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Genetics of sleep and sleep disorders

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Abstract. Genetic factors affect sleep. Studies in twin pairs demonstrate that the strong hereditary influences on sleep architecture and some sleep disorders are transmitted through families. Evidence like this strongly suggests that sleep regulation receives significant influence from genetic factors. Although recent molecular technologies have revealed evidence that genetic traits or gene products trigger particular changes in sleep electroencephalogram activity, we are still far from finding candidate genes or multiple mutations responsible for individual sleep disorders. Sleep is a very complex phenotype. Genetic susceptibility and environmental factors should be also considered as contributors to sleep phenotype. The aim of this review is to present a current summary and future prospects for genetic studies on sleep and selected sleep-associated disorders.

Keywords. Chromosome, familial sleep disorders, electroencephalography (EEG), genotype, heritability, inbread mice, mutations, polymorphism.

Introduction

In recent years, genetic approaches have become especially popular in many fields of science. To find causative genes for particular diseases is a hot target in biomedical sciences, and similar efforts have been made in the field of sleep research [1, 2]. One of the most clear-cut successes in terms of sleep genetics so far is hypocretins/orexins, internal ligands of a G-coupled orphan receptor in the hypothalamus. Hypocretins/orexins were first demonstrated to function as appetite promoters [3], and it was then discovered that lacking this system initiates narcoleptic symptoms [4–8]. However, since familial clustering had been observed in narcolepsy with a strong association of human leukocyte antigens, e.g., HLA-DQB1 and HLA-DQA1, the discovery of gene products triggering or blocking narcolepsy was anticipated earlier [9]. Apart from this example, identifying a gene or its products responsible for sleep disorders is quite difficult because of the complexity of most sleep disorders.

However, there is an increasing demand for finding genetic factors in sleep pathology [10, 11]. It has long been known that sleep problems tend to be inherited. Further, twin studies have demonstrated that normal sleep components are significantly influenced by genetic background. Thus, sleep regulation or dysregulation is likely to be closely linked with genetic control. To prescreen a risk factor, find an adequate cure, or even classify the complexity of sleep phenotypes for further treatments, genetic information can contribute to our in-depth understanding of the pathophysiology of major sleep disorders. Indeed, some 'sleep-related' genes and mutations have been demonstrated in animal models, and with the help of advanced molecular-genetic approaches, sleep genetics will soon expand into human models and pharmacogenomic development for individualized treatment of sleep disorders.

In this review, we will describe first the genetic influence on normal sleep and its regulatory mechanisms, and then discuss recently understood clinical

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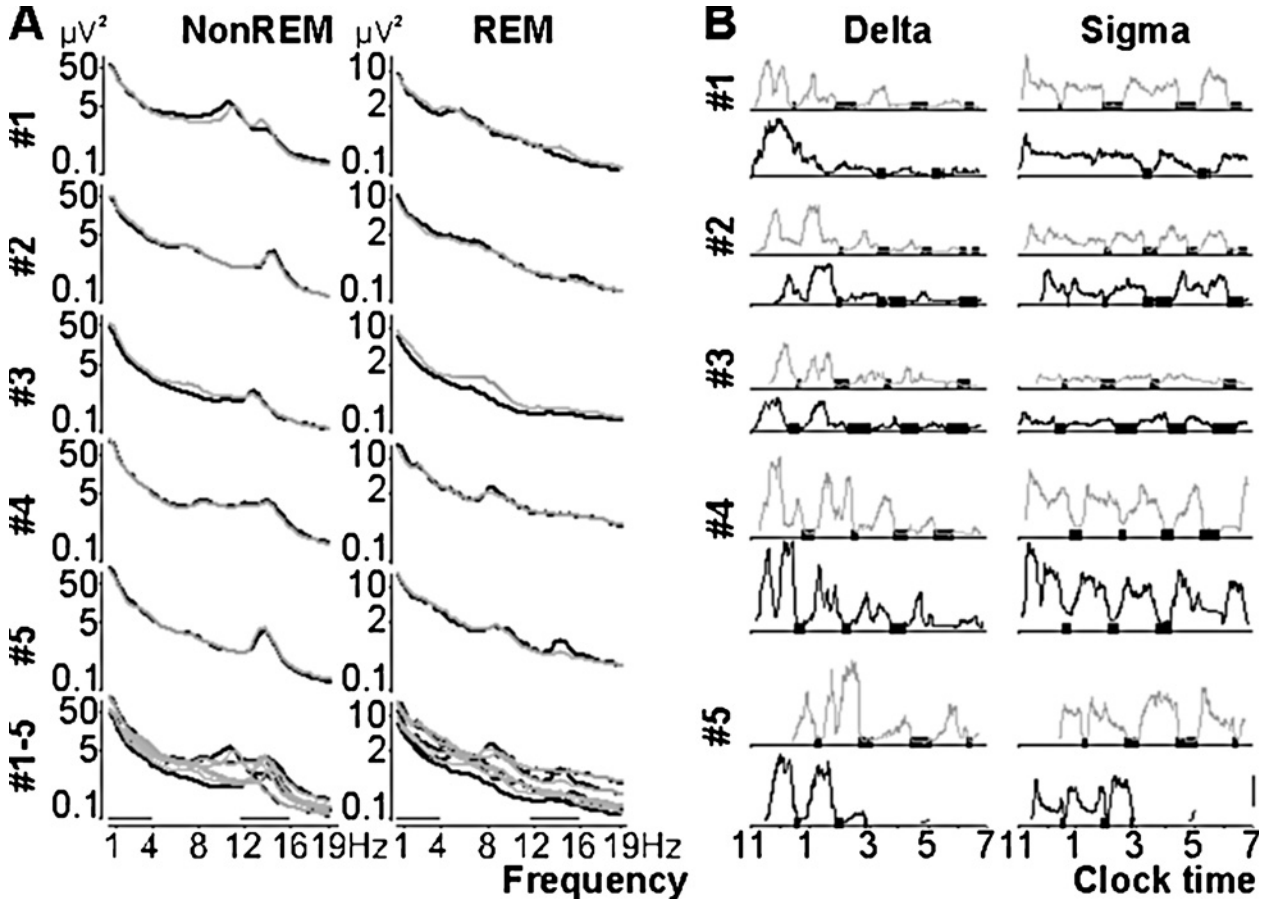

