Genetic basis of sleep disorders

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Summary

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Sleep as all other complex phenotypes is regulated by genes and environment. Although many sleep disorders run in families, only few have an established genetic basis but their number is increasing. Recent progress in molecular genetics has led to the discovery of the orexin deficiency in narcolepsy and indicates that similar approaches are needed in order to understand the molecular basis of other sleep disorders. Among the best candidates are common sleep disorders such as sleep apnoea, sleepwalking, restless-legs syndrome and primary nocturnal enuresis. Most sleep disorders are complex and many genes, environment and gene-environment interactions might contribute to the final phenotype. Even at the genetic level, these disorders are still too complex for detailed analysis and sequential approaches, taking into account different aspects of the disorder, are needed. Sleep apnoea is the best example for which morphological, chemosensitivity, arousability and many other simple phenotypes should be considered one by one for a thorough genetic dissection. Here we review key sleep disorders with strong evidence for a major genetic contribution. We believe that molecular genetics constitute our best hope for future development of appropriate pharmacogenetically-based treatments.

Keywords: narcolepsy; sleepwalking; Kleine-Levin; fatal familial insomnia; enuresis; OSAS

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Introduction

Although substantial progress has been made in our understanding of the mechanisms underlying different aspects of sleep physiology, its functions remain unknown. We do know that the expression and regulation of sleep and some sleep disorders have strong genetic components. Sleep disorders are highly frequent in the general population and have dramatic health, social and economic impacts. Their treatments remain largely symptomatic owing to our ignorance of their molecular pathophysiology. A large number of sleep disorders run in families suggesting that genetic factors might play an important role. Expectations are high that the molecular pathways underlying several sleep disorders and sleep regulation or even function will be uncovered soon. Sleep is a complex behaviour and its various aspects differ in their regulation and interact with each other and the environment. Each of these aspects is likely to be under the control of a multitude of genes and each component of sleep must therefore be considered a complex trait. Any dysfunction in the expression and the regulation of sleep results in a complex sleep disorder that needs integrated clinical and laboratory investigations. The genetic dissection of well-characterised sleep disorders might improve our ability for better treatments and also provide fundamental insights into the underlying neurobiological bases of normal sleep and wakefulness. We here review key sleep disorders with well-established genetic basis and provide insights into future directions.

Fatal familial insomnia

The first sleep disorder for which a gene mutation has been identified is fatal familial insomnia (FFI), described by Lugaresi and colleagues in 1986 [1]. This neurodegenerative disorder is caused by a point mutation in the Prion protein gene (PrP) and is responsible for a degeneration of specific

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thalamic nuclei. Fatal familial insomnia affects both sexes equally in an autosomal dominant manner with high penetrance and is uniformly fatal [2]. Neuropathologic lesions are limited to spongiform degeneration of the anterior ventral and mediodorsal thalamic nuclei. It has been shown that the degeneration seen in FFI patients is associated with protease-resistant PrP in the brain tissue [3]. A gene on human chromosome 20 encodes the prion protein. The identified mutation at codon 178 [4, 5] results in the substitution of Asparagine for Aspartic acid. Familial Creutzfeld-Jacob [6] disease (CJD) is also associated with codon 178 mutation and spongiform neurodegeneration leading to dementia. The two conditions, however, differ at codon 129, with all FFI patients having a Methionine and CJD patients a Valine at this position. Furthermore, homozygosity at codon 129 was associated with a more rapid disease course in both FFI and CJD patients and lower age of onset in CJD patients. The normal function of PrP remains unknown and PrP knock-out animals do not present pathological changes but have a longer circadian period and a stronger reaction to sleep deprivation [7].

Narcolepsy

Narcolepsy-cataplexy is rare but a highly disabling disorder of vigilance affecting 0.02–0.06% of the general population. It has been defined as

> A syndrome of unknown origin that is characterized by abnormal sleep tendencies, including excessive daytime sleepiness and often disturbed nocturnal sleep and pathological manifestation of REM sleep. The REM sleep abnormalities include sleep-onset REM periods and the dissociated REM sleep inhibitory processes, cataplexy and sleep paralysis. Excessive daytime sleepiness, cataplexy and less often sleep paralysis and hypnagogic hallucinations are the major symptoms of the disease. [8]

Excessive daytime sleepiness characteristically leads to irresistible and daily repeated sleep periods. Cataplexy is defined as a "sudden bilateral loss of postural muscle tone in association with intense emotion" [8, 9] and in its typical form is pathognomic.

