The genetics of sleep disorders

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The contribution of genetic components to the pathology of sleep disorders is increasingly recognised as important. Genetic studies have identified genes that may be important in the regulation of circadian rhythms, which in turn determine the time of sleep onset and waking. Recent studies have shown that mutations in *hPER2* are associated with autosomal-dominant familial advanced-sleep-phase syndrome. Genetic studies in a canine model of narcolepsy and in knock-out mice have led to the identification of the hypothalamic hypocretin (orexin) neurotransmitter system as a key target for human narcolepsy. The contribution of genetic factors to obstructive sleep apnoea syndrome (OSAS) has led to a better understanding of this complex disorder that may be part of a larger syndrome associated with respiratory, cardiovascular, and metabolic dysfunction. The aim of this review is to discuss the current knowledge on the role of genetic factors in sleep disorders, in particular circadian disorders, narcolepsy, restless-legs syndrome, and OSAS.

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In human beings, sleep occupies about a third of adult life. Sleep is essential; the precise physiological reasons for this are unknown, but even subtle changes in duration and quality of sleep can impinge greatly on health.[1] Epidemiological studies have stimulated debate by reporting an association between sleep duration, insomnia, and mortality.[2] The importance of sleep was clearly shown in studies with rodents in which total sleep deprivation resulted in death within 2–4 weeks.[3] The complexity of regulation of sleep and wakefulness is reflected by differences in the expression of various genes between these states, which indicates changes at the cellular level.[4] A study of the genes involved in various sleep disorders and how various genetic disorders may cause sleep disturbance is central to our understanding of the intriguing and complex mechanisms that regulate sleep.

Electrophysiological studies have shown that normal sleep can be divided into two states: rapid-eye-movement (REM) sleep and non-REM sleep. Non-REM sleep is subdivided into four stages: stages I and II (light, non-REM sleep) and stages III and IV (deep, slow-wave sleep).[1] Since REM sleep is associated with an electroencephalographic (EEG) pattern that resembles the awake state, it is also called paradoxical sleep. The various sleep stages are intimately linked with specific changes in thermoregulation and cardiovascular, respiratory, gastrointestinal, and endocrine functions.[5]

Two important and interconnected mechanisms determine the timing, duration, and intensity of sleep: circadian (clock-dependent) and homoeostatic (sleep-debt-dependent).[6–10] Circadian rhythms are mainly generated in the suprachiasmatic nucleus of the hypothalamus, which contains pacemaker neurons with a genetically identified biological clock.[11,12] The suprachiasmatic nucleus is entrained by light through neural inputs from the retina (retinohypothalamic tract). In the absence of cues (zeitgebers), most importantly light, the biological clock fluctuates with a periodicity that ranges between 23·8 to 27·1 h, called the free-running circadian period, τ. Recent studies show that in human beings τ may be only slightly longer than 24 h, depending on the specific protocol used to measure endogenous circadian phase.[13]

The mechanisms for the homoeostatic regulatory process (also called process S) are more diffusely located within the brain and determine the need for sleep after sleep deprivation. The neuroanatomical, genetic, and neurochemical mechanisms involved in this process are largely unknown. Slow-wave sleep and EEG slow-wave activity during non-REM sleep have classically been used as markers of the sleep homoeostatic process.[7] Other investigators have, however, stressed the importance of sleep continuity, on the basis of observations that benzodiazepine administration produces restorative sleep yet actually reduces deep slow-wave sleep.[14] Some animals such as birds, dolphins, and some seals can experience slow-wave sleep in one hemisphere;[15,16] slow-wave activity that can be generated unilaterally in the brain is most probably brought about by the regulation of established thalamocortical circuits.[15] Although the slow-wave process and resulting EEG phenotype might be generated through these circuits, other findings indicate the importance of other brain regions such as the hypothalamus, the basal forebrain, and the brainstem in the generation of sleep.[17–24]

Genetic studies are likely to clarify some of the complexities of sleep and lead to novel approaches for the treatment of sleep disorders. Genes are less likely to be involved in state-to-state changes observed electrophysiologically during the sleep cycle; they are more likely to contribute to circadian rhythmicity and to sleep

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homoeostasis. The study of circadian mechanisms has benefited from the identification of the molecular basis of rhythmicity through mutagenesis and positional cloning studies in drosophila and rodents.[11,12] Recently, study of the genetics of canine narcolepsy has identified the importance of hypocretin (also called orexin) deficiency in human narcolepsy.[23,25]

