. N Engl J Med 2007, 357: 639–647.

[97] Hallmayer J, Faraco J, Lin L, Hesselson S, Winkelmann J, Kawashima M, *et al.* Narcolepsy is strongly associated with the T-cell receptor alpha locus. Nat Genet 2009, 41: 708–711.

[98] 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: 807–814.

[99] 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, 147B: 1047–1055.

[100] Kripke DF, Nievergelt CM, Tranah GJ, Murray SS, Rex KM, Grizas AP, *et al.* FMR1, circadian genes and depression: suggestive associations or false discovery? J Circadian Rhythms 2013, 11: 3.

[101] Johansson C, Willeit M, Smedh C, Ekholm J, Paunio T, Kieseppa T, *et al.* Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. Neuropsychopharmacology 2003, 28: 734–739.

[102] Partonen T, Treutlein J, Alpman A, Frank J, Johansson C, Depner M, *et al.* Three circadian clock genes Per2, Arntl, and Npas2 contribute to winter depression. Ann Med 2007, 39: 229–238.

[103] Kovanen L, Saarikoski ST, Haukka J, Pirkola S, Aromaa A, Lonnqvist J, *et al.* Circadian clock gene polymorphisms in alcohol use disorders and alcohol consumption. Alcohol Alcohol 2010, 45: 303–311.

[104] Levran O, Londono D, O'Hara K, Nielsen DA, Peles E, Rotrosen J, *et al.* Genetic susceptibility to heroin addiction: a candidate gene association study. Genes Brain Behav 2008, 7: 720–729.

[105] 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: 701–710.

[106] 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: 1279–1289.

[107] Utge SJ, Soronen P, Loukola A, Kronholm E, Ollila HM, Pirkola S, *et al*. Systematic analysis of circadian genes in a population-based sample reveals association of TIMELESS with depression and sleep disturbance. PLoS One 2010, 5: e9259.

[108] McCarthy MJ, Nievergelt CM, Kelsoe JR, Welsh DK. A survey of genomic studies supports association of circadian clock genes with bipolar disorder spectrum illnesses and lithium response. PLoS One 2012, 7: e32091.

[109] Wetherill L, Agrawal A, Kapoor M, Bertelsen S, Bierut LJ, Brooks A, *et al*. Association of substance dependence phenotypes in the COGA sample. Addict.Biol 2014,

[110] Schosser A, Butler AW, Uher R, Ng MY, Cohen-Woods S, Craddock N, *et al.* Genome-wide association study of co-occurring anxiety in major depression. World J Biol Psychiatry 2013, 14: 611–621.

[111] Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, *et al.* Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet 2013, 45: 984–994.

[112] Trzaskowski M, Eley TC, Davis OS, Doherty SJ, Hanscombe KB, Meaburn EL, *et al.* First genome-wide association study on anxiety-related behaviours in childhood. PLoS One 2013, 8: e58676.

[113] Chen X, Cho K, Singer BH, Zhang H. The nuclear transcription factor PKNOX2 is a candidate gene for substance dependence in European-origin women. PLoS One 2011, 6: e16002.

[114] Etchegaray JP, Lee C, Wade PA, Reppert SM. Rhythmic histone acetylation underlies transcription in the mammalian circadian clock. Nature 2003, 421: 177–182.

[115] Doi M, Hirayama J, Sassone-Corsi P. Circadian regulator CLOCK is a histone acetyltransferase. Cell 2006, 125: 497–508.

[116] Hirayama J, Sahar S, Grimaldi B, Tamaru T, Takamatsu K, Nakahata Y, *et al.* CLOCK-mediated acetylation of BMAL1 controls circadian function. Nature 2007, 450: 1086–1090.

[117] Johansson AS, Brask J, Owe-Larsson B, Hetta J, Lundkvist GB. Valproic acid phase shifts the rhythmic expression of Period2::Luciferase. J Biol Rhythms 2011, 26: 541–551.

[118] Alenghat T, Meyers K, Mullican SE, Leitner K, iji-Adele A, Avila J, *et al.* Nuclear receptor corepressor and histone deacetylase 3 govern circadian metabolic physiology. Nature 2008, 456: 997–1000.

[119] Feng D, Liu T, Sun Z, Bugge A, Mullican SE, Alenghat T, *et al.* A circadian rhythm orchestrated by histone deacetylase 3 controls hepatic lipid metabolism. Science 2011, 331: 1315–1319.

[120] Asher G, Gatfield D, Stratmann M, Reinke H, Dibner C, Kreppel F, *et al.* SIRT1 regulates circadian clock gene expression through PER2 deacetylation. Cell 2008, 134: 317–328.

[121] Gan L, Mucke L. Paths of convergence: sirtuins in aging and neurodegeneration. Neuron 2008, 58: 10–14.

[122] Chang HC, Guarente L. SIRT1 mediates central circadian control in the SCN by a mechanism that decays with aging. Cell 2013, 153: 1448–1460.

[123] Michan S, Li Y, Chou MM, Parrella E, Ge H, Long JM, *et al.* SIRT1 is essential for normal cognitive function and synaptic plasticity. J Neurosci 2010, 30: 9695–9707.

[124] Gao J, Wang WY, Mao YW, Graff J, Guan JS, Pan L, *et al.* A novel pathway regulates memory and plasticity via SIRT1 and miR-134. Nature 2010, 466: 1105–1109.

[125] DiTacchio L, Le HD, Vollmers C, Hatori M, Witcher M, Secombe J, *et al.* Histone lysine demethylase JARID1a activates CLOCK-BMAL1 and influences the circadian clock. Science 2011, 333: 1881–1885.

[126] Bonsch D, Hothorn T, Krieglstein C, Koch M, Nehmer C, Lenz B, *et al.* Daily variations of homocysteine concentration may influence methylation of DNA in normal healthy individuals. Chronobiol Int 2007, 24: 315–326.

[127] Krishna SM, Dear A, Craig JM, Norman PE, Golledge J. The potential role of homocysteine mediated DNA methylation and associated epigenetic changes in abdominal aortic aneurysm formation. Atherosclerosis 2013, 228: 295–305.

[128] Azzi A, Dallmann R, Casserly A, Rehrauer H, Patrignani A, Maier B, *et al.* Circadian behavior is light-reprogrammed by plastic DNA methylation. Nat Neurosci 2014, 17: 377–382.

[129] Massart R, Freyburger M, Suderman M, Paquet J, El HJ, Belanger-Nelson E, *et al.* The genome-wide landscape of DNA methylation and hydroxymethylation in response to sleep deprivation impacts on synaptic plasticity genes. Transl Psychiatry 2014, 4: e347.

[130] Chen R, D'Alessandro M, Lee C. miRNAs are required for generating a time delay critical for the circadian oscillator. Curr Biol 2013, 23: 1959–1968.

[131] Cheng HY, Papp JW, Varlamova O, Dziema H, Russell B, Curfman JP, *et al.* microRNA modulation of circadian-clock period and entrainment. Neuron 2007, 54: 813–829.

[132] varez-Saavedra M, Antoun G, Yanagiya A, Oliva-Hernandez R, Cornejo-Palma D, Perez-Iratxeta C, *et al.* miRNA-132 orchestrates chromatin remodeling and translational control of the circadian clock. Hum Mol Genet 2011, 20: 731–751.

[133] Coon SL, Munson PJ, Cherukuri PF, Sugden D, Rath MF, Moller M, *et al.* Circadian changes in long noncoding RNAs in the pineal gland. Proc Natl Acad Sci U S A 2012, 109: 13319–13324.

[134] Xue Z, Ye Q, Anson SR, Yang J, Xiao G, Kowbel D, *et al.*

Transcriptional interference by antisense RNA is required for circadian clock function. Nature 2014,

[135] Hughes ME, Grant GR, Paquin C, Qian J, Nitabach MN. Deep sequencing the circadianand diurnal transcriptome of Drosophila brain HUGHES2012. Genome Res 2012, 22: 1266–1281.

[136] Johnsson P, Lipovich L, Grander D, Morris KV. Evolutionary conservation of long non-coding RNAs, sequence, structure, function. Biochim Biophys Acta 2014, 1840: 1063–1071.

[137] Pang KC, Frith MC, Mattick JS. Rapid evolution of noncoding RNAs: lack of conservation does not mean lack of function. Trends Genet 2006, 22: 1–5.

[138] Fustin JM, Doi M, Yamaguchi Y, Hida H, Nishimura S, Yoshida M, *et al*. RNA-methylation-dependent RNA processing controls the speed of the circadian clock. Cell 2013, 155: 793–806.

[139] Suter M, Bocock P, Showalter L, Hu M, Shope C, McKnight R, *et al.* Epigenomics: maternal high-fat diet exposure in utero disrupts peripheral circadian gene expression in nonhuman primates. FASEB J 2011, 25: 714–726.

[140] Ciarleglio CM, Axley JC, Strauss BR, Gamble KL, McMahon DG. Perinatal photoperiod imprints the circadian clock CIARLEGLIO2011. Nat Neurosci 2011, 14: 25–27.