Genetics of narcolepsy is the best studied in the field of sleep disorders and recently substantial progress has been made owing to a valuable canine model. Up to 10% of narcolepsies are familial and different studies have shown that besides the typical phenotype attenuated forms of the condition characterised by isolated excessive daytime sleepiness do exist at much higher rates; 10–40% of first-degree relatives of narcoleptics may be affected [10].

In 1983 a first study reported 100% association between narcolepsy and the HLA-DR2/DQw1 haplotype in Japanese patients [11], a finding that was immediately confirmed in Caucasians (reviewed in [12]). Four alleles corresponding to DRB1*1501, DRB5*0101, DQA1*0102 and DQB1*0602 constitute the susceptibility haplotype associated with human narcolepsy in Caucasian populations. However, shortly after this extraordinary finding, it was demonstrated that the DR2 association is dependant on the ethnic origin with African-American narcoleptics presenting a weaker (60–65%) association [13]. In this ethnic group the strongest association is found with DQA1*0102, DQB1*0602 haplotype typically in linkage disequilibrium with DRB*1503, suggesting that the susceptibility gene should be closer to the DQ loci [14]. However, these genes have been sequenced and no mutation was identified indicating that they are either necessary or sufficient to trigger narcolepsy. Therefore, non-HLA genes also confer susceptibility to narcolepsy. Accordingly, reported positive associations with monoamine oxydase-A (MAO-A) [15], tumour necrosis factor alpha (TNF-A) [16] and catechol-O-metyltransferase (COMT) [17] genes indicate that in addition or independent of the HLA other susceptibility genes can be found. Also, a recent study reported a suggestive linkage to chromosome 4p13-q21 in several Japanese families [18]. The identified region contains the candidate genes circadian locomotor output cycles kaput (CLOCK) and λ-aminobutyric acid receptor β-1 (GABRB1).

Narcolepsy is also found in dogs and is clinically and electro-physiologically similar to the human disease. Canine narcolepsy is transmitted as a single autosomal recessive trait with full penetrance. After intensive work over the past 15 years on the genetics of canine narcolepsy at Stanford University, Mignot's group identified, through linkage analysis and positional cloning, mutations in the hypocretin-2 receptor as the cause of narcolepsy [19]. Hypocretin-1 and -2 are hypothalamic neuropeptides acting on two receptor subtypes and first found to be involved in feeding behaviour [20]. Simultaneously, Yanagisawa's group discovered in the mouse a phenotype similar to canine and human narcolepsy after a targeted deletion of the prepro-hypocretin gene [21]. Recently, it was discovered that narcoleptics have undetectable hypocretin-1 levels in their CSF [22] and that there is a dramatic reduction in the number of hypocretin-containing neurons in a small number of post-mortem narcoleptic cases [23, 24]. Also transgenic mice carrying the promotor of the human prepro-hypocretin gene ligated to truncated hu-

man ataxin-3, a gene that can induce apoptosis of hypocretin-containing neurons, present symptoms similar to human narcolepsy [25]. Among fourteen polymorphisms identified in genes encoding the prepro-hypocretin and its two receptors, none segregates with human narcolepsy [23]. Therefore, together with the tight association with the HLA antigens, the most likely cause of hypocretin deficiency in narcolepsy might be an autoimmune process resulting in acute or progressive degeneration of hypocretin-containing neurons in the hypothalamus. As over 90% of narcoleptics have no family history of narcolepsy and monozygotic twins are mostly discordant, environmental factors might play an important role [26]. The environmental factor(s) might trigger narcolepsy by inducing an autoimmune reaction that targets hypocretin neurons.

Familial advanced sleep phase syndrome

Familial advanced sleep phase syndrome (FASPS) is an abnormality of human circadian behaviour that segregates in a highly penetrant autosomal dominant manner and produces a striking 3–4-hour advance of the daily sleep-wake rhythm. Genetic studies in Drosophila, fungi, plants and animals led to the identification and characterisation of clock genes responsible for circadian behaviour [27–29]. In mammals four genes are determinant for circadian oscillation: CLOCK, BMAL1, PER and TIM.

hPer2, a human homolog of the Drosophila period gene, was found to be mutated in affected members of one family with FASPS [30]. A missense mutation at position 2106 (A to G) of the hPer2 cDNA predicting a substitution of a Serine at amino acid 662 with a Glycine (S662G) is therefore responsible for FASPS. hPER2 protein is a substrate of casein kinase Iepsilon and mutations affecting the function of casein kinase Iepsilon disrupt endogenous circadian clock function and alter period length or arrhythmicity. The causal mutation is located within the casein kinase Iepsilon binding site of hPER2. The mutation leads to decreased phosphorylation by casein kinase Iepsilon. However, not all the families tested and not all the members of the same family are linked with the hPer2 locus, suggesting a genetic heterogeneity in FASPS.

