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MINI REVIEW

Genes for normal sleep and sleep disorders

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Abstract
Sleep and wakefulness are complex behaviors that are influenced by many genetic and environmental factors, which are beginning to be discovered. The contribution of genetic components to sleep disorders is also increasingly recognized as important. Point mutations in the prion protein, period 2, and the prepro-hypocretin/orexin gene have been found as the cause of a few sleep disorders but the possibility that other gene defects may contribute to the pathophysiology of major sleep disorders is worth in-depth investigations. However, single gene disorders are rare and most common disorders are complex in terms of their genetic susceptibility, environmental effects, gene-gene, and gene-environment interactions. We review here the current progress in the genetics of normal and pathological sleep.

Key words: *Apnea, association, circadian, human leucocyte antigen, insomnia, Kleine-Levin syndrome, linkage, narcolepsy, prion protein, sleepwalking, twin*

Introduction

One third of the population is affected by a sleep disorder with a major social, medical, and economic impact. Although very little is known about the genetics of normal sleep, familial and twin studies indicate an important influence of genetic factors. Recent linkage and candidate gene association studies also resulted in the discovery of gene mutations, gene localizations, or evidence for susceptibility genes in several sleep disorders. However, only a few sleep disorders have an established genetic basis, although their number is increasing. Fatal familial insomnia, familial advanced sleep phase syndrome, and narcolepsy may be single gene disorders. The genetic dissection of sleep and sleep disorders may constitute a promising approach in understanding the complexity of normal and pathological sleep and in finding new treatment modalities. In this review we will focus on advances towards genetic approaches in normal sleep and sleep disorders in humans. Sleep disorders will be classified as monogenic disorders, disorders associated with human leucocyte antigen (HLA) complex, and disorders associated with non-HLA genes.

Genetic aspects of normal sleep

Sleep and wakefulness are complex behaviors regulated at many different levels and each of these is likely to be under genetic control. Each component of sleep needs to be considered as a complex phenotype. Twin studies are of major interest to determine the respective contribution of genetic and environmental factors to a given phenotype. Geyer in 1937 and Gedda in 1951 were probably the first authors to report a higher concordance between sleep habits in monozygotic (MZ) than in dizygotic (DZ) twins (1,2). In 1979, Gedda and Brenci found a higher correlation for sleep duration in MZ than in DZ twins (3) with the number of hours of sleep similarly correlated in MZ twins living together or living apart, discounting the influence of environmental effects (4). Partinen and colleagues analyzed self-reported sleep data from 2238 MZ and 4545 DZ adult twins and found significant heritability estimates for sleep length (heritability, h^2: percent of variance explained by the additive effects of genes=0.44) and sleep quality (h^2=0.44) (5). More recently, Heath and colleagues reported that in 1800 MZ, 1103 same-sex DZ and 907 unlike-sex

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DZ twins, genetic differences accounted for at least 33% of the variance in sleep quality and sleep disturbance and 40% of the variance in sleep pattern (6).

Only a few polysomnographic studies have been performed in twins with nevertheless a striking similarity and concordance between all-night sleep patterns (sleep latency, awakening measures, stage changes, and rapid eye movement amounts) of the MZ in contrast to DZ twins (7). In summary, results from twin studies have shown that the sleep patterns of MZ twins have a much higher resemblance than those of DZ twins, confirming that this highly complex phenotype might be tightly controlled by genes (8).

Family studies and quantitative electroencephalographic (EEG) analysis of sleep are completely lacking although two reports indicated a highly stable 'within subject' but different 'between subject' topographic EEG power densities that can be used as a 'genetic fingerprint' (9,10).