Figure 1. Comparison of spectral profiles in non-REM and REM sleep (**A**) and temporal dynamics of delta and sigma EEG activity during non-REM sleep (**B**) in five twin pairs. #1–#4; monozygotic twins; #5, dizygotic twin [19].

evidence for the role of genetic factors in selected sleep disorders.

Genetic influence on normal sleep and sleep-wake regulation

Evidence for genes

Where can we observe genetic aspects of normal sleep in healthy subjects? As in many fields, a search for genetic influences in human sleep begins with studies employing twin pairs [12]. Under visual inspection, monozygotic (MZ) twins show a very similar hypnogram if they do not generally differ in environmental factors. The similarities of the sleep patterns in MZ twins are observed particularly in terms of sleep latency, duration of sleep cycles, and appearance of rapid-eye-movement (REM) sleep [13]. The majority of twin studies have been based on questionnaire data, such as self-reported sleep habits, subjective mood after night sleep, etc., and mostly demonstrate higher concordance for sleep characteristics in MZ than dizygotic (DZ) twins [14, 15]. More advanced polygraphic analyses give deeper impact shed greater light on the evidence for genes in sleep regulation of twins [16]. For example, resemblance in alpha rhythms during waking was observed within MZ but not DZ twin pairs [17, 18]. Recently, quantitative electroencephalogram (EEG) measures revealed that spectral profiles during non-REM sleep were almost identical in respective DZ twin pairs and also in separated MZ twins who were raised under different environmental conditions [19] (Fig. 1). Apart from the strong evidence of similarities between MZ but not DZ twins, more general findings of similarities in siblings suggest broader genetic hereditary in sleep architecture [20].

From the brief review above, we conclude that genetic factors affect normal sleep. Can sleep disorders be transmitted within families? In the case of insomnia, familial occurrence is common [21]. Although not every sibling in an affected family experiences insomniac symptoms, individuals in a family with and without insomnia would show very similar power spectral distribution in their EEG [19]. Therefore, genetic vulnerability to insomnia would be hidden

even in normal sleep cycles, and the signs for potential sleep problems could be assessed by polysomnography. A recent study found vulnerabilities in healthy probands who have family members diagnosed with anxious and/or depressed insomnia [22]; affected and nonaffected family members all show higher REM density. It should be noted, though, that because insomnia can be a manifestation prior to the onset of affective disorders that are also inheritable, these results do not point specifically to genetic influences on insomnia *per se*.

In fact, insomnia, or other symptoms of disordered sleep, is associated with many other diseases and conditions, including simple stress. Some of other conditions may also have genetic aspects or causes. We cannot really separate which genomic factor influences the most or first, but it is worth recalling that sleep is a complex of phenotypes. Many gene factors may be involved in sleep, and in total balancing or counterbalancing their functions maintains the homeostasis of sleep-wake regulation. Thus, there must be many possible genetic avenues for sleep disturbance.