Primary nocturnal enuresis

Primary nocturnal enuresis is one of the most important health problems in children worldwide affecting 10–15% of 7-year-old children [31]. Nocturnal enuresis is bed-wetting beyond the age of 5 years, when nocturnal bladder control would normally be expected. Nocturnal enuresis is referred to as primary if the child has not previously had at least 6 months of nocturnal continence. The condition was often considered as a benign developmental process until epidemiological studies showed that 1% of adults might suffer from enuresis and an affected child has a 5–10-fold increase in risk of enuresis in adulthood [32]. Several pathophysiologic mechanisms have been proposed, e.g. a small bladder volume [33], bladder dysfunction [34], abnormal circadian vasopressin levels [35], nocturnal polyuria and abnormal sleep patterns and arousability [36].

Familial and twin studies have suggested a genetic background for enuresis. Bakwin [37] showed that the incidence of enuresis is highest in families in which both parents have been enuretic (77%). A recent Finnish study [38] in twins reported a concordance rate of 0.43 for monozygotic against 0.19 for dizygotic twins in childhood, whereas it was 0.25 against 0, respectively, in adulthood. Segregation studies have shown that, in some families, enuresis is inherited as a dominant trait with high penetrance [39]. However, familial primary enuresis is genetically heterogeneous since significant positive linkage has been found with markers on chromosomes 8q, 12q, 13q13–q14.3 (ENUR1) and 22q11 (ENUR3), suggesting that the molecular cause of enuresis might involve different levels in a common pathway including the bladder, the kidney or the central control (brain) [40–42]. In several families putative linkage with more than one of the four chromosomal regions was detected. This may indicate a polygenic inheritance with the presence of two or more genes. Further narrowing of the identified regions should ultimately lead to the identification of underlying genes [43].

Restless-legs syndrome

Restless-legs syndrome (RLS) is one of the most common sleep and movement disorders. Age at onset is variable and early onset and anticipation phenomenon have been reported in familial cases [44]. Restless-legs syndrome affects both genders equally and symptoms tend to worsen with age. Recent studies report a prevalence of 2–5% in the general population. According to the diagnostic criteria, restless-legs syndrome is defined as an irresistible desire to move limbs, usually associated with paraesthesias/dysaesthesias and motor

restlessness. The symptoms start or worsen at rest and improve with activity. In over 87% of the cases restless-legs syndrome is associated with periodic limb movement in sleep (PLMS) [45].

Although the pathophysiology of restless-legs syndrome is still unknown, a genetic basis is supported by studies reporting a positive family history in 63–92% of patients. A twin study reported that 83% of monozygotic twins were concordant for restless-legs syndrome [46], strongly suggesting that a significant portion of the familial aggregation is due to genetic factors, proposed to be transmitted in an autosomal dominant mode of inheritance. Recently, an RLS susceptibility locus has been mapped on the short arm of chromosome 12 in a large French-Canadian family [47]. Candidate genes within this region include the putative orthologue of the drosophila clock gene, timeless, and the gene encoding the tridecapeptide neurotensin. This tridecapeptide may influence dopaminergic neurotransmission [48], which is central to the pathophysiology of restless-legs syndrome [49]. Other mapping studies in different ethnic groups are needed because the RLS locus on chromosome 12 has been mapped based on a recessive mode of inheritance while in most familial cases a dominant mode of inheritance and variable expressivity is evident and may suggest genetic heterogeneity. Finally, a putative association between a polymorphism of the monoamine oxidase A and restless-legs syndrome has recently been reported [50].

Obstructive sleep apnoea syndrome

Obstructive sleep apnoea syndrome (OSAS) is a complex chronic condition influenced by multiple factors including genes, environmental influences and developmental features. OSAS is the most common sleep disorder with impacts on sleep, daytime sleepiness and cardiovascular function [51]. OSAS is defined by a large number of symptoms, specifically the occurrence of repetitive episodes of complete or partial obstruction of the upper airway during sleep resulting in snoring, sleep fragmentation, transient hypoxia, nocturnal hypertension and excessive daytime sleepiness. Many of the key risk factors have a large heritable component and OSAS has a strong familial basis. Genetic factors associated with craniofacial structure, upper airway soft tissues, body fat distribution, neural control of the upper airway and central regulation of breathing are likely to interact and influence the expression of the disease.

