Sleep Disturbances Linked to Genetic Disorders

Rimawati Tedjasukmana, MD, PhD, RPSGT[a,b,*]

KEYWORDS

• Sleep • Sleep disturbance • Sleep regulation • Genetics • Circadian clock

KEY POINTS

- Sleep is a very complex behavior, regulated by processes that have underlying genetical factors.
- However, up till now, no sleep genes are identified.
- Some sleep disturbances are inherited and have underlying genetic factors.
- Sleep disturbances are caused by the interplay of genetic, neurobiological, and environmental factors.

INTRODUCTION

The understanding of sleep remains elusive, it must have an important purpose, as it survived many evolutionary cycles. Genetic factors are surmised to regulate sleep as evidenced by the heritability of sleep traits, specific genetic polymorphisms of these traits, and existence of familial sleep disorders.[1]

Recent studies in human and animal models have uncovered some genetic factors underlying sleep disturbances. However, there are more questions than answers. Studying the genetic factors underlying sleep disturbance will aid in understanding the underlying mechanism of sleep. Identification of the first familial circadian phenotype (familial advanced sleep phase syndrome [FASPS]) in the late 1990s made it possible to begin genetic mapping and cloning of genes or mutations that have strong effects on human circadian timing, thus starting the quest for understanding the genetics of sleep.[2] In this review, an overview of genetical regulation of sleep and genetic factors underlying several sleep disturbances will be presented.

Genetic Factors of Sleep

Although mechanisms regulating sleep are conserved across species from flies to mammals, studies find that genes regulating sleep remain ambiguous. The probable cause may be that sleep is not one phenotype; there are variabilities in rapid eye movement (REM) and non-REM (NREM) sleep for instance. Diessler and colleagues found more than 300 sleep phenotypes in mice.[3] Sleep is a very complex behavior that is regulated by the circadian rhythm (process C) and homeostatic drive (process S). Process S keeps track of prior sleep-wake history and controls the homeostatic need for sleep, whereas process C sets the time-of-day that sleep preferably occurs.[4]

Circadian rhythm plays a role in sleep regulation, especially in sleep timing. In mammals, the circadian clock genes consist of activators CLOCK and BMAL1, repressors PER (period) and CRY (cryptochrome).[5] The mechanism consists of clock proteins that regulate their own transcription in an autoregulatory feedback loop.[1,6] The degradation of PER and CRY proteins is also regulated by the serine/threonine kinases, casein kinase 1δ (CK1δ) and CK1ε, the F-box proteins, FBXL3 and FBXL21. Several additional genes and feedback loops have been uncovered, increasing the complexity of the mammalian circadian clock gene network. In a second feedback loop, CLOCK and BMAL1 also regulate the transcription of genes for the nuclear receptors REV-ERBα and REV-ERBβ. A third feedback loop is mediated by

[a] Department of Neurology, Universitas Kristen Krida Wacana (Krida Wacana Christian University), Jakarta, Indonesia; [b] Medistra Hospital, Jl. Gatot Subroto Kav 59, Jakarta 12950, Indonesia
* Medistra Hospital, Jl. Gatot Subroto Kav 59, Jakarta 12950, Indonesia
E-mail address: rima.tedja@gmail.com

Sleep Med Clin ■ (2021) ■–■
https://doi.org/10.1016/j.jsmc.2021.10.005

CLOCK/BMAL1-mediated transcription of the gene DBP and the ROR/REV-ERB-mediated transcription of *Nfil3*[7] (**Fig. 1**).

Sleep homeostasis is a process where sleep need accumulates during wakefulness and decreases during sleep. Both circadian rhythm and sleep homeostasis regulate sleep. However, the differences between these 2 processes are not clear cut. The clock genes NPAS2 and CLOCK are sleep-wake driven and not circadian. It was discovered also that sleep deprivation can cause long-term dampening of clock genes expression.[8,9] A variation of PER3 gene is associated with sleep deprivation.[10] Franken and colleagues discovered that PER1, PER2, and DBP are implicated in sleep homeostasis.[4,11] Clock genes also act as sensors of homeostasis in peripheral tissues.[4] These findings suggest that circadian rhythm and sleep homeostasis are closely interlocked. Sleep homeostasis is also caused by build-up and decay of adenosine, which is regulated by 2 genes, the Adora1 and Adk. These genes, respectively, encode the adenosine receptor and its metabolizing enzyme.[12] In conclusion, both processes S and C are genetically regulated.

To make matters even more complicated, other genes also regulate sleep. Voltage-gated potassium channels have a major function in sleep. A genetic screen in *Drosophila* by Cirelli and colleagues identified sleep-inhibiting effects of mutations in the Shaker potassium channel.[13] Also, injury or infection may increase sleep, and some immune genes are involved in sleep promotion. The cytokines IL-1 and TNFα play a role in sleep physiology.[1,14,15] Nuclear factor-κB (NF-κB) increases after sleep deprivation,[16] and Williams and colleagues discovered in *Drosophila* that the immune gene Relish (encoding the Drosophila NF-κB) plays a role in the control of sleep.[17] The EEG features of sleep can also be modulated by the genes that regulate the duration and timing of sleep. DEC2 Y362H mutation carriers showed higher delta power during NREM and less REM sleep compared with the noncarriers.[2] Slow-wave activity in NREM sleep, theta and alpha activity during wakefulness, and REM sleep were all increased in $PER3^{5/5}$ compared with $PER3^{4/4}$ individuals.[10]

Sleep appears to be genetically regulated. However, it is clear from all these observations that despite the increasing number of studies we still cannot elucidate "sleep genes."