Genetic aspects of the human and animal EEG

Humans

EEG is currently the most useful and convenient tool to examine genetic influences on individual differences in central nervous system (CNS) functioning and human behaviors. EEG records reflect rhythmic electrical activity of the brain and provide a direct measure of the functional state of the brain and of its different levels of arousal. EEGs are described by various parameters, such as amplitude (power in μV^2) and rhythm (frequency in Hz). These EEG variants have been shown to reflect genetic traits. For example, from the EEG recordings for three consecutive nights in 26 twin pairs living apart, Linkowski and associates found hereditary signs in stages 2 and 4 of non-REM sleep, but not in REM sleep [23, 24]. In their study, variance in stage REM sleep appeared to represent a substantial influence from environment rather than genetic components. However, when the heritability of EEGs was investigated in 213 twin pairs across four main frequency bands, van Beijsterveldt et al. [25] reported that all delta, theta, alpha, and beta frequencies showed significantly high heritabilities. On the other hand, Vogel [26] performed extensive studies in 1970 and hypothesized at that time that normal EEG rhythm appears to be influenced by many genes. Subsequently, his group focused on low-voltage EEG (lack of α waves) in 17 families with 191 individuals, and identified a linkage region for a putative gene underlying the normal human EEG variant to chromosome 20q [27]. Their results provide strong evidence for a close linkage with the high polymorphic marker CMM6 (D20S19) and for genetic heterogeneity in low-voltage EEG. Recently, Rétey et al. [28] demonstrated a functional polymorphism of the gene encoding adenosine deaminase on chromosome 20, which revealed an association with interindividual variability in sleep architecture and sleep EEG. Their healthy young subjects who possess a G-to-A transition at nucleotide 22 (G/A genotype compared with G/G) were characterized by more slow-wave sleep (SWS) and more intensity, indicating a direct role of a single gene in homeostatic human sleep regulation.

Regarding polymorphisms, it has been demonstrated that the genetic cause of fetal familial insomnia (FFI) is a mutation at codon 178 of the prion protein gene, located on human chromosome 20, cosegregating with the methionine polymorphism at codon 129 (129M) of the mutated allele [29, 30]. These mutations are also found in another prion disease, Creutzfeldt-Jakob disease (CJD), in which a valine residue segregates at the codon 129 (129V). Although the polymorphism at codon 129 is very critical to separate either FFI or CJD, the 129 polymorphism without the mutation at the codon 178 occurs very commonly in the general population and does not cause any prion diseases. One study recently conducted EEG recordings and insomnia questionnaires in 884 middle-aged men and women to examine whether the 129V/M polymorphism influences sleep, with special emphasis on items related to insomnia complaints and any sleep disruption [31]. The results failed to clarify any differences in polysomnographic measures among three genotypes (129VV, 129MV, and 129MM), indicating that the prion 129 polymorphism does not really affect normal sleep. Other pathogenic mechanisms, implicating the normal allele of prion protein gene, still need to be considered.

Animals

A role of the prion protein in sleep regulation has been also investigated with a genetically modified animal model, the prion protein null mouse [32]. The involvement of the prion protein in the neuropathogenesis of human and animal transmissible spongiform encephalopaties is well known [33], although the normal function of this protein is still undefined. Compared with wild types (129/Ola mice or 129/Sv and C57BL/6J mixture, Prn-$p^{+/+}$), prion gene-disrupted homozygous mice (Prn-$p^{0/0}$) display abnormalities in circadian activity rhythm and sleep structure. EEGs have revealed that Prn-$p^{0/0}$ mice also exhibit a larger degree of sleep fragmentation and a larger response to sleep deprivation. The response to sleep deprivation is commonly indicated by the magnitude of EEG slow-wave activity (SWA, power density in the delta band) during and after sleep deprivation [34, 35], and in Prn-

$p^{0/0}$ mice during recovery sleep SWA increases twice as much as that in Prn-$p^{+/+}$ after 6 h of sleep deprivation. The data from the gene-knockout (KO) model suggest that the prion protein may participate in maintaining sleep continuity and regulating sleep intensity [36].

Similar to the MZ/DZ twin study results, in the case of mouse strains, systematic and quantitative studies of sleep EEG can also distinguish genetic influence on particular rhythmic brain activity [37, 38]. Franken and Tafti's group has screened many inbred mice and categorized them according to the spectral dynamics of their EEG activity [39]. First, the time of a 24-h circadian cycle spent in each vigilance state was compared across six commonly used inbred strains (Fig. 2). They showed slight but significant differences in the amount of sleep and wakefulness (W), in which the relative amount of W looks counterbalanced by that of SWS (= non-REM sleep). Among these six strains, AKR/J (AK) mice had the most SWS (least W), whereas DBA/2J (D2) mice had the least SWS (most W) per day. When spectral profiles were compared, delta power (ca. 1.5–4.0 Hz) typical for SWS was highest in AK and lowest in D2 mice, respectively, while the distribution of peak delta frequencies was quite similar among six strains. However, peak frequency for the theta band (ca. 5.5–8.5 Hz) during paradoxical sleep (PS = REM sleep) was distributed in a strain-dependent manner, which did not coincide proportionally with relative power or episode duration of PS (Fig. 3). Therefore, it is very plausible that theta-peak frequency (TPF) associated with PS varies with genotype. Based on these findings, Tafti et al. [40] analyzed TPF in F_1 and F_2 generations crossing or back-crossing a slow-theta strain (BALB/cByJ, C) with a fast-theta strain (C57BL/6J, B6) and finally established that theta oscillations during REM sleep are controlled by a single autosomal recessive gene, identified as the acylcoenzyme-A dehydrogenase for short-chain fatty acids (encoded by *Acads*). TPF also suggests that brain fatty acid metabolism is important for cognitive function and sleep represents a condition favoring or requiring β-oxidation.