Familial aggregation of OSAS has been repeatedly reported [52–55]. The prevalence of OSAS among first-degree relatives of 47 subjects with laboratory-confirmed sleep-disordered breathing was estimated to be almost twice as that among control subjects and the probability of sleep-disordered breathing increased progressively with increasing numbers of affected relatives. In a recent report an oligogenic inheritance of OSAS in Caucasians, partly due to a major gene, with a small contribution from modifying genes has been proposed [55].

A study reported a possible link between the Apolipoprotein E epsilon4 and OSAS. Apolipoprotein E is a polymorphic protein encoded by 3 alleles at a single gene locus on chromosome 19q13. The same allele has been associated with Alzheimer's disease and cardiovascular disease in the general population [56, 57]. This potential association might reflect the increased prevalence of OSAS with age and its associated cardiovascular consequences. Since OSAS is a complex syndrome, future genetic studies would benefit from a better dissection of the disease into discrete phenotypes and risk factors. For instance, both hypercapnic and hypoxic responses are reduced in OSAS family members [53] and both phenotypes are found to be highly heritable traits [58]. Additional genetic effects on central and peripheral chemosensitivity, body fat and craniofacial or upper airway anatomy need further investigation.

Sleep paralysis

Sleep paralysis (SP) is a brief inability to move while awake, during the process of falling asleep or at awaking. Sleep paralysis is also considered as an abnormal REM-sleep phenomenon [59]. Episodes of up to 30 minutes have been reported. Sleep paralysis is reported by 17 to 80% of narcoleptic patients but is also occasionally observed in normal individuals or in association with other sleep pathologies. Sleep paralysis is a common condition with a prevalence of 5–62% and is highly familial with autosomal dominant transmission in some cases [60–62]. The prevalence of isolated sleep paralysis greatly varies among ethnic groups with the highest incidence found in African-Americans and in association with panic disorder [63].

Bruxism

Bruxism is a stereotyped movement disorder characterised by grinding or clenching of the teeth during sleep [8]. The prevalence of occasion-

al bruxism is very high (90%) in the general population and in approximately 5% of the cases it will present as a clinical condition [8]. In children bruxism occurs always or often in 5–20% and at least sometimes in 10–50% [64]. In young adults the respective figures are 2–5% and 10–50%, and in adults or elderly 1–5% and 6–50%. The prevalence of tooth grinding decreases linearly with age [65] and there is no gender preference in sleep bruxism [66].

The aetiology of sleep bruxism is not known, and many hypotheses have been proposed, including a genetic basis [67]. So far, no genetic marker has been found for bruxism, and no study has been undertaken to specify the mode of transmission [68]. Children of sleep bruxists are more likely to be affected than those of individuals who never suffered from this condition [69]. The concordance rate has been found to be significantly higher in monozygotic than in dizygotic twin pairs [70, 71], suggesting that hereditary factors play a role in bruxism. In a large population-based twin sample, substantial genetic effects in bruxism were found [72]. Of the total phenotypic variance in childhood bruxism, the proportion attributable to genetic influences was 49% in males and 64% in females. In bruxism among adults, the proportion of variance attributable to genetic effects also was higher in females (53%) than in males (39%). These figures are population-specific estimates, affected by a multitude of both environmental influences and genetic factors. So far no specific genes for bruxism have been found, and the environmental factors that may affect gene expression are unknown. The bivariate modelling suggests that the same genetic influences are responsible both in childhood and adulthood. Abe and Shimakawa [73] had already found that tooth grinding present in childhood persisted in 35% in adulthood, and the incidence of tooth grinding in the offspring of parents with tooth grinding is significantly higher, suggesting with the recent studies that bruxism is a persistent and highly genetic disorder.

Sleeptalking

Sleeptalking is an utterance of speech or sounds during sleep without subjective detailed awareness of the event [8]. This parasomnia can occur in REM and non-REM sleep at any time during the night [74]. Sleeptalking seems to be very common. In childhood sleeptalking occurs always or often in 5–20% and at least sometimes in 20–90% and respectively in young adults in 6 and 40% and in adults and elderly in 1–5% and 14–40% [64]. Occasional sleeptalking is benign but chronic sleeptalking may be related to significant psychopathology [75, 76]. Frequent sleeptalking in adulthood is significantly associated with psychiatric comorbidity.