The genetics of sleep

Twin studies

Twin studies have attempted to assess the heritable component of normal sleep. Such studies either have been based on questionnaires comparing sleep habits (duration of sleep, schedules and quality of night sleep, and frequency of napping) in monozygotic and dizygotic twins,[26,27] or have studied EEG in small numbers of twins.[28,29] Relations between most variables assessed by questionnaires are significantly stronger for monozygotic than for dizygotic twins, even when the twins do not share the same environment. However, environmental factors and noise also contribute significantly to the variance. EEG studies generally confirm the findings of questionnaire-based studies. In a study of 26 twin pairs over three consecutive nights, significant differences were observed between monozygotic and dizygotic twin-pair correlations for all stages of sleep except REM sleep.[28] Another study looking at awake-resting EEG frequencies in a large number of monozygotic and dizygotic twins reported high average heritabilities (0·76 to 0·89) for all analysed EEG frequency bands.[29] Few studies have investigated the genetic contribution to circadian and homoeostatic processes. In one study, using the Horne-Ostberg morningness–eveningness score in 238 twin pairs, higher correlations were found for monozygotic pairs, which indicate the existence of human circadian genetic factors.[30]

Circadian-rhythm genes

Circadian rhythmicity is an almost universal property observed in most organisms, including some unicellular organisms. In mammals, circadian clocks are located mainly, but not exclusively, in the hypothalamic suprachiasmatic nucleus. The clocks in the cells of this nucleus operate through transcription–translation (genes and their protein products) autoregulatory feedback loops.[11,12] *Clock* was the first mammalian clock gene to be functionally identified—mutations were produced through N-ethyl-N-nitrosourea germline mutagenesis in mice.[31,32] *Clock* mutations were found to be associated with a long free-running period, τ, and were mapped to the midportion of mouse chromosome 5, in a region of conserved synteny with human chromosome 4. Clock is one of the basic helix-loop-helix family of proteins. When partnered with Bmal1 (another basic helix-loop-helix protein), Clock binds DNA to stimulate the expression of period proteins (Per1 and Per2) and cryptochromes (Cry1 and Cry2). Period proteins and the cryptochromes in turn suppress the transcriptional activity of Clock–Bmal1, thus completing the negative feedback loop.[11,12]

Until recently, the importance of circadian clock genes in human beings was unclear, although, from rodent and drosophila studies, there was a suspicion that genetic variation in circadian period might explain why some people are "morning larks" while others are "night owls". In drosophila and rodents, long-period mutants are generally phase-delayed with respect to an entraining light–dark cycle, whereas short-period mutants are mostly phase-advanced. By use of the Horne-Ostberg morningness–eveningness score and examining a single nucleotide polymorphism located in the 3' flanking region of the human *CLOCK* gene, Katzenberg and colleagues[33] showed that people with the 3111C *CLOCK* allele had lower Horne-Ostberg scores and a 10–44 min delay in preferred timing for activity or sleep episodes.

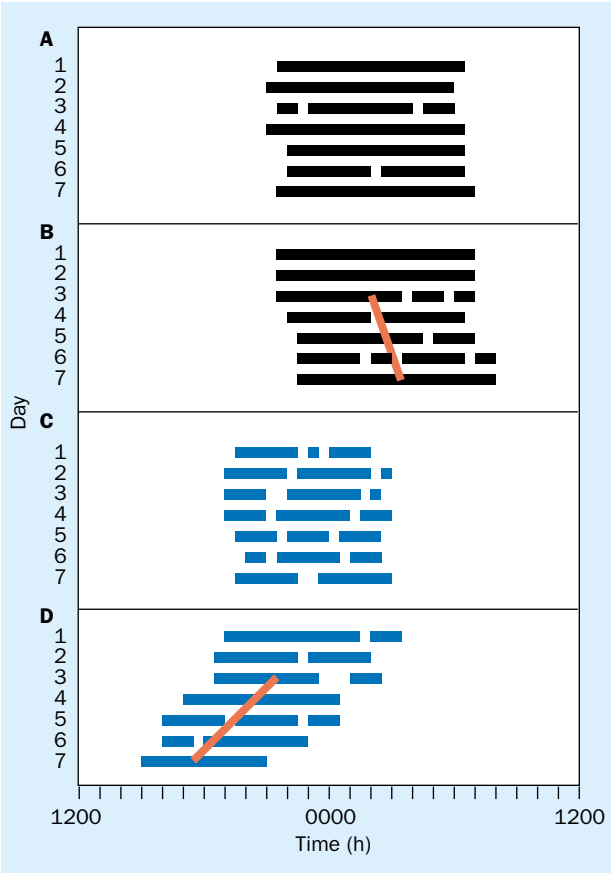

Figure 1. Schematic sleep logs over 7 days carried out in controls under entrained light–dark conditions (A) and free-running conditions in the absence of time cues (B). Controls sleep at usual hours (entrained) and will show an endogenous rhythm close to 24 h under free-running conditions. Similar data are shown for individuals with advanced-sleep-phase syndrome (ASPS). In ASPS, times of both going to sleep and awakening are advanced under entrained conditions (C) and the free-running period is shorter than 24 h (D). Black and blue bars represent sleep.

