Genetic Basis for Sleep Regulation and Sleep Disorders

David M. Raizen, M.D., Ph.D.,[1,2] Thornton B.A. Mason, M.D., Ph.D., M.S.C.E.,[2,3] and Allan I. Pack, M.B., Ch.B., Ph.D.[1,4]

ABSTRACT

Sleep disorders arise by an interaction between the environment and the genetic makeup of the individual but the relative contribution of nature and nurture varies with diseases. At one extreme are the disorders with simple Mendelian patterns of inheritance such as familial advanced sleep phase syndrome, and at the other extreme are diseases such as insomnia, which can be associated with a multitude of medical and psychiatric conditions. In this article, we review data on the relative contribution of genetic and environmental factors in the pathogenesis of various sleep disorders. The understanding of many of these disorders has been advanced by the study of sleep and circadian rhythms in model laboratory organisms. We summarize this model system research and how it relates to human sleep disorders. The current challenge in this field is the identification of susceptibility genetic loci for complex diseases such as obstructive sleep apnea. We anticipate such identification will increase our ability to assess risk for disease before symptom onset and by doing so will shift the focus from treatment to prevention of disease.

KEYWORDS: Sleep, genetics, circadian, homeostatic

CIRCADIAN REGULATION OF SLEEP AND CIRCADIAN SLEEP DISORDERS

The Circadian Clock

Virtually all organisms display biologic rhythms, called circadian rhythms, which are synchronized to the 24-hour earth rotation cycle. In addition to having an approximate 24-hour period, circadian clocks have a few other key properties. First, they are free running. That is, they continue to keep time even in the absence of external cues. However, normally clocks are entrained to external cues provided by the environment. The best understood entraining signal is light, which changes with sun exposure. In mammals, a retinal photoreceptor molecule—melanopsin, which is found in retinal ganglion cells but not rods and cones—transduces the light entrainment signal. This signal is carried to the suprachiasmatic nucleus (SCN), the site of the central circadian clock, by the retinohypothalamic tract (for review, see Peirson and Foster[1]). Another entrainment signal, restricted feeding, does not require the SCN.[2] Finally, circadian clocks show temperature compensation, where the period remains constant at different temperatures. Control of circadian rhythm of three physiological variables—sleep, core body temperature, and melatonin secretion—is anatomically housed in neurons of the SCN in the hypothalamus.

[1]Center for Sleep and Respiratory Neurobiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [2]Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [3]Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [4]Division of Sleep Medicine, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Address for correspondence and reprint requests: Allan I. Pack, M.B., Ch.B., Ph.D., Center for Sleep and Respiratory Neurobiology, University of Pennsylvania School of Medicine, 125 South 31st Street, Suite 2100, Philadelphia, PA 19104-3403.

Genetics of Common Neurologic Diseases; Guest Editor, John K. Fink, M.D.

Semin Neurol 2006;26:467–483.

DOI 10.1055/s-2006-951619. ISSN 0271-8235.

In 1971, Ron Konopka and Seymour Benzer ushered in the modern era of circadian research when they published a description of the first three circadian mutants, which they had identified in the fruit fly *Drosophila melanogaster*.[3] These three mutants turned out to be different mutations in the same gene, which they named *period* or *per*. *Per* turned out to be an integral part of the core molecular machinery that makes up the clock. There is one *per* gene in Drosophila but three separate *per* genes in mammals.

The 35 years of intense research that followed the identification of *per* mutants have led to a remarkably detailed understanding of the molecular underpinnings of the circadian clock.[4] This clock mechanism, which is phylogenetically conserved and similar in flies and mammals, consists of a cell-autonomous transcriptional-translational negative feedback loop. At the core of the clock are a pair of transcription factors, CLOCK and BMAL1, that activate *per* gene transcription as well as transcription of other genes, *cryptochrome* or *cry* (the identity of this second gene is one arena in which mammals and fruit flies differ as in Drosophila, the PER partner is TIMELESS). The mRNA from these genes is transported to the cell cytoplasm, where it is translated into protein. In the cytoplasm, PER proteins form a heterodimer with CRY proteins; when this protein complex reaches a critical concentration, it translocates back into the nucleus. In the nucleus, this complex then negatively regulates the positive transcriptional activity of CLK:BMAL1, at which point the negative feedback loop is completed.

A major determinant of the duration of this molecular oscillation is the time it takes PER proteins to reach the critical concentration in the cytoplasm to be transported back into the nucleus. Proteolytic degradation lowers PER concentrations and therefore turns out to be a key site for regulation of this process. PER proteins are marked for degradation by phosphorylation by one or more protein kinases. Therefore, mutations in either the kinases themselves or in the amino acids in PER, which the kinases phosphorylate, would be predicted to stabilize PER protein, expedite its nuclear entry, and therefore shorten the period of the clock.

Advanced Sleep Phase Syndrome

Thirty years after the publication of Konopka and Benzer's pioneering work on *per* mutants in Drosophila, a mutation in one of the three human *per* genes, *per2*, was found to account for an autosomal-dominant circadian sleep disorder called familial advanced sleep phase syndrome (FASPS).[5] Affected members of this extended family have a sleep onset and waking time that are 3 to 4 hours earlier than unaffected family members.[6] When Ptacek and colleagues mapped the FASPS trait to a region of chromosome 2q known to contain one of the three human *per* genes, the possibility that there was a mutation in the *per2* gene itself was immediately appreciated. Indeed, there was a mutation of a conserved serine amino acid, in a region of the protein known to bind caseine kinase 1ε.[5] Toh et al went on to demonstrate in vitro that this mutation causes reduced phosphorylation of PER by caseine kinase 1ε.[5] Given what was known from work in Drosophila and rodents about the mechanism of regulation of circadian period, a possible explanation for the short period that has been shown in these FASPS patients is that the PER protein mutation results in reduced phosphorylation of this protein, increasing its stability and cytoplasmic concentration, and therefore promoting its precocious entry into the nucleus. Research is ongoing to test this model.

Recently, a genetic association study showed that another single nucleotide polymorphism in the 5′-untranslated region of *per2* was more likely to be found in patients with extreme morning preference than in patients with evening preference.[7] The biochemical and cell biologic consequences of this polymorphism are unknown.