A Finnish twin cohort study showed that sleeptalking is very common in the adult population. Childhood sleeptalking was equally common in both genders but as adults, sleeptalking was more frequent in males than in females. The majority of sleeptalkers had talked in their sleep in childhood. Considerable differences in concordance rates were found between monozygotic and dizygotic twin pairs, and between childhood and adulthood sleeptalking. The proportion attributable to genetic influences was over 50% in both males and females in childhood sleeptalking and higher in females (48%) than in males (37%) in adulthood [76]. No molecular genetic study is yet available in sleeptalking.

Sleepwalking and night terrors

These two parasomnias are partial arousal disorders, which occur in slow-wave sleep, usually during the first third of the sleep period [8, 77]. The frequency of these parasomnias is greatest in childhood, decreases significantly in adolescence and is lowest in adulthood [78, 79]. In children aged 5–12 years, more than 15% present sleepwalking and 2–3% night terrors. Twin studies have shown 50% of concordance in monozygotic and 10–15% for dizygotic twins [77, 80, 81]. Prevalence of sleepwalking in first-degree relatives of an affected subject has been estimated to be at least 10 times greater than that in the general population [81]. Two modes of inheritance have been proposed, multi-factorial and autosomal recessive with incomplete penetrance [80].

In a recent study on 60 Caucasian subjects and their families we reported a positive association between the HLA-DQB1*05 subtype and sleepwalking [82]. The frequency of DQB1*0501 was increased in sleepwalking patients 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 HLA-DQB1 polymorphism with sleepwalking. DQB1*05 has also been implicated in REM-sleep behaviour disorder [83]. A common genetic predisposition to sleepwalking and REM-sleep behaviour disorder may explain the coexistence of both disorders in some patients with the

so-called parasomnia overlap disorder. A hypothesis of a close relationship between the immune system and sleep may be proposed and might involve some immune-related regulation of motor control during sleep. Further replication and family studies are needed to confirm this association.

Kleine-Levin syndrome

Kleine-Levin syndrome (KLS) is a rare and probably underdiagnosed disorder of uncertain aetiology, affecting mainly young males. Kleine-Levin syndrome is characterised by periodic episodes of hypersomnia, cognitive and mood disturbances, compulsive hyperphagia and behavioural changes with frequent hypersexuality and signs of dysautonomia [8, 84, 85]. The aetiology of Kleine-Levin syndrome remains unknown, although the combination of its clinical features raised the possibility of periodic hypothalamic dysfunction [86]. In 30 unrelated patients with Kleine-Levin syndrome and their families we have recently reported that HLA-DQB1*0201 allele frequency was significantly increased [87]. Three patients with Kleine-Levin syndrome but none of the control subjects were DQB1*0201 homozygous. In 17 DQB1*0201 heterozygous parents, 11 (64,7%) had transmitted this allele, suggesting a preferential transmission. The recurrence of episodes, frequent infectious precipitating factors at onset, young age at onset, and for the first time an association with HLA-DQB*0201, are in favour of an autoimmune disorder [87].

Conclusions

The list of sleep disorders with a genetic contribution is expending fast and those reviewed here constitute significant examples only. Other common sleep disorders such as insomnia and nightmares and rare disorders such as idiopathic hypersomnia might well be controlled by genetic factors. Moreover, normal sleep *per se* is under strong genetic control both in animals and humans (see recent reviews in [88–90]). Also, significant changes in the sleep EEG can be identified and associated with single genes [88, 89]. The most striking finding remains the HLA association found in narcolepsy, sleepwalking, Kleine-Levin syndrome and REM-sleep behaviour disorder. Although not a major common feature can be proposed in these disorders, this finding suggests a fundamental relationship between sleep and the immune system [91], which remains to be discovered. As mentioned in the introduction, increasing our knowledge of molecular basis of sleep and sleep disorders should ultimately help developing appropriate treatments. We first showed that a functional polymorphism of the catechol-O-methyltransferase gene (involved in the metabolism of dopamine) presents a sexual dimorphism and is strongly associated with the severity of narcolepsy [17]. More recently, we have reported that this sexual dimorphism in narcolepsy is associated with response to modafinil with women being less severely affected with excessive daytime sleepiness and responding better to stimulant treatments [92]. Pharmacogenetics is therefore our best hope once molecular genetics of sleep disorders makes significant progress [93].

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