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Genetics of the sleep-wake cycle and its disorders

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Abstract

The sleep-wake cycle is under the control of the circadian clock. Recent advances in rhythm biology have identified molecular clocks and their key regulating genes. Circadian clock genes (*Clock*, *Per*) were first isolated in *Drosophila*, and their homologous counterparts have been found in mammals. Some of the circadian master genes have been shown to influence sleeping behavior. For instance, a point mutation in a human clock gene (*Per2*) was shown to produce the rare advanced sleep phase syndrome, whereas a functional polymorphism in *Per3* is associated with the more frequent delayed sleep phase syndrome. Furthermore, a study examining the association between *Clock* gene polymorphisms and insomnia revealed a higher recurrence of initial, middle, and terminal insomnia in patients homozygous for the *Clock* genotype. Other genes have been shown to contribute to sleep pathologies. A point mutation in the prion protein gene appears to be the cause of fatal familial insomnia. A missense mutation has been found in the gene encoding the GABA-A β 3 subunit in a patient with chronic insomnia. In both animal models and humans, a deficiency in the hypocretin/orexin system was proposed to be responsible for narcolepsy. Selective destruction of hypocretin neurons is the most probable culprit in humans. These findings suggest that the genetic contribution to sleep disorders and wake determinants is more important than originally thought. Beyond sleep, light/dark cycles and sleep deprivation appear also to be associated with eating habits, and epidemics of obesity have to be evaluated in the context of shortened sleep duration.

1. Introduction

A strong genetic basis of normal sleep has been established in both humans and animals. The genetic inheritance of sleep traits in animals was shown in the early 1970s by cross-breeding mouse strains, and several loci found to be involved in sleep regulation have been mapped in the last few years [1-4]. In humans, studies on families and twins have indicated the important influence of genetic factors [5]. Recent linkage and association studies have resulted in the identification of gene mutations, gene localizations, or evidence of susceptibility genes in several sleep disorders.

In this review, we will focus on new gene discoveries in animal models and the genetic dissection of sleep disorders as a promising approach to understanding the complexity of normal and pathologic sleep. We will also examine the genetic regulation of circadian rhythms and its impact on mood disorders while reflecting on new knowledge of its metabolic consequences for energy intake and potentially obesity.

2. Circadian rhythm

The Latin words *circa diem* (meaning about a day), which became the word circadian, represent a cycle with a period length (τ) of approximately 24 hours. Demonstrated initially in the pineal gland for melatonin secretion and its nocturnal surges [6,7], it is now apparent that whereas central nervous system suprachiasmatic nuclei are major controllers of the circadian cycle, peripheral tissues are also able to express cycling functions with or without external cues, such as light sensitivity, and obey endogenous biologic clocks [6]. Extremes of period lengths (τ), such as of ultradian rhythms of heartbeats, range from about 1 second in humans to a much shorter time in rodents: 400 and 600 heartbeats per minute in rats and mice, respectively. Other periodicities of infradian rhythms, such as the female estrous cycles, span about 1 month, but may be extended by external light to several months, eg, in Inuit living in subarctic areas. Generally, these cycles are called biological clocks, and their genetics is now being uncovered. Although often very subtle, some biological clocks have highly measurable components, such as the circannual sexual cycle of Siberian hamsters where males manifest 20-fold oscillations of testicular weight controlled by seasonal changes in melatonin secretion [8]. In general, to be considered real biological clocks, these processes have to

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continue to oscillate, even in the absence of external time cues, such as temporal changes in light intensity, at least for a defined adaptation period [6].

3. Circadian clock genes

Sleep occupies about one third of our life. Total sleep deprivation can be fatal, and even partial sleep deprivation can have serious health consequences. Sleep is tightly regulated and gated by the circadian system, which ensures that it occurs at the appropriate time of day.

The circadian system is a good example of how a complex phenomenon can be dissected into its individual genetic factors. Starting with the discovery of the *Period* (*per*) gene in *Drosophila* [9] and mutagenesis studies in flies and mice, at least 10 genes whose mutations critically affect circadian rhythms have been identified [6]. Core circadian clock genes are defined as genes whose protein products are necessary components for the generation and regulation of circadian rhythms, ie, proteins that form the primary molecular circadian oscillatory mechanism within the individual cells of organisms [10].