Circadian disorders

Advanced-sleep-phase syndrome is a rare disorder characterised by very early sleep onset (1900 h) and very early waking (0430 h). In familial cases patients have a very short circadian period with a 4 h advance of daily sleep–wake rhythm (figure 1). Furthermore, the syndrome was shown to segregate as a highly penetrant autosomal dominant trait (figure 2).[34] Familial advanced-sleep-phase syndrome is

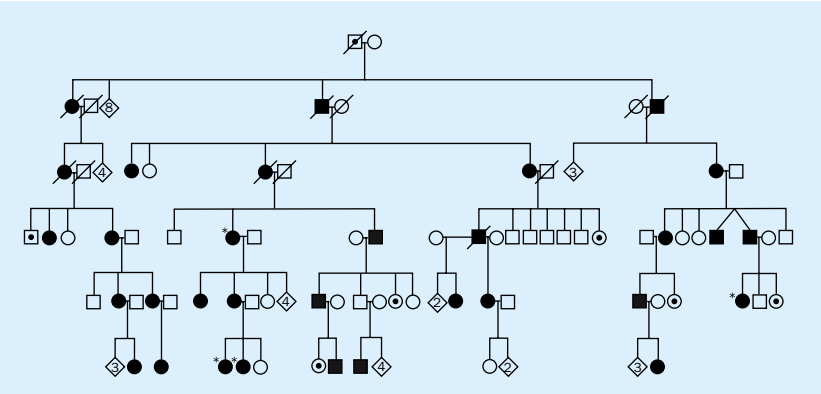

*Figure 2. Pedigree of a family that demonstrates autosomal dominant inheritance of advanced-sleep-phase syndrome. Circle=male; square=female. Filled symbols=affected individuals; open symbols=unaffected individuals; symbols with central dots=individuals of unknown phenotype; diamonds=sibships of children with unknown phenotype (number in diamond=sibship size). Slash through symbol=dead; arrow=index case. *Patient included in the inpatient study by Jones and colleagues[34] studying activity, sleep variables, core body temperature, and melatonin concentrations. Patients with ASPS had significantly earlier sleep onset and awakening, and phase-advanced dim-light plasma melatonin and temperature rhythms. Reproduced with the permission of Louis Ptacek.[34]*

associated with a mutation (S662G) in the human period 2 (PER2) peptide. The gene, *hPER2*, is located on chromosome 2q, and the mutation occurs in exon 17.[35] The mutation affects a phosphorylation site of the PER protein by the enzyme human casein kinase Iε (CK Iε), a homologue of the protein encoded by the drosophila circadian gene *doubletime*. Mutations in *Per2* in the mouse produce a short-period phenotype similar to advanced-sleep-phase syndome.[36] A mis-sense mutation in CK Iε (the *tau* mutation) in Syrian hamsters shortens period length and results in a similar syndrome to advanced-sleep-phase syndrome.[37] Some cases of familial advanced-sleep-phase syndrome, however, are not caused by mutation in the *hPER2* locus, which suggests that other genes are involved.[35] The opposite of advanced-sleep-phase syndrome, delayed-sleep-phase syndrome, is associated with delayed bedtime and delayed wake time. The problem is most commonly found in young adults. Recently, delayed-sleep-phase syndrome has been associated with structural polymorphisms in the human period 3 (*hPER3*) gene.[38]

Narcolepsy–cataplexy and dissociated REM sleep events

Narcolepsy–cataplexy syndrome affects 0·02–0·06% of the general population in the USA and western European countries.[39] It may be more common in Japan and less common in Israel,[39] although this variation in prevalence could be due to methodological differences. Narcolepsy generally begins in the second or third decade of life[40] and is characterised by excessive daytime sleepiness (usually the most disabling symptom), cataplexy (sudden loss of muscle tone in response to strong emotion), hypnagogic hallucinations (dream-like experiences occurring at sleep onset), and sleep paralysis (the inability to move while falling asleep or on awakening). Narcolepsy therefore consists of an inability to maintain wakefulness combined with intrusion of REM-sleep-associated phenomena (hallucinations, sleep paralysis, and possibly cataplexy) into wakefulness. Sleepiness is estimated with the multiple sleep latency test.[41] In this test, the time taken to fall asleep is measured for each of four to five short naps taken every 2 h during the daytime, and the presence or absence of an REM-sleep transition is recorded. Untreated patients typically display short mean sleep latency (about 8 min) and two or more sleep-onset REM periods during naps. Cataplexy is indicative of narcolepsy[40] but is difficult to demonstrate objectively. It consists of brief episodes of muscle weakness when the patient is emotionally excited (eg, laughing) and results in knees buckling, jaw sagging, head dropping, or less frequently, full body paralysis. Full consciousness is maintained, and tendon reflexes are generally absent during an attack.