Not long after the identification of the disease gene in this first FASPS family, a second gene causing FASPS was identified in a different family. However, this time the trait was not linked to any of the three human *per* genes. It was instead linked to the protein kinase casein kinase 1δ.[8] A mutation in a conserved threonine resulted in reduced activity of the enzyme in vitro. To show that this mutation was causing the patient syndrome and was not simply a linked polymorphism, Xu and colleagues made elegant use of the previously established animal models for circadian rhythm studies by demonstrating an alteration of the circadian clock in both mice and fruit flies.[8] Although the in vivo phosphorylation substrate for casein kinase 1δ remains unknown, these findings show that protein phosphorylation is a major determinant of the period of human circadian rhythms, just as it is in Drosophila, mice, and hamsters.

Delayed Sleep Phase Syndrome: Is There a Genetic Etiology?

The identification of two genes, which are implicated in the circadian clock of model organisms as the cause for FASPS, leads to an optimistic expectation that for the opposite phenotype, delayed sleep phase syndrome, underlying genetic lesions will also be identified. This optimism is tempered, however, by a few points. First, delayed sleep phase syndrome is more common than advanced sleep phase syndrome; therefore, if there is a genetic predisposition, it is more likely to be genetically heterogeneous. Second, it is evident that environmental psychosocial variables influence the likelihood of

delayed sleep phase. Social activities, television shows, and Internet browsing tend to be late evening endeavors, in particular among teenagers. Finally, poor sleep hygiene, including reduced or mistimed exposure to the phase-advancing effects of morning light, can result in a mildly delayed sleep phase because the endogenous free-running human circadian period in most people is slightly longer than 24 hours.[9] In support of a more complicated pathogenesis for delayed sleep phase syndrome is the fact that a large family with convincing Mendelian segregation of a delayed sleep phase trait has yet to be described.

Despite this likely genetic heterogeneity and the input of environment, close to 50% of patients with delayed sleep phase report a relative with similar circadian tendencies.[10] Moreover, monozygotic twins have matching circadian tendencies[11] and a single family pedigree with higher than normal reports of eveningness has been described,[12] suggesting an underlying genetic predisposition. Attempts have been made to identify genetic polymorphisms in candidate circadian genes in subjects with delayed sleep phase syndrome. Lower scores on the Horne-Ostberg morningness-eveningness scale[13] indicating delayed sleep phase tendencies have been reported to be associated with a polymorphism in the 3′-untranslated region of the human CLOCK gene,[14] although a follow-up study failed to reproduce this association.[15] A structural polymorphism in the human *per3* gene has also been shown to be associated with delayed sleep phase,[16] although the functional consequences of this amino acid change or even the role of the PER3 protein in the function of the central clock remains unclear.

Other Circadian Sleep Disorders

Blind patients who lack a functional retina cannot entrain their circadian cycle to light. Their circadian cycle is therefore free running; because the majority of humans have a circadian period that is slightly longer than 24 hours,[9] blind patients will be phase delayed by 20 to 30 minutes every day such that after 5 weeks, their physiology will be 12 hours out of phase with the day-night cycle.[17] Instead of light, alternative cues have been attempted to entrain the circadian rhythm of blind patients. Melatonin, a pineal hormone that has weak and time-of-day-dependent effects on the circadian phase in people with normal light input and normal melatonin levels,[18] can entrain the central clock of blind patients.[19] To date, there have been few searches for association between mutations in components of the light or melatonin entrainment system, although it is likely that such mutations exist. In fact, one study showed an association between delayed sleep phase and a polymorphism in the rate-limiting enzyme in melatonin synthesis.[20]

HOMEOSTATIC REGULATION OF SLEEP AND ITS GENETIC UNDERPINNINGS

Process S: The Homeostatic Sleep Process

Although we know much about the molecular basis of the circadian clock, we know little about the molecular genetic basis of the sleep homeostatic process. A current popular model posits that sleep is controlled by two interacting processes, the circadian process described above and a sleep promoting process (process S).[21] The pressure for sleep increases as a function of the duration of prior wakefulness. The process is homeostatic in that longer durations of wakefulness lead to increased amounts of subsequent recovery sleep. Increases in electroencephalogram (EEG) waves of the delta frequencies are frequently used as a measure of the sleep homeostatic drive.

Studies to assess sleep homeostasis often involve sleep deprivation for fixed periods and examining behavioral impairment during sleep deprivation and/or delta power during recovery sleep. Studies in healthy humans have shown that there are major differences between individuals in the degree of behavioral impairment during 36 hours of sleep deprivation. Within individual subjects, however, the response is highly reproducible.[22,23] Thus, the degree of sleep drive is a biologic trait. Further studies are needed to determine if this trait in humans is genetically determined.

There is strong evidence that in another mammal, the laboratory mouse, sleep drive is indeed genetically determined. Franken et al[24] studied increases in EEG delta power in different inbred mouse strains. The increase in delta power was reproducible within a strain but different between strains. Franken et al[24] studied 32 recombinant inbred lines of mice that were derived from crosses between DBA and C57BL/6 mice (DBA and C57BL/6 mice have different responses to sleep deprivation). They found that there were substantial differences in increases in delta power between the recombinant inbred lines and they were able to identify a quantitative trait locus (QTL) for this difference on mouse chromosome 13. This QTL has a logarithm of odds (LOD) score of 3.6, which is highly significant. The gene responsible for this quantitative trait remains to be determined.

This research in mice suggests that there will also be variants of the genes for sleep promotion in humans and that these variants will affect the response to sleep deprivation. Moreover, it is conceivable that certain variants in these genes would result in excessive sleepiness and other variants would result in excessive wakefulness and hence insomnia (see further below).

The Use of *Drosophila* sp. to Study Sleep Regulation and Its Genetic Determinants

The phenomenal success of using Drosophila in identifying circadian clock genes of relevance to human

disorders raised the possibility that Drosophila would also prove to be a valuable genetic model system for the study of sleep. In 2000, two groups described the remarkable similarity between rest in Drosophila and sleep in mammals.[25,26] Like humans, Drosophila have a consolidated sleep period during the night,[25,26] they exhibit recovery sleep following sleep deprivation, and they are less responsive during sleep.[25,26] Moreover, there are similar pharmacological responses in Drosophila: caffeine reduces the amount of sleep,[25,26] antihistamines increase sleep,[26] and modafinil reduces the duration of sleep bouts.[27]

Drosophila studies have shown that the transcription factor cyclic adenosine monophosphate response element binding protein (CREB) plays a role in sleep-wake control. Mutants with reduced CREB have increased sleep, and continuous activation of the PKA/CREB pathway reduces sleep.[28] This finding indicates that genes whose transcription is affected by CREB promote wakefulness. A phylogenetically conserved role for CREB in promoting wakefulness was demonstrated by showing that mice lacking two of the three isoforms of CREB have reduced wakefulness.[29]

Although the studies of the effects of CREB signaling on sleep-wake regulation were hypothesis-driven experiments, Drosophila also offers the power of identifying genes in a hypothesis-independent fashion by using genetic screens. Indeed, such a screen has led to the identification of the Shaker potassium channel gene as a promoter of sleep.[30]

Currently, the chief disadvantage of Drosophila for understanding sleep regulation is that the neuroanatomy of insects is poorly understood in comparison to that of mammals. Sleep, unlike cell-autonomous circadian clocks, is the product of a circuit composed of multiple neuronal groups. Two articles have, however, recently described a role of the mushroom body in the fly brain for sleep-wake control.[31,32]

Thus, moving forward, we can anticipate the field of sleep research in Drosophila to yield new insights into the molecular/genetic basis of sleep regulation.