Other genetic studies have focused on normal circadian typology, which is closely linked with sleep regulation. Drennan and colleagues examined the circadian typology (morning or evening type) in 238 MZ pairs using the Horne and Ostberg (H&O) questionnaire and obtained higher correlations in MZ twins (11). This result thus points to the implication of genetic factors in circadian modulation of sleep in humans. Katzenberg and colleagues (12) found an association between a *CLOCK* gene polymorphism and different circadian tendencies attested by the H&O questionnaire; however this result was replicated in a Japanese (13) but not another Caucasian population (14). In addition, no polymorphism of other clock genes *TIMELESS* or *PER1* was reported in association with a particular circadian typology (15,16) but a link between extreme diurnal preference and polymorphisms of *PER2* and *PER3* is suspected (17,18). Overall there is no strong evidence of any direct association of circadian gene polymorphisms and timing of sleep and wakefulness.

Genetic aspects of sleep disorders

Monogenic sleep disorders

Four diseases are reported to result from single gene mutations: fatal familial insomnia, familial advance sleep phase syndrome, chronic primary insomnia, and narcolepsy with cataplexy. However, single mutations observed in the two latter conditions are exceptional (single cases) and do not clearly explain the pathogenesis of these disorders in most affected subjects.

Key messages

- Although its biological function remains elusive, sleep is crucial for our daytime functioning and well-being.
- We know very little about the molecular bases of sleep and sleep disorders.
- Molecular genetics is our best hope to understand sleep and to develop appropriate treatments for sleep disorders.

Fatal familial insomnia (FFI). FFI is a rare prion disease clinically characterized by inability to sleep, dysautonomia and motor disturbances, rapidly leading to death (19). The major sleep features of FFI include a progressive reduction of total sleep time, an early disappearance of sleep spindles, a loss of slow wave sleep, and the disintegration of the cyclic organization of sleep (19,20). A point mutation (codon 178) in the prion protein gene (*PRNP*) on chromosome 20 and rarely a mutation at codon 200 (21) have been identified in FFI. Single pathogenic mutation at codon 178 of *PRNP* is responsible for two distinct pathogenic phenotypes, FFI and a subtype of familial Creutzfeldt-Jakob disease in relation to a common polymorphism at codon 129 on the mutated allele: methionine and valine, respectively. Moreover phenotypic and neuropathologic variabilities have been recently described between FFI homozygotes and heterozygotes at polymorphic codon 129, with a progressive disturbance of sleep clinically apparent in homozygous forms only (22,23). A pseudohypersomnia behavior could be observed instead of an insomnia complaint in FFI with heterozygosity at *PRNP* codon 129 (23). A severe neuronal loss and astrogliosis were found in the mediodorsal thalamic nuclei in association with relatively modest amounts of abnormal prion protein in FFI patients. Selective atrophy, loss of neurons, and astrogliosis of the anteroventral thalamic nucleus cause behavioral changes whereas impairment of the mediodorsal thalamic nucleus disrupts sleep and wakefulness and is associated with the loss of EEG spindle activity (24).

Familial advanced sleep phase syndrome (FASPS). An advanced sleep phase tendency is often found in the general population (morning type individuals) whereas FASPS is a particularly rare disorder. FASPS is an abnormality of human circadian behavior that segregates in a highly penetrant autosomal dominant manner. Polysomnographic recordings of sleep and measures of plasma

melatonin and body temperature rhythms all show a phase advance of about 4 hours (25). In mammals a few genes are determinant for circadian oscillation: *CLOCK*, *BMAL1*, *PER*, and *TIMELESS*. The first mutation responsible for FASPS was described in 2001 within the *PER2* gene on chromosome 2q (26). *PER2* gene is a human homolog of the Drosophila period gene and is responsible for this circadian syndrome in a large kindred with autosomal dominant transmission and high penetrance. The mutation is supposed to change the phosphorylation site within the casein kinase I epsilon (CKIε) binding domain of *PER2*. In the mammalian clock model, Per2 is a positive regulator of Bmal1 feedback loop, raising the possibility that the mutation in FASPS may affect the endogenous circadian clock function and the period length or rhythmicity (27). However, most cases of FASPS are not caused by any *PER2* gene mutation (27) suggesting a genetic heterogeneity with probably the involvement of other circadian-related genes. A recent study identified a missense mutation in the human *CKIdelta* gene in a three-generation family affected by FASPS (28). An A to G mutation was identified to be responsible for a threonine-to-alanine alteration at amino acid 44 in this protein. These two examples clearly indicate that single gene mutations in circadian genes might be involved in the etiology of human circadian disorders as repeatedly reported in several animal models.