Several cases of familial narcolepsy have been reported, and first-degree relatives of patients with narcolepsy have a 10–40 times greater than normal risk of developing narcolepsy–cataplexy.[39] Narcolepsy is not, however, a simple genetic disorder. No more than a third of monozygotic twins are concordant for narcolepsy,[39] so non-genetic factors must also play a major part. A genetic factor that predisposes for narcolepsy is located in the MHC DQ region. 90–100% of patients with narcolepsy–cataplexy are positive for the HLA class II allele, DQB1*0602 (most often in combination with DR2) compared with 12–38% of the general population.[40,42,43] Other HLA subtypes also have a modulating effect. For example, DQB1*0301 increases susceptibility whereas alleles such as DQB1*0601 and DQB1*0501 are protective.[43] Surprisingly, DQB1*0601 is very similar to DQB1*0602 yet it is protective; this difference suggests that tiny changes in the peptide binding pockets of these molecules may have strong effects in narcolepsy. Familial aggregation in narcolepsy cannot be explained by shared HLA haplotypes alone because some families are not positive for HLA DQB1*0602.[39] Non-HLA susceptibility genes are probably also important. The strong association with an HLA marker has suggested that narcolepsy–cataplexy is an autoimmune disorder. However, to date, no concrete evidence to support this hypothesis has been reported.

Hypocretins (orexins)

A colony of narcoleptic dogs has been intensively studied at Stanford University since 1976. Canine narcolepsy is transmitted as a single autosomal recessive trait with full penetrance, which is not linked to MHC class II. A decade-long search for the genetic abnormalities in canine narcolepsy recently resulted in the discovery that canine narcolepsy is caused by mutations in one of the receptors (hcrtr2) for the newly discovered lateral hypothalamic neuropeptides, the hypocretins (also called orexins).[25] At around the same time, mice with targeted disruption of the hypocretin precursor

(preprohypocretin) gene were shown to have periods of behavioural arrest and EEG patterns that resemble human narcolepsy.[44] These findings in animals have now been extended to human beings and most of the narcolepsy–cataplexy patients studied have been shown to have low or undetectable hypocretin in their CSF.[42,45] Few post-mortem studies of human brain have been done, but these studies have shown that patients with narcolepsy have much lower than normal hypocretin levels in the brain.[46,47]

So far, only one case of narcolepsy has been associated with a mutation in the gene that encodes preprohypocretin (figure 3).[46] This case is unusual in that the onset of narcolepsy was at a very early age (cataplexy at age 6 months). The mutation in the preprohypocretin gene results in abnormal trafficking of the mutant peptide precursor (figure 4).[46] No mutations have been observed in the genes for the two hypocretin receptors *HCRTR1* and *HCRTR2*.[46] Similarly, no association between narcolepsy and polymorphisms in hypocretin genes has been found.[46,48,49] Narcolepsy–cataplexy is therefore associated with deficiency in hypocretin neurotransmission, but in most cases, this deficiency is not due to mutations or polymorphisms in preprohypocretin and hypocretin receptor genes. The fact that narcolepsy–cataplexy is associated with specific HLA alleles in sporadic cases,[43] with generally adolescent onset, suggests that most cases may be due to autoimmune targeting of hypocretin cells. Polymorphisms in other genes such as catechol-O-methyltransferase[50] and the tumour necrosis factor system[51] may also be involved.

Whereas narcolepsy–cataplexy is associated with HLA DQB1*0602 and hypocretin deficiency, the situation is more complex in hypersomnia cases without cataplexy. In these related disorders, investigators have reported a partial HLA DQB1*0602 association (eg, 40%) but most of these patients have normal concentrations of hypocretin-1 in CSF.[42] This suggests disease heterogeneity and partial hypocretin deficiency that does not result in significantly decreased CSF hypocretin levels.[42] Cataplexy without sleepiness is exceptional, but rare familial cases have been reported with or without associated sleep paralysis.[52,53] In some of these cases, however, clinical presentation differs strongly from narcolepsy–cataplexy (cataplexy presents in the first months of life). HLA typing and hypocretin measurements have not been carried out for these families. Isolated narcolepsy, cataplexy, or cataplexy-like symptoms can be associated with genetic disorders such as Prader-Willi syndrome, Niemann-Pick disease type C, and Norrie's disease.[53–57] In some of these cases, decreased hypocretin transmission has been reported, which suggests genuine secondary cases of narcolepsy.[42]