DISORDERS OF BEHAVIORAL STATE INSTABILITY: NARCOLEPSY

Clinical Features

Narcolepsy is a disease characterized by five cardinal features: excessive daytime sleepiness, cataplexy, fragmented nocturnal sleep, sleep paralysis, and hypnogogic or hypnopompic hallucinations. Cataplexy refers to the sudden loss of muscle tone associated with emotional outbursts, usually with laughing. Cataplectic spells can be as subtle as brief jaw drop or slight knee buckling or as severe as complete paralysis lasting minutes. It is believed that cataplexy represents the normal muscle atonia seen during rapid eye movement (REM) sleep expressed inappropriately during wakefulness. Sleep paralysis is a similar phenomenon to cataplexy except that the atonia involves the whole body (except the diaphragm and extraocular muscles) and it occurs at sleep-wake transitions. Although the presence of cataplexy is highly suggestive of the diagnosis of narcolepsy, sleep paralysis is far less specific and can occur in association with other sleep disorders or in normal individuals. Interestingly, twin studies suggest that the propensity for sleep paralysis is heritable[33] and familial cases of autosomal-dominant sleep paralysis have been described.[34,35] Hypnogogic and hypnopompic hallucinations are dreamlike thoughts during wakefulness that occur during wake-sleep transitions (hypnogogic) or sleep-wake transitions (hypnopompic). The current gold standard diagnostic test for narcolepsy is the multiple sleep latency test (MSLT). Narcoleptics show reduced mean sleep latencies as well as sleep-onset REM periods, in which REM sleep is recorded within 15 minutes of sleep onset.

Based on these five clinical features and the MSLT findings, a popular notion is that narcolepsy represents a disease in which there is behavioral state instability. Sleepiness is the result of instability of the wake state; nocturnal sleep fragmentation is the result of instability of the sleep state; and cataplexy, sleep paralysis, and hypnogogic hallucinations represent intrusion of features of REM sleep into wakefulness.

Narcolepsy Pathogenesis

Prior to 1999, little was known about the pathogenesis of narcolepsy. Studies of families and twins indicate that narcolepsy arises by an interaction of the environment on a predisposed genetic substrate. Twin studies showed concordance rates of ~30%,[36] suggesting both a genetic as well as environmental factors in the pathogenesis or on expression of the disorder. The influence of genetics is illustrated by the greater than 10-fold increased risk for narcolepsy with an affected first-degree relative.[36] Although not causal for the disorder, genetic predisposition to narcolepsy is conferred by HLA class II allele, DQB1*0602, usually in combination with DR2.[36] Approximately 90% of patients with narcolepsy and cataplexy carry this allele, whereas less than 40% of people in the general population carry the allele. The association of the disease with a gene encoding a major histocompatibility antigen combined with the apparent environmental factors in the pathogenesis has led to the suggestion that the immune system plays a role in the pathogenesis of narcolepsy, much like juvenile diabetes or rheumatoid arthritis. However, no convincing evidence for inflammation has ever been demonstrated, immune-modifying therapy has had little if any impact on disease progression, and extensive

searches for autoantibodies in narcoleptics have come up empty-handed.[37] Therefore, a role for the immune system in the pathogenesis remains unproven.

A Defect in Hypocretin Neurotransmission

In August of 1999, two articles published in the journal *Cell* led to a giant advance in the understanding of the pathogenesis of narcolepsy as well as in the understanding of the basic neurobiology of sleep. In the first article, Mignot and colleagues showed that in a canine colony in which narcolepsy segregated in an autosomal-recessive fashion, the causative mutation was in a receptor for a hypothalamic peptide called hypocretin,[38] which is found in the posterior hypothalamus in neurons that project to many of the wake promoting brain nuclei.[39] In the second article, Chemelli and colleagues showed that mice with targeted disruption of the gene encoding preprohypocretin, the precursor protein to hypocretin (also known as orexin), displayed narcoleptic features, including direct transitions between wakefulness and REM sleep, a transition never observed normally.[40]

The demonstration that defective hypocretin neurotransmission results in narcolepsy in animal models was rapidly translated to the clinic with the finding that cerebrospinal fluid (CSF) hypocretin levels are reduced in narcoleptics patients.[41] This reduction might be explained by degeneration of the neurons that make hypocretin as a postmortem pathological study of narcoleptic's brains have shown an absence of hypocretin immunoreactivity in the hypothalamus.[42,43] A follow-up study showed absence of other immunological antigens expressed by hypocretinergic neurons,[44] demonstrating an absence of these neurons. The finding of low CSF hypocretin can be diagnostically useful in the appropriate clinical setting.[45] Interestingly, patients with all the features of narcolepsy, including sleep onset REM periods but without cataplexy, can have normal levels of CSF hypocretin, suggesting that the pathogenesis of narcolepsy without cataplexy is different from the pathogenesis of narcolepsy with cataplexy.[45] Further supporting a pathophysiological distinction between these two clinical entities is the finding that the association of HLA DQB1*0602 is far stronger among narcolepsy patients with cataplexy than among those without cataplexy.[46]

Can one relate the previously known association of narcolepsy with an HLA haplotype to the finding of apparent degeneration of hypocretin neurons? One possible way to tie these together is to propose that in narcoleptics there is an autoimmune attack on hypocretin neurons. Despite the absence of direct evidence for immune system activation, there has been a continued search for environmental triggers. In this regard, it is interesting that there may be an effect of birth month on the likelihood of developing narcolepsy.[47]

In summary, narcolepsy results from loss of hypothalamic neurons that contain hypocretin. Based on the clinical features of narcolepsy and the available neuroanatomic and neurophysiological data, Saper, Chou, and Scammell have proposed a "flip-flop" model for sleep-wake regulation and that the main role of hypocretin is to stabilize behavioral state.[48] Further elaborations of the underlying neuronal circuitry for this flip-flop switch control of REM sleep have been elucidated.[49] Therefore, the discovery of hypocretin signaling with the use of genetic studies in animal models 7 years ago has led to remarkable advances in our understanding of the pathophysiology of narcolepsy and in our understanding of sleep regulation in general. As in the case of circadian disorders, the hypocretin story underlines the power of genetic model systems to discover and understand genes that have relevance to sleep disorders.

