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Genetics of Narcolepsy and Other Sleep Disorders

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Introduction

Sleep-disorders medicine has emerged as a genuine clinical field, yet few studies have examined sleep disorders from the human-genetic perspective. Sleep itself is a vital behavior of unknown function that consumes one-third of any given human life; animals die if totally deprived of sleep (Rechtschaffen et al. 1983; Kushida et al. 1989). A genetic approach in sleep-disorders research thus not only might have therapeutic applications but also could indirectly help our understanding of this important physiological behavior.

The complexity of sleep as a physiological phenomenon is matched by an increasing number of pathologies (>50; see Thorpy 1994) now catalogued by international classifications. Electrophysiological studies have long shown that sleep is a heterogeneous state, most classically separated into rapid-eye movement (REM) and non-REM sleep. In humans, non-REM sleep can also be subdivided into light non-REM sleep (stage I and stage II) and slow-wave sleep (SWS; stage III and stage IV). Independent of this organization by sleep stage, the propensity to sleep or to stay awake is regulated independently by homeostatic (sleep-debt dependent) and circadian (clock dependent) processes. The importance of circadian factors can be best illustrated in the absence of time cues. In these conditions, sleep, wakefulness, core temperature, and various other behaviors still fluctuate with a periodicity close to 24 h, called the "free-running circadian period" (τ). Circadian and homeostatic factors have distinct anatomical substrates, circadian factors regulating sleep and wakefulness being mostly if not exclusively localized in the hypothalamus, within the suprachiasmatic nuclei. Finally, sleep is associated with a host of physiological changes that have a pathological impact. These include well-established sleep-state-specific or circadian-controlled changes in endocrine release, convulsive thresholds, regulation of breathing, cardiovascular control, gastrointestinal physiology, and muscle tone.

Clinically, the most frequent sleep disorders are insomnia (whether or not of chronobiological origin), obstructive sleep apnea, restless-leg syndrome/periodic leg movements, and narcolepsy. In this review, I will briefly demonstrate the involvement of genetic factors in the regulation of normal and abnormal sleep and will review the potential of the field of genetics in the study of sleep disorders.

Genetic Control of Normal Human Sleep: Twin Studies

Research in this area is primarily based on questionnaire studies comparing sleep habits (duration of sleep, schedules and quality of night sleep, and frequency of napping) in MZ and DZ twin pairs (Gedda and Brenci 1983; Partinen et al. 1983; Heath et al. 1990; Drennan et al. 1992). For most of the variables analyzed, correlations are higher for MZ twins than for DZ twins. This effect remains significant even when twins do not share the same environment (Partinen et al. 1983) and does not correlate strongly with depression or anxiety (Kendler et al. 1987). Environmental factors, however, do contribute significantly to the variance (Partinen et al. 1983; Heath et al. 1990). Measures of the residual variance between MZ twins ($1 - r_{mz}$) quantify the influence of environmental factors specific to each twin pair (Hrubec and Robinette 1984). In all studies, correlations barely reach .60, thus suggesting that half of the variance is associated with environmental factors. Since twins live in similar environments, this difference probably corresponds to short-term environmental variance.

Several authors have studied sleep in MZ and DZ twins, using polygraphic techniques (Webb and Campbell 1983; Hori 1986; Linkowski et al. 1989, 1991). These studies generally confirm the results obtained with questionnaires, but sample sizes are always small. Linkowski et al. (1989, 1991), studying 26 pairs during 3 consecutive nights, could demonstrate significant differences between MZ and DZ twin-pair correlations, for all stages of sleep but REM sleep. Vogel (1986), studying

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more particularly alpha-occipital rhythms during awake resting electroencephalogram (EEG), suggested dominant transmission for this trait, thus showing that EEG genetic variations are not only quantitative but also qualitative (Vogel 1986; Anokhin et al. 1992); a linkage marker for low-voltage alpha EEG has now been identified on human chromosome 20q (Anokhin et al. 1992; Steinlein et al. 1992). More recently, Van Beijsterveldt et al. (1996), studying awake resting EEG frequencies in a large number of MZ and DZ twins, could also demonstrate high average heritabilities (.76–.89) for all analyzed EEG frequency bands.

Most of the early studies did not take into account the fact that sleep is independently regulated by circadian and homeostatic factors. Linkowski et al. (1992, 1993) tried to address this issue by measuring cortisol and prolactin levels in twins. Results suggest that genetic factors play a major role in the regulation of cortisol secretion but not in that of prolactin secretion. Drennan et al. (1992) used the Horne-Ostberg questionnaire to examine morningness/eveningness in 238 twin pairs and found higher correlations in MZ pairs, thus suggesting the existence of human circadian genetic factors. Such studies certainly could be extended. As of today, there has been no twin study measuring SWS/REM sleep homeostasis or circadian-rhythm properties under optimal experimental conditions.