Genetic Factors Underlying Narcolepsy and Other Hypersomnia Disorders

Narcolepsy is a chronic neurologic sleep disorder that manifests as a difficulty in maintaining

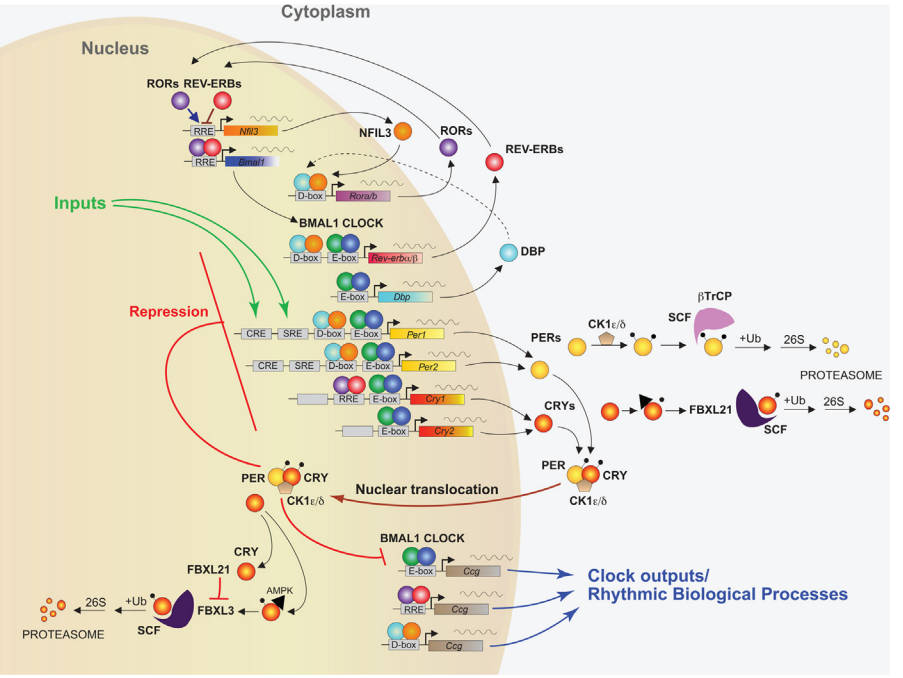

Fig. 1. Components of the mammalian circadian clock. The mammalian clock consisted of 3 feedback loops of clock genes (see text). (*From* Cox KH, Takahashi JS. Circadian clock genes and the transcriptional architecture of the clock mechanism. Journal of Molecular Endocrinology. 2019;63(4):R93-R102. https://doi.org/10.1530/JME-19-0153; with permission.)

continuous wakefulness and sleep. Narcolepsy type 1 (NT1) is characterized by excessive daytime sleepiness, cataplexy, hypnagogic/hypnopompic hallucinations, and sleep paralysis. It is caused by a marked reduction in neurons in the hypothalamus that produce orexin (hypocretin), which is a wakefulness-associated neuropeptide. Narcolepsy type 2 (NT2) has the same symptoms as NT1 excluding cataplexy and has normal cerebrospinal fluid (CSF) hypocretin.[18]

In animal models, this disease can be reproduced by disrupting hypocretin (orexin) transmission by defects in either the hypocretin receptor 2 (HCRTR2) or the hypocretin ligand genes.[19,20] However, it is a different story in human narcolepsy. Although the link between hypocretin deficiency and narcolepsy is consistent in both humans and animal models, the mechanisms underlying the dysfunction are different.[21] Human narcolepsy is sporadic, there is low concordance in monozygotic twins (25%–30%), and only 1% to 2% of first-degree relatives of an NT1 patient have the same disease. However, the relative risk for first-degree family members of patients with NT1 is 10- to 40-fold higher than that in the general population.[22] Narcolepsy is a very complex disease with both genetical and environmental factors. Recent studies have identified susceptibility loci for NT1, but genetical analysis of NT2 is still progressing.[21]

There is hypocretin deficiency in the CSF of NT1 patients. Hypocretin 1 (orexin A) and hypocretin 2 (orexin B) are neuropeptides that control wakefulness and appetite. They are produced by neurons in the lateral hypothalamus.[23,24] However, unlike canine narcolepsy models, most human NT1 patients do not have variants in the prepro-orexin and orexin receptor genes.[21] Loss of hypocretin neurons is probably caused by autoimmune pathology. This fact is apparent by the close association between human leukocyte antigen (HLA) and T cell receptor (TCR) variants of narcolepsy. HLA class II antigens in immune cells present foreign peptides to T cells via TCR. Nearly all NT1 cases carry HLA-DQB1*06:02 gene allele[25] and also 30% to 50% of NT2 cases.[26] The problem is that this is a very common allele in general population and thus is not sufficient as a cause of disease.[27]

Recent data from H1N1 influenza infection and vaccination suggests narcolepsy can develop by interaction between HLA and an immune trigger. Increased prevalence of NT1 was discovered after H1N1 infection in Chinese children[28] and after anti-H1N1 vaccination in European countries.[29,30] On the other hand, genome-wide association (GWA) studies found single-nucleotide polymorphism (SNP) rs5770917 located between CPT1B (carnitine palmitoyltransferase 1B) and CHKB (Choline Kinase B) was associated with NT1. CPT1B regulates β-oxidation, a pathway involved in regulating theta frequency during REM sleep, and CHKB is an enzyme involved in the metabolism of choline, a precursor of the REM- and wake-regulating neurotransmitter acetylcholine.[31] So, either of these genes is a plausible candidate for the development of narcolepsy.

Idiopathic hypersomnia is clinically difficult to differentiate with NT2. The frequency of DQB1*0602 (40%) in patients with idiopathic hypersomnia is intermediate between that in the general population (12%–38%) and that in narcolepsy-cataplexy (70%–100%). Idiopathic hypersomnia may be closely linked to narcolepsy, because a narcolepsy polymorphism located between CPT1B and CHKB may be associated with both narcolepsy and hypersomnia in Japanese cohorts.[32]

Kleine-Levin syndrome is a rare disorder characterized by episodes of hypersomnia and cognitive and behavioral changes. This disorder usually affects adolescent males (frequently reported in Ashkenazi Jews), with some family members are also affected. This data suggests that there is a major susceptibility gene and exposure to an unknown environmental trigger.[1]

Genetics of Circadian Rhythm Sleep-Wake Disorders

Circadian rhythm sleep-wake disorder (CRSWD) is defined as a condition that is "caused by alterations of the circadian time keeping system, its entrainment mechanisms, or a misalignment of the endogenous circadian rhythm and the external environment."[33] One disorder has a well-established cause in clock gene mutations, it is the FASPS.

Advanced sleep phase (ASP) is characterized by a phase-advanced circadian sleep-wake rhythm relative to local solar time. It is suspected to be FASPS when ASP is demonstrated in multiple family members. Advanced sleep-wake phase disorder (ASWPD) is defined as a phase advance of the sleep-wake cycle accompanied by a sleep-related complaint. FASPS is a subtype of ASP and overlaps with ASWPD. Prevalence of ASP is 0.33%, FASPS 0.21%, and ASWPD at least 0.04%. Most cases of young-onset ASP were familial.[34]

FASPS patients tend to sleep and wake very early, their melatonin and core body temperature rhythms are advanced by 4 to 6 hours, and their circadian rhythms are 1 hour shorter compared with conventional sleepers. They have defects in

phosphorylation of PER2, with mutations identified in both PER2 and Casein Kinase 1 genes (CK1δ).[1,35,36] The FASPS hPER2 S662 G mutation resulted in PER2 being hypophosphorylated by CKI in vitro. Xu and colleagues showed that phosphorylation at S662 leads to increased PER2 transcription and suggest that phosphorylation at another site leads to PER2 degradation.[37]

Contrary to ASWPD patients, individuals with delayed sleep-wake phase disorder (DSWPD) have later sleep and wake onset compared with the rest of the population. They are often sleep deprived because sleep onset is delayed by the biological clock, whereas morning waking time is enforced by the alarm clock and social/work responsibilities.[38] It is common in adolescents and young adults with an estimated prevalence of 7% to 16%. Archer and colleagues reported a length polymorphism in PER3 and PER3 promoter linked to DSWPD.[39,40] However, another study by Osland and colleagues was not able to reproduce these findings.[41] Another study discovered that this disorder was caused by mutation in the core circadian clock gene CRY1 that causes its translation product to constitutively repress the circadian transcriptional activators CLOCK and BMAL1.[42]

Genetics of Restless Legs Syndrome

Restless legs syndrome (RLS)/Willis-Ekbom disease is characterized by an urgency to move the legs occurring with abnormal leg sensations. These disturbing sensations can be relieved by movement. These symptoms have a definite circadian presentation; they are worse at night time. The pathophysiology involves iron-dopamine connectivity, iron regulation in the brain, opioid signaling, as well as brain and spinal cord circuitry.[43,44]

Sixty percent of RLS patients reported other family members with this disorder, also there was high concordance (83%) in monozygotic twins.[1,43] GWA studies discovered transcription factors MEIS1, important for nervous system development and affecting dopamine signaling, and BTBD9, which regulates the activity of the striatum.[45,46] MEIS1 is the most important gene involved in RLS pathology. This gene is expressed in dopaminergic neurons of the substantia nigra, the spinal cord, and the red nucleus (regulates coordination of limb movement and that also contains lower iron levels in RLS). MEIS1 is part of a regulatory network that specifies motor neuron pool identity and the pattern of target-muscle connectivity.[1] BTBD9 regulates striatal activity. Recent studies suggest that changes in the striatum may underlie the pathogenesis of RLS.[47] Brain imaging studies show decreased striatal dopamine transporter[48] and D_2 dopamine receptor binding potential.[49] Also, this gene is associated with periodic limb movement in sleep, inferring that it is important for the motor symptoms of RLS.[50]

GWA studies also discovered a third locus containing the genes encoding mitogen-activated protein kinase MAP2K5 and the transcription factor SKOR1(LBXCOR1) on chromosomes 2p, 6p, and 15q, respectively.[45] SKOR1 is expressed selectively in a subset of dorsal horn interneurons in the developing spinal cord, which relay pain and touch. This locus may contribute to the sensory component of RLS by affecting modulation of sensory and pain inputs.