DISORDERS OF MOTOR CONTROL DURING SLEEP: THE PARASOMNIAS

Clinical Features

According to the International Classification of Sleep Disorders (ICSD-2), parasomnias are "undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep." Parasomnias are classified as disorders of arousal from non-REM sleep, parasomnias usually associated with REM sleep, and other parasomnias.

The disorders of arousal occur during non-REM sleep. These parasomnias are more common in childhood and may be considered part of a continuum because they share overlapping features. They include sleepwalking, confusional arousals, and sleep terrors. These parasomnias usually occur during slow wave sleep but can also occur during stage 2 non-REM sleep.[50] Common among these disorders is an incomplete transition from slow wave sleep, altered perception of the environment, automatic behavior, and variable degrees of amnesia for the event. Because of the association with slow wave sleep, the arousal parasomnias tend to occur in the first third of the night, when slow wave sleep is most prominent. Arousal parasomnias may represent an abnormal transition between slow wave sleep and lighter stages of non-REM sleep, with the patient "stuck" between deep sleep and wakefulness.[51]

Sleepwalking (somnambulism) can be either calm or agitated, with varying degrees of complexity and duration.[52] Confusional arousals have more associated agitation than what would be expected with sleepwalking: a typical episode may begin with movements and moaning, then evolve to confused behavior with calling out, crying, or thrashing.[53] Attempts to wake a patient during a non-REM parasomnia are

usually unsuccessful; the individual appears confused, with eyes open or closed, and is very agitated or even combative. A confusional arousal episode may last 5 to 15 minutes (although sometimes longer) before the patient calms and returns to a restful sleep. Sleep terrors are the most dramatic disorder of arousals from slow wave sleep. Patients may sit up suddenly and scream, with an intense, blood-curdling "battle cry." Autonomic activation is present, with mydriasis, diaphoresis, and tachycardia.[54] There is increased respiratory tidal volume and an intense look of fear on the face. Moreover, there is a "curious paradox" of endogenous arousal coexistent with external unarousability.[52]

Genetics of non-REM Parasomnias

Several studies support a genetic predisposition to the expression of arousal parasomnias. A three-generation family has been described in which night terrors appeared to be transmitted in an autosomal-dominant fashion.[55] Kales et al reported that the prevalence of sleep terrors and sleepwalking in first-degree relatives of individuals with sleep terrors was 10 times greater than in the general population. If both parents were affected, they estimated that there was a 60% chance that a child would be affected.[56] A study of monozygotic and dizygotic twins also demonstrated that sleep terrors are under moderate to strong genetic control.[57] Proposed modes of inheritance for sleepwalking include multifactorial models, autosomal-recessive inheritance with variable penetrance, and autosomal-dominant inheritance with variable penetrance.[58] Working from the Finnish Twin Cohort, Hublin et al reported that greater than one-third of sleepwalking in adults and greater than one-half of sleepwalking in children is attributable to genetic factors; both additive and dominant genetic effects were proposed.[59] A family-based study found a positive association between the HLA-DQB1*05 subtype and sleepwalking, suggesting (beyond narcolepsy, see above) a possible further interaction between the immune system and sleep.[58]

Some of the apparent genetic complexity of non-REM parasomnia may be explained by the many known triggers, which include sleep deprivation and intrinsic sleep disorders such as obstructive sleep apnea (OSA) and periodic limb movements in sleep.[60] Parasomnias such as sleepwalking and sleep terrors seem significantly more common in children with OSA than in normal children.[61,62] Moreover, Guilleminault et al reported that in children, sleep-disordered breathing or periodic limb movements in sleep (restless legs syndrome [RLS]) may trigger sleepwalking or sleep terrors, as these parasomnias disappeared after treatment for these conditions.[63] Therefore, two considerations are important in evaluating genetic contributions to arousal disorder parasomnias, particularly in children. First, a shared family environment leading, for example, to poor sleep and sleep deprivation complicates interpretation of heritability; second, the heritability of arousal parasomnias could occur indirectly as there is evidence of familial aggregation of sleep-disordered breathing as well as of RLS (as detailed further in this article, see below).

REM Sleep Behavior Disorder

As its name indicates, REM sleep behavior disorder (RBD; also known as REM sleep motor disorder) consists of motor manifestations during REM sleep. Instead of the normal atonia of REM sleep, patients with RBD have complex movements that can be vigorous and even violent (for review, see Schenck and Mahowald[64]). Accordingly, affected patients may injure themselves or their bed partners by punching, grabbing, or kicking.[65,66] Although there is variable loss of the general muscle paralysis typically associated with REM sleep, all other major features of REM sleep remain intact. RBD is more common in male patients (80 to 90% are male patients), with onset usually in the sixth to seventh decade of life.[67] There is often a prodrome where vocalizations and partial limb movements without complex behavior occur during REM sleep.

The pathogenesis of the disorder in many patients is explained by a neurodegenerative disease process that affects key brain stem areas that promote the atonia during REM sleep.[68,69] In animals, lesions of key areas in the pons result in a similar syndrome in which lesioned animals exhibit complex motor behaviors during REM sleep.[70] This model of the pathogenesis is supported by the observation that a large number of patients with RBD go on to develop other neurological signs and symptoms of a neurodegenerative disease.[68,69,71] Neurodegenerative diseases that have been shown to be associated with RBD include the synucleinopathies Parkinson's disease, Lewy-body dementia, and multisystem atrophy.[68,69,72] Although there are currently no studies on family aggregation of RBD, several susceptibility loci have been identified for Parkinson's disease (for review, see Schapira[73]).