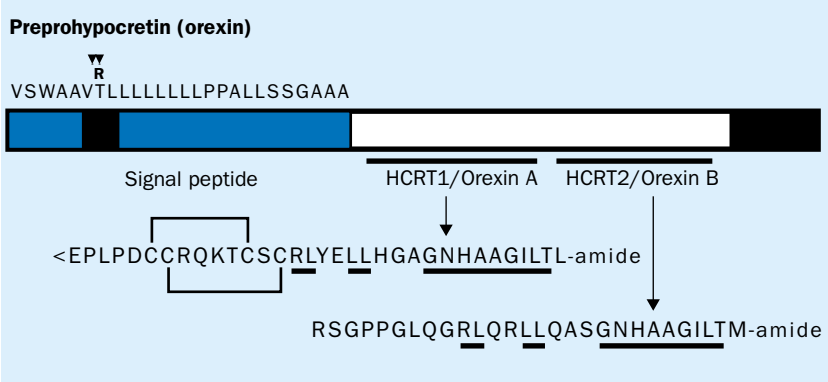

Figure 3. Mutation in preprohypocretin that leads to narcolepsy.The mutation produces a polar substitution in the hydrophobic core of preprohypocretin (orexin). Note arginine insertion in the polyleucine stretch of neutral, hydrophobic amino acids (double arrows). The amino-acid structures of the biologically active products, human hypocretin-1 (HCRT-1; orexin A) and hypocretin 2 (HCRT-2; orexin B), are also shown. HCRT-1 has two disulphide bonds. <E = pyroglutamyl residue. Note the C-terminal amidation of both peptides, which is essential for their biological activity. Amino acids common to both peptides are underlined.

Sleep paralysis and hypnagogic hallucinations—symptoms of dissociated REM sleep—without narcolepsy are commonly reported. Sleep paralysis is highly familial, with autosomal dominant transmission in some cases.[54,58–60] Twin studies suggest a much higher concordance in monozygotic than in dizygotic twins for this symptom,[61] which has no clear association with HLA DQB1*0602,[62] but may be more frequent in African Americans.[60] In REM-sleep-behaviour disorder, motor behaviours arise during REM sleep, which disturb sleep continuity. REM-sleep-behaviour disorder is frequently associated with other disorders such as narcolepsy but also occurs in isolation. It is a common early sign of a parkinsonian disorder.[63] REM-sleep-behaviour disorder may also be weakly associated with HLA DQ1.[64]

Restless-legs syndrome

Restless-legs syndrome (also called Ekbom's syndrome) is a common disorder affecting 2–5% of the general population.[65] It begins in early adult life in most cases and affects both sexes equally. Symptoms tend to worsen with age. The syndrome is both a sensory and a motor disorder. Most patients complain of paraesthesias accompanied by an urge to move their limbs (usually legs). This urge (akathisia) is generally greatest at rest and is relieved by movement. Symptoms tend to worsen during the day such that they are worst at bedtime thus disrupting sleep. Symptoms then improve in the early morning allowing some respite, but return in the afternoon, evening, or bedtime. Sleep disruption results in daytime fatigue. In 85% of patients, restless-legs syndrome is associated with periodic leg movements during sleep (and also wakefulness) that occur mostly during stage II sleep; the periodic leg movements recur every 20–40 s. The pathophysiology of the syndrome has not been fully elucidated but may involve dopaminergic dysfunction and abnormalities in brain iron metabolism.[65]

Several studies have highlighted the familial occurrence of restless-legs syndrome.[66,67] The hereditary form of the syndrome may have an earlier onset than the idiopathic

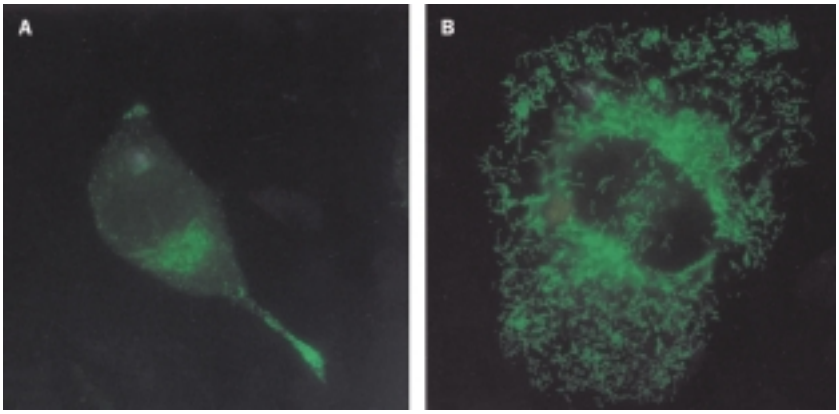

Figure 4. Fluorescent images of a single transfected cell. In vitro transfection studies show that the mutation impairs peptide trafficking, resulting in the abnormal accumulation of a mutant polypeptide. (A) Wild-type protein fused to green fluorescent protein is processed into mature secretory vesicles. (B) Mutant protein fused to GFP is retained in a tubular network and is not processed into secretory vesicles. This case illustrates the need for coordinated genetic, biochemical, and clinical studies. Reproduced with the permission of the Nature Publishing Group.[46]

form. The prevalence and the proportion of familial cases vary widely with geographical origin. This variation may reflect founder effects—such as in Quebec, where there is a high proportion of familial cases and a higher prevalence—or the influence of local environmental factors.[67] Up to a third of cases may transmit the disorder as an autosomal dominant trait with possible genetic anticipation. A recent twin study reported that ten of 12 self-selected monozygotic twin pairs were concordant for restless-legs syndrome, hence some familial aggregation may be due to genetic factors.[66] Linkage studies of microsatellite markers and candidate genes in multiplex families are underway to identify the genes involved.[68] Because of the association of restless-legs syndrome with dopaminergic dysfunction, a recent study analysed eight genes that encode receptors and enzymes related to dopaminergic transmission.[69] No significant differences were found between patients and controls. Recently, the mapping of a large French-Canadian kindred group provided evidence for a susceptibility locus within a 14·71 cM region on chromosome 12q.[68] 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 transmission,[70] which is central to the pathophysiology of restless-legs syndrome.