Genetic Influences on Animal Sleep

Animal studies also support the concept of genetic influences on sleep. Major differences in overall sleep amount and distribution or in SWS versus REM sleep as percentage of total sleep time can be observed within the same species, these differences being resistant to prolonged manipulations such as forced immobilization or sleep-deprivation amount (Webb and Friedmann 1971; Kitahama and Valatx 1980; Valatx 1984; Rosenberg et al. 1987). Significant variations in sleep/wake architecture and EEG profiles are also observed between rodent inbred strains (Valatx et al. 1972; Friedmann 1974; Van Twyver et al. 1973; Valatx and Buget 1974; Kitahama and Valatx 1980; Valatx 1984; Rosenberg et al. 1987; Benca et al. 1991; Leung et al. 1992). C57BL or C57BR strains are characterized by long REM-sleep episodes, short SWS episodes, and significant circadian variation under light:dark conditions (Valatx and Buget 1974; Valatx 1984). At the opposite end of the spectrum, BALB/c is characterized by REM-sleep episodes of very short duration and weak circadian fluctuations, and DBA mice are intermediary for these characteristics (Valatx and Buget 1974; Valatx 1984). The characteristic free-running period is also 50 min longer in C57BL/6J than in BALB/cByJ (Schwartz and Zimmerman 1990). Qualitative differences in EEG signals are also observed. DBA and BALB/c but not C57BR display high-amplitude spindles, whereas REM-associated theta frequency varies significantly between strains (Valatx and Buget 1974; Valatx 1984).

These phenotypic differences are genetically transmitted. Diallelic methods (Friedmann 1974), simple segregation analysis in a backcross setting (Valatx and Buget 1974), and recombinant inbred-strain studies (Schwartz and Zimmerman 1990; Hofstetter et al. 1995) suggest that many genes are involved in the expression of each trait (Valatx et al. 1972; Friedmann 1974; Rosenberg et al. 1987; Schwartz and Zimmerman 1990; Hofstetter et al. 1995). The interactions observed are complex and not strictly additive, with hybrids of inbred strains occasionally presenting important deviations when compared with the average in parental strains (Friedmann 1974).

Pharmacogenetic Approaches in Rodents

The basis of this technique is the selection of animal strains relatively sensitive or resistant to pharmacological agents, for example, ethanol (McClearn and Kakihana 1973; Morzorati et al. 1988; Phillips et al. 1989), benzodiazepines (Korpi et al. 1993), barbiturates (Stino 1992), or cholinergic compounds (Overstreet et al. 1990; Shiromani et al. 1991). These models can then be studied pharmacologically, physiologically, and genetically. Mice that have been selected for their hypersensitivity to cholinergic compounds display, for example, an increase in paradoxical sleep (Shiromani et al. 1991), which confirms the role of acetylcholine in REM-sleep regulation.

The Long-Sleep (LS) and Short-Sleep (SS) mouse strains have been the most intensively studied (Phillips et al. 1989; Markel et al. 1996). These mouse strains were created in the 1970s by selecting mice more or less sensitive to the sedative effects of ehtanol, measured as the duration of loss of the righting reflex ("sleep time") after administration of ethanol (McLearn and Kakihana 1973). After 18 generations of selection, the resulting strains now present an average "sleep" time of 10 min (SS) or 2 h (LS) after ingestion of a similar dose of ethanol. These animals have been particularly useful in two research areas. First, it is well established that there is pharmacological overlap between anesthetics, ethanol, and most benzodiazepine and barbituric hypnotics. Partial or total cross-tolerance is observed for numerous pharmacological properties (Khanna et al. 1991; Khanna and Kalant 1992), suggesting that all these compounds act directly or indirectly through the GABAergic system. Studying the differential sensitivity of the LS and SS strains to various hypnotics or anesthetic agents has allowed investigation of whether the genetic control of these compounds overlaps with that of

ethanol (Marley et al. 1988; Erwin et al. 1990; Philips and Dudek 1991; De Fiebre and Collins 1992; De Fiebre et al. 1992; Wehner et al. 1991, 1992). These studies demonstrate that there is some overlap for the hypnotic effect of the less liposoluble anesthetic compounds (e.g., urethane and trifluorethanol) with ethanol. In contrast, liposoluble anesthetics, such as barbiturates, seem to produce similar effects in SS and LS strains (De Fiebre et al. 1992), suggesting independent genetic control (Stino 1992). A preferred interaction between the effects of ethanol and cholinergic (Erwin et al. 1988; Overstreet et al. 1990; De Fiebre and Collins 1992) and dopaminergic (Phillips et al. 1989) transmission has also been suggested.

Second, these mouse stains are particularly useful for purely genetic studies. A detailed phenotypic comparison of the SS and LS strains, as well as other strains hypersensitive to ethanol, suggests that the various pharmacological effects of ethanol (sedation, hypothermy, and toxicity) are controlled by different genes (Phillips et al. 1989; Erwin et al. 1990; Phillips and Dudek 1991). Traditional segregation studies and phenotypic analysis of SS×LS hybrids suggest that at least seven or eight genes are involved in the hypnotic effects of ethanol (Dudek and Abbott 1984; DeFries et al. 1989). Quantitative-trait locus (QTL) analysis has already been performed in recombinant inbred strains, and multiple QTLs have been identified (Crabbe et al. 1994; Markel et al. 1996).