SENSORIMOTOR DISORDER AT SLEEP TIME: RLS

Clinical Features of RLS

The prevalence of RLS, a disorder first described by Ekbom,[74] varies widely by geographic origin but in some studies affects as many 10 to 15% of the population.[75–77] Although methodological differences may account for some of the variation in prevalence values,[78,79] it is likely that this geographic variation in prevalence indicates that there are both environmental and genetics factors in the pathogenesis of the disorder.

The diagnosis of RLS can be made on the basis of the patient history alone. Polysomnographic supportive evidence in the form of periodic limb movements during wakefulness and sleep is not essential for the diagnosis but is a useful biomarker for the purpose of research studies. For example, the presence of periodic limb movements during sleep may distinguish one type of familial RLS from another.[80] In RLS, symptoms consist of an ill-described sensation in the limbs, usually in the legs, that comes on with rest and results in an urge to move the affected limb. This sensation is relieved with movement. The symptoms are strongly influenced by the circadian clock as they begin in the evening and wane in the morning. With increasing severity of the disease, symptoms occur earlier in the day and can be experienced at all times of day and in all limbs.

Pathophysiology of RLS

RLS has both sensory and motor manifestations; therefore, the precise neuroanatomic and neurochemical defect is unclear. Aspects of the disorder that bear relevance to the underlying pathophysiological mechanisms include the following: association with low body iron stores when it arises secondary to other conditions; low brain iron levels in some patients with the primary disorder; the structural normality of the brain; and the therapeutic effect of dopaminergic agonists.

A distinction is often made between primary and secondary RLS because it is felt that the former is more likely to have a genetic underlying basis. Nevertheless, the known risk factors for secondary RLS likely have relevance to the pathophysiology of primary RLS also. For example, iron deficiency is a common cause for secondary RLS,[81,82] a finding that may explain the high prevalence of RLS during pregnancy.[83] Pathological specimens from patients with primary RLS have reduced iron stores in the substantia nigra[84] consistent with results of a prior magnetic resonance imaging (MRI) study.[85] A subset of patients with normal serum iron levels have been found to have reduced iron stores in the CSF,[86,87] suggesting that part of the defect in these patients is specifically in central nervous system iron homeostasis. Moreover, Nordlander has shown in a small case series that high intravenous doses of iron can ameliorate RLS symptoms even in patients with normal serum iron.[88] A larger study led by Early and colleagues to test the role of iron therapy on RLS therapy is currently under way.[89]

Neuroimaging and postmortem studies, aside from showing differences in iron levels, have failed to detect gross structural defects in brains of RLS patients. This suggests that the defect in RLS is at the neurochemical level, perhaps due to a defect in a specific neurotransmitter system that depends on iron.

Finally, one of the main treatment modalities for RLS is the use of dopaminergic agonists. The therapeutic effect of dopamine agonists have led to the idea that defective dopamine neurotransmission may play a role in expression of the disorder. Dopaminergic neurotransmission may also explain the circadian manifestation of RLS, because dopamine and its metabolites show circadian variation in human plasma[90] and expression of the mRNA for the rate-limiting enzyme in dopamine biosynthesis, tyrosine hydroxylase, shows circadian variation.[91,92] In an attempt to explain the apparent excitability changes in the spinal cord and the therapeutic effect of dopamine, the A11 dopaminergic neurons, which are located in the hypothalamus and provide descending inhibitory input to the spinal cord, have been proposed to have abnormal function in RLS patients.[93] Recently, a new dopaminergic cell group was identified in the ventral periaqueductal gray that shows state-dependent changes in activity.[94] The relevance of this neuronal group to RLS is unknown.

At this point, however, there is no compelling mechanism to tie iron deficiency with defective dopaminergic neurotransmission.[95] Analysis of eight genes related to dopaminergic neurotransmission found no mutations in DNA from RLS patients.[96]

Genetics of RLS

Frequent familial occurrence of RLS,[97–99] in particular of RLS of early onset,[100] suggests an underlying genetic etiology. In fact, a positive family history of RLS is used as supportive evidence of the diagnosis of RLS.[79] High heritability is indicated by a small twin study, in which there was concordance for RLS symptoms in 10 out of 12 of the twin pairs.[101] An important observation made in this twin study with relevance to attempts to identify genes that cause RLS is that despite the high concordance rate, the age of onset and symptom severity varied between individuals in a given twin pair, suggesting environmental factors in expression of the disorder. Based on observations of single families, it has been proposed that a frequent mode of inheritance is autosomal-dominant.[102–104] An alternative model to explain RLS inheritance is that it is transmitted as an autosomal-recessive trait but because of the high defective gene carrier frequency, it appears to be dominant within families.[105] Although the penetrance is high in these families with early onset of the disorder, the expressivity within families is variable,[102,103,106] suggesting the presence of modifying genetic loci, environmental factors, or both in the pathogenesis of the disorder. Studies of families have also raised the possibility of genetic anticipation,[102,103] a hallmark of trinucleotide repeat disorders, although ascertainment bias in RLS, a subjective disorder without overt physical exam findings, is likely to make accurate identification of anticipation challenging.

Three genome-wide association studies have been performed to map RLS susceptibility genes. In a single French-Canadian family, a susceptibility locus was found on chromosome 12q.[105] In a follow-up large-scale study of 19 families in Quebec, Canada, confirmation of linkage to 12q was provided in five families of French-Canadian heritage.[80] In collaboration with deCODE Genetics, Rye and colleagues reported recently, albeit thus far only in a meeting abstract, the confirmation of the 12q RLS susceptibility locus in the Icelandic population. The unique genealogy strategy for linkage studies offered in Iceland may provide the needed tools for future identification of the 12q RLS susceptibility tools.

In contrast to the results of these studies in North America and Iceland, two large South Tyrolean families did not show linkage of RLS to chromosome 12q.[107] A study of a large Italian family identified a different RLS susceptibility locus on chromosome 14q,[108] and an RLS susceptibility locus on chromosome 9p was identified in a North American family.[109] Furthermore, there are likely to be genetic loci that modify expression of the disease. A polymorphism in a gene encoding monoamine oxidase has been shown to be associated with an increased risk of severe RLS in Canadian women.[110] Therefore, it is likely that more than one gene contributes to the pathogenesis or expression of RLS. Interestingly, Desautels et al reported that RLS patients with linkage to chromosome 12q had significantly higher indices of periodic limb movements of sleep than RLS patients without linkage to chromosome 12q.[80] In addition, the diagnosis of RLS has been made in a subset of patients with a hereditary neuropathy, those with Charcot-Marie-Tooth type 2,[111] as well as in a subset of patients with autosomal-dominant cerebellar ataxia.[112] Therefore, future genetic mapping studies may be able to minimize the confounding effect of genetic heterogeneity by careful phenotypic description of affected patients. It is anticipated that identification of one or more susceptibility genes for RLS will provide a tremendous boost to our understanding of the pathogenesis of the disorder and will lead to new diagnostic and therapeutic possibilities.