In mammals, 2 core clock genes, circadian locomotor output cycle kaput (*Clock*) and *Bmal1* (*Mop3*) encode proteins that are members of the basic helix-loop-helix (b-HLH)-period-Arnt-Single-minded (PAS) transcription factor family. Whereas *Clock* messenger RNA and protein are constitutively expressed in the suprachiasmatic nucleus, *Bmal1* transcript levels peak in the middle of the circadian night. CLOCK and BMAL1 proteins heterodimerize in the cytoplasm to form a complex that, after translocation to the nucleus, activates the transcription of target genes containing E-box cis-regulatory enhancer sequences. Important targets for the CLOCK-BMAL1 complex are core clock genes. These include the *Period* genes (*Per1*, *Per2*, and *Per3*), paralogous members of the PAS protein family, and 2 Cryptochrome genes (*Cry1* and *Cry2*). PER, CRYs, and other proteins form a heteromultimeric complex that translocates to the nucleus and directly inhibits transcriptional activity of the CLOCK-BMAL1 complex, thereby lowering Per and Cry messenger RNA levels. Thus, it is the daily transcriptional activity of CLOCK-BMAL1 heterodimers that forms the positive feedback loop of the mammalian molecular clock. It is extremely critical in establishing the rhythm, and represents an important point for regulation by CRY-PER complexes. The cessation of CLOCK-BMAL1–mediated transcription by CRYs and associated proteins, directly inhibiting their own transcription, establishes the negative feedback loop. In a simplified model of the mammalian oscillator, the negative components are 4 genes encoding the repressors *Cry1*, *Cry2*, *Per1*, and *Per2*, which are activated by the 2 PAS domain transcription factors CLOCK and BMAL1. For a complete review, see Ref. [10].

Other modulatory components include the orphan nuclear receptor and repressor REV-ERBα, and posttranslational mechanisms, such as protein phosphorylation by casein kinase 1 (CKI), contribute to negative and positive control of the generation of 24-hour rhythms. A recent study showed that deletion of mammalian BMAL1/Mop3 alters the baseline sleep architecture and the response to sleep deprivation [11]. Mice deficient in the *Bmal1/Mop3* gene become immediately arrhythmic in constant darkness and exhibit reduced locomotor activity levels, increased total sleep time, sleep fragmentation, and an attenuated compensatory response to acute sleep deprivation. This study suggests that molecular components of the circadian system play a central role in the generation of sleep and wakefulness beyond just the timing of these behavioral vigilance states.

Because we sleep one third of our life, some of us hyperactive achievers would like to sleep less to not lose precious time. A recent screening of 9000 mutant lines of *Drosophila* led to the discovery of a minisleep (mns) line that sleeps for one third the amount of that of the wild type [12]. Mns flies normally perform a number of tasks and have preserved sleep homeostasis, but are not impaired by sleep deprivation. The study showed that mns flies carry a point mutation in a conserved domain of the *Shaker* gene [12]. Because there was no recombination between the *Shaker* gene and the short-sleeping phenotype, the mutation observed in the Shaker locus appears to code for both phenotypes. The gene encodes an α subunit of the tetrameric voltage-dependent potassium channel controlling membrane repolarization and transmitter release. Unfortunately, the presence of this mutation resulted in 10% to 15% shortening of life span, supporting the importance of adequate sleep duration for a healthy life [13].

4. Genetics of sleep disorders

Sleep and sleep disorders are complex traits that involve many genes and their interactions with environmental factors. Twin- and family-based studies have found high heritability estimates for sleep length (h^2 = 0.44) [14]. A recent study showed a genetic contribution of 33% of variance in sleep quality and sleep disturbance and 40% of variance in sleep pattern [15]. Sleep disorders can be divided into monogenic and polygenic disorders. Monogenic causes are rare and generally more severe. They include familial advance sleep phase syndrome, fatal familial insomnia, chronic primary insomnia, and narcolepsy with cataplexy [14].