[141] Chavez SL, McElroy SL, Bossert NL, De Jonge CJ, Rodriguez MV, Leong DE, *et al*. Comparison of epigenetic mediator expression and function in mouse and human embryonic blastomeres. Hum Mol Genet 2014, 23: 4970–4984.

[142] Moller-Levet CS, Archer SN, Bucca G, Laing EE, Slak A, Kabiljo R, *et al*. Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. Proc Natl Acad Sci U S A 2013, 110: E1132–E1141.

[143] Archer SN, Laing EE, Moller-Levet CS, van d, V, Bucca G, Lazar AS, *et al.* Mistimed sleep disrupts circadian regulation of the human transcriptome. Proc Natl Acad Sci U S A 2014, 111: E682–E691.

[144] Bollati V, Baccarelli A, Sartori S, Tarantini L, Motta V, Rota F, *et al*. Epigenetic effects of shiftwork on blood DNA methylation. Chronobiol Int 2010, 27: 1093–1104.

[145] Dykens E, Shah B. Psychiatric disorders in Prader-Willi syndrome: epidemiology and management. CNS Drugs 2003, 17: 167–178.

[146] Sahoo T, del GD, German JR, Shinawi M, Peters SU, Person RE, *et al.* Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster. Nat Genet 2008, 40: 719–721.

[147] Powell WT, Coulson RL, Crary FK, Wong SS, Ach RA, Tsang P, *et al.* A Prader-Willi locus lncRNA cloud modulates diurnal genes and energy expenditure. Hum Mol Genet 2013, 22: 4318–4328.

[148] Saus E, Soria V, Escaramis G, Vivarelli F, Crespo JM, Kagerbauer B, *et al*. Genetic variants and abnormal processing of pre-miR-182, a circadian clock modulator, in major depression patients with late insomnia. Hum Mol Genet 2010, 19: 4017–4025.

[149] Grennan KS, Chen C, Gershon ES, Liu C. Molecular network analysis enhances understanding of the biology of mental disorders. Bioessays 2014, 36: 606–616.

[150] Hayes KR, Baggs JE, Hogenesch JB. Circadian clocks are seeing the systems biology light. Genome Biol 2005, 6: 219.

[151] Patel VR, Eckel-Mahan K, Sassone-Corsi P, Baldi P. CircadiOmics: integrating circadian genomics, transcriptomics, proteomics and metabolomics. Nat Methods 2012, 9: 772–773.

[152] Ukai H, Ueda HR. Systems biology of mammalian circadian clocks. Annu Rev Physiol 2010, 72: 579–603.

[153] McDonald MJ, Rosbash M. Microarray analysis and organization of circadian gene expression in Drosophila. Cell 2001, 107: 567–578.

[154] Ueda HR. A systems-biological approach in drug discovery for circadian rhythm disorders. Nihon Yakurigaku Zasshi 2002, 120: 37P–40P.

[155] Zvonic S, Ptitsyn AA, Conrad SA, Scott LK, Floyd ZE, Kilroy G, *et al.* Characterization of peripheral circadian clocks in adipose tissues. Diabetes 2006, 55: 962–970.

[156] Oster H, Damerow S, Hut RA, Eichele G. Transcriptional profiling in the adrenal gland reveals circadian regulation of hormone biosynthesis genes and nucleosome assembly genes. J Biol Rhythms 2006, 21: 350–361.

[157] Lemos DR, Downs JL, Urbanski HF. Twenty-four-hour rhythmic gene expression in the rhesus macaque adrenal gland. Mol Endocrinol 2006, 20: 1164–1176.

[158] Zvonic S, Ptitsyn AA, Kilroy G, Wu X, Conrad SA, Scott LK, *et al.* Circadian oscillation of gene expression in murine calvarial bone. J Bone Miner Res 2007, 22: 357–365.

[159] Yang S, Wang K, Valladares O, Hannenhalli S, Bucan M. Genome-wide expression profiling and bioinformatics analysis of diurnally regulated genes in the mouse prefrontal cortex. Genome Biol 2007, 8: R247.

[160] Maret S, Dorsaz S, Gurcel L, Pradervand S, Petit B, Pfister C, *et al.* Homer1a is a core brain molecular correlate of sleep loss. Proc Natl Acad Sci U S A 2007, 104: 20090–20095.

[161] Bray MS, Shaw CA, Moore MW, Garcia RA, Zanquetta MM, Durgan DJ, *et al.* Disruption of the circadian clock within the cardiomyocyte influences myocardial contractile function, metabolism, and gene expression. Am J Physiol Heart Circ Physiol 2008, 294: H1036–H1047.

[162] Kronfeld-Schor N, Einat H. Circadian rhythms and depression: human psychopathology and animal models.

Neuropharmacology 2012, 62: 101–114.
[163] Mendlewicz J, Kerkhofs M. Sleep electroencephalography in depressive illness. A collaborative study by the World Health Organization. Br J Psychiatry 1991, 159: 505–509.
[164] Kupfer DJ. REM latency: a psychobiologic marker for primary depressive disease. Biol Psychiatry 1976, 11: 159–174.
[165] Emens J, Lewy A, Kinzie JM, Arntz D, Rough J. Circadian misalignment in major depressive disorder. Psychiatry Res 2009, 168: 259–261.
[166] Robillard R, Naismith SL, Hickie IB. Recent advances in sleep-wake cycle and biological rhythms in bipolar disorder. Curr Psychiatry Rep 2013, 15: 402.
[167] Plante DT, Winkelman JW. Sleep disturbance in bipolar disorder: therapeutic implications. Am J Psychiatry 2008, 165: 830–843.
[168] Monk TH, Burk LR, Klein MH, Kupfer DJ, Soehner AM, Essex MJ. Behavioral circadian regularity at age 1 month predicts anxiety levels during school-age years. Psychiatry Res 2010, 178: 370–373.
[169] Shibley HL, Malcolm RJ, Veatch LM. Adolescents with insomnia and substance abuse: consequences and comorbidities SHIBLEY2008. J Psychiatr Pract 2008, 14: 146–153.
[170] Lam RW, Levitan RD. Pathophysiology of seasonal affective disorder: a review. J Psychiatry Neurosci 2000, 25: 469–480.
[171] Leibenluft E, Wehr TA. Is sleep deprivation useful in the treatment of depression? Am J Psychiatry 1992, 149: 159–168.
[172] Colombo C, Benedetti F, Barbini B, Campori E, Smeraldi E. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. Psychiatry Res 1999, 86: 267–270.
[173] Iwahana E, Hamada T, Uchida A, Shibata S. Differential effect of lithium on the circadian oscillator in young and old hamsters. Biochem Biophys Res Commun. 2007, 354: 752–756.
[174] 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: e318.
[175] Osland TM, Ferno J, Havik B, Heuch I, Ruoff P, Laerum OD, *et al.* Lithium differentially affects clock gene expression in serum-shocked NIH-3T3 cells. J Psychopharmacol 2011, 25: 924–933.
[176] Demyttenaere K. Agomelatine in treating generalized anxiety disorder. Expert Opin Investig Drugs 2014, 23: 857–864.
[177] Stein DJ, Ahokas A, Marquez MS, Hoschl C, Oh KS, *et al.* Agomelatine in generalized anxiety disorder: an active comparator and placebo-controlled study. J Clin Psychiatry 2014, 75: 362–368.
[178] 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: 571–584.
[179] 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): 201–209.
[180] Broms U, Pennanen M, Patja K, Ollila H, Korhonen T, Kankaanpaa A, *et al.* Diurnal Evening Type is Associated with Current Smoking, Nicotine Dependence and Nicotine Intake in the Population Based National FINRISK 2007 Study. J Addict Res Ther 2012, S2
[181] Adan A. Chronotype and personality factors in the daily consumption of alcohol and psychostimulants. Addiction 1994, 89: 455–462.
[182] Malkoff-Schwartz S, Frank E, Anderson BP, Hlastala SA, Luther JF, Sherrill JT, *et al.* Social rhythm disruption and stressful life events in the onset of bipolar and unipolar episodes. Psychol Med 2000, 30: 1005–1016.
[183] Ashman SB, Monk TH, Kupfer DJ, Clark CH, Myers FS, Frank E, Leibenluft. Relationship between social rhythms and mood in patients with rapid cycling bipolar disorder. Psychiatry Res 1999, 86: 1–8.
[184] Malkoff-Schwartz S, Frank E, Anderson B, Sherrill JT, Siegel L, Patterson D, *et al.* Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes: a preliminary investigation. Arch Gen Psychiatry 1998, 55: 702–707.
[185] Shear MK, Randall J, Monk TH, Ritenour A, Tu X, Frank E, *et al.* Social rhythm in anxiety disorder patients. Anxiety 1994, 1: 90–95.
[186] Cassidy F, Carroll BJ. Seasonal variation of mixed and pure episodes of bipolar disorder. J Affect Disord 2002, 68: 25–31.
[187] Silverstone T, Romans S, Hunt N, McPherson H. Is there a seasonal pattern of relapse in bipolar affective disorders? A dual northern and southern hemisphere cohort study. Br J Psychiatry 1995, 167: 58–60.
[188] Sandyk R, Kanofsky JD. Cocaine addiction: relationship to seasonal affective disorder. Int J Neurosci 1992, 64 (1-4): 195–201.
[189] Nurnberger JI, Jr., Adkins S, Lahiri DK, Mayeda A, Hu K, Lewy A, *et al.* Melatonin suppression by light in euthymic bipolar and unipolar patients. Arch Gen Psychiatry 2000, 57: 572–579.
[190] Lewy AJ, Nurnberger JI, Jr., Wehr TA, Pack D, Becker LE, Powell RL, *et al.* Supersensitivity to light: possible trait marker for manic-depressive illness. Am J Psychiatry 1985, 142: 725–727.
[191] Crofford LJ, Young EA, Engleberg NC, Korszun A, Brucksch CB, McClure LA, *et al.* Basal circadian and pulsatile ACTH