DISORDERS OF SLEEP ONSET AND SLEEP MAINTENANCE: INSOMNIA

Insomnia Definition and Clinical Features

Insomnia, chronic sleeping difficulty, is an extremely common condition (for review of prevalence, see Roth[113]). Insomnia is often divided into a primary form (i.e., psychophysiological insomnia) and a secondary form where insomnia is thought to be secondary to other comorbid conditions. Recent data from cognitive-behavioral treatment, however, have challenged this dichotomy.[114] Insomnia is often a complaint in patients with psychiatric disorders, in particular depression (for review, see Fava[115]) and may occur secondary to disorders such as chronic pain. That the diagnosis of insomnia is based on self-report of a complaint and may arise as part of both medical and psychiatric disorders make genetic studies particularly challenging. There is clearly a need to develop more in-depth characterization of the phenotype to facilitate genetic studies of insomnia. Apart from the rare fatal familial insomnia (FFI) that we describe below, very little is known about the genetics of insomnia. A recent, albeit relatively small, study of subjects with primary insomnia ($n = 77$) found that there was a higher prevalence of insomnia in their first-degree relatives as compared with controls (spouses of those with insomnia) or population-based estimates of prevalence.[116] Thus, there is some suggestive evidence of family aggregation of primary insomnia. Further family-based studies with more in-depth phenotyping are needed.

Prion Diseases: FFI

FFI is a prion disorder that results from spongiform brain degeneration. Prion diseases can occur by inheritance as in the cases of Gerstmann-Straussler-Scheinker syndrome and FFI, sporadically as in the case of Creutzfeldt-Jacob disease (CJD) and fatal sporadic insomnia, and by infection as in the case of Kuru and new-variant CJD.[117,118] Common to all these diseases is the finding that the disease can be transmitted to animals; therefore, these diseases are collectively known as transmissible spongiform encephalopathies. The causative agent has been proposed to be a normal cellular protein PrP that is converted by a poorly understood process to a neurotoxic protein.[118]

Patients with FFI initially may complain of mild insomnia and nonrefreshing sleep and show evidence of autonomic nervous system hyperactivity (pyrexia, diaphoresis, myosis, and sphincter disturbances). These symptoms worsen to the point that the patients complain of an inability to fall asleep and eventually show clouded cognition and confusion. Some patients may die after a few months without overt motor manifestations. Those who progress to motor involvement will show features typically seen in CJD, including myoclonus, pyramidal tract signs, and cerebellar ataxia. The course is invariably fatal. The disease results in profound reductions of sleep, both non-REM and REM sleep, and loss of the normal circadian oscillation of melatonin, growth hormone, and cortisol. Other functions controlled by the central circadian clock are preserved, including body temperature and sleep propensity, indicating a selective defect in sleep regulation and in the neurohormonal outputs of the circadian clock.[119]

Unlike the brains of patients with CJD, which show spongiform degeneration of the cerebral cortex, the

histopathology of FFI is restricted to atrophy of the anteroventral and mediodorsal nuclei of the thalamus.[120] The clinicopathologic findings in FFI implicate these neuronal cell groups in sleep initiation or maintenance, in autonomic functions, and in neuroendocrine circadian rhythm.

FFI is transmitted in an autosomal-dominant pattern[121] and is genetically determined by the identity of two amino acids of the prion protein. FFI patients have a mutation at position 178 that changes a normal aspartate to an asparagine, which results in disease. Interestingly, this mutation must be coupled with a methionine polymorphism at position 129 to express the insomnia and neuropathology that is typical of FFI. The same D178N mutation, when coupled with a valine at position 129, results in a clinical presentation and neuropathology typical of CJD and not FFI.[122] In addition, patients who are homozygous for methionine 129 show more prominent oneiric episodes, insomnia, and dysautonomia at disease onset, whereas patients heterozygous for met/val129 show ataxia and dysarthria at disease onset, earlier sphincter loss, and seizures.[123]

The FFI disease phenotype could arise from the effect of the selective neurodegeneration seen in the disease, from the effect of the D178N mutation, from the loss of normal PrP function with conversion to the pathological form of the protein, or from some combination of these three. The D178N mutation does not appear to be essential for disease manifestation because there have been reports of patients who presented with FFI symptoms and whose postmortem pathological analysis showed the signature brain pathology of FFI, yet were the only members of their families with disease and did not carry the D178N mutation.[124,125] Furthermore, a case series has been described in which patients with sporadic CJD who have little thalamic pathology and no mutation in PrP had sleep-wake disturbances similar to those reported for FFI patients.[126] This observation challenges the interpretation that FFI symptoms arise solely from the effects of neurodegeneration of key neuronal groups in the thalamus. A final interpretation is that the PrP gene product itself plays a role in sleep regulation and that disruption of this role contributes to the insomnia phenotype of FFI. In support of a potential role for PrP in normal sleep physiology is the finding by Tobler and colleagues that mice lacking the PrP gene have fragmented sleep.[127]

EPILEPTIC DISORDERS THAT ARISE DURING SLEEP

Epileptic Disorders

The relationships between sleep and epilepsy are complex. Seizures may decrease REM sleep, increase non-REM stage 1 sleep, and decrease sleep efficiency.[128] Different stages of sleep have varying effects on neuronal excitability and ultimately seizure threshold. Although non-REM sleep promotes interictal activity via increased neuronal synchrony, REM sleep apparently inhibits the incidence and extension of epileptiform discharges. Herman et al reported that the effects of sleep on focal onset seizures may depend in part on the epileptic focus location: frontal lobe seizures are most likely to occur during sleep, followed in decreasing frequency by temporal lobe, occipital, and parietal lobe seizures.[129] Chronic sleep deprivation may exacerbate seizure frequency, and case series have supported improved seizure control in patients following treatment of OSA.[130,131]