The utility of these model strains for studying the genetic control of sleep remains uncertain. Indeed, as of today, LS and SS animals have not been studied for sleep and circadian rhythms, whether by use of either polygraphic recordings or wheel-running activity. Moreover, the effect of benzodiazepines and alcohol on sleep seems to be indirect and very dependent on previously accumulated sleep debt (Roehrs et al. 1989; Zwyghuizen-Doorenbos et al. 1990; Edgar et al. 1991; Mignot et al. 1992). A better analysis of the sleep and circadian physiology of these model animals during baseline conditions and after deprivation will be needed.

Circadian Control in *Drosophila, Neurospora,* and Other Nonmamalian Organisms

Circadian rhythmicity is an almost universal property observed in most organisms, including some unicellular organisms (Takahashi 1995). A variety of mutations have been reported to alter circadian rhythmicity in *Drosophila, Neurospora,* and *Arabidosis* (Dunlap 1993; Millar et al. 1995). Research in this field has already led to the isolation of two genes ("period," or *per,* and "timeless," or *tim*) in *Drosophila* and of one gene ("frequency," or *frq*) in *Neurospora,* whose mutations can suppress, decrease, or increase the circadian free-running period *t* (Hall 1995; Takahashi 1995; Dunlap 1996; Sehgal et al. 1996). How these genes contribute to the generation of 24-h rythmicity is still uncertain (Hall 1996), but transcription-translation autoregulatory feedback loops are probably involved (Takahashi 1995). In *Drosophila,* for example, PER protein and *per* mRNA levels fluctuate with a 3–4-h difference in phase, and TIM is necessary for these fluctuations to occur. It thus has been hypothesized that TIM interacts with PER to enter into the nucleus and directly or indirectly regulates the transcription of the *per* locus, with a delay, to produce the 24-h rhythmicity (Dunlap 1996; Hall 1996; Sehgal et al. 1996).

Circadian Rythmicity in Mammals and the Suprachiasmatic Nucleus

In mammals, research in the area is facilitated by the fact that most circadian rhythms are generated in a discrete region of the hypothalamus, the suprachiasmatic nuclei ("SCN"; for review, see Klein et al. 1991). Lesions of these nuclei suppress all behavioral rhythms in absence of time cues, whereas transplantation of fetal hypothalamic tissue into lesioned animals restores circadian fluctuations. Mouse strains and mutant hamsters with abnormal free-running periods (*t* either too long or too short) have been identified (Klein et al. 1991; Vitaterna et al. 1994). Transplanting mutant SCN tissue into the third ventricle of a normal animal whose suprachiasmatic nuclei had a former lesion induces an abnormal rhythmicity in the transplanted animal (Klein et al. 1991). The neuronal, metabolic, and neurochemical activity of SCN tissue also varies with a circadian periodicity in vitro (Klein et al. 1991). The mechanism by which the SCN generates rhythmicity is still debated. The transplant probably generates rhythmicity independent of any synaptic connection with the host tissue. Rhythmicity within the nuclei also seems independent of the existence of synaptic connections, as individual neurons and glial cells can generate circadian fluctuations independently. These results appear to be parallel to what has been found in avian pineal glands or retina and in the marine mollusk bulla (Takahashi 1995). On the basis of the knowledge gathered from lower organisms, it is likely that transcription-translation mechanisms within individual cells are a core phenomenon initiating overall behavioral circadian rhythmicity across the animal kingdom. Synaptic organization in the SCN nucleus may thus coordinate and relay, rather than generate, rhythmicity.

Clock, Gene Regulation, and Circadian Rythmicity in Mammals

It generally is assumed that the genetic control of circadian rhythmicity is polygenic in mammals, as it is in

lower organisms, and several mutations with a strong effect on free-running period have been reported (Ralph and Menaker 1988; Vitaterna et al. 1994; Nolan et al. 1995; Takahashi 1995). One of these phenotypes is the product of a spontaneous semidominant mutation, *Tau* (Ralph and Menaker 1988), in the golden hamster, which induces a shorter free-running period and no other apparent abnormalities. The two others, *Clock* and *Wheel,* are dominant mutations in mice that are produced through N-ethyl-N-nitrosurea germ-line mutagenesis. *Wheel* is a complex neurological mutation that associates a complex array of abnormal behaviors such as circling, hyperactivity, and abnormal circadian rhythmicity and that has been mapped to mouse chromosome 4 (Nolan et al. 1995). *Clock* is a pure circadian mutation, associated with long free-running period, that has been mapped to the midportion of mouse chromosome 5, in a region of conserved synteny with human chromosome 4.

The positional cloning of *Clock* has recently been sucessfully completed (Antoch et al. 1997; King et al. 1997). Interestingly, CLOCK is a member of the bHLH-PAS protein family and shares sequence similarity with PER in the PAS domain that is known to be a protein-dimerization interface. In contrast to PER in *Drosophila,* however, CLOCK also has a DNA binding motif (bHLH), suggesting an ability to regulate gene transcription. Protein-protein interactions and regulation of transcription are thus likely to be involved in generating circadian rythmicity across the animal kingdom.