and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. Brain Behav Immun 2004, 18: 314–325.

[192] Lovallo WR. Cortisol secretion patterns in addiction and addiction risk. Int J Psychophysiol 2006, 59: 195–202.

[193] Gonzalez R. The relationship between bipolar disorder and biological rhythms. J Clin Psychiatry 2014, 75: e323–e331.

[194] Sipila T, Kananen L, Greco D, Donner J, Silander K, Terwilliger JD, *et al.* An association analysis of circadian genes in anxiety disorders. Biol Psychiatry 2010, 67: 1163–1170.

[195] Blomeyer D, Buchmann AF, Lascorz J, Zimmermann US, Esser G, Desrivieres S, *et al.* Association of PER2 genotype and stressful life events with alcohol drinking in young adults. PLoS One 2013, 8: e59136.

[196] Shumay E, Fowler JS, Wang GJ, Logan J, ia-Klein N, Goldstein RZ, *et al.* Repeat variation in the human PER2 gene as a new genetic marker associated with cocaine addiction and brain dopamine D2 receptor availability. Transl Psychiatry 2012, 2: e86.

[197] Dong L, Bilbao A, Laucht M, Henriksson R, Yakovleva T, Ridinger M, *et al.* Effects of the circadian rhythm gene period 1 (per1) on psychosocial stress-induced alcohol drinking. Am J Psychiatry 2011, 168: 1090–1098.

[198] Comasco E, Nordquist N, Gokturk C, Aslund C, Hallman J, Oreland L, *et al.* The clock gene PER2 and sleep problems: association with alcohol consumption among Swedish adolescents. Ups J Med Sci 2010, 115: 41–48.

[199] Malison RT, Kranzler HR, Yang BZ, Gelernter J. Human clock, PER1 and PER2 polymorphisms: lack of association with cocaine dependence susceptibility and cocaine-induced paranoia. Psychiatr Genet 2006, 16: 245–249.

[200] Spanagel R, Pendyala G, Abarca C, Zghoul T, Sanchis-Segura C, Magnone MC, *et al.* The clock gene Per2 influences the glutamatergic system and modulates alcohol consumption. Nat Med 2005, 11: 35–42.

[201] Chung S, Lee EJ, Yun S, Choe HK, Park SB, Son HJ, *et al.* Impact of circadian nuclear receptor REV-ERBalpha on midbrain dopamine production and mood regulation. Cell 2014, 157: 858–868.

[202] Spencer S, Falcon E, Kumar J, Krishnan V, Mukherjee S, Birnbaum SG, *et al.* Circadian genes Period 1 and Period 2 in the nucleus accumbens regulate anxiety-related behavior. Eur J Neurosci 2013, 37: 242–250.

[203] Logan RW, Williams WP, III, McClung CA. Circadian rhythms and addiction: mechanistic insights and future directions. Behav.Neurosci. 2014, 128: 387–412.

[204] 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: 43–55.

[205] Akiyama M, Kirihara T, Takahashi S, Minami Y, Yoshinobu Y, Moriya T, *et al.* Modulation of mPer1 gene expression by anxiolytic drugs in mouse cerebellum. Br J Pharmacol 1999, 128: 1616–1622.

[206] Honma K, Honma S. The SCN-independent clocks, methamphetamine and food restriction. Eur J Neurosci 2009, 30: 1707–1717.

[207] Gouin JP, Connors J, Kiecolt-Glaser JK, Glaser R, Malarkey WB, Atkinson C, *et al.* Altered expression of circadian rhythm genes among individuals with a history of depression. J Affect Disord 2010, 126: 161–166.

[208] Zambon AC, McDearmon EL, Salomonis N, Vranizan KM, Johansen KL, Adey D, *et al.* Time- and exercise-dependent gene regulation in human skeletal muscle. Genome Biol 2003, 4: R61.