Sleep has an activating role in several specific epilepsy disorders, including benign Rolandic epilepsy of childhood, electrical status epilepticus during sleep, and autosomal-dominant nocturnal frontal lobe epilepsy. Benign Rolandic epilepsy, also referred to as benign epilepsy with centrotemporal spikes, begins in childhood and remits in adolescence. Seizures consist of unilateral clonic jerking (often upper extremity and face), hypersalivation, speech difficulty, and preserved alertness. Seizures predominate at night and begin exclusively during sleep in about half of cases.[128] Although a strong genetic basis for benign Rolandic epilepsy had been suggested in earlier reports (autosomal-dominant inheritance, multifactorial inheritance), a recent analysis based on international twin registries suggests that the mode(s) of inheritance are complex and that the environment plays a role in the pathogenesis or expression of the disorder.[132]

Nocturnal frontal lobe epilepsy can manifest in three patterns that may lie along a continuum: (1) paroxysmal arousals, which involve abrupt, frequently recurring arousals from sleep with stereotyped movements (elevating the head, sitting, screaming, or looking about as if frightened); dystonic posture of the limbs often occurs, with a typical event duration of less than 20 seconds; (2) nocturnal paroxysmal dystonia, where sudden arousals occur with complex, stereotyped, and sometimes bizarre sequences of movements (dystonic or asymmetric tonic postures, cycling movements, kicking, twisting, or rocking of the pelvis); the event duration is usually less than 2 minutes; and (3) episodic nocturnal wanderings, where sudden awakenings with abnormal motor features are followed by agitated somnambulism (jumping, twisting, moving aimlessly), possibly accompanied by screaming or agitated behavior; the duration is usually less than 3 minutes.[133,134] The mean age of onset for nocturnal frontal lobe epilepsy is 10 to 12 years, and affected patients usually have a history of normal psychomotor development. Establishing the diagnosis may be difficult as neuroimaging is usually normal. Patients may not have ictal or interictal EEG changes. Anticonvulsants are often effective, especially carbamazepine.

Autosomal-dominant frontal lobe epilepsy has been associated with mutations in the nicotinic acetylcholine receptor α_4 and β_2 subunits.[135,136] A gain of function of these mutant receptors may underlie the nocturnal seizures occurring in affected patients.[137] Recently, two nucleotide variations in the promoter of the corticotrophin-releasing hormone (CRH) gene have also been identified and could play a pathogenic role in patients without demonstrable acetylcholine receptor mutations, although further investigation is needed.[138]

OSA

OSA is a common condition in which there is intermittent narrowing or frank closure of the upper airway during sleep (for review of advances, see Pack[139]). Closure occurs with the loss of upper airway dilator muscle activity during sleep. Closure arises behind the soft palate or at the base of tongue, or in both locations. Complete closure of the airway leads to cessation of respiration (i.e., apnea), and partial closure results in substantial reduction of respiration (i.e., hypopnea). In both of these events, oxygen levels decline, carbon dioxide levels increase, and the episode is generally terminated by an arousal, which results in sleep interruption accompanied by restoration of upper airway motor tone. Symptomatic sleep apnea (i.e., with complaints of excessive daytime sleepiness) occurs in 4% of middle-aged males and 2% of females, although sleep apnea in the absence of sleepiness is much more common.[140] (For review of epidemiology of OSA, see Young et al[141].)

Clinical Features of OSA

OSA typically presents with complaints of loud, habitual (i.e., nightly) snoring, and apneas may be witnessed by bed partners. There are several risk factors for the condition[142]: obesity, in particular excess fat in the neck; altered craniofacial structures (e.g., retrognathia); nasal septal deviation and nasal allergies; enlarged tonsils and adenoids, which is a key risk factor in children; and hypothyroidism. Premenopausal women are relatively protected from the disorder.[143] The disorder is progressive and its severity changes slowly over time. Major determinants of disease progression are degree of obesity as well as change in weight.[144]

OSA has several consequences. It can result in excessive daytime sleepiness and this is often the reason that individuals with OSA seek help. OSA is a risk factor for hypertension and randomized trials comparing the current major therapy (i.e., use of nasal continuous positive airway pressure [CPAP] to sham CPAP) have revealed reductions in blood pressure.[145,146] OSA is also associated with atrial fibrillation.[147] Individuals with severe untreated OSA have a higher rate of cardiovascular events or death over a 10-year period than controls with similar degrees of obesity or patients with severe OSA who are treated with CPAP.[148] There is no difference in cardiovascular event rates or deaths between controls and those with severe OSA who are treated with CPAP. Finally, there is growing evidence that OSA is associated with insulin resistance[149–151] and that treatment of obese type II diabetics with OSA by nasal CPAP can improve glucose control.[152]

The common association of OSA with these other conditions—obesity, hypertension, myocardial infarction, diabetes, and so on—is going to make identifying the genes conferring risk for OSA challenging.

Genetics of OSA

EVIDENCE OF FAMILY AGGREGATION

The first indication that OSA may have a genetic component came from finding large family pedigrees in whom OSA was common.[153] Family aggregation of symptoms of OSA was then demonstrated[154] and subsequently sleep-disordered breathing by objective testing.[155] Family aggregation of sleep-disordered breathing has now been demonstrated in four different populations: (1) in the Cleveland Family Study[155]; (2) in Scotland[156]; (3) in Israel[157]; and (4) in Iceland using the genealogy database.[158] Such family aggregation might simply be due to obesity. In the Cleveland Family Study, body mass index (BMI) was used as a covariate and controlling for this did not alter the degree of family aggregation.[155] In the Scottish study, the investigation was done only on relatively less obese individuals with OSA (i.e., BMI < 30 kg/m^2).[156] Thus, family aggregation of OSA is independent of obesity.

INTERMEDIATE TRAITS FOR OSA (FRACTIONATING THE PHENOTYPE)

The risk factors for OSA described above lead one to conclude that there may be several distinct traits that are genetically determined that are associated with an increased risk of OSA. Thus, elucidating the genes for OSA likely involves determining the genes for these intermediate traits.

Many of these traits are structural, involving anatomic changes that act to compromise upper airway size (for review, see Schwab[159]). In OSA, the size of the upper airway is decreased even in wakefulness.[160] Among the anatomic risk factors that are in part genetically determined are craniofacial structure, size of upper airway soft tissue structures, and regional distribution of fat, in particular fat deposited in the parapharyngeal fat pads.[161]

OSA has a high prevalence in individuals with specific craniofacial disorders such as Treacher Collins syndrome, Apert's syndrome, and Pierre Robin syndrome. It is also common in subjects with achondroplasia and Down's syndrome. Even, however, in the absence

of these specific genetic conditions, individuals with OSA have craniofacial abnormalities, albeit ones that are more subtle.[162,163] The most common abnormality is retroposed mandibles with inferior position of the hyoid bone. These abnormalities are heritable and are found in first-degree relatives of individuals with OSA.[156,164]

Soft tissue structures are also important. MRI studies reveal that individuals with OSA have increased tongue size, increased volume of the lateral pharyngeal walls, and increased total soft tissue in the upper airway.[165] These differences are heritable and first-degree relatives (same gender siblings) have increased size of these structures compared with same-gender neighborhood controls and their same-gender siblings.[166] Differences in size of these structures between OSA and controls and their heritability is not explained by obesity.[165,166] Heritability of the size of these structures is 35 to 40%.