Cloning Sleep and Circadian Genes in Mammals by Use of Rodent Models

Even for a relatively simple, anatomically localized function such as the regulation of circadian rhythmicity in the suprachiasmatic nucleus, multiple genes are involved. The situation is thus likely to be even more complex for normal and abnormal sleep regulation. Mutations and variations in some of these genes will cause pathological phenotypes in animals and humans, whereas others may contribute to interindividual differences or variations in sleep patterns within the same species.

In the search for these genes, mouse models are likely to be one of the best tools for discovering sleep-related genes (Takahashi et al. 1994). Not only are rodents easy to breed and study, but high-density marker maps, such as the Whitehead Institute/MIT map, are now available. One possible approach, already exemplified for circadian rhythmicity, is to use mutagenesis to produce mutants with sleep or circadian abnormalities and to isolate the mutant genes through positional cloning. This is clearly one of the most promising avenues, but the feasibility of this approach is limited by the relatively large number of animals (200–1,000) that need to be screened to find a mutation of interest (Takahashi 1995). Another strategy is to use QTL analysis and inbred mouse strains. This usually involves first studying recombinant inbred strains to identify possible genetic effects and phenotypes of interest and then verifying the QTLs by breeding experiments, genetic typing, and building of congenic lines. These protocols have been used successfully for numerous other multifactorial traits, from autoimmune diabetes in the nonobese diabetic (nod) mouse (Todd et al. 1991) to drug response for addiction research (Crabbe et al. 1994; Dudek and Tritto 1995). Candidate QTLs for circadian rhythmicity in mice recently have been reported in studies using available recombinant inbred strains (Hofstetter et al. 1995; Maeda et al. 1996). One important limitation of the QTL approach is that genetic effects may be weak or very dependent on genetic background. This makes the next step, gene isolation, extremely difficult, if not impossible, in many cases. An advantage of the QTL technique is that it may lead to the isolation of naturally polymorphic factors that are involved in phenotypic variations; it is thus a technique complementary to mutagenesis.

Another approach consists of direct examination of "candidate" genes in phenotypically distinct animal strains. Korpi et al. (1993), for example, recently demonstrated that a strain of rats particularly more resistant to benzodiazepines and alcohol carried a specific mutation of the alpha-6 subunit of the GABA-A receptor. This result agrees with the idea that sensitivity to alcohol and to benzodiazepines proceeds from a common GABAergic mechanism. Nevertheless, other genes and factors also seem to be involved, because mutations at this locus are not found in other strains of rodents sensitive to sedatives or to alcohol (Korpi et al. 1993). The candidate-gene approach will become more feasible as more and more genes are isolated and sequenced and is likely to be most powerful in humans. In this species, gene isolation and sequencing is moving forward at a faster pace than in mice, and human disorders offer a wide-open field of investigation.

Another research strategy that looks promising uses genetically manipulated animal strains (transgenic or "knockout") (Roemer et al. 1991; Travis 1992). If the animal is viable, the analysis of the obtained phenotype provides information on the normal function of the modified gene. A recent example of this research stategy was provided by the study of the prion knockout mouse (Tobler et al. 1996). In this study, mice with a null mutation in the prion protein gene ($PrP^{0/0}$), a gene associated with fatal familial insomnia and Creutzfeldt-Jakob disease, were reported to display alterations in both circadian activity and sleep patterns (Tobler et al. 1996), thus suggesting a role for the prion protein in sleep regu-

lation. New mouse strains manipulated for one or multiple candidate genes (neuroreceptors and enzymes and candidate disease genes) are being developed at an increasing pace. Ultimately, sleep and circadian rhythms will also be studied in these mutants, and conclusions will be drawn regarding the involvement of a given system in the control of sleep.

The study of genetically altered strains will soon lead to the identification of numerous genetic factors involved in the physiological control of sleep in rodents. The potential clinical implications of these research avenues are still difficult to measure. Only a fraction of the genes identified in rodents will play a role in human disease. The rodent models will, however, remain attractive for the design of better-controlled behavioral and genetic studies.

Genetic Aspects of Pathological Human Sleep

Numerous sleep pathologies, such as narcolepsy, fatal familial insomnia, sleep paralysis, hypnagogic hallucinations, sleep apnea, and restless-leg syndrome, are well known for recurring with a high frequency in certain families (Bornstein 1961; Roth et al. 1968; Kales et al. 1980; Montplaisir et al. 1985; Lugaresi et al. 1986; Guilleminault et al. 1989; El Bayadi et al. 1990; Heath et al. 1990). All these results confirm the existence of a group of genes whose function is more specifically related to sleep. Genome screening is therefore another possible research strategy for identification of pathological factors in sleep disorders.