Narcolepsy. Narcolepsy is a disabling disorder characterized by excessive daytime sleepiness (EDS), cataplexy (sudden loss of muscle tone triggered by strong emotions), sleep paralysis, hypnagogic hallucinations, and sleep onset rapid-eye movement (REM) periods. In Western countries the prevalence is 0.026% of the general population (29), in Japan the prevalence is the highest (30) and in Israel the lowest (31). The onset of the disease is situated between 15 and 30 years old generally with both genders equally affected. A selective degeneration of hypocretin-producing neurons in the hypothalamus is the most plausible cause of human narcolepsy (32,33). Narcolepsy-cataplexy patients have an 85%–95% reduction in the number of hypocretin neurons and most narcoleptics have undetectable cerebrospinal fluid (CSF) hypocretin-1 levels (34,35). Up to 10% of narcolepsies are familial and the risk of narcolepsy in first-degree relatives is 20 to 40 times higher than in the general population. However, in several families (10%–30%), first or second-degree relatives of narcolepsy patients are affected with an attenuated phenotype characterized by isolated recurrent daytime naps and/or lapses into sleep. This finding suggests a strong genetic influence on the development of narcolepsy. However twin studies indicate concordance rates of only 25% to 31% in MZ pairs, clearly indicating a major contribution of environmental factors.

Narcolepsy is also found in Dobermans and Labradors in a clinically and electro-physiologically comparable manner to the human disease. Canine narcolepsy is transmitted as a single autosomal recessive trait with full penetrance. Mutations of the gene encoding the type 2 hypocretin/orexin receptor were found to be responsible for canine narcolepsy (36). Moreover, mutant mice with loss-of-function of the pre-prohypocretin as well as hypocretin/ataxin 3 transgenic mice (with progressive loss of hypocretin neurons) present a phenotype similar to human narcolepsy (37,38). The human 131 amino acid pre-prohypocretin/orexin gene is located on chromosome 17q21 and the hypocretin 1 and 2 are synthesized by neurons located exclusively in the lateral, posterior and perifornical hypothalamus (32,39). Only one mutation, a G to T substitution resulting in leucine to arginine change in the signal peptide of the pre-prohypocretin gene is so far reported in an atypical case of narcolepsy with a very young age at onset and a severe phenotype (32). No pathogenic mutation is found in the hypocretin receptor 1 or 2 genes. These findings indicate that although the hypocretin deficiency constitutes the best biological marker of sporadic narcolepsy, the molecular cause remains elusive and that mutations in the 3 hypocretinergic genes are exceptional in human narcolepsy.

Chronic primary insomnia. A few authors have suggested the involvement of genetic factors in early onset insomnia. Two recent studies reported high rates of familial incidence of primary insomnia, especially in the cases with early age at onset and sleep onset insomnia (40,41). Molecular studies of primary insomnias are lacking but in a single patient with chronic insomnia, a missense mutation was found in the gene encoding the gamma-aminobutyric acid A (*GABAA*) beta3 subunit (42). The substitution of the amino acid residue arginine for histidine at position 192 alters the GABAA receptor function *in vitro* (42).

Sleep disorders with HLA association:

Several sleep disorders are associated with HLA and the involvement of an autoimmune process has repeatedly been suggested. Although the mechanism

of this involvement remains unknown there remains little doubt that some HLA alleles are critically implicated in the increased genetic susceptibility risk to several sleep disorders.