Genetics of Insomnia

Insomnia is characterized with persistent difficulty in initiating or maintaining sleep, with corresponding daytime dysfunction. It occurs in 10% to 20% of the general population. Insomnia increases the risk of developing anxiety disorders, alcohol abuse, major depression, and cardiometabolic disease.[51] Insomnia runs in families and has higher concordance in monozygotic twins.[1]

GWA studies identified 57 loci for self-reported insomnia symptoms in the UK Biobank, some of them are MEIS1, CYCL1, TMEM132E, and SCFD2. There was evidence of shared genetic factors between frequent insomnia symptoms and RLS, aging, cardiometabolic, behavioral, psychiatric, and reproductive traits. This study also found a possible causal link between insomnia symptoms and coronary artery disease, depressive symptoms and subjective well-being.[51]

Fatal familial insomnia (FFI) is a rare disorder characterized by severe sleep disorder, dysautonomia, motor signs, and abnormal behavior. Primary atrophy of selected thalamic nuclei and inferior olives is usually found in this disorder, and expansion to other brain regions with disease progression. It is an autosomal dominant inherited prion disease caused by D178N mutation in the prion protein gene (*PRNP* D178N) accompanied by the presence of a methionine at the codon 129 polymorphic site on the mutated allele.[52,53] Loss of sleep, sympathetic hyperactivity, and flattening of vegetative and hormonal circadian oscillations characterize FFI. These symptoms resulted from homeostatic imbalance caused by the interruption of the thalamocortical limbic circuits, the phylogenetically most advanced structures involved in the control of the sleep-wake cycle and the body's homeostasis.[54]

Short sleeper is usually classified under the heading of insomnia as isolated symptoms and normal variants.[33] Familial natural short sleeper is an extreme early bird phenotype. Similar to individuals with FASPS, they wake up at an extremely early hour in the morning. However, their sleep onset time was comparable to conventional sleepers, thus shortening their total sleep duration by 2 hours each day compared to conventional sleepers. Their sleep time requirement is approximately 6 hours.[38,55] These individuals have a mutation in DEC2, which plays a role in circadian rhythm (as a repressor of CLOCK/BMAL activity[55]) and act as a transcriptional repressor of hypocretin (Hcrt) encoding the neuropeptides HCRT1 and 2[55–57].

Genetics of Sleep-Related Breathing Disorders

Sleep-related breathing disorders (SRBDs) are characterized by abnormalities of respiration during sleep. They may experience repetitive episodes of decreased or arrested respiratory airflow during sleep.[33,58] SRBDs include obstructive sleep apnea (OSA) disorders, central sleep apnea disorders, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders.[33]

OSA is a syndrome characterized by repetitive upper airway obstruction caused by reduced patency of the upper airway during sleep. OSA is heritable, because first-degree relatives of an OSA patient are more likely to snore or have observed apneas, after controlling for obesity, age, and gender.[59] There is evidence of both direct genetic contributions to OSA susceptibility and indirect contributions via "intermediate" phenotypes such as obesity, craniofacial structure, neurologic control of upper airway muscles and of sleep and circadian rhythm.[60] Approximately 40% of the variance in the apnea-hypopnea index may be explained by familial factors.[61] Studies in twin and family suggest that ventilatory responsiveness to either hypoxemia or hypercapnia, obesity, upper airway dimension, and craniofacial morphology are also under a high degree of genetic control.[62–65]

Despite the evidence of heritability, no risk locus for OSA has reached a genome-wide level of significance. Some studies identified candidate genes for OSA, they are associated with inflammation, hypoxia signaling, and sleep pathways.[58] Polymorphism in the angiopoietin-2 gene (ANGPT2),[66] TNF-α gene,[67] prostaglandin E2 receptor (PTGER3) gene, and lysophosphatidic acid receptor 1 (LPAR1) gene, G-protein receptor gene (GPR83), β-arrestin 1 (ARRB1) gene, an important regulator of hypoxia-inducible factor 1 alpha (HIF-1α), were associated with OSA.[60] In conclusion, OSA is a complex disease, it is probably caused by a combination of many genetic and environmental factors.

Congenital central hypoventilation syndrome (CCHS) or Ondine's curse is a life-threatening disorder involving an impaired ventilatory response to hypercarbia and hypoxemia. It is characterized by alveolar hypoventilation and autonomic dysregulation. Mutations in the paired-like homeobox 2B (PHOX2B) gene underly CCHS. PHOX2B is a master gene for the formation and/or function of the neuronal network for autonomous control of ventilation.[68,69]

Genetics of Sleep Disturbance in Psychiatric Disorders

SNPs in core circadian clock genes have been associated with psychiatric disorders. Several studies have highlighted that circadian clock genes may have a more widespread physiologic effect on cognition, mood, and reward-related behaviors.[70] An SNP in the 3-flanking region of the Clock gene (3111 T to C) is associated with a higher recurrence rate of bipolar episodes. This SNP was also associated in bipolar disorder with sleep problems (insomnia and decreased need for sleep).[71] Several SNPs in the Clock gene (3117 G to T, 3125 A to G) have been reported to be associated with major depression and sleep disturbances.[70] Schizophrenia patients presented disruptions in diurnal rhythms of the expression of PER1, PER2, PER3, and NPAS2 in white blood cells,[72] also a loss of rhythmic expression of CRY1 and PER2 in fibroblasts.[73] Mice deficient for CRY1 and 2 proteins show an abnormally high level of anxiety.[74] In conclusion, the effects resulting from altered clock genes may play a role in sleep problems and the emergence of symptoms present in certain psychiatric disorders.