Molecular Genetics and Narcolepsy-Cataplexy

Narcolepsy is a disorder characterized by excessive daytime sleepiness and abnormal REM sleep. Disease onset usually occurs at 15–25 years of age and only exceptionally before puberty. Daytime somnolence is usually the most disabling symptom; it frequently requires life-long treatment with amphetamine-like stimulants. Sleepiness can be objectively demonstrated in a sleep laboratory using the Multiple Sleep Latency Test (MSLT). In this simple test, latencies to falling asleep are measured during four or five short naps taken at 2-h intervals during the daytime, and the presence or absence of a REM-sleep transition is recorded. In narcolepsy, sleep latencies are decreased (mean <8 min), and multiple (i.e., more than two) REM-sleep transitions are observed. Cataplexy, sleep paralysis, and hypnagogic hallucinations are frequently associated symptoms. In cataplexy, brief episodes of muscle weakness resulting in knees buckling, jaw sagging, head dropping, or, less frequently, full-body paralysis are observed when the patient is laughing or elated. In sleep paralysis, the patient finds him- or herself unable to move for a few seconds to several minutes when waking up or when falling asleep. Sleep paralysis and cataplexy are both pathological manifestations of REM-sleep atonia, but only cataplexy is specific for the narcolepsy syndrome. Hypnagogic hallucinations are dreamlike experiences occurring at sleep onset or during sleep attacks.

Narcolepsy with cataplexy affects 0.02%–0.06% of the general population in the United States and western European countries (Solomon 1945; Dement et al. 1973; Aldrich 1992; Mignot, in press). It may be more frequent (0.16%–0.18%) in Japan (Honda 1979; Mignot, in press) and rarer in Israel (Lavie and Peled 1987). Since its description in 1880 by Gélineau (1880), familial cases have been reported by numerous authors (Daly and Yoss 1959; Nevsimalova-Bruhova 1973; Kessler et al. 1979; Guilleminault et al. 1989; Singh et al. 1990; Billiard et al. 1994), thus suggesting a genetic basis for narcolepsy. This pathology thus offers a unique opportunity to discover genes involved in the control of sleep.

More recent studies, however, suggest that narcolepsy is not a simple genetic disorder (for review, see Mignot, in press). The development of human narcolepsy involves environmental factors on a specific genetic background, and only 25%–31% of MZ twins reported in the literature are concordant for narcolepsy (Mignot, in press). One of the predisposing genetic factors is located in the major histocompatibility complex (MHC) DQ region. Ninety to 100% of narcoleptic patients with definite cataplexy share a specific human leukocyte antigen (HLA) class II allele, HLA DQB1*0602 (most often in combination with HLA DR2), versus 12%–38% of the general population in various ethnic groups (Honda 1983; Honda and Matsuki 1990; Matsuki et al. 1992; Rogers et al. 1997; Mignot et al., in press). The finding of an HLA association in narcolepsy, together with the fact that HLA DQB1*0602 is likely to be the actual HLA narcolepsy-susceptibility gene (Mignot et al. 1997; Mignot, in press), suggests that narcolepsy might be an autoimmune disorder. However, to date, all attempts to demonstrate an immunopathology in narcolepsy have failed, and the mode of action of HLA DQB1*0602 is still uncertain (Matsuki et al. 1988; Rubin et al. 1988; Fredrikson et al. 1990; Carlander et al. 1993; Mignot et al. 1995; Tafti et al. 1996).

Twelve to 38% of the general population carry HLA DQB1*0602, and only a small fraction have narcolepsy; DQB1*0602 is thus a weakly penetrant genetic factor ($\lambda_{HLA} = 2$), even if genetic association with the disorder is high. Other genetic factors, possibly more penetrant than HLA, are likely to be involved. One to 2% of the first-degree relatives of a patient with narcolepsy-cataplexy are affected by the disorder, versus 0.02%–0.06% in the general population in various ethnic groups, yielding a $\lambda_{siblings}$ of 20–40-fold increased risk (Guilleminault et al. 1989; Billiard et al. 1994; Mignot, in press). Familial aggregation cannot be explained by

the sharing of HLA haplotypes alone (Mignot, in press), and some families are non-HLA DQB1*0602 positive (Guilleminault et al. 1989), thus suggesting the importance of non–HLA susceptibility genes that could be positionally cloned by use of genome-screening approaches in human multiplex families or in isolated populations.

Studies using a canine model of narcolepsy also illustrate the importance of non-MHC genes. In this model, narcolepsy-cataplexy is transmitted as a single autosomal recessive trait with full penetrance, *canarc-1* (Baker and Dement 1985; Mignot et al. 1992, 1993). This high-penetrance narcolepsy gene is unlinked to MHC class II but cosegregates with a DNA segment with high homology to the human immunoglobulin μ-switch sequence (Mignot et al. 1991). This linkage marker is located very close to the narcolepsy gene (current LOD score 15.3 at 0% recombination), and gene isolation is ongoing both in canines and in the corresponding human region of conserved synteny.

Genetics and Dissociated-REM-Sleep Events

Sleep paralysis and hypnagogic hallucinations, two symptoms of dissociated REM sleep, occur frequently in the general population, independently of narcolepsy (Dalhitz et al. 1992; Oyahon et al. 1996). Sleep paralysis is highly familial, and autosomal dominant transmission has been observed in some cases (Goode 1962; Roth et al. 1968; Nevsimalova-Bruhova 1973; Bell et al. 1986). For this symptom, twin studies suggest a much higher concordance in MZ twins versus DZ twins (Hori and Hirose 1995), which may be more frequent in the black population (Bell et al. 1986). There is no association with HLA DQB1*0602 (Dalhitz et al. 1992).