5. Advanced sleep phase syndrome

Advanced sleep phase tendency is often found in the general population (morning type) but familial advanced sleep phase syndrome (ASPS) is a rare disorder that results in abnormal circadian behavior. Individuals sleep and wake earlier than desired (from about 1900 hours in the evening to 0400 hours in the morning). The first gene mutation for familial ASPS was described in 2001 in one of the core clock genes, *Per2*. As mentioned, *Per2* is the positive regulator of the BMAL1 feedback loop [16]. The mutation

modifies a phosphorylation site within the CKI-binding domain of *Per2*. However, most cases of familial ASPS are not caused by this mutation. Recently, a missense mutation was identified in the CKIdelta gene [17].

6. Delayed sleep phase syndrome

Delayed sleep phase syndrome (DSPS) is the most frequent sleep disorder among young adults. It is characterized by persistently delayed sleep-wake timing (sleep from 0400 hours in the morning to noon). The melatonin cycle appears to be delayed in these subjects [18]. Melatonin and its receptor are expressed in suprachiasmatic nuclei (circadian pacemaker). An association was found with melatonin receptor 1a (*MEL1A*) and the absence of 24-hour sleep-wake rhythm synchronization [5]. Another report showed an association with a polymorphism in arylalkylamine *N*-acetyltransferase gene, an enzyme involved in the synthesis of melatonin [19].

Delayed sleep syndrome was also associated with HLA antigen DR1 allele and *Per3* gene. PER3 protein was shown to heterodimerize with PER1 and PER2 and CRY1 and CRY2. It then enters the nucleus and inhibits the CLOCK/BMAL1 complex. These 2 examples constitute sleep disorders of circadian rhythms where the involvement of clock genes has been shown.

7. Insomnia

Insomnia is the most common sleep disorder, with about 20% of the adult population affected by chronic insomnia [20]. The etiologies of insomnia are complex, including medical, psychological, and psychiatric disorders. Few studies have focused on the familial aspect of insomnia except for the rare subtype, fatal familial insomnia (FFI). FFI is a rare disease characterized by the inability to sleep, dysautonomia, and motor disturbances rapidly leading to death. A point mutation (codon 178) in a prion protein gene has been identified in severe FFI. Genetic factors have also been involved in early-onset childhood insomnia. A familial history of insomnia increases vulnerability to insomnia, especially in primary insomnia [20]. However, very few genetic studies have been reported to date. A missense mutation in GABA-A β3 subunit changing one amino acid and GABA receptor function has been reported. Interestingly, a higher recurrence of failure to fall asleep (initial insomnia), to maintain sleep (middle insomnia), and early wakening (terminal insomnia) was found in patients homozygous (CC) for the *Clock* genotype.

8. Narcolepsy

Narcolepsy is an underdiagnosed, disabling neurologic condition affecting from 0.02% to 0.07% of the overall population in the United States and European Union countries [21]. It typically has an onset around puberty (age, 15-25 years). This disorder is characterized by excessive daytime sleepiness, disturbed nocturnal sleep, and abnormal rapid eye movement (REM) sleep. Human narcolepsy is a genetically complex disorder. Familial cases are rare (less than 10%), but the risk of narcolepsy with cataplexy appears to be 10 to 40 times higher in first-degree relatives of patients with narcolepsy, and an attenuated phenotype of recurrent daytime naps and/or lapse into sleep has been observed in second-degree relatives. As about 80% of narcolepsy cases are sporadic, and monozygotic twins are usually discordant for narcolepsy, it is therefore plausible that environmental factors play a significant role [21,22]. Narcolepsy is associated with the HLA system, suggesting that it may have an autoimmune basis [23]. The principal predisposing allele is DQB1*0602, which is found in 95% of patients with narcolepsy with clear cataplexy across all ethnic groups, but this allele seems not to be necessary or sufficient for developing narcolepsy (and even less for the development of narcolepsy without cataplexy and in familial forms) [14]. Other HLA alleles have been reported to increase the risk of developing narcolepsy, but their effects seem to be weaker than that of the DBP1*0602 allele. DRB1 and DQB1 genes have been sequenced, but no mutations have been found in narcolepsy patients. The mechanisms by which DQB1*0602 predisposes to narcolepsy remains unknown. Other genes, including those coding for tumor necrosis factor α and its receptor, have been associated with greater susceptibility to narcolepsy. In a natural canine model and transgenic mice, a deficiency of the orexin/hypocretin (Hcrt) system was proposed to be responsible for narcolepsy. Selective destruction of hypocretin neurons is the most implicated in humans. Most cases, however, are not linked to Hcrt ligand or receptor mutations, but are associated with undetectable cerebrospinal fluid Hcrt-1 levels [21]. Narcolepsy with cataplexy could thus be due to Hcrt deficiency. Autoimmune activity against hypothalamic Hcrt-containing cells has been suggested as a likely pathophysiologic mechanism, but there is no clear evidence of an autoimmune etiology for narcolepsy to date [21].