Obstructive sleep apnoea syndrome (OSAS)

The most common form of sleep-disordered breathing is OSAS, in which the upper airway collapses repetitively during sleep resulting in snoring, sleep-related decreases and pauses in respiration, transient hypoxia, sleep fragmentation, and excessive daytime sleepiness.[71,72] Associated nocturnal symptoms include restlessness, excessive salivation and sweating, nocturia, and gastro-oesophageal reflux. The patient frequently wakes in the morning with headache and a dry mouth or throat. Excessive daytime sleepiness is likely to be secondary to sleep deprivation at night, which, together with recurrent hypoxia and sympathetic activation during sleep, may lead to adverse metabolic consequences of OSAS. Patients with OSAS have consistently been shown to be at increased risk of high blood pressure and cardiovascular events.[73,74]

The diagnosis of OSAS is confirmed by polysomnography, in which electrical activity from the brain, eyes, heart, and chin and leg muscles is monitored, in addition to respiratory variables such as oronasal airflow, chest and abdominal movement, blood oxygen saturation, snoring intensity, and in some cases oesophageal pressure. OSAS is diagnosed when the patient reports snoring and daytime sleepiness, and has an apnoea–hypopnoea index ([apnoeas + hypopnoeas]/duration of sleep [h]) of 5 or more. An obstructive apnoea is defined as a 10 s pause in oronasal airflow despite chest and abdominal movement, accompanied by decreases in oxygen saturation and arousals from sleep. An obstructive hypopnoea is defined by the same criteria of duration and oxygen saturation as the obstructive apnoea, except that there is a partial (at least 50%), rather than complete, obstruction in oronasal airflow. OSAS is more frequent in men, is found in all age groups, and becomes more prevalent with age. Among people over 55 years of age, 30–60% meet the polysomnographic diagnostic criterion of an apnoea–hypopnea index of 5 or more.[75] The prevalence of OSAS in children is more uncertain but is estimated to be 2–8%.[76]

Recent twin studies have shown higher concordance in monozygotic than in dizygotic twins for habitual snoring.[77] Several families of patients with OSAS have also been studied.[78–88] First-degree relatives of patients with OSAS have consistently been shown to be at increased risk.[82–87] Familial aggregation is generally explained by the fact that most risk factors involved in the pathophysiology of OSAS are, to a large extent, genetically determined.[82–84,89,90] The major risk factors for OSAS include obesity, ventilatory control abnormalities, and craniofacial dysmorphism (disproportionate craniofacial anatomy).[72]

Obesity probably results in sleep-disordered breathing through increased fat deposition in the nasopharyngeal area and reduced chest-wall compliance. Twin studies have shown that an estimated 70% of the variance in obesity within the general population can be attributed to genetic factors.[89,90] Obesity is believed to be secondary to abnormalities in autonomic, endocrine, and hypothalamic function, which, in turn, are associated with genetic factors that influence metabolic rate, fat storage, and eating behaviour. About a quarter of the between-twin variability in regional body-fat distribution may be influenced by genetic factors.[90] Hence, upper-body obesity may be a relatively greater risk factor for OSAS than total body fat mass. Since OSAS is associated with obesity, type 2 diabetes mellitus (possibly independently of obesity), and

hypertension,[73,74,86,91] the impact of the combined pathology on the cardiovascular system is high. The term "syndrome Z" has been introduced for the combination of hypertension, central obesity, insulin resistance, hyperlipidaemia, and OSAS.[92] Some studies have shown combined metabolic abnormalities in patients with obesity (metabolic syndrome or syndrome X),[93] and sleep deprivation itself has been shown to have metabolic consequences.[94] Increasingly, OSAS is considered as one facet of a more complex set of disturbances, and the challenge is to identify the major causal pathways, many of which will ultimately be traceable to genetic factors.

In some cases, the mutation involved is the main cause of abnormal ventilatory control by the CNS.[80,82] Abnormalities in ventilatory responsiveness to either hypoxia or hypercapnia have been shown in first-degree relatives of probands with various pulmonary diseases.[95] A possible genetic overlap between OSAS, sudden infant death syndrome,[80,81,96] and apparent life-threatening events,[97] combined with the high degree of concordance in chemoreceptor responses observed in monozygotic twins,[98,99] emphasises the importance of genetic factors in the central control of ventilation in OSAS.

To address the issue of genetic predisposition to OSAS, two basic designs are currently used: a systematic genome scan in multiplex families; and the study of candidate gene markers by case-control designs. One study found a substantial increase in HLA*A2 and HLA*B39 in Japanese patients with OSAS.[100] This finding may indirectly reflect the effect of HLA DQ on nocturnal sleep in the general population but has not been confirmed.[101] Jennum and colleagues[102] systematically explored various blood groups in an epidemiological sample and found an increased frequency of the Lewis blood group phenotype Le(a+b-) in snorers compared with non-snorers. Zhang and co-workers[103] have found that a polymorphism in angiotensin-converting enzyme, known to be associated with hypertension,[104] was associated with increased blood pressure in patients with moderate sleep apnoea.

A role of apolipoprotein E markers in OSAS has also been reported but remains to be clarified. Apolipoprotein E is a polymorphic protein arising from three alleles at a single gene locus on chromosome 19q13. Three studies, with very different samples and research designs, have investigated the possible link between the apolipoprotein E genotype, ε4, and OSAS. The rationale for these studies was a possible relation between OSAS, cardiovascular disease, and dementia. The ε4 genotype predisposes strongly to Alzheimer's disease and cardiovascular disease in the general population.[105,106] OSAS prevalence is also known to increase with age and may be increased in patients with dementia.[107] Saarelainen and colleagues[108] looked at the frequency of apolipoprotein E alleles in 291 patients with OSAS and 728 controls matched for age and sex: the ε4 carrier frequency did not differ from that in controls but a higher proportion of homozygotes was observed in the sleep apnoea group (5·8% *vs* 3·6%; odds ratio 1·68 [95% CI 0·90–3·13], p=0·1). Importantly, however, mild OSAS cases were included in the study and patients with "any other neurological and cerebrovascular diseases" were excluded (potentially lowering the number of apolipoprotein ε4 carriers with sleep apnoea in the study). The absence of OSAS in the mostly male (78%) control group was not established (24% of the male population have an apnoea–hypopnea index ⩾5). A second study was population based and included 800 participants from the Wisconsin sleep cohort who were studied one to three times in the sleep laboratory over a 4–8 year period.[105] The participants were almost all middle aged (32–68 years, mean 49 years) and overweight (mean body-mass index 30 kg/m^2). The risk of a apnoea–hypopnea index of 15 or more was doubled and independent of sex and body-mass index.[109] In a third study, by Foley and colleagues,[110] in the very old (79–97 years) no association was found; this raises the interesting possibility of survival effects or distinct pathophysiology for OSAS in the very old.

Insomnia and fatal familial insomnia

9–15% of the general adult population suffer from chronic insomnia and an additional 15–20% of the adult population complain of occasional sleep difficulties.[111,112] Insomnia is more common in women than men and increases with age.[111,112] Familial occurrence is common[113] but well-controlled family studies are lacking. A potentially interesting but controversial model for insomnia is fatal familial insomnia. This rare neurological condition is characterised by severe insomnia, neurovegetative symptoms, intellectual deterioration, and death.[114-116] Insomnia is an early sign, and sleep disruption is associated with a disappearance of stage II and slow-wave sleep while brief episodes of REM sleep are maintained. Neuropathological lesions are mostly limited to spongiform degeneration of the anterior ventral and mediodorsal thalamic nuclei and of the inferior olive. This pathology is typically associated with a mutation of the codon 178 in the prion gene. These mutations are also found in some forms of dementia including Creutzfeldt-Jakob disease, but a polymorphism on codon 129 seems to determine the phenotypic expression into fatal familial insomnia. Other investigators have questioned the existence of genuine phenotypic differences between fatal familial insomnia and Creutzfeldt-Jakob disease.[117,118] Some of the confusion stems from the definition of insomnia in fatal familial insomnia as the inability to generate slow-wave sleep, which is more commonly related to agrypnia.[116]

The prion is encoded by a gene located on human chromosome 20. The normal function of the protein is unknown, but the gene is expressed in neurons. Mice homozygous for mutations that disrupt the prion gene are behaviourally normal but may display sleep abnormalities.[119] Prions are involved in a group of human and animal disorders with more or less anatomically confined spongiform degeneration and neuronal atrophy (spongiform encephalopathies). A proteinase-resistant form of the prion is involved in the pathogenesis.[120] These diseases can appear in a familial context or in an infectious context, in which the prion acts as the transmitting agent. The mechanism by which certain isoforms of the prion are infectious remains a widely discussed topic.