Changes in the accumulation of EEG delta power can be used to detect a trace of genetic factors in recombinant inbred mice. As described earlier as well as in the other review articles of this volume, delta power increases proportionally over the course of recovery sleep after a certain period of sleep loss (or prior wakefulness). Therefore, the requirement of SWS is predictive through the magnitude of delta power that indicates SWS intensity, i.e., homeostatic drive for non-REM sleep. Using quantitative trait loci (QTL) analysis, Franken et al. [41] examined 25 BXD (B6 x D2 mice) recombinant inbred strains and looked

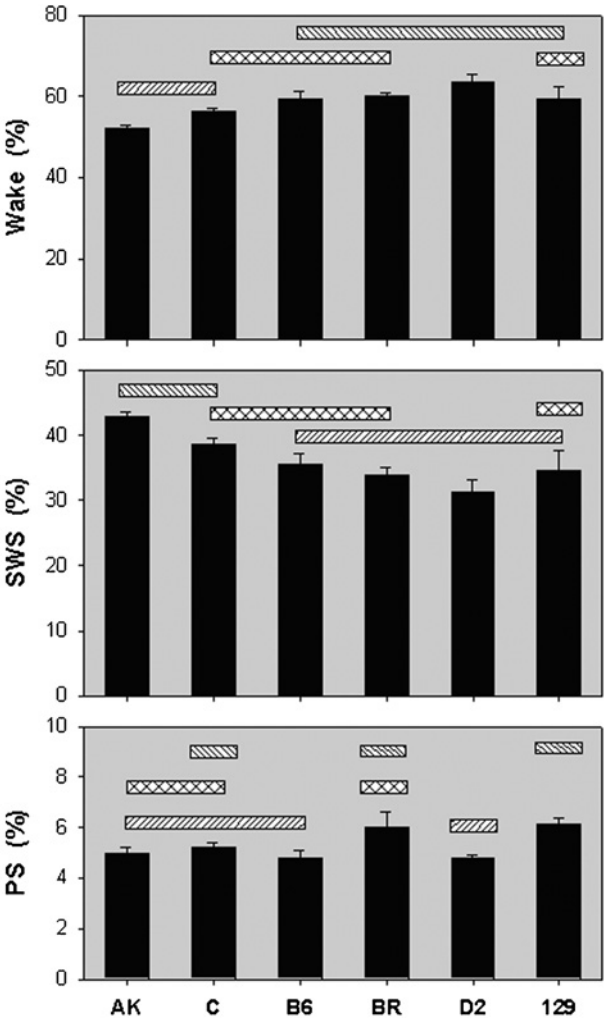

Figure 2. Comparison of time spent in each vigilance state across six inbred mouse strains. AK; AKR/J, C; BALB/cByJ, B6; C57BL/6J, BR; C57BR/6J, D2; DBA/2J, 129; 129/Ola mice. Hatched bars represent significant differences from other strains. Drawn based on [39].

for genomic regions that might affect the increase of delta power after 6 h of sleep deprivation. Then, one significant locus was identified on chromosome 13 that accounted for 49% of the genetic variance in this trait. In contrast, the decrease of delta power afterwards did not vary with genotype. These results support the conclusion that the homeostatic regulation of SWS has some genetic control [42]. In addition, QTL analysis has also demonstrated PS-related loci on chromosomes 7 during the light period, 5 during the dark period, and 2, 17, and 19 across the 24-h period from CXB (C x B6 recombinant mice) lines [43].