9. Sleepwalking and nocturnal terrors

The familial nature of these parasomnias is recognized, but no clear mode of transmission has been identified. There is a higher concordance in MZ than in HZ twins, and association with an HLA (DQB1*0501) allele has been shown in the familial form, demonstrating the first genetic susceptibility factor for this parasomnia [24]. An overlap between sleep walking and REM sleep disorders has been reported [25], and a common genetic predisposition (HLA DQB1*05) between the 2 has been suggested.

10. Primary nocturnal enuresis

It is another common type of parasomnia in children. Most often, nocturnal enuresis has an autosomal dominant

mode of inheritance with high penetrance (90%). Four gene loci have been identified on chromosomes 8q, 13q, 12q, and 22q11. Recent linkage studies in 6 families have identified a quantitative trait loci with logarithm of odds (LOD) scores of 4.2 at 12q around the aquaporin-2 gene (water channel) [26], but no mutations were found in the coding sequence, making this gene a weaker candidate yet not excluding its regulatory regions at the moment [5].

11. Restless legs and periodic limb movement syndrome

The restless legs syndrome (RLS) is defined by some people as a syndrome, by some as a sleep disorder; some refuse to accept it as a problem altogether, and only a few know that it has a clear clinical definition [27]. Clinical diagnostic criteria were established in 2002 and reviewed in 2003. A list of these criteria can be found in Reference [27]. RLS is a common disorder (5%) characterized by an irresistible desire to move the limbs, usually associated with paresthesias/dysesthesias and motor restlessness, and resulting in nocturnal insomnia and chronic sleep deprivation. Familial forms are common. In the province of Quebec, Canada, the prevalence and proportion of families with RLS are particularly high, suggesting a founder effect [28,29]. RLS is an autosomal dominant disorder with incomplete penetrance in one third of cases, pointing to genetic heterogeneity [30]. The excellent therapeutic response to dopaminergic drugs indicates a central role of dopamine in its pathophysiology [31]. Eight genes coding for receptors and enzymes related to the dopaminergic systems have thus far been tested but without any significant results [14]. However, the high-activity allele of the *MAOA* gene may act as a modifying factor [32].

12. Sleep apnea syndrome

Sleep apnea syndrome (SAS) is a complex syndrome affecting 4% to 5% of the general population. The most common type of sleep apnea is obstructive sleep apnea, in which the upper airways become obstructed during sleep. Although not nearly as prevalent, central sleep apnea is caused by a dysfunction in the thalamus area of the brain and the mechanism that controls breathing, and can be caused by stroke.

Few studies have focused on the genetics of SAS [33]. Numerous forms of familial SAS have been reported. This can be explained by the fact that most of the risk factors involved in the pathophysiology of SAS are genetically determined (eg, upper body obesity). Genomewide scans have identified several (only suggestive) quantitative trait loci. A few candidate gene studies have been published. For instance, an association has been shown for angiotensin-converting enzyme (*Ace*) gene and hypertension in moderate SAS [33]. Other studies suggest a possible link between *ApoE4* gene and obstructive SAS [34,35]. Yet another study disclosed an association between haptoglobin gene polymorphism and susceptibility to cardiovascular disorders in obstructive SAS [14].