Anxiety, stress, and depressive symptoms are often associated with insomnia. Insomnia symptoms are associated with MEIS1 in animal models, it is located near TMEM132E and CYCL1. TMEM132E is a gene family with roles in brain development, panic/anxiety, and bipolar disorder, suggesting a link between insomnia symptoms and an underlying broader sensitivity to anxiety and stress. CYCL1 is a locus previously associated with alcohol dependence comorbid with depressive symptoms.[75]

Symptoms in depression include early morning awakenings and fatigue, these features also indicate disturbed sleep. Neurotransmitters involved in depression are also linked to sleep regulation,

Table 1
Neurodevelopmental syndromes and associated sleep disturbances

Syndromes	SRBD	Insomnia	EDS	Sleep Enuresis	Sleep Bruxism
Angelman	+	+	+	+	+
CHARGE	+	–	-	-	-
Cornelia de Lange	+	+	+	-	-
Cri du Chat	–	–	-	-	-
Down	+	+	+	+	+
Fragile X	+	+	+	+	+
Hurler	+	–	-	-	-
Jacobsen	–	–	-	-	-
Juvenile Neuronal Ceroid Lipofuscinosis	–	–	-	-	-
Mucopolysaccharidoses	+	–	-	-	-
Neurofibromatosis	+	+	+	-	-
Prader-Willi	+	+	+	+	
Rett	+	+	+	-	+
Smith-Magenis	–	+	+	-	-
Smith-Lemli-Opitz	–	–	-	-	-
Tuberous Sclerosis Complex	–	+	+	-	-
Williams	+	+	+	+	+

Abbreviations: EDS, excessive daytime sleepiness; SRBD, sleep-related breathing disorder.
Data from Agar G, Brown C, Sutherland D, Coulborn S, Oliver C, Richards C. Sleep disorders in rare genetic syndromes: a meta-analysis of prevalence and profile. Mol Autism. 2021;12(1):18. https://doi.org/10.1186/s13229-021-00426-w [81]

including serotonergic and glutamatergic neurotransmission and the hypothalamic-pituitary-adrenal axis. GWA studies from Finland found suggestive associations in women for GAD1, GRIA3, and BDNF with depression accompanied by fatigue, and for CRHR1 with depression accompanied by early morning awakenings.[76]

Almost 80% of schizophrenic patients have sleep disturbance, which are associated with greater symptom severity, increased relapse rates, worse prognoses, and a diminished quality of life.[77] These sleep disturbances may be caused by exogenous effects of psychoactive agents (psychotropic medications, alcohol, illegal substances) or the endogenous effects of disease-related pathophysiological processes on sleep continuity and architecture. Schizophrenic patients report various sleep disorders, mainly insomnia, RLS, and OSA syndrome.[78] Several genetic polymorphisms were associated with schizophrenia-related sleep disorders. Antipsychotic-induced RLS was linked to polymorphisms located on CLOCK (Circadian Locomotor Output Cycles Kaput), BTBD9 (BTB Domain Containing 9), GNB3 (G Protein Subunit Beta 3), and TH (Tyrosine Hydroxylase) genes. Clozapine-induced somnolence was correlated with polymorphisms of HNMT (histamine N-methyltransferase) gene, whereas insomnia symptoms were associated with polymorphisms of the MTNR1 (Melatonin Receptor 1A) gene.[79]

Sleep Disturbance in Neurodevelopmental Disorders

Sleep disturbances are extremely prevalent in children with neurodevelopmental disorders compared with typically developing children. The diagnostic criteria for many neurodevelopmental disorders include sleep disturbances. Sleep disturbance in this population is often multifactorial and caused by the interplay of genetic, neurobiological, and environmental overlap. These disturbances often present either as insomnia or hypersomnia.[80] Insomnia was reported in most syndromes, but it was not associated with specific genetic risk.[81] **Table 1** lists the neurodevelopmental syndromes and their associated sleep disturbances.

SUMMARY

Sleep is a very complex behavior that is influenced by genetic and environmental factors. We still have