Differences in the level of delta power during non-REM sleep can also indicate gene mutation. For example, double-KO mice lacking both *cryptochromes* 1 and 2 (*cry*$1,2^{-/-}$) show greater delta power during non-REM sleep across 24 h compared with

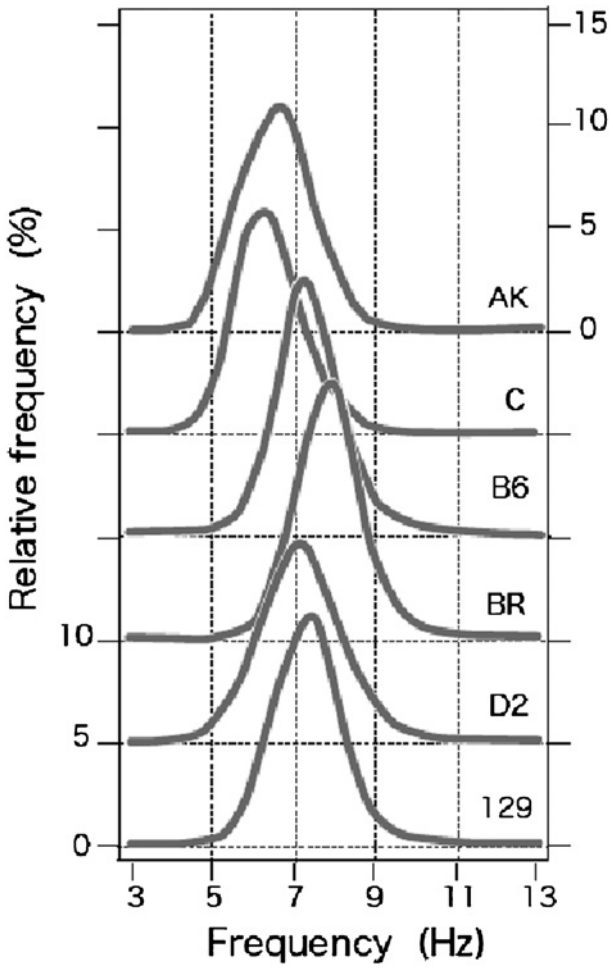

Figure 3. Distributions of peak frequency in paradoxical sleep of six inbred mouse strains. AK; AKR/J, C; BALB/cByJ, B6; C57BL/6J, BR; C57BR/6J, D2; DBA/2J, 129; 129/Ola mice. Curves illustrate changes in maximum power spectra for each frequency bin. Modified from [39]. Copyright 1998 American Physiological Society.

respective wild types [44]. The *cryptochrome* genes as well as *period* genes (*per*) are mainly involved in circadian rhythm generation under the control of transcriptional factors such as CLOCK and BMAL1; therefore, genetic inactivation of *cryptochromes* results in circadian arrhythmicity. Although *cryptochromes* are clock-related genes, the experimental data from *cry*1,2$^{-/-}$ mice suggest their additional non-circadian role in the homeostatic regulation of sleep [45, 46]. In this mutant mouse, however, *per* 1 and 2 genes are overexpressed reversely. Therefore, it is not yet clear which genes or gene products would be responsible for high non-REM sleep drive. On the other hand, low non-REM sleep drive is seen in another mouse mutant with T-type calcium channel deficiency [47]. In this model ($\alpha 1_G{}^{-/-}$), low-threshold spikes in the thalamocortical relay neurons are absent, suggesting that the $\alpha 1_G$-subunit of T-type calcium channels is critical for the genesis of sleep spindles and delta oscillations [48]. In fact, the recent study reported a lack of delta waves with much lower power density during non-REM sleep in $\alpha 1_G{}^{-/-}$ mice compared with wild types, and sleep disturbances were significantly characterized by brief awakening interrupting non-REM but not REM stage [47]. At least from this study, we understand that the gene related to calcium channels appears to stabilize non-REM sleep. Regarding the case of REM sleep regulation, using a gene-modified (transgenic) mouse model, in which corticotropin-releasing hormone (CRH) is site specifically overexpressed in the brain, we demonstrated that CRH overexpression causes a heavy drive towards REM sleep [49]. In this model, delta power accumulation during sleep deprivation is lower in homo- and heterozygous mice than in respective control and wild-type mice. Although the total time spent in non-REM sleep is not much different across genotypes, findings on changes in EEG delta power are very interesting, indicating that a single gene manipulation could possibly modify sleep homeostasis, if not sleep itself.

Microarrays

In recent years, microarray technology is being integrated into the mainstream of genetic sleep research and represents opportunities for new discoveries in the field. Most of the studies so far have been done under sleep deprivation, and then complementary DNA (cDNA) arrays are applied to find genes in the whole brain that are upregulated or downregulated as a result of the deprivation or as the effects of deprivation [50]. In the past, 'sleep-inducing factors' were historically hypothesized to accumulate in the brain during prolonged wakefulness, and some of these putative sleep-promoting substances were isolated from the brains of sleep-deprived animals. More enhanced 'sleep pressure' (increasing power densities of delta waves), as described in the two-process model, is more associated with increases in the levels of related sleep-inducing messenger RNA (mRNA). cDNA microarrays can detect such an intensified transcription of particular genes in response to sleep needs. Earlier studies have reported in rats [51] and fruit flies [52] that either 3-, 6-, or 8-h sleep deprivation increases expression of several genes that can be divided into some categories: immediate early gene/transcription factors, energy balance-related genes, growth factors, heat shock proteins (chaperones), neurotransmitter/hormone receptors, kinases, etc. [53, 54]. Most properties and functions of these molecules are not yet known with respect to sleep regulation. However, microarray technology has the potential to find a gene product that can contribute to developing