13. Circadian rhythm and mood disorders

As much as light and its cycling are involved in sleep periodicity, it has been recognized since antiquity that sleep is related to mood and its disorders [36]. Environmental light is considered to be the time giver (zeitgeber) of circadian behavior. Recent gene expression studies in constant darkness have uncovered a circadian metabolite rhythm in mammals [37] contrasting light with dark periods and identifying the circadian regulator 5′ -AMP as a molecular mediator. Lincoln et al [38] have reported the temporal expression of 7 clock genes in the suprachiasmatic nucleus and pars tuberalis of the pituitary gland in sheep, providing evidence of an internal coincidence timer. The genes *Bmal1*, *Clock*, *Per1*, *Per2*, *Cry1*, *Cry2*, and *CK1* were tested by in situ hybridization in the suprachiasmatic nucleus and pars tuberalis of the pituitary gland collected every 4 hours through a day cycle. The animals were kept in short or long photoperiods. It was observed that locomotor activity was inversely related to melatonin secretion and that prolactin levels increased during the light periods. *Clock* gene was expressed in parallel with *Bmal1*, and in antiphase with *Per1* and *Per2*. *Cry1* and *Cry2* present oscillations of low amplitude. Photoperiods affected the wave form of *Per1* and *Per2* expression. *Per1* and *Per2* gene expression peaked during the day, whereas expression of *Cry1* and *Cry2* peaked early during the night. These authors suggest that melatonin is responsible, through the photoperiod, for the marked effect on the phase relationship between *Per* and *Cry* genes. This study proposed that external coincidence models explain the photoperiod impact of waveforms of clock genes expressed in suprachiasmatic nuclei as the central pacemaker. It also proposed that the internal coincidence models explained the way melatonin affects the phasing of clock genes in pars tuberalis, which should then be responsible for photoperiod control of summer and winter physiology [38].

These investigations led to the conclusion that the core Clock gene system is used differently in the circadian clock and in the photoperiod in a relay within the pituitary gland.

With the accumulated knowledge that clock genes are responsible for 24-hour rhythmicity, the importance of synchronizers (zeitgebers) has helped us to understand winter depression, an understanding that elicited the first successful chronobiological treatment in psychiatry with nonpharmacologic agents such as light therapy and sleep deprivation as well as novel approaches to drug development, including agomelatine [39].

Light therapy has become a treatment for seasonal affective disorder in people who incur depression with shortened daylight. Spontaneous remission then occurs during the longer daylight period of summer. A similar effect was observed with melatonin [7], which has resulted in agomelatine, an agonist of melatoninergic MT1 and MT2

receptors, and eventually an antagonist of 5-HT_{2C} receptors [40]. All these therapies aim at resynchronization of the disturbed phase relationship between the clock and sleep with concomitant improvement in mood.

14. Potential metabolic consequences of sleep deprivation

Data from the National Sleep Foundation, Washington, DC, indicate that since 1960, the prevalence of short sleepers (sleep duration less than 7 hours) has increased from 16% to 37% in young adults. Based on this information, Spiegel et al [41] performed an experiment on the metabolic consequences of sleep deprivation in a short term: 2 days of sleep restriction (vs 2 days sleep extension) was associated with a significant decrease of the anorexigenic hormone leptin, contrasting with an increase of the orexigenic factor ghrelin accompanied by increased hunger and appetite, particularly for high-energy foods with high-carbohydrate content. Actually, these data have to be put into the context of the complexity of chronic impact, as we have observed gene-environment interaction in a genetic rat model possessing less than 1% of the genomic cross-background of hypertensive rats including a segment of RT1 (histocompatibility complex). Animals possessing this new segment (RT1) gained more weight in response to high-fat and high-carbohydrate diets, despite higher leptin levels, and the leptin gene locus itself did not appear to be involved [42].

It has been shown that constant darkness constitutes a circadian metabolic signal in mammals [37]. Ablation of the suprachiasmatic nucleus, the master clock synchronizer, abolished torpor, a state similar to hibernation, implicating the circadian clock in this phenomenon. It has also been found that constant darkness induces the gene expression of fat catabolic enzymes, such as procolipase (mClps) and pancreatic lipase-related protein 2. This mechanism is dysregulated in *Per1* knockout mice. Zhang et al [37] identified 5′ -AMP as a key metabolic controller inducing torpor. Hibernation torpor is actually an energy-saving strategy of survival in low-temperature and low-light periods. Differential gene expression microarrays have revealed that the Alaskan ground squirrel expresses in its brown adipose tissues most of the genes leading to non-shivering thermogenesis during hibernation when its body temperature decreases to 0°C, allowing it to survive from one period to another. The physiology of hibernation teaches us the relationship between sleep and energy metabolism.