Narcolepsy. Narcolepsy has one of the tightest associations with a specific HLA allele. First an association with HLA class I (Bw35) was reported in Japanese patients whereas another subtype (Bw7) was found associated in Caucasians (43,44). In the early 1980s, a 100% association with HLA DR2/DQw1 was shown in Japanese patients (43,45) while it was at 85%–95% in Caucasians (29,44). Four alleles corresponding to DRBQ1*1501, DRB5*0101, DQA1*0102 and DQB1*602 are associated with the disease. 88%–98% of patients affected with narcolepsy with clear cataplexy are HLA-DQB1*0602 positive against 40%–60% of narcolepsy patients with mild or atypical or no cataplexy (46). Since up to 10% of narcolepsy patients are DQB1*0602 negative and 15% to 25 % of the general population are DQB1*0602 positive, this allele is neither necessary nor sufficient for the development of narcolepsy (even less in the cases of narcolepsy without typical cataplexy and in familial forms). Other alleles reported to increase the risk for narcolepsy are DQB1*0301 and DQB1*0407 while DQB1*0501 or DQB1*0601 seem protective (46). These effects are nevertheless far weaker than those of DQB1*0602 and the global contribution of HLA to the total genetic risk of narcolepsy is only partial. Finally, DRB1 and DQB1 genes have been sequenced and no mutation has been found in narcolepsy patients. Altogether, as in other HLA-associated disorders, the underlying mechanism remains unknown.

REM sleep behavior disorder (RBD). RBD is a relatively rare parasomnia, more common in male elderly subjects and often occurring in a context of neurodegenerative disorders. It occurs only during REM sleep and is characterized by the loss of skeletal muscle atonia associated with REM sleep resulting in complex and vigorous dream-enacting behaviors (47). RBD-type behaviors may be seen in up to 25% of Parkinson's disease patients (48) and may appear before the onset of motor symptoms in approximately 40% of older onset RBD patients (49). RBD is also associated with dementia with Lewy bodies (50). These two associations reflect an underlying synucleinopathy. A single genetic study has been published to date, reporting an association between RBD and HLA DQw1, more specifically DQB1*05 and DQB1*06 (51). Replication studies are needed and should be facilitated by the increasing number of patients diagnosed with RBD.

Sleepwalking (SW). SW is a highly frequent parasomnia affecting up to 20% of children (52) and 1%–3% of adults (53). SW is a parasomnia occurring during slow wave sleep, generally 1 to 3 hours after sleep onset and resulting in walking with partial or complete amnesia the next day. Its familial nature (up to 80% of cases) is recognized by most authors without a clear mode of transmission (54,55). Furthermore the prevalence of SW in first-degree relatives of an affected subject is estimated to be at least 10 times higher than that in the general population (55). Twin studies have shown higher concordance for sleepwalking in MZ than in DZ twins (50% against 10%–15%) (53,56). There seems to be an important overlap in genetic predisposition to sleepwalking, sleep talking and to a lesser extent, to night terrors.

In a recent study in 60 Caucasian subjects and their families we have found a positive association between the HLA DQB1*05 subtypes and sleepwalking (notably in the familial forms) (57). The frequency of DQB1*05 was increased in sleepwalking subjects while DQB1*0602 (associated with narcolepsy) was slightly decreased. Detailed analysis in families indicates that the polymorphic amino acid Ser74, shared by all DQB1*04 and*05 alleles, is the most tightly associated DQB1 polymorphism with SW. An overlap between sleepwalking and RBD has previously been reported. A common genetic predisposition to sleepwalking and RBD (HLA DQB1*05) is therefore suggested (57). We have hypothesized that based on a close relationship between the immune system and sleep these findings suggest some immune-related regulation of motor control during sleep.