In REM-sleep behavior disorder (RBD), motor behaviors arise during REM sleep and disturb sleep continuity (Mahowald and Schenck 1994). RBD is frequently associated with other pathologies, such as narcolepsy, but may occur in isolation (Mahowald and Schenck 1994). The familiality of isolated RBD is not established, but the disorder may be weakly associated with HLA DQ1 (Schenck et al. 1996)

Cataplexy without sleepiness is exceptional (Aldrich 1992), but some rare familial cases with or without associated sleep paralysis have been described (Gelardi and Brown 1967; Vela Bueno et al. 1978; Hartse et al. 1988). In many of these cases, however, clinical presentation seems to differ quite significantly from narcolepsy-cataplexy and cataplexy presented in the first months of life (Vela Bueno et al. 1978; Hartse et al. 1988). HLA typing has not been done for these families.

Molecular Genetics and Fatal Familial Insomnia

Fatal familial insomnia is a rare neurological condition characterized by severe insomnia, neurovegetative symptoms, intellectual deterioration, and death (Lugaresi et al. 1986; Julien et al. 1990; Goldfarb et al. 1992; Manetto et al. 1992). Insomnia is an early sign, and sleep disruption is associated with a disappearance of stage II light sleep and SWS, whereas brief episodes of REM sleep are usually maintained. Neuropathological lesions are mostly limited to a spongiform degeneration of the anterior ventral and mediodorsal thalamic nuclei and of the inferior olive (Manetto et al. 1992). This pathology is typically associated with a mutation of the codon 178 in the prion protein gene, but one recent report detected a codon 200 mutation (Chapman et al. 1996). These same mutations are also found in Creutzfeldt-Jakob disease, but a polymorphism at codon 129 seems to determine the phenotypic expression of fatal familial insomnia rather than Creutzfeldt-Jakob dementia (Goldfarb et al. 1992; Chapman et al. 1996).

The prion protein 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 disrupting the prion protein gene are behaviorally normal but may display sleep abnormalities (Tobler et al. 1996). Prions are involved in a group of human and animal disorders with more or less anatomically confined spongious degeneration and neuronal atrophy (spongiform encephalopathies). A proteinase-resistant form of the prion protein is probably involved in the pathology (Prusiner et al. 1991). These diseases can appear either in a familial context or in an infectious context, the prion protein (or an agent that cannot be distinguished from the proteic element) acting as the transmitting agent. The mechanism by which certain isoforms of the protein are infectious remains a widely discussed topic (Weissman 1991; Mestel 1996).

How a simple additional polymorphism on codon 129 alters the symptomatology from Creutzfeldt-Jakob disease to fatal familial insomnia is not understood, but molecular studies are underway to evaluate the effect that these mutations have on the metabolism of the protein (Petersen et al. 1996). The differences in symptomatology are probably due to a differential anatomic localization of the lesions. In fatal familial insomnia, degeneration primarily localizes in the anterior ventral and mediodorsal thalamic nuclei, whereas lesions are much more diffuse in Creutzfeldt-Jakob disease (Weissman 1991; Lugaresi 1992). The well-established role of the thalamus (albeit mostly of the intralaminar thalamus) and of its cortical projections in the generation of the cortical synchronization of SWS and sleep spindles (Stériade 1992) suggests that thalamic lesions may cause the insomnia in this disorder (Lugaresi 1992). As of today, however, no study has convincingly demonstrated that the destruction of these nuclei can produce a fatal insomnia in animal models. Bilateral lesions of

these nuclei produce a persistent insomnia that is not fatal (Marini et al. 1988). Therefore, other, more discrete anatomical lesions or a distinct pathophysiological mechanism could also play a role. Transgenic mice carrying the human prion allele specific for fatal familial insomnia have now been generated and are under study to answer these questions.

The implication of the thalamus in the pathophysiology of fatal familial insomnia suggests that this brain structure may be involved in the genesis of other, more frequent insomnias. Insomnia is a very frequent symptom that affects $\geq$10% of the general population (National Institute of Mental Health 1984; Angst et al. 1989). Many insomnias appear to be constitutional (Hauri 1989), and genetic factors influencing the thalamus and homeostatic abnormalities in the regulation of sleep may be involved in some cases. Other genetic factors, such as those regulating circadian rhythmicity at the level of suprachiasmatic nuclei, could be involved in other cases.