15. Conclusion and perspectives

The fields of sleep genetics, genomics, and transcriptomics are only just emerging. Despite the identification of a few mutations in rare sleep disorders, the complexity of sleep-wake regulation and the underlying gene-gene and gene-environment interactions make the elaboration of their molecular bases a challenge. Case-control and family-based studies are promising approaches, especially with the development of whole-genome association tools using high-density single nucleotide polymorphism chips. The scope has to be enlarged to global genomics, not just limited to candidate genes [43]. As for other complex traits, our strategies should focus on reduction of heterogeneity. Exploration of gene-environment interactions will require the development of new paradigms and better assessment of environmental factors. The physiologic genomics of sleep disorders are being uncovered, and their relevance to human pathophysiology, from mood to metabolic disorders, is being progressively appreciated.

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References

[1] Valatx JL, Bugat R. Genetic factors as determinants of the waking-sleep cycle in the mouse (author's transl). Brain Res 1974;69:315-30.
[2] Valatx JL, Bugat R, Jouvet M. Genetic studies of sleep in mice. Nature 1972;238:226-7.
[3] Dunlap JC. Molecular bases for circadian clocks. Cell 1999;96:271-90.
[4] Schibler U, Tafti M. Molecular approaches towards the isolation of sleep-related genes. J Sleep Res 1999;8(Suppl 1):1-10.
[5] Dauvilliers Y, Maret S, Tafti M. Genetics of normal and pathological sleep in humans. Sleep Med Rev 2005;9:91-100.
[6] Gachon F, Nagoshi E, Brown SA, et al. The mammalian circadian timing system: from gene expression to physiology. Chromosoma 2004;113:103-12.
[7] Wurtman P. Melatonin. In: Coates P, et al, editors. Encyclopedia of dietary supplements, vol. P. New York: Marcel Dekker Inc., 2005. p. 457-66.
[8] Bartness TJ, Powers JB, Hastings MH, et al. The timed infusion paradigm for melatonin delivery: what has it taught us about the melatonin signal, its reception, and the photoperiodic control of seasonal responses? J Pineal Res 1993;15:161-90.
[9] Konopka RJ, Benzer S. Clock mutants of *Drosophila melanogaster*. Proc Natl Acad Sci U S A 1971;68:2112-6.
[10] Lowrey PL, Takahashi JS. Mammalian circadian biology: elucidating genome-wide levels of temporal organization. Annu Rev Genomics Hum Genet 2004;5:407-41.
[11] 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;28:395-409.
[12] Cirelli C, Bushey D, Hill S, et al. Reduced sleep in *Drosophila* Shaker mutants. Nature 2005;434:1087-92.
[13] Hendricks JC. Shaking up sleep research. Nat Neurosci 2005;8:703-5.
[14] Tafti M, Maret S, Dauvilliers Y. Genes for normal sleep and sleep disorders. Ann Med 2005;37:580-9.
[15] Heath AC, Kendler KS, Eaves LJ, et al. Evidence for genetic influences on sleep disturbance and sleep pattern in twins. Sleep 1990;13:318-35.
[16] Shearman LP, Sriram S, Weaver DR, et al. Interacting molecular loops in the mammalian circadian clock. Science 2000;288:1013-9.
[17] Xu Y, Padiath QS, Shapiro RE, et al. Functional consequences of a CKIdelta mutation causing familial advanced sleep phase syndrome. Nature 2005;434:640-4.
[18] Shibui K, Uchiyama M, Okawa M. Melatonin rhythms in delayed sleep phase syndrome. J Biol Rhythms 1999;14:72-6.