Kleine-Levin syndrome (KLS). KLS is a rare disorder mainly affecting adolescent men, characterized by hypersomnia and different behavioral abnormalities such as cognitive and mood disturbances, compulsive hyperphagia, hypersexuality and signs of dysautonomia (58–60). The etiology of KLS remains unknown although a controversial intermittent dysfunction at the diencephalic-hypothalamic level was suggested (61,62). A familial case with two siblings affected and both sharing the HLA DR2 and DQ1 antigens was reported (63) although KLS is mainly a sporadic condition. In a study in 30 unrelated patients and their families we have observed an increased frequency of the HLA-DQB1*0201 allele (28.3% against 12.5% in controls) (60). Three of the

patients but none of the controls were homozygous for this allele and in one of them the mother was also affected and homozygous DQB1*0201. In 17 heterozygous parents, 11 (64.7%) had transmitted this allele, suggesting a preferential transmission. Based on the recurrence of the episodes, the frequent infectious precipitating factors at onset, young age at onset and the association with DQB*0201, we have hypothesized an autoimmune etiology for this disorder (60). More recently, we have identified three new KLS cases, two of them DQB1*0201 positive.

Delayed sleep phase syndrome (DSPS). Delayed sleep phase syndrome (DSPS) is characterized by a persistently delayed sleep-wake timing. Shibui and colleagues found that the melatonin rhythm in these patients was delayed compared to controls (64). However, the mechanism underlying this disease is still unknown although different hypotheses have been proposed: a prolonged intrinsic circadian period beyond the range of entrainment to 24-hour day, a reduced sensitivity of the oscillator to photic entrainment, or an abnormal coupling of the sleep-wake cycle to the circadian oscillator (65–67). Although DSPS seems to have a heterogeneous etiology, it appears associated with HLA DR1 (68).

Myotonic dystrophy type 1 (DM1). DM1 is a multisystem disorder with myotonia, muscle weakness, cataracts, endocrine dysfunction and intellectual impairment. The disorder is caused by a CTG triplet expansion in the 3' untranslated region of the *DMPK* (DM1 protein kinase) gene on 19q13. DM1 is frequently associated with hypersomnia. Sleep abnormalities, such as central and obstructive sleep apnea, have also been reported. However many DM1 patients suffer from objective sleepiness in the absence of any identified respiratory disturbances but with frequent abnormal REM sleep pressure. An intrinsic hypersomnia may therefore be associated, sharing with narcolepsy a short sleep latency and the presence of sleep onset REM periods during the multiple sleep latency test. DM1 with objective hypersomnia is not associated with DQB1*0602 as in narcolepsy but may be associated with a higher frequency of DQw1 and particularly of DRw6-DQw1 haplotype (69).

Sleep disorders associated with non-HLA genes

Narcolepsy. Since narcolepsy is mainly sporadic and MZ twins are usually discordant (in terms of clinical phenotype and CSF hypocretin 1 levels) (29,70), the development of the disease should involve environmental factors interacting with genetic susceptibility factors. As indicated above the HLA DQB1*0602 is neither necessary nor sufficient to trigger narcolepsy and therefore non-HLA genes also confer susceptibility. Consistent with the imbalance between monoaminergic and cholinergic systems in narcolepsy and the fact that most available treatments act on monoaminergic neurotransmission, several studies have sought for association between polymorphisms in monoaminergic genes and sporadic narcolepsy. Significant associations between narcolepsy and the dopaminergic/noradrenergic pathways involving monoamine oxydase A (MAOA) and the catechol-o-methyltransferase (COMT) gene were reported (71,72). A sexual dimorphism of the COMT polymorphism as well as its effect on the severity of daytime sleepiness and response to stimulant (modafinil) treatment strengthens an alteration of the dopaminergic/noradrenergic rather than serotonergic pathways in narcolepsy (72,73). COMT genotype seems to influence sleep onset REM periods and sleep paralysis as well.

A tumor necrosis factor alpha (*TNF*) promoter polymorphism was also found to be associated with narcolepsy (74). *TNF* may constitute a second susceptibility gene in association with DRB1*1501 (75). Another association with the tumor necrosis factor receptor 2 was also reported in Japanese patients indicating the possibility of an additive effect with *TNF* alpha (76).