Genetic Aspects of Restless-Leg Syndrome and Periodic Limb Movements

Restless-leg syndrome (RLS) is a frequent (2%–5% of general population) (Ekbom et al. 1960; Strang 1967; Montplaisir et al. 1994) syndrome that worsens with age and affects both sexes. RLS is almost always associated with periodic leg movements (PLM) during sleep. RLS is best defined as unconfortable or painful sensations in the legs, which force the patient to get up several times each night (Montplaisir et al. 1994; Walters and International RLS Study Group 1995). PLM are brief and repetitive muscular jerks of the lower limbs, occurring mostly during stage II sleep (Montplaisir et al. 1994). When these movements increase in strength and frequency, sleep is altered. RLS is highly familial and as many as one-third of the reported cases may transmit the condition as an autosomal dominant trait (Bornstein 1961; Ambrosetto et al. 1965; Montagna et al. 1983; Jacobsen et al. 1986; Walters et al. 1990, 1994; Trenkwalder et al. 1996) with possible genetic anticipation (Trenkwalder et al. 1996). Unfortunately, no twin study is available, and both the prevalence and the proportion of familial cases seem to vary widely according to the geographical origin of the population studied. These differences may reflect either founder effects, such as in Quebec, where one finds a high proportion of familial cases (Montplaisir et al. 1994) and a higher prevalence (Lavigne and Montplaisir 1994), or the influence of local environmental factors.

Population-based risk estimations in first- and second-degree relatives are not yet available for this interesting pathology. In a recent study published only as an abtract, risks to first- and second-degree relatives were 19.9% and 4.1%, respectively (Labuda 1997). This compared with 3.5% and 0.5%, respectively, for first- and second-degree relatives of control subjects and suggested a $\lambda_{siblings}$ of $\sim$5 (Labuda 1997). Linkage studies using either microsatellite markers or candidate genes in multiplex families are ongoing in order to identify the gene(s) involved (Johnson et al. 1992; J. Montplaisir, personal communication). Possible candidate genes are enzymes and receptors of the dopaminergic and enkephalinergic metabolisms, two neurotransmitters involved in the pharmacological treatment of the syndrome. As of today, however, no result suggestive of linkage has been published.

Genetic Aspects of Sleepwalking, Sleeptalking, and Night Terrors

These parasomnias generally occur during SWS (stage III and stage IV) (Keefauver and Guilleminault 1994). They are usually grouped together and considered to share a common or related pathophysiological mechanism (Broughton 1968), although this notion is sometimes disputed (Keefauver and Guilleminault 1994). The prevalence of these symptoms is several percent among children and only scarcely requires a medical consultation. Symptoms generally disappear in adulthood (Abe and Shimakawa 1966; Keefauver and Guilleminault 1994).

The familial nature of these symptoms has been recognized by most authors (Debray and Huon 1973; Hälstrom et al. 1972; Kales et al. 1980; Abe et al. 1984), but the exact mode of transmission is uncertain. Twin studies have shown a high degree of concordance for sleepwalking and night terror (50% in MZ twins and 10%–15% in DZ twins) (Bakwin 1970; Hori and Hirose 1995; Hublin et al. 1997). The genetic predisposition to sleepwalking, sleeptalking, and, to a lesser degree, night terrors and enuresis may overlap. Indeed, the frequency of sleep terrors and enuresis might be more frequent in families with somnambulism (Debray and Huon 1973; Kales et al. 1980; Abe et al. 1984). This suggests a related pathophysiological mechanism and similar genetic control. As of today, however, there has not been any molecular study initiated on these pathologies.

Obstructive Sleep–Apnea Syndrome and Related Breathing Abnormalities during Sleep

Obstructive-sleep-apnea syndrome (OSAS) is a complex syndrome in which the upper airway collapses repetitively during sleep, thus blocking breathing (Gastaud et al. 1965). Snoring is one of the cardinal symptoms. Repeated apneas prevent the patient from sleeping soundly, and the patient is frequently excessively sleepy the following day. Four to 5% of the general population suffer from OSAS (Lugaresi et al. 1986; Young et al. 1993), which, in the longer term, leads to high blood

pressure and increased risk for cardiovascular accidents (Guilleminault et al. 1975; Koskenvuo et al. 1985; Hall and Bradley 1995). Recent studies suggest increased vulnerability in African Americans (Redline et al. 1997).

Twin studies are lacking in OSAS, but, for habitual snoring, two recent studies have shown higher concordance in MZ twins versus DZ twins (Ferini-Strambi et al. 1995; Hori and Hirose 1995). Multiplex families of patients suffering from OSAS have also been reported in the literature (Strohl et al. 1978; Adickes et al. 1986; Oren et al. 1987; Manon-Espaillat et al. 1988; Wittig et al. 1988; El Bayadi et al. 1990; Mathur and Douglas 1995; Pillar and Lavie 1995; Redline et al. 1995), and one study found a substantial increase of HLA A2 and HLA B39 in Japanese patients with OSAS (Yoshizawa et al. 1993). Familial aggregation is generally explained by the fact that most risk factors involved in the physiopathology of sleep apnea are, in large part, genetically determined. These include obesity, alcoholism, and facial soft-tissue and bone anatomy, which all predispose to upper-airway obstruction (for discussion, see El Bayadi et al. 1990; Guilleminault et al. 1995; Mathur and Douglas 1995; Redline et al. 1995; Kronholm et al. 1996). In some cases, the genetic factor primarily involves abnormal ventilatory control by the CNS (Adickes et al. 1986; El Bayadi et al. 1990). A possible genetic overlap between OSAS and sudden infant death (Adickes et al. 1986; Oren et al. 1987; Tishler et al. 1996) and the high degree of concordance in chemoreceptor responses observed in MZ twins (Kawakami et al. 1982; Thomas et al. 1993) suggests the importance of genetic factors regulating the central control of ventilation in OSAS.