[19] Hohjoh H, Takasu M, Shishikura K, et al. Significant association of the arylalkylamine *N*-acetyltransferase (AA-NAT) gene with delayed sleep phase syndrome. Neurogenetics 2003;4:151-3.
[20] Dauvilliers Y, Morin C, Cervena K, et al. Family studies in insomnia. J Psychosom Res 2005;58:271-8.
[21] Mignot E. Sleep, sleep disorders and hypocretin (orexin). Sleep Med 2004;5(Suppl 1):S2-S8.
[22] Hungs M, Lin L, Okun M, et al. Polymorphisms in the vicinity of the hypocretin/orexin are not associated with human narcolepsy. Neurology 2001;57:1893-5.
[23] Lin L, Hungs M, Mignot E. Narcolepsy and the HLA region. J Neuroimmunol 2001;117:9-20.
[24] Lecendreux M, Bassetti C, Dauvilliers Y, et al. HLA and genetic susceptibility to sleepwalking. Mol Psychiatry 2003;8:114-7.
[25] Schenck CH, Boyd JL, Mahowald MW. A parasomnia overlap disorder involving sleepwalking, sleep terrors, and REM sleep behavior disorder in 33 polysomnographically confirmed cases. Sleep 1997;20:972-81.
[26] Deen PM, Dahl N, Caplan MJ. The aquaporin-2 water channel in autosomal dominant primary nocturnal enuresis. J Urol 2002;167:1447-50.
[27] Trenkwalder C, Paulus W, Walters AS. The restless legs syndrome. Lancet Neurol 2005;4:465-75.
[28] Lavigne GJ, Montplaisir JY. Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. Sleep 1994;17:739-43.
[29] Montplaisir J, Boucher S, Poirier G, et al. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997;12:61-5.
[30] Desautels A, Turecki G, Montplaisir J, et al. Restless legs syndrome: confirmation of linkage to chromosome 12q, genetic heterogeneity, and evidence of complexity. Arch Neurol 2005;62:591-6.
[31] Barriere G, Cazalets JR, Bioulac B, et al. The restless legs syndrome. Prog Neurobiol 2005;77:139-65.
[32] Desautels A, Turecki G, Montplaisir J, et al. Evidence for a genetic association between monoamine oxidase A and restless legs syndrome. Neurology 2002;59:215-9.
[33] Zhang J, Zhao B, Gesongluobu, et al. Angiotensin-converting enzyme gene insertion/deletion (I/D) polymorphism in hypertensive patients with different degrees of obstructive sleep apnea. Hypertens Res 2000;23:407-11.
[34] Kadotani H, Kadotani T, Young T, et al. Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. JAMA 2001;285:2888-90.
[35] Foley DJ, Masaki K, White L, et al. Relationship between apolipoprotein E epsilon4 and sleep-disordered breathing at different ages. JAMA 2001;286:1447-8.
[36] Soldatos CR, Paparrigopoulos TJ. Sleep physiology and pathology: pertinence to psychiatry. Int Rev Psychiatry 2005;17:213-28.
[37] Zhang J, Kaasik K, Blackburn MR, et al. Constant darkness is a circadian metabolic signal in mammals. Nature 2006;439:340-3.
[38] Lincoln G, Messager S, Andersson H, et al. Temporal expression of seven clock genes in the suprachiasmatic nucleus and the pars tuberalis of the sheep: evidence for an internal coincidence timer. Proc Natl Acad Sci U S A 2002;99:13890-5.
[39] Wirz-Justice A. Biological rhythm disturbances in mood disorders. Int Clin Psychopharmacol 2006;21(Suppl 1):S11-5.
[40] Loo H, Hale A, D'haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. Int Clin Psychopharmacol 2002;17:239-47.
[41] Spiegel K, Tasali E, Penev P, et al. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med 2004;141:846-50.
[42] Sedova L, Berube J, Gaudet D, et al. Diet-induced obesity delays cardiovascular recovery from stress in spontaneously hypertensive rats. Obes Res 2004;12:1951-8.
[43] Seda O, Tremblay J, Sedova L, et al. Integrating genomics and transcriptomics with geo-ethnicity and the environment for the resolution of complex cardiovascular diseases. Curr Opin Mol Ther 2005;7:583-7.