Obesity is also heritable.[167] Adoption studies of twins raised apart provide the most compelling evidence of this.[168,169] It is, however, not just the overall level of obesity but the distribution of fat that is genetically determined.[170–172] This has particularly been shown for amounts of abdominal visceral fat.[170–172] Currently we do not know whether the volume of the parapharyngeal fat pads is heritable, although this is likely to be the case.

CHALLENGES TO ELUCIDATING GENES CONFERRING RISK FOR OSA

There are significant challenges in determining genes conferring risk for OSA. First, OSA is an age-dependent phenotype. As described, it is a slowly progressive disorder.[144] Thus, individuals with genes conferring risk would not be expected to show much apneic activity during sleep when they are younger (i.e., in their twenties). This is particularly so in women because they have the added factor of being premenopausal, which protects them from OSA.[143] Both of these issues are of particular importance for the strategy of examining linkage to the quantitative trait of the apnea-hypopnea index, a measure of disease severity. This is the strategy being employed in the Cleveland Family Study to study genes conferring risk for OSA.

Another important challenge is obesity. Because obesity and regional distribution of fat are heritable, we may simply find genes for obesity. This has led investigators to control for obesity as a covariate in ongoing genetic studies.

Individuals with OSA also commonly have other disorders (e.g., hypertension, diabetes, and cardiovascular disease). Thus, they have a complex phenotype. It may be that the genes that are found in genetic studies of OSA are susceptibility genes for hypertension rather than OSA. This does not imply that hypertension is a risk factor for OSA. This is a challenge for the affected-only approach to linkage for OSA that is currently being pursued in Iceland (unpublished data). Thus, a challenge to elucidating genes for OSA is that there are likely to be genes affecting the consequences of the condition, including the presence of excessive sleepiness, and hence whether individuals seek clinical evaluation.

CURRENT KNOWLEDGE ABOUT GENES FOR OSA

Both candidate gene association studies and linkage studies are being applied to study genes conferring risk for OSA. Much of the effort to date in candidate gene studies has focused on APOε4. There are some studies that show an association between the presence of APOε4 allele and OSA,[173,174] although other studies do not find this.[175–177] This may, in part, be related to age, as in the Sleep Heart Health study an association was found in individuals under the age of 65 years but not in those over this age.[174] This is compatible with the concept that sleep-disordered breathing in the elderly is a somewhat different disorder. It has also been reported that the presence of APOε4 may affect consequences of OSA.[178] There is a relationship between declines in performance in a memory task with increasing severity of OSA in individuals with the APOε4 allele, but not in those with other genotypes.[178] Thus, the role of APOε4 in OSA at the present time remains a matter of debate and there is a need for further inquiry.

Candidate gene studies have also looked at variants of serotonin receptors because serotonin is involved in the state-dependent neural control of the upper airway. These candidate genes studies were negative.[179] A somewhat more positive result was found examining the tumor necrosis factor-α (TNFα; ~308A) allele. This polymorphism is in the promoter region of TNFα and leads to enhanced levels of the proinflammatory cytokine. This allele was found more commonly in subjects with OSA than unspecified controls from a blood bank.[180] Because TNFα may be part of the mechanism by which OSA leads to sleepiness,[181] this association may be related to enhanced sleepiness in individuals with a given degree of OSA leading them to present clinically.

Although candidate gene association studies for OSA are currently limited, there is also a paucity of linkage studies. Currently, to our knowledge, there are only two such studies: the Cleveland Family Study and a recently established study in Iceland that uses the genealogical database. As described previously, the Cleveland Family Study is looking at linkage to apnea-hypopnea index as a quantitative trait, using individuals across the life span.[182,183] Initial studies with this cohort suggested that the transmission of this trait was different in Caucasians and African-Americans.[184] In Caucasians, evidence of a major gene effect was markedly reduced when BMI was introduced as a variable in models of segregation analysis, whereas in African-Americans inclusion of BMI strengthened the evidence. This has led

to the conclusion that genes conferring risk for OSA may be different in Caucasians and African Americans, and hence the need to do linkage studies separately in the two groups. This genetic heterogeneity, which reduces the power of the Cleveland Family Study, combined with the challenges described above have led to linkages that are rather weak—LOD score of 1.09 on chromosome 8q in African-Americans[182] and an LOD score of 1.33 on chromosome 2p in Caucasians and 1.45 on chromosome 19p.[183] (No fine mapping has been reported to date.) Thus, currently linkage studies in OSA are not close to finding genes conferring risk for this disorder.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Throughout this article we have noted the impact of genetics on the normal variations of sleep and in a large number of sleep disorders. We have alluded to the power of using model genetic organisms for understanding single genes effects on sleep. The data obtained from model systems has proven useful not only in understanding sleep disorders with simple Mendelian modes of inheritance such as FASPS but also in understanding diseases such as narcolepsy, in which the genetic influence is weak. We believe that these approaches over the next decade will be complemented by genome-wide human diseases association studies to identify genes that confer risk for complex sleep disorders, such as OSA. Developing such association studies will require large collaborative clinical networks, some of which could be international in scope. As has already been demonstrated in the case of RLS, and is likely to be demonstrated in the case of OSA and insomnia, progress in association studies will require careful attention to phenotypic description of affected individuals and to the influence of confounding variables. Genes identified in association studies, in turn, can have their function assessed in studies in model organisms. New knowledge about the genes conferring risk for sleep disorders will allow sleep medicine to take advantage of the vision of personalized medicine, where medicine in the future will focus on managing risk for disease rather than disease.[185]

ACKNOWLEDGMENTS

We are grateful to Mr. Daniel Barrett for his outstanding help in putting this review together. The authors are supported by NIH grants K08 NS-48914 (D.M.R.), K23 RR-016566 (T.B.A.M.), and AG-17628, HL-60287, and RR-00040 (A.I.P.).

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