Table 2
Genes associated with sleep disorders

Sleep Disorder	Gene
Hypersomnia	
• Narcolepsy	Hypocretin receptor 2 (HCRTR2) or the hypocretin ligand genes (animal models) HLA-DQB1*06:02 gene allele (human) SNP rs5770917 located between CPT1B (carnitine palmitoyltransferase 1B) and CHKB (Choline Kinase B)
• Idiopathic Hypersomnia	HLA-DQB1*06:02 Polymorphism located between CPT1B and CHKB
CRSWD	
• ASWPD	PER2 S662G mutation (in FASPS)
• DSWPD	PER3 and PER3 promoter, CRY1
Restless Legs Syndrome	MEIS1, BTBD9 MAP2K5 and SKOR1(LBXCOR1)
Insomnia	
• Insomnia	MEIS1, CYCL1, TMEM132E, SCFD2
• FNSS	DEC2
SRBD	
• OSA	Angiopoietin-2 gene (ANGPT2), TNF-α gene, prostaglandin E2 receptor (PTGER3) gene, lysophosphatidic acid receptor 1 (LPAR1) gene, G-protein receptor gene (GPR83), β-arrestin 1 (ARRB1) gene
• CCHS	Paired-like homeobox 2B (PHOX2B)
Psychiatric disorder	
• Bipolar disorder	SNP in the 3-flanking region of the Clock gene (3111 T to C), TMEM132 E
• Major depressive disorder	SNPs in the Clock gene (3117 G to T, 3125 A to G), GAD1, GRIA3, BDNF
• Schizophrenia	PER1, PER2, PER3, CRY1, NPAS2, MTNR1 (Melatonin Receptor 1A)
• Anxiety	CRY1, CRY2, TMEM132E
• Alcohol dependence comorbid with depressive symptoms	CYCL1

Abbreviations: ASWPD, advanced sleep-wake phase disorder; CCHS, congenital central hypoventilation syndrome; CRSWD, circadian rhythm sleep-wake disorder; DSWPD, delayed sleep-wake phase disorder; FNSS, familial natural short sleeper; OSA, obstructive sleep apnea; SRDB, sleep-related breathing disorder.

not discovered sleep genes. Many sleep disturbances have underlying genetic factors, but most are caused by the interplay between genetical, environmental, and biological factors. Table 2 lists sleep disorders and their underlying genetic basis. Some sleep disturbances have polymorphisms in the circadian clock. Moreover, sleep is still an expanding field, there is still a lot more to be

discerned. Understanding the genetic factors underlying sleep disturbance may help us to discover the mechanisms of sleep.

CLINICS CARE POINTS

- Recent studies in humans and animal models have uncovered some genetic factors underlying sleep disturbances.
- Sleep is a very complex behavior that is, regulated by circadian rhythm, homeostatic drive, and other processes, all of which have genetic regulation.
- Many sleep disturbances have underlying genetic factors, some caused by polymorphisms of the circadian clock.
- However, most sleep disturbances mechanisms are caused by interaction between genetical, biological and environmental factors.

DISCLOSURE

The author has nothing to disclose.

REFERENCES

1. Sehgal A, Mignot E. Genetics of sleep and sleep disorders. Cell 2011;146(2):194–207.
2. Shi G, Wu D, Ptáček LJ, et al. Human genetics and sleep behavior. Curr Opin Neurobiol 2017;44:43–9.
3. Diessler S, Jan M, Emmenegger Y, et al. A systems genetics resource and analysis of sleep regulation in the mouse. PLoS Biol 2018;16(8):e2005750.
4. Franken P. A role for clock genes in sleep homeostasis. Curr Opin Neurobiol 2013;23(5):864–72.
5. Laposky A, Easton A, Dugovic C, et al. Deletion of the mammalian circadian clock gene BMAL1/Mop3 alters baseline sleep architecture and the response to sleep deprivation. Sleep 2005;28(4):395–409.
6. Zheng X, Sehgal A. Probing the relative importance of molecular oscillations in the circadian clock. Genetics 2008;178(3):1147–55.
7. Cox KH, Takahashi JS. Circadian clock genes and the transcriptional architecture of the clock mechanism. J Mol Endocrinol 2019;63(4):R93–102.
8. Jan M, O'Hara BF, Franken P. Recent advances in understanding the genetics of sleep. F1000Res 2020;9. https://doi.org/10.12688/f1000research.22028.1.
9. Hor CN, Yeung J, Jan M, et al. Sleep–wake-driven and circadian contributions to daily rhythms in gene expression and chromatin accessibility in the murine cortex. Proc Natl Acad Sci U S A 2019;116(51):25773–83.
10. Viola AU, Archer SN, James LM, et al. PER3 polymorphism predicts sleep structure and waking performance. Curr Biol 2007;17(7):613–8.
11. Franken P, Thomason R, Heller HC, et al. A non-circadian role for clock-genes in sleep homeostasis:a strain comparison. BMC Neurosci 2007;8(1):87.
12. Greene RW, Bjorness TE, Suzzuki A. The adenosine-mediated, neuronal-glial, homeostatic sleep response. Curr Opin Neurobiol 2017;44:236–42.
13. Cirelli C, Bushey D, Hill S, et al. Reduced sleep in Drosophila Shaker mutants. Nature 2005;434(7037):1087–92.
14. Imeri L, Opp MR. How (and why) the immune system makes us sleep. Nat Rev Neurosci 2009;10(3):199–210.
15. Asif N, Iqbal R, Nazir CF. Human immune system during sleep. Am J Clin Exp Immunol 2017;6(6):92–6.
16. Chen Z, Gardi J, Kushikata T, et al. Nuclear factor-κB-like activity increases in murine cerebral cortex after sleep deprivation. Am J Physiol 1999;276(6):R1812–8.
17. Williams JA, Sathyanarayanan S, Hendricks JC, et al. Interaction between sleep and the immune response in Drosophila: a role for the NFκB relish. Sleep 2007;30(4):389–400.
18. Ruoff C, Rye D. The ICSD-3 and DSM-5 guidelines for diagnosing narcolepsy: clinical relevance and practicality. Curr Med Res Opin 2016;32(10):1611–22.
19. Lin L, Faraco J, Li R, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 1999;98(3):365–76.
20. Chemelli RM, Willie JT, Sinton CM, et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 1999;98(4):437–51.
21. Miyagawa T, Tokunaga K. Genetics of narcolepsy. Hum Genome Var 2019;6(1):1–8.
22. Mignot E. Genetic and familial aspects of narcolepsy. Neurology 1998;50(2 Suppl 1):S16–22.
23. Sakurai T, Amemiya A, Ishii M, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 1998;92(4):573–85.
24. Sakurai T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nat Rev Neurosci 2007;8(3):171–81.
25. Mignot E, Hayduk R, Black J, et al. HLA DQB1*0602 is associated with cataplexy in 509 narcoleptic patients. Sleep 1997;20(11):1012–20.
26. Miyagawa T, Toyoda H, Kanbayashi T, et al. An association analysis of HLA-DQB1 with narcolepsy without cataplexy and idiopathic hypersomnia with/without long sleep time in a Japanese population. Hum Genome Variation 2015;2(1):1–4.