A multiplicity of genetic factors is likely to correspond to the multifactorial aspect of OSAS. A genetic-linkage approach in OSAS would thus be facilitated by a careful phenotypic analysis—for example, study of sleepy or nonsleepy subjects, nonobsese versus obese OSAS patients (Guilleminault et al. 1995), or subjects with selected mophological features (Kushida et al. 1996).

Chromosomal and Genetic Abnormalities and Sleep Disturbances

The coincidental association of specific chromosomal breakpoints with specific pathologies can be very useful to help localize the susceptibility gene(s). In practice, however, karyotypes are rarely requested when a sleep disorder is the primary abnormality, and very few sleep studies have been performed in patients with chromosomal or genetic abnormalities. These disorders frequently produce behavioral and medical problems that have secondary effects on sleep, particularly disturbed nocturnal sleep, so it may difficult to identify a disease-specific sleep phenotype (Carskadon et al. 1993). In spite of these limitations, fragile X subjects have been reported to experience sleep disturbances and low melatonin levels (O'Hare et al. 1986; Staley-Gane et al. 1996), whereas subjects with either Norrie disease (genetic alterations in a region encompassing the monoamine oxidase genes at Xp11.3) or Nieman-Pick type C (18q11-q12) may experience cataplexy and sleep disturbances (Challamel et al. 1994; Vossler et al. 1996). An interesting family with autosomal dominant cerebral ataxia, deafness, normal karyotype, and clinically defined narcolepsy with cataplexy also has been described and shown to be non–HLA DR2 associated (Melberg et al. 1995). OSAS are also frequently observed as a result of anatomic malformations, adenotonsilar enlargement, or morbid obesity (e.g., see Goldberg et al. 1980; Kaplan et al. 1991; Carskadon et al. 1993). In a few instances, however, polygraphic studies suggest that central factors are also involved in addition to or independently of abnormal breathing during sleep. This may be the case for the Prader-Willi and Angelman syndromes (del[15q]) (Kaplan et al. 1991; Summers et al. 1992; Vgontzas et al. 1996) or the Smith Magenis syndrome (del[17][p11.2]) (Greenberg et al. 1991; Fischer et al. 1993).

In spite of their relatively high population frequency, the effects of sex-chromosomal aneuploidies on sleep have been only marginally studied, but XXY subjects may display increased 24-h sleep time (Higurashi et al. 1986). The general topic of abnormal hormonal control and sleep in these patients would be worth investigating more thoroughly, because puberty is associated with established changes in sleep needs (Carskadon 1990). Moreover, narcolepsy often starts with adolescence, and in two cases narcolepsy started at the unusual age of 6 years, in a Turner syndrome patient (XO) (George and Singh 1991), or in coincidence with a precocious puberty (Chilshlom et al. 1985).

Other Sleep Pathologies

Insomnia, obstructive sleep apnea, narcolepsy, periodic movements and RLS syndrome, parasomnias, and circadian disorders are the most frequent sleep pathologies. There are few or no studies on other forms of hypersomnias or parasomnias. One twin study suggests increased frequency of bruxism (teeth grinding during sleep) in MZ twins versus DZ twins (Hori and Hirose 1995), and bruxism has been reported in a multiplex context (Hartman 1989). Familial forms of essential hypersomnia (Nevsimalova-Bruhova 1973), of hypersomnias associated with either dystrophia myotonica (Manni et al. 1991) or sleep-responsive extrapyramidal dystonias (Byrne et al. 1991; Ishikawa and Miyatake 1995), and of jactatio capitis nocturna (Thorpy and Glovinsky 1989) have also been reported. A possible association of idiopathic hypersomnias with HLA Cw2 and of hypersomnia in dystrophia myotonica with DR6

has also been found (Poirier et al. 1986; Manni et al. 1991) but would need independent confirmation.

Perspectives in Human Genetic Research in Sleep Disorders

The complexity of sleep as a physiological phenomenon is matched by a vast number of pathologies. Most of these pathologies are multifactorial and, to a large extent, genetically determined. The recent progress of molecular genetics has enabled researchers to undertake a purely genetic approach to understand the pathophysiology of these disorders. This approach will most likely first lead to the identification of genes involved in etiologically homogeneous sleep disorders such as narcolepsy. Genome-screening studies in more frequent and complex sleep disorders, such as OSAS or RLS, will require the inclusion of a large number of multiplex families but are now feasible. These disorders may also benefit from studies in isolated populations or even from association studies using very large numbers of single-case families; this last design has the benefit of being easily used for candidate-gene studies. Those are likely to become a more viable research strategy as more and more genes are cloned and positioned on the human map and as possible candidate genes are identified in mouse models.

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