sleep medicine. As QTL analysis reveals, slight differences in genotypes may result in a large difference in phenotypes in terms of characteristics of sleep patterns, including EEG modulation. cDNA array studies will provide a novel direction for identifying causal mechanisms of sleep disorders and suggest interventions on an individual basis. Currently, although gene hunting for human sleep disorders is not yet established, the microarray technique has demonstrated genetic factors in selectively bred animals for short and long sleepers [55]. In the near future, using this gene technology, might help to interpret differences in sleep architecture even across different ethnic groups [56, 57].

Familial sleep disorders

Restless leg syndrome

Restless legs syndrome (RLS) is a prime example of a sleep disorder with a strong genetic component. RLS is characterized by an unpleasant sensation and an urge to move the lower limbs, occurring exclusively at rest in the evening or at night. Moving the affected extremity improves the symptoms. The diagnosis is based on the clinical description of the symptoms by the patient and the presence of four essential diagnostic criteria that make up the core clinical features of the disease [58]. It has been reported that between 60 and 90% of RLS patients have a positive family history [59–61]. In addition, an investigation of 12 MZ twins revealed 10 (83%) to be concordant for RLS, further supporting the importance of a genetic contribution to the disease [62]. Nevertheless, besides this obvious genetic influence, no disease-associated gene has yet been identified. Comparing all clinical characteristics between familial and non-familial RLS-patients, it has been consistently demonstrated that patients with a positive family history have an earlier age-at-onset of the disease compared with patients with a negative family history [60, 61, 63]. Several families with RLS have been described showing a large phenotypic variability. Within a single family there can be family members having very severe symptoms and sleep disturbances due to dysaesthesias at night as well as family members with only mild symptoms only occasionally in their lives.

Linkage studies are family-based techniques to analyze possible cosegregation with a genetic marker and a specific phenotype. A prerequisite is an accurate assumption regarding potential genetic models with the disease penetrance and phenocopy rate. To date, three loci for RLS have been published: Chr.12q (RLS1), Chr.14q (RLS2), and Chr. 9p (RLS3). In a French Canadian family linkage to chromosome 12q was identified based on a recessive mode of inheritance, and this was confirmed in a further five French Canadian families [64, 65]. Possible phenocopies and non-penetrants made it difficult to detect a common segregating haplotype in these families, and it is not clear whether a founder effect of the French Canadian population plays a role [65]. Based on an autosomal dominant mode of inheritance, a second locus was identified on chromosome 14q13–21 (RLS2) in a North Italian RLS family [66] and confirmed in an independent family of French Canadian origin [67]. Investigating 15 extended American families, including 134 RLS-affected persons, a third RLS locus on chromosome 9p24–23 (RLS3) was identified [68]. Although the statistical analysis was criticized [69], this linkage was confirmed within a German RLS family under the assumption of intrafamilial heterogeneity and stratification according to an early-age-at-onset phenotype [70]. Defining the exact candidate region in RLS is difficult due to intrafamilial, allelic, and non-allelic heterogeneity. This suggests locus heterogeneity, and it appears likely that several genes contain several disease-associated variants contributing different effects to the RLS phenotypes [65].

Association studies analyze the frequencies of alleles or genotypes at the site of interest and compare these in case and control samples (although family-based designs can also be used). A higher frequency in cases is taken as evidence that the allele or genotype is associated with an increased risk for the disease.

One association study investigated a putative functional single nucleotide polymorphism (SNP) within eight genes coding for receptors and enzymes related to the dopaminergic transmission (dopamine receptors D1-D5, dopamine transporter, tyrosine hydroxylase and dopamine β-hydroxylase) [71]. No significant association signals were found in 92 French Canadian RLS patients and 182 controls. In a subsequent study within the same population, polymorphisms of two mitochondrial genes coding for the enzymes monoamine oxidase A and B (MAOA and MAOB) were genotyped [72]. These enzymes are involved in the dopamine catabolism through oxidative deamination. Certain polymorphisms of these genes are correlated with different enzyme activities. The authors concluded that an association with the 'high-activity allele' of the MAOA gene in females could contribute to the susceptibility of RLS. In contrast, no association was found either with the high- or the low-activity allele in males. It should, however, be noted that neither of these studies meet the criteria for performing reliable association studies [73]. The number of individuals investigated was small for such a heterogeneous disease, and no further

replication in multiple independent samples has been performed. Taking this into consideration, the results of these studies should be interpreted with caution.

Narcolepsy

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy (sudden loss of muscle tone triggered by emotions), hypnagogic hallucinations and sleep paralysis [10]. The disease is mainly sporadic, and pathophysiological studies point towards an involvement of both environmental and genetic susceptibility factors interacting with each other. Familial cases of narcolepsy are rare and first-degree relatives have a risk of 2% to develop narcolepsy, which is up to 10–40% times higher than the prevalence (0.02–0.06%) in the general population of Western European countries as well as the USA [74]. Up to one-third of monozygotic twins are concordant for narcolepsy, further demonstrating that non-genetic factors must also play a significant role in the aetiology of the disorder [10].

Narcolepsy has a high association to a specific HLA (human leukocyte antigen) allele: 88–98% of the patients with narcolepsy-cataplexy are positive for the HLA class II allele DQB1*0602, most often in combination with DR2 [75]. Up to 60% of patients with milder symptoms or without cataplexy show this haplotype in comparison to only 12–38% of the general population. However, narcoleptic patients can also be negative for the DQB1*0602 allele, and familial cases are not all explained by a shared HLA haplotype [76] pointing to the involvement of further susceptibility genes. The strong association to specific HLA haplotypes suggested an autoimmune process in the aetiology; however, DRB1 and DQB1 genes have been sequenced in narcoleptic patients and no mutation was found [77]. Thus, the importance of an autoimmune process is still under discussion, and the final mechanism of the HLA genotype contributing to the pathophysiology of narcolepsy remains to be elucidated. Further alleles contributing to the risk are DQB1*0301 and DQB1*0407, while the DQB1*0501 or DQB1*0601 alleles are likely to be protective against narcolepsy [75].

Families with narcolepsy-cataplexy over several generations generally show a variable phenotype, and individuals with and without cataplexy within a single family complicate the clinical classification within these studies. Only a few linkage studies of narcoleptic families have been performed to date. In eight narcolepsy families of Japanese origin suggestive evidence for linkage was found on chromosome 4p13–21q [78]. A second locus was identified on chromosome 21q in a French family based on an autosomal dominant mode of inheritance [76]. Interestingly, these authors were able to show that the primary excessive daytime sleepiness in individuals of the narcolepsy family was a reliable minimal clinical condition for the genetically affected phenotype in multiplex families [76].

Today a causal relation of narcolepsy and hypocretin/orexin, a neuropeptide produced in the lateral hypothalamus, is well established for narcolepsy. It has been repeatedly shown that most narcoleptics have undetectable levels of hypocretin/orexin in the cerebrospinal fluid (CSF). Originally, a mutation in the gene encoding the type 2 hypocretin/orexin receptor was found to be responsible for narcolepsy in canines, where the disease follows an autosomal recessive mode of inheritance [5]. Further behavioral assessments of transgenic mice with a null mutation of the prepro-hypocretin/orexin gene showed symptoms like behavioral arrests and EEG patterns similar to human narcolepsy [4]. However, no association of SNPs in the prepro-hypocretin gene, nor in the hypocretin 1 and hypocretin 2 genes, have been reported in humans. So far, only a single case with a mutation in the prepro-hypocretin gene has been identified [9]. This patient was DQBq*01602 negative and had undetectable levels of hypocretin 1 in the CSF; the case first showed symptoms of cataplexy at the age of 6 months.

These findings indicate that although the hypocretin deficiency constitutes the best biological marker of sporadic narcolepsy, the molecular cause remains elusive and mutations within the three hypocretinergic genes are exceptional in human narcolepsy [77].

Sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) is a common disorder affecting up to 2–4% of middle-aged adults [79]. It is characterized by recurrent episodes of apnea (no airflow) and hypopnea (partially obstructed airflow) that occur during sleep, and is followed by oxygen desaturation, sleep fragmentation, and disruptive snoring, all of which are associated with daytime sleepiness [80]. The diagnosis is based on standard clinical criteria, and is generally validated by an overnight sleep study with measurement of the apnea-hypopnea index (AHI), the number of apneas and hypopnoeas per hour of sleep [80]. OSAS is a complex phenotype and associated with other conditions like obesity, alteration of craniofacial morphology, enlargement of critical upper airway soft tissue, significant cardiovascular morbidity, and daytime sleepiness. Moreover, OSAS is an independent risk factor for hypertension, myocardial infarction, and insulin resistance. A number of studies have showed that a familial aggregation of some associated conditions is involved in the pathogenesis of sleep

apnea. For example, an extensive family study was performed by Guilleminault et al. investigating 157 OSAS patients using a detailed assessment of clinical symptoms, physical evaluation, cephalometric X-ray films, and polysomnography. In addition, 531 living first-degree relatives and 189 age-matched controls were also investigated [81]. Interestingly, the latter study demonstrated that none of the very obese patients had any familial aggregate of OSAS, while patients with specific craniofacial features mostly involving the maxillomandibular growth did have a familial aggregate [81].

A biometric genetic study based on data of 68 monozygotic and 54 dizygotic twin pairs demonstrates that sleep-disordered breathing, even in old age, is determined, in part, by genetic factors [82, 83]. Differences in age of presentation and anatomic risk factors for obstructive sleep apnea (OSA) in Caucasians and African Americans suggest possible racial differences in the genetic underpinnings of the disorder [84]. Performing a segregation analysis Buxbaum et al. [84] assessed the transmission patterns in 177 Caucasian and 125 African American families for apnea hypopnea index (AHI). Analysis of the Caucasian sample showed that the transmission pattern is consistent with a major gene that is stronger in an age-adjusted than in an age- and BMI (body mass index) -adjusted model. In the African American families, adjusting for BMI gave strong evidence for the segregation of a codominant gene. These results provide support for an underlying genetic basis for OSA in African Americans independent of the contribution of BMI [84].

To identify susceptibility loci for OSA, Palmer et al. [85] performed a genomewide model free linkage analysis on AHI and BMI in 59 African American OSA pedigrees. A region on chromosome 8q gave the only evidence for linkage to the AHI, while the BMI was linked to multiple regions, most significantly to markers on chromosome 4q and 8q, suggesting that there are both shared and unshared genetic factors underlying susceptibility to OSA and obesity [85].

Furthermore, at the central level there might also be an associated genetic factor. Congenital central hypoventilation syndrome (CCHS) is a life-threatening disorder involving an impaired ventilatory response to hypercarbia and hypoxemia. This phenotype is associated with lower-penetrance anomalies of the autonomic nervous system (ANS), including Hirschsprung disease and tumors such as ganglioneuromas and neuroblastomas. In mice, the development of ANS reflex circuits is dependent on the paired-like homeobox gene Phox2b; Amiel et al. [86] identified the human ortholog PHOX2B as a candidate gene in heterozygous de novo mutations in 18 of 29 CCHS patients. This indicates an essential role of PHOX2B in the normal patterning of the autonomous ventilation system in humans [86]. Further investigation of candidate genes suggested a polymorphism in the angiotensin-converting enzyme in association with hypertension in the case of moderate OSAS [87]. Another investigation regarding a possible association to an allele in the apolipoprotein E epsilon4 gene to obstructive OSAS brought inconsistent results in independent populations [10].

Circadian sleep disorders

Advanced sleep phase syndrome (APS) is characterized by continuously advanced sleep onset and awakenings that are earlier than desired. It is a rare disorder, and only a few familial cases have been described. It is suggested that the phenotype is transmitted in a classic Mendelian autosomal dominant mode of inheritance. A mutation responsible for the disorder was identified in the PER2 gene on chromosome 2q [88]. However, other cases of familial advanced sleep phase syndrome are not caused by a mutation in the PER2 gene, suggesting genetic heterogeneity of the disorder. Delayed-phase syndrome (DPS) is characterized by persistent delayed sleep-wake timing. Although DPS seems to be phenotypically heterogeneous, an association with HLA DR1 and a PER gene polymorphism have been suggested [89, 90].

Kleine-Levine syndrome

Kleine-Levine Syndrome (KLS) is a very rare disorder with the cardinal clinical features of recurring spells of hypersomnia, cognitive and mood disturbances accompanied by altered behavior like hyperphagia, hypersexuality, and autonomic alterations [91]. The pathophysiological hypotheses suggest dysfunction at the hypothalamus. KLS is usually sporadic, but recently two siblings with the syndrome were described [91]. An analysis of polymorphism in candidate genes in 30 unrelated KLS patients demonstrated that the human leukocyte antigen HLS-DQB1*0201 allele frequency is significantly increased in patients with KLS. The authors suggested the possibility of an autoimmune aetiology for the disorder [92].

Perspectives

Sleep-related genes have been identified in monogenic disorders. However, most of the sleep disorders described in this review have complex phenotypes. One avenue for further investigation of the genetics of these disorders is association studies in large populations. New technologies like high-throughput SNP

genotyping methods will provide a perquisite for performing such studies. Moreover, beyond investigating single linkage loci, genomewide association studies have become possible and popular only recently. However, one must first investigate hundreds or even thousands of patients and controls to detect subtle genetic effects or genetic susceptibility factors. The need for multiple large and independent populations, which have been carefully phenotyped, is an absolute prerequisite. To further explore the genetics of sleep disorders, epigenetic factors should also be considered that might explain the complexity of phenotypes.

Two further loci for RLS have been reported during our publishing process (2q 20p).

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