27. Mignot E, Lin L, Rogers W, et al. Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. Am J Hum Genet 2001;68(3):686–99.
28. Han F, Lin L, Warby SC, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. Ann Neurol 2011;70(3):410–7.
29. Nohynek H, Jokinen J, Partinen M, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS One 2012;7(3):e33536.
30. Dauvilliers Y, Arnulf I, Lecendreux M, et al. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. Brain 2013;136(8):2486–96.
31. Miyagawa T, Kawashima M, Nishida N, et al. Variant between CPT1B and CHKB associated with susceptibility to narcolepsy. Nat Genet 2008;40(11):1324–8.
32. Miyagawa T, Honda M, Kawashima M, et al. Polymorphism located between CPT1B and CHKB, and HLA-DRB1*1501-DQB1*0602 haplotype confer susceptibility to CNS hypersomnias (essential hypersomnia). PLOS ONE 2009;4(4):e5394.
33.. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd edition. Darien (IL): American Academy of Sleep Medicine; 2014.
34. Curtis BJ, Ashbrook LH, Young T, et al. Extreme morning chronotypes are often familial and not exceedingly rare: the estimated prevalence of advanced sleep phase, familial advanced sleep phase, and advanced sleep–wake phase disorder in a sleep clinic population. Sleep 2019;42(10):zsz148.
35. Toh KL, Jones CR, He Y, et al. An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. Science 2001;291(5506):1040–3.
36. Xu Y, Padiath QS, Shapiro RE, et al. Functional consequences of a CKIδ mutation causing familial advanced sleep phase syndrome. Nature 2005;434(7033):640–4.
37. Xu Y, Toh KL, Jones CR, et al. Modeling of a human circadian mutation yields insights into clock regulation by PER2. Cell 2007;128(1):59–70.
38. Jones CR, Huang AL, Ptáček LJ, et al. Genetic basis of human circadian rhythm disorders. Exp Neurol 2013;243:28–33.
39. Archer SN, Robilliard DL, Skene DJ, et al. A length polymorphism in the circadian clock gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. Sleep 2003;26(4):413–5.
40. Archer SN, Carpen JD, Gibson M, et al. Polymorphism in the PER3 promoter associates with diurnal preference and delayed sleep phase disorder. Sleep 2010;33(5):695–701.
41. Osland TM, Bjorvatn BR, Steen VM, et al. Association study of a variable-number tandem repeat polymorphism in the clock gene PERIOD3 and chronotype in Norwegian university students. Chronobiol Int 2011;28(9):764–70.
42. Patke A, Murphy PJ, Onat OE, et al. Mutation of the human circadian clock gene CRY1 in familial delayed sleep phase disorder. Cell 2017;169(2):203–15.e13.
43. Salas RE, Gamaldo CE, Allen RP. Update in restless legs syndrome. Curr Opin Neurol 2010;23(4):401–6.
44. Gonzalez-Latapi P, Malkani R. Update on restless legs syndrome: from mechanisms to treatment. Curr Neurol Neurosci Rep 2019;19(8):54.
45. Winkelmann J, Schormair B, Lichtner P, et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet 2007;39(8):1000–6.
46. Lyu S, Xing H, DeAndrade MP, et al. The Role of BTBD9 in Striatum and Restless Legs Syndrome. eNeuro 2019;6(5). ENEURO.0277-19.2019.
47. Rizzo G, Li X, Galantucci S, et al. Brain imaging and networks in restless legs syndrome. Sleep Med 2017;31:39–48.
48. Earley CJ, Kuwabara H, Wong DF, et al. The dopamine transporter is decreased in the striatum of subjects with restless legs syndrome. Sleep 2011;34(3):341–7.
49. Michaud M, Soucy J-P, Chabli A, et al. SPECT imaging of striatal pre- and postsynaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. J Neurol 2002;249(2):164–70.
50. Stefansson H, Rye DB, Hicks A, et al. A genetic risk factor for periodic limb movements in sleep. N Engl J Med 2007;357(7):639–47.
51. Lane JM, Jones SE, Dashti HS, et al. Biological and clinical insights from genetics of insomnia symptoms. Nat Genet 2019;51(3):387–93.
52. Llorens F, Zarranz J-J, Fischer A, et al. Fatal familial insomnia: clinical aspects and molecular alterations. Curr Neurol Neurosci Rep 2017;17(4):30.
53. Medori R, Tritschler HJ, LeBlanc A, et al. Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. N Engl J Med 1992;326(7):444–9.
54. Cortelli P, Gambetti P, Montagna P, et al. Fatal familial insomnia: clinical features and molecular genetics. J Sleep Res 1999;8(Suppl 1):23–9.
55. He Y, Jones CR, Fujiki N, et al. The transcriptional repressor DEC2 regulates sleep length in mammals. Science 2009;325(5942):866–70.
56. Honma S, Kawamoto T, Takagi Y, et al. Dec1 and Dec2 are regulators of the mammalian molecular clock. Nature 2002;419(6909):841–4.
57. Hirano A, Hsu P-K, Zhang L, et al. DEC2 modulates orexin expression and regulates sleep. Proc Natl Acad Sci U S A 2018;115(13):3434–9.
58. Tanizawa K, Chin K. Genetic factors in sleep-disordered breathing. Respir Investig 2018;56(2):111–9.