Search strategy

Data for this article were identified from the authors' knowledge of the subject, personal files, and sleep congress abstract books. Textbooks of sleep medicine (and references therein) were consulted. Medline and Current Contents searches were carried out with the terms "sleep", "sleep disorders", "sleep apnoea", "sleep disordered breathing", "narcolepsy", "sleep paralysis", "parasomnia", "circadian", "sleep walking", "fatal familial insomnia", "insomnia", "restless leg syndrome", "REM behaviour disorder", "genetic", "gene", "polymorphisms", "familial", "twins". Abstracts were included only when the data were important and not yet available in a peer-reviewed publication.

How a simple additional polymorphism on codon 129 alters the symptom pattern from Creutzfeldt-Jakob disease to fatal familial insomnia is not understood, but molecular studies are underway to assess the effect of these mutations on the metabolism of the protein.[121] The differences in symptoms are probably due to the anatomical localisation of the lesions. In fatal familial insomnia, degeneration is mostly localised in the anterior ventral and mediodorsal thalamic nuclei, but lesions are more diffuse in Creutzfeldt-Jakob disease.[114–116] The well-established role of the thalamus (albeit mostly of the intralaminar thalamus) and of its cortical projections in the generation of cortical synchronisation of the slow-wave sleep and sleep spindles[17] suggests that thalamic lesions may cause insomnia in the fatal familial form. No study has convincingly shown that the destruction of these nuclei can produce fatal insomnia in animal models. A bilateral lesion of these nuclei produces persistent insomnia that is not fatal.[122] More discrete anatomical lesions or a distinct pathophysiological mechanism could also play a part. Mice carrying transgenes with the human prion allele for fatal familial insomnia have now been generated to answer these questions.

The implication of the thalamus in the physiopathology of fatal familial insomnia suggests that it may be involved in the genesis of other, more common insomnias. Many cases of insomnia seem to be caused by constitutional and genetic factors acting in the thalamus; homoeostatic abnormalities in the regulation of sleep could be involved in some cases. Other genetic factors, such as those that regulate circadian rhythmicity at the level of the suprachiasmatic nuclei, could also be involved.

Sleepwalking, night terrors, and nocturnal frontal-lobe epilepsy

These parasomnias generally occur during slow-wave sleep (stages III and IV).[123] They are generally grouped together and considered to share a common or related disease mechanism,[124] even if this view is sometimes disputed.[125] The prevalence of these symptoms is about 10% among children and rarely requires a medical consultation. Symptoms generally disappear in adulthood.[123,125] The familial nature of these symptoms has been emphasised by most researchers[126-129] but the exact mode of transmission is uncertain. Twin studies have shown a high degree of concordance for sleepwalking and night terrors (50% for monozygotes, 10–15% for dizygotes).[130,131] The genetic predisposition to sleepwalking, sleeptalking, and to a lesser degree, night terrors seems to overlap since the frequency of night terrors and enuresis may be more frequent in families with somnambulism.[126,128,129] This link suggests a related disease mechanism and a similar genetic control. To date, very few investigators have initiated molecular studies for these disorders although a possible association with HLA DQB1*05 has been reported.[132]

An important new clinical entity is the genetically heterogeneous, but clinically homogeneous, autosomal-dominant nocturnal frontal-lobe epilepsy, characterised by clusters of frontal-lobe seizures during sleep.[133,134] This disorder is inherited in an autosomal dominant fashion with 75% penetrance and commonly starts in childhood. It may be mistaken for nightmares or night terrors. There are at least three forms of this condition characterised by different mutations. The gene for type 1 has been mapped to chromosome 20q13.2.[135] The mutation causes a molecular defect in the nicotinic acetylcholine receptor α4 (*CHRNA4*) subunit, causing abnormal function.[136–138] The type 2 gene has been mapped to chromosome 15q24, *CHRNA3–CHRNA5–CHRNB4* cluster.[139] Type 3 is associated with mutations in the *CHRNB2* gene on chromosome 1p21.[140,141]

Conclusions

Most of the current progress in the study of sleep genetics has been made with the help of animal models. In one case, regulation of circadian rhythms, knowledge was first generated in drosophila and later shown to be applicable to mammals.[12,142] This knowledge is now being transferred to human medicine, with the recent demonstration of similar mutations and phenotypes in human beings.[33,35,38] In another case, the study of a single-gene animal model[25] and the generation of a knock-out animal[44] led to the discovery of the cause of human narcolepsy,[23,42,45-47] a major neurological disorder. In this case, the human disorder was genetically complex and thus not easily amendable to a genetic approach.[39] The discovery also led to the identification of a major pathway regulating sleep and energy metabolism.[23,143] We expect that other striking discoveries will be made in the area of sleep regulation and sleep disorders with animal models such as flies, zebrafish, and mice. These studies will complement more traditional genome-screening and association studies in sleep disorders, which, with bigger sample sizes and better genetic and genomic tools, will ultimately lead to major advances in the understanding of sleep and its disorders.

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Authors' contributions

Both authors planned the review. ST wrote the first draft of the article and collated the figures. Subsequently, both authors made revisions, added text, and produced the final version.

Conflict of interest

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