Few genetic studies have been published on the familial forms of narcolepsy. In familial forms, several subjects affected over several generations are rare, making mapping studies through linkage analysis very difficult. Nevertheless, two studies are available; the first one included 8 small Japanese families and found only a suggestive linkage (Lod score=3.09) to 4p13-q21 (77); the second one, from our laboratory, included a single extended French family, 4 with narcolepsy with clear-cut cataplexy and 10 others affected with the minor form of narcolepsy (EDS with questionable cataplexy or without cataplexy). In this study a single significant (multipoint Lod score=4.00) locus was identified in a 5Mb region on chromosome 21q (78).

Circadian rhythm sleep disorders. In addition to a possible predisposition effect of HLA DR1, several recent studies have sought for association between delayed sleep phase syndrome (DSPS) and *PER3* gene polymorphisms (18,79–80). A higher frequency of the long repeat allele (5-repeat) of *PER3* gene was found in DSPS. The exact role of *PER3* is not clearly established but this protein

heterodimerizes with *PER1* and *2* and *CRY1* and *2* before entering the nucleus and inhibiting the CLOCK/BMAL1 transcriptional complex (81,82). An alteration of PER3 phosphorylation may change its function and affect the cellular circadian machinery. A recent study reported an association between DSPS and the arylalkylamine N-acetyltransferase polymorphism (83), a gene involved in the synthesis of melatonin. A significant difference in allele frequency at a single nucleotide polymorphism resulting in a substitution of alanine 129 to threonine has been found in DSPS patients (83), suggesting a potential role of melatonin in the pathophysiology of DSPS.

Sleep apnea syndrome (SAS). Few studies have focused on the implication of genetic factors in SAS. Palmer and colleagues (84) performed a 9-cM genome scan in 66 Caucasian pedigrees and found suggestive linkage between apnea-hypopnea index and chromosome 1p (Lod score 1.39), 2p (Lod score=1.64), 12p (Lod score=1.43) and 19p (Lod score=1.4). Body mass index was linked to markers on 2p (Lod score=3.08), 7p (Lod score=2.53) and 12p (Lod score=3.41). After adjustment for body mass index, suggestive Lod scores for SAS persisted only on chromosome 2p (Lod score=1.33) and 19p (Lod score=1.45).

In some cases of SAS, the implied genetic factor seems to act at the central level (control of ventilation). A recent study reported a large kindred with 11 patients affected both by Charcot-Marie-Tooth 1A disease (duplication of *PMP22* gene) and SAS, suggesting a pathophysiological mechanism common to both conditions (85). Moreover, the marked concordance in chemo-respiratory responses observed in MZ twins also appears to underscore the importance of central factors in the genetic control of respiration. The homeobox *PHOX2B* gene, for instance, is involved in the normal patterning of the autonomous ventilatory system and heterozygous *de novo* mutations in *PHOX2B* (5-9 alanine expansions within a 20-residue polyalanine) were found in 18 out of 29 patients affected with congenital central hypoventilation syndrome (86).

Other studies reported a possible link between Apolipoprotein E epsilon4 and obstructive SAS (87,88). The probability of moderate to severe sleep disordered breathing is significantly higher in subjects with apoE4 genotype, independently of sex, body mass index and ethnicity. A polymorphism in angiotensin-converting enzyme was also reported associated with moderate obstructive SAS especially in hypertensive patients (89). Another recent study looked for an association between a haptoglobin polymorphism and the obstructive SAS complicated with cardiovascular disease (90). The results indicated that haptoglobin genotype is an important risk factor in determining susceptibility to cardiovascular disorders in obstructive SAS (90).

Restless-legs syndrome (RLS). RLS is one of the most common sleep and movement disorders affecting 2%–5% of the general population (91). RLS is characterized by an irresistible desire to move limbs, usually associated with paresthesias/dysesthesias and motor restlessness and results in nocturnal insomnia and chronic sleep deprivation (92). Symptoms start or worsen at rest and improve with activity. In over 87% of the cases, RLS is associated with periodic limb movement in sleep (PLMS) (93). The pathophysiology of RLS is still unknown although abnormalities in dopaminergic systems and brain iron metabolism may be implicated (91). Hence, eight genes coding for receptors and enzymes related to the dopaminergic neurotransmission were investigated without any significant result (94). Nevertheless, the high activity allele of the *MAOA* gene may represent a modifying factor involved in the severity of RLS manifestations in female patients only (95).

Familial forms of RLS are common, notably for the idiopathic forms, but the occurrence rate may vary depending on the geographical origins of the populations. In Quebec, the prevalence and proportion of these families seem to be particularly high suggesting a so-called founding effect. The age at onset seems to be younger in familial forms. Several studies reported that more than 50% of patients with RLS had a positive family history and that a person affected is 3–6 times more likely to have a family history than a non-affected individual (96). An autosomal dominant mode of inheritance with incomplete penetrance is evidenced in most cases with an anticipation effect (92,96,97). A strong genetic contribution is supported by frequent positive family history and high concordance of RLS in MZ twins (83%) (98). An RLS susceptibility locus has been mapped on the short arm of chromosome 12 in a large French-Canadian family (Lod score=3.59) (94). One main candidate gene within the region was neurotensin (12q21), an important modulator of dopaminergic transmission; however, a recent study excluded this gene as responsible for RLS in chromosome 12-linked families (99). A recent study confirms this locus in 5 new kindred out of 19 new French-Canadian families analyzed (100). Two more recent linkage studies reported two new loci on chromosomes 14q13-21 (101) and 9p24-22

(102), suggesting the presence of genetic heterogeneity in RLS.

Primary nocturnal enuresis. Primary nocturnal enuresis is another common type of parasomnia affecting 10% of children under the age of 7 years and up to 1%–2% of adolescents. Familial and twins studies have suggested a strong genetic contribution to enuresis although psychosocial factors have a major modulatory effect (103). A Finnish twin study reported a concordance rate of 0.43 for MZ against 0.19 for DZ twins in childhood, whereas the rate was 0.25 against 0 in adulthood (104). Backwin has shown that the incidence of the illness is highest in families in which both parents have been affected (77%) (105). Most commonly, nocturnal enuresis is inherited through an autosomal dominant mode of transmission with high penetrance (90%) (103). Four loci on chromosomes 8q, 13q, 12q and 22q11 have been identified to be involved in primary nocturnal enuresis, indicating genetic heterogeneity and suggestive of the involvement of different pathways with abnormalities including the bladder, the kidney, or the central control (106–108). A recent linkage analysis reported a 2-point Lod score of 4.2 in 6 families around the aquaporin-2 (*AQP2*) water channel locus (12q)(109). However no pathogenic mutation in *AQP2* was detected, excluding this gene in families in which the disease co-segregates with chromosome 12q locus (109).

Conclusion

Sleep is a complex phenotype regulated by many genes, gene interactions, environment and gene-environment interactions. Sleep disorders are highly frequent with important consequences for daytime functioning. Several sleep disorders have a genetic component. Recent progress in molecular genetics and the development of detailed human genome mapping have already led to the identification of genetic factors in several complex disorders. A single gene defect may cause a dysregulation of sleep and lead to a very disabling disorder but only a few genes are known for which a mutation causes a rare sleep disorder. Nevertheless, genetic linkage studies in a large number of multiplex families affected by a well defined sleep disorder should be more systematically carried out in the future.

An interesting and striking feature of an increasing number of sleep disorders is that they are associated with HLA, suggesting an interrelation between sleep and the immune system that still needs to be discovered. This relationship is not necessarily auto-immune but may involve endocrine, endotoxin and cytokine mediators that affect the basic processes of sleep regulation. Finally two other poorly explored fields relevant to the sleep research are pharmacogenomics and pharmacogenetics (73,110).

We know very little about the molecular basis of normal sleep in both animal models and humans. Most of the current progress in the field of the genetics of sleep comes from animal models, strongly indicating that a continuous effort to support and promote basic research remains an indispensable guarantee of success to further our understanding of basic mechanisms of sleep and sleep disorders. Finally, understanding the molecular genetics of sleep and sleep disorders constitutes our best hope for future development of appropriate treatments.

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