59. Redline S, Tosteson T, Tishler PV, et al. Studies in the genetics of obstructive sleep apnea. Familial aggregation of symptoms associated with sleep-related breathing disturbances. Am Rev Respir Dis 1992; 145(2 Pt 1):440–4.
60. Mukherjee S, Saxena R, Palmer LJ. The genetics of obstructive sleep apnoea. Respirology 2018;23(1): 18–27.
61. Redline S, Tishler PV. The genetics of sleep apnea. Sleep Med Rev 2000;4(6):583–602.
62. Patel SR, Frame JM, Larkin EK, et al. Heritability of upper airway dimensions derived using acoustic pharyngometry. Eur Respir J 2008;32(5):1304–8.
63. Herrera BM, Lindgren CM. The genetics of obesity. Curr Diab Rep 2010;10(6):498–505.
64. Roosenboom J, Hens G, Mattern BC, et al. Exploring the underlying genetics of craniofacial morphology through various sources of knowledge. Biomed Res Int 2016;2016:3054578.
65. Weil JV. Variation in human ventilatory control—genetic influence on the hypoxic ventilatory response. Respir Physiol Neurobiol 2003;135(2):239–46.
66. Wang H, Cade BE, Chen H, et al. Variants in angiopoietin-2 (ANGPT2) contribute to variation in nocturnal oxyhaemoglobin saturation level. Hum Mol Genet 2016;25(23):5244–53.
67. Bhushan B, Guleria R, Misra A, et al. TNF-alpha gene polymorphism and TNF-alpha levels in obese Asian Indians with obstructive sleep apnea. Respir Med 2009;103(3):386–92.
68. Amiel J, Laudier B, Attié-Bitach T, et al. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene PHOX2B in congenital central hypoventilation syndrome. Nat Genet 2003;33(4): 459–61.
69. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al. An official ATS clinical policy statement: congenital central hypoventilation syndrome. Am J Respir Crit Care Med 2010;181(6):626–44.
70. Charrier A, Olliac B, Roubertoux P, et al. Clock genes and altered sleep–wake rhythms: their role in the development of psychiatric disorders. Int J Mol Sci 2017;18(5):938.
71. Benedetti F, Dallaspezia S, Fulgosi MC, 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.
72. Sun H-Q, Li S-X, Chen F-B, et al. Diurnal neurobiological alterations after exposure to clozapine in first-episode schizophrenia patients. Psychoneuroendocrinology 2016;64:108–16.
73. Johansson A-S, Owe-Larsson B, Hetta J, et al. Altered circadian clock gene expression in patients with schizophrenia. Schizophr Res 2016;174(1–3): 17–23.
74. De Bundel D, Gangarossa G, Biever A, et al. Cognitive dysfunction, elevated anxiety, and reduced cocaine response in circadian clock-deficient cryptochrome knockout mice. Front Behav Neurosci 2013;7. https://doi.org/10.3389/fnbeh.2013.00152.
75. Lane JM, Liang J, Vlasac I, et al. Genome-wide association analyses of sleep disturbance traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits. Nat Genet 2017;49(2):274–81.
76. Utge S, Soronen P, Partonen T, et al. A population-based association study of candidate genes for depression and sleep disturbance. Am J Med Genet B Neuropsychiatr Genet 2010;153B(2):468–76.
77. Afonso P, Brissos S, Figueira ML, et al. Schizophrenia patients with predominantly positive symptoms have more disturbed sleep-wake cycles measured by actigraphy. Psychiatry Res 2011; 189(1):62–6.
78. Kaskie RE, Graziano B, Ferrarelli F. Schizophrenia and sleep disorders: links, risks, and management challenges. Nat Sci Sleep 2017;9:227–39.
79. Assimakopoulos K, Karaivazoglou K, Skokou M, et al. Genetic variations associated with sleep disorders in patients with schizophrenia: a systematic review. Medicines (Basel) 2018;5(2):27.
80. Robinson-Shelton A, Malow BA. Sleep disturbances in neurodevelopmental disorders. Curr Psychiatry Rep 2015;18(1):6.
81. Agar G, Brown C, Sutherland D, et al. Sleep disorders in rare genetic syndromes: a meta-analysis of prevalence and profile. Mol Autism 2021;12(1):18.