Am. J. Hum. Genet. 60:1289–1302, 1997

BEHAVIORAL GENETICS '97
Genetics of Narcolepsy and Other Sleep Disorders

Emmanuel Mignot

Center for Narcolepsy, Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford

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

Received April 14, 1997; accepted for publication April 15, 1997.

Address for correspondence and reprints: Dr. Emmanuel Mignot, Stanford Center For Narcolepsy, Department of Psychiatry and Behavioral Sciences, MSLS Building, 1201 Welch Road, Room P112, Stanford, CA 94305. E-mail: mignot@leland.stanford.edu

This article represents the opinion of the author and has not been peer reviewed.

0002-9297/97/6006-0005$02.00

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 ~ 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.

Acknowledgments

Part of the work described in this review has been funded by NIH grant NS23724, from the National Institute of Neurological Disease and Stroke, to the author. I thank Dr. Juliette Faraco for her critical reading of the manuscript.

References

Abe K, Amatomi M, Oda N (1984) Sleepwalking and recurrent sleeptalking in children of childhood sleepwalkers. Am J Psychiatry 141:800–801

Abe K, Shimakawa M (1966) Genetic and developmental aspects of sleeptalking and teeth-grinding. Acta Paedopsychiatr 33(11): 339–344

Adickes ED, Buehler BA, Sanger WG (1986) Familial sleep apnea. Hum Genet 73:39–43

Aldrich M (1992) Narcolepsy. Neurology 42 Suppl 6:34–43

Ambrosetto C, Lugaresi E, Coccagna G, Tassinari CA (1965) Clinical and polygraphic remarks on the restless leg syndrome. Riv Pathol Nerv Ment 86:244–251

Angst J, Vollrath M, Koch R, Dobbler-Mikola A (1989) The Zurick study. VII. Insomnia: symptoms, classification and prevalence. Eur Arch Psychiatr Neurol Sci 238:285–293

Anokhin A, Steinlein O, Fischer C, Mao Y, Vogt P, Schalt E, Vogel F (1992) A genetic study of the human low-voltage electroencephalogram. Hum Genet 90:99–112

Antoch MP, Song EJ, Chang AM, Vitaterna MH, Zhao Y, Wilsbacher LD, Sangoram AM, et al (1997) Functional identification of the mouse circadian Clock gene by transgenic BAC rescue. Cell 89:655–667

Baker TL, Dement WC (1985) Canine narcolepsy-cataplexy syndrome: evidence for an inherited monoaminergic-cholinergic imbalance. In: McGinty DJ, Drucker-Colin R, Morrisson A (eds) Brain mechanisms of sleep. Raven Press, New York, pp 199–233

Bakwin H (1970) Sleepwalking in twins. Lancet 2:466–467

Bell GC, Dixie-Bell DD, Thompson B (1986) Further studies on the prevalence of isolated sleep paralysis in black subjects. J Natl Med Assoc 78(7): 649–659

Benca RM, Bergman BM, Leung C, Nummy D, Rechtschaffen A (1991) Rat strain differences in response to dark pulse triggering of paradoxical sleep. Physiol Behav 49:83–87

Billiard M, Pasquie-Magentto, Heckman M, Carlander B, Besset A, Zachariev Z, Eliaou JF, et al (1994) Family studies in narcolepsy. Sleep Suppl 17:S54–S59

Bornstein B (1961) Restless leg syndrome. Psychiatr Neurol 141:165–201

Broughton RJ (1968) Sleep disorders: disorders of arousal? Science 159:1070–1078

Byrne E, White O, Cook M (1991) Familial dystonic choreoathetosis with myyokymia: a sleep responsive disorder. J Neurol Neurosurg Psychiatry 54:1090–1092

Carlander B, Eliaou JF, Billiard M (1993) Autoimmune hypothesis in narcolepsy. Neurophysiol Clin 23:15–22

Carskadon MA (1990) Patterns of sleep and sleepiness in adolescents. Pediatrician 17(1): 5–12

Carskadon MA, Pueschel SM, Millman RP (1993) Sleep-disordered breathing and behavior in three risk groups: preliminary findings from parental reports. Childs Nerv Syst 9(8): 452–457

Challamel MJ, Mazzola ME, Nevsimalova S, Cannard C, Louis J, Revol M (1994) Narcolespy in children. Sleep Suppl 17:S17–S20

Chapman J, Arlazoroff A, Goldfarb LG, Cervenakova L, Neufeld MY, Werber E, Herbert M, et al (1996) Fatal insomnia in a case of familial Creuzfeld-Jakob disease with codon 200(lys) mutation. Neurology 46(3): 758–761

Chilshlom RC, Brooks CJ, Harrison GF, Lyon L, Zukaitis D (1985) Prepubescent narcolepsy in a six year old girl. Sleep Res 15:113

Crabbe JC, Belknap J, Buck KJ (1994) Genetic animal models of alcohol and drug abuse. Science 264:1715–1723

Dalhitz M, Parles JD, Vaughan R, Page G (1992) The sleep paralysis-excessive daytime sleepiness syndrome. J Sleep Res 1 Suppl 1:52

Daly D, Yoss R (1959) A family with narcolepsy. Proc Staff Meet Mayo Clin 34:313–320

Debray P, Huon H (1973) À propos de trois cas de somnambulisme familial. Ann Med Intern 124(1): 27–29

De Fiebre CM, Collins A (1992) Classical genetic analyses of responses to nicotine and ethanol in crosses derived from long- and short-sleep mice. J Pharmacol Exp Ther 261(1): 173–180

De Fiebre CM, Marley RJ, Miner LL, De Fiebre NEC, Wehener JM, Collins A (1992) Classical genetic analyses of responses to sedative-hypnotic drugs in crosses derived from long-sleep and short-sleep mice. Alcohol Clin Exp Res 16(3): 511–521

DeFries JC, Wilson JR, Erwin VG, Petersen DR (1989) LS × SS recombinant inbred strains of mice: initial characterization. Alcohol Clin Exp Res 13:196–200

Dement WC, Carskadon M, Ley R (1973) The prevalence of narcolepsy. II. Sleep Res 2:147

Drennan MD, Shelby J, Kripke DF, Kelsoe J, Gillin JC (1992) Morningness/eveningness is heritable. Soc Neurosci Abstr Book 8:196

Dudek BC, Abbott ME (1984) A biometrical genetic analysis of ethanol response in selectively bred long-sleep and short-sleep mice. Behav Genet 14:1–19

Dudek BC, Tritto T (1995) Classical and nonclassical approaches to the genetic analysis of alcohol-related phenotypes. Alcohol Clin Exp Res 19(4): 802–810

Dunlap JC (1993) Genetic analysis of circadian clocks. Annu Rev Physiol 55:683–728

——— (1996) Genetic and molecular analysis of circadian clocks. Annu Rev Genet 30:579–601

Edgar DM, Seidel WF, Martin CE, Sayeski PP, Dement WC (1991) Triazolam fails to induce sleep in suprachiasmatic nucleus-lesioned rats. Neurosci Lett 125:125–128

Ekbom K (1960) Restless legs syndrome. Neurology 10:868–873

El Bayadi S, Millman RP, Tishler PV, Rosenberg C, Saliski W, Boucher MA, Redline S (1990) A family study of sleep apnea: anatomic and physiologic interactions. Chest 98:(3): 554–559

Erwin VG, Jones BC, Radcliffe R (1990) Further characterization of LS×SS recombinant inbred strains of mice: activating and hypothermic effects of ethanol. Alcohol Clin Exp Res 14(2): 200–204

Erwin VG, Korte A, Jones BC (1988) Central muscarinic cholinergic influences on ethanol sensitivity in long-sleep and short-sleep mice. J Pharmacol Exp Ther 247(3): 857–862

Fischer H, Oswald HP, Duba HC, Doczy L, Simma B, Uterman G, Hass OA (1993) Constitutional interstitial deletion of 17 (p11.2) (Smith Magenis syndrome): a clinically recognizable microdeletion syndrome: report of two cases and review of the literature. Klin Padiatr 205(3): 162–166

Ferini-Strambi L, Calori G, Oldani A, Della Marca G, Zucconi M, Castronovo V, Gallus G, et al (1995) Snoring in twins. Respir Med 89:337–340

Fredrikson S, Carlander B, Billiard M, Link H (1990) CSF immune variable in patients with narcolepsy. Acta Neurol Scand 81:253–254

Friedmann JK (1974) A diallell analysis of the genetic underpinnings of mouse sleep. Physiol Behav 12:169–175

Gastaut H, Tassinari C, Duron B (1965) Étude polygraphique des manifestations épisodiques (hypniques et respiratoires) diurnes et nocturnes du syndrome de Pickwick. Rev Neurol (Paris) 112:573–579

Gedda L, Brenci G (1983) Twins living apart test: progress report. Acta Genet Med Gemellol (Roma) 32:17–22

Gelardi JAM, Brown JW (1967) Hereditary cataplexy. J Neurol Neurosurg Psychiatry 30:455–457

Gélineau J (1880) De la narcolepsie. Gaz Hop Paris 53:626–628, 54:635–637

George CF, Singh SM (1991) Juvenile onset narcolepsy in an individual with Turner syndrome: a case report. Sleep 14(3): 267–269

Goldberg R, Fish B, Ship A, Shprintzen RJ (1980) Deletion of a portion of the long arm of chromosome 6. Am J Med Genet 5:73–80

Goldfarb LG, Petersen RB, Tabaton M (1980) Fatal familial insomnia and familial Creutzfeldt-Jakob disease: a disease phenotype determined by a DNA polymorphism. Science 258:806–808

Goode GB (1962) Sleep paralysis. Arch Neurol 6(3): 228–234

Greenberg F, Guzzetta V, Montes de Oca-Luna R, Magenis RE, Smith ACM, Richter SF, Kondo I (1991) Molecular analysis of the Smith-Magenis ayndrome: a possible contiguous-gene syndrome associated with del(17)(p11.2). Am J Hum Genet 49:1207–1218

Guilleminault C, Eldridge FL, Simmons FB (1975) Sleep apnea syndrome: can it induce hemodynamic changes? West J Med 123:7–16

Guilleminault C, Mignot E, Grumet FC (1989) Familial patterns of narcolepsy. Lancet 2(8676): 1376–1379

Guilleminault C, Partinen, M, Hollman K, Powell N, Stroohs R (1995) Familial aggregates in obstructive sleep apnea syndrome. Chest 107:1545–1551

Hall JC (1995) Tripping along the trail to the molecular mechanism of biological clocks. Trends Neurosci 18:230–240

Hall JC (1996) Are cycling gene products as internal zeitgebers no longer the zeitgeist of chronobiology. Neuron 17:799–800

Hall MJ, Bradley TD (1995) Cardiovacular disease and sleep apnea. Curr Opin Pulm Med 1(6): 512–518

Hälstrom T (1972) Night terror in adults through three generations. Acta Psychiatr Scand 48:350–352

Hartman E (1989) Bruxism. In: Kryeger M, Roth T, Dement WC (eds) Principles and practice of sleep medicine. WB Saunders, Philadelphia, pp 385–388

Hartse KM, Zorick FJ, Sicklesteel JM, Roth T (1988) Isolated cataplexy: a family study. Henry Ford Hosp Med J 36(1): 24–27

Hauri P (1989) Primary insomnia. In: Kryeger M, Roth T, Dement WC (eds) Principles and practice of sleep medicine. WB Saunders, Philadelphia, pp 442–447

Heath A, Kendler KS, Eaves LJ, Roth T (1990) Evidence for genetic influences on sleep disturbance and sleep patterns in twins. Sleep 13:318–335

Higurashi M, Kawai H, Segawa M, Iijima K, Ikeda Y, Tanaka F, Egi S (1986) Growth, psychologic characteristics, and sleep-wakefulness cycle of children with sex chromosomal abnormalities. Birth Defects 22(3): 251–275

Hofstetter JR, Mayeda AR, Possidented B, Nurnberger JI (1995) Quantitative trait loci for circadian rhythms of locomotor activity in mice. Behav Genet 25(6): 545–556

Honda Y (1979) Consensus of narcolepsy, cataplexy and sleep life among teenagers in Fujisawa city. Sleep Res 8:191

Honda Y, Asaka A, Tanaka Y, Juji T (1983) Discrimination of narcolepsy by using genetic markers and HLA. Sleep Res 12:254

Honda Y, Matsuki K (1990) Genetic aspects of narcolepsy. In: Thorpy MJ (ed) Handbook of sleep disorders. Marcel Dekker, New York, pp 217–234

Hori A (1986) Sleep characteristics in twins. Jpn J Psychiatr Neurol 40(1): 35–46

Hori A, Hirose G (1995) Twin studies on parasomnias. Sleep Res Suppl 24A:324
Hrubec Z, Robinette CD (1984) The study of human twins in medical research. N Engl J Med 310:435–441
Hublin C, Kaprio J, Partinen M, Heikkila K, Koskenvuo M (1997) Prevalence and genetics of sleepwalking: a population based twin study. Neurology 48(1): 177–181
Ishikawa A, Miyatake T (1995) A family with hereditary juvenile dystonia-parkinsonism. Mov Disord 10(4): 482–488
Jacobsen JH, Rosenberg RS, Huttenlocher PR, Spire JP (1986) Familial nocturnal cramping. Sleep 9(1): 54–60
Johnson W, Walter A, Lehner T, Coccagna G, Ehrenberg B, Lazzarini A, Stenroos E, et al (1992) Affected only linkage analysis of autosomal dominant restless legs syndrome. Sleep Res 21:214
Julien J, Vital C, Deleplanque B, Lagueny A, Ferrer X (1990) Athrophie thalamique subaigue familiale: troubles mnésiques et insomnie totale. Rev Neurol (Paris) 146(3): 173–178
Kales A, Soldatos CR, Bixler EO, Ladda RL, Charney DS, Weber G, Schweitzer PK (1980) Hereditary factors in sleepwalking and night terrors. Br J Psychiatr 137:111–118
Kaplan J, Frederickson PA, Richardson JW (1991) Sleep and breathing in patients with the Prader-Willi syndrome. Mayo Clin Proc 66:1124–1126
Kawakami Y, Yamamoto H, Yoshikawa T, Shida A (1982) Chemical and behavioral control of breathing in twins. Am Rev Respir Dis 129:703–707
Keefauver SP, Guilleminault C (1994) Sleep terrors and sleep walking. In: Kryeger M, Roth T, Dement WC (eds) Principles and practice of sleep medicine, 2d ed. WB Saunders, Philadelphia, pp 567–573
Kendler KS, Heath AC, Martin NG, Eaves LJ (1987) Symptoms of anxiety and symptoms of depression: same genes, different environments? Arch Gen Psychiatry 122:451–457
Kessler S, Guilleminault C, Dement WC (1979) A family study of 50 REM narcoleptics. Acta Neurol Scand 50:503–512
Khanna JM, Kalant H (1992) Effects of chronic treatment with ethanol on the development of cross-tolerance to other alcohols and pentobarbital. J Pharmacol Exp Ther 263(2): 480–485
Khanna JM, Kalant H, Shah G, Chua A (1991) Tolerance to ethanol and cross-tolerance to pentobarbital and barbital in four rat strains. Pharmacol Biochem Behav 39:705–709
King DP, Zhao Y, Sangoram AM, Wilsbacher LD, Tanaka M, Antoch MP, Steeves TDL (1997) Positional cloning of the mouse circadian clock gene. Cell 89:641–653
Kitahama K, Valatx JL (1980) Instrumental and pharmacological paradoxical sleep deprivation in mice: strain differences. Neuropharmacology 19:529–535
Klein D, Moore RY, Reppert SM (1991) Suprachiasmatic nucleus: the mind's clock. Oxford University Press, New York
Korpi ER, Kleingoor C, Kettenmann H, Seeburg PH (1993) Benzodiazepine-induced motor impairment linked to point mutation in cerebellar GABA-A receptor. Nature 361:356–359
Koskenvuo M, Kaprio J, Partinen M (1985) Snoring as a risk for hypertension and angina pectoris. Lancet 1:893–896
Kronholm E, Aunola S, Hyyppa MT, Alanen E, Halonen P, Partinen M (1996) Sleep in monozygotic twin pairs discordant for obesity. J Appl Physiol 80(1): 14–19
Kushida CA, Bergman BM, Rechtschaffen A (1989) Sleep deprivation in the rat. IV. Paradoxical sleep deprivation. Sleep 12:22–30
Kushida CA, Guilleminault C, Mignot E, Amhed O, Won C, O'Hara B, Clerk AA (1996) Genetics and craniofacial dysmorphism in family studies of obstructive sleep apnea. Sleep Res 25:275
Labuda MC (1997) Epidemiology, family patterns, and genetics of restless legs syndrome. Paper presented at the RLS Foundation conference, Washington DC, February 22
Lavie P, Peled R (1987) Narcolepsy is a rare disease in Isreal. Sleep 10:608–609
Lavigne G, Montplaisir J (1994) Restless legs syndrome and sleep bruxism: prevalence and assoication among Canadians. Sleep 17:739–743
Leung C, Bergmann BM, Rechtschaffen A, Benca RM (1992) Heritalility of dark pulse trigerring of paradoxical sleep in rats. Physiol Behav 52:127–131
Linkowski P, Kerkhofs M, Hauspie R, Mendlewicz J (1991) Genetic determinants of EEG sleep: a study in twins living apart. Electroencephalogr Clin Neurophysiol 79:114–118
Linkowski P, Kerkhofs M, Hauspie R, Susanne C, Mendlewicz J (1989) EEG sleep patterns in man: a twin study. Electroencephalogr Clin Neurophysiol 73:279–284
Linkowski P, Kerkhofs M, Van Cauter E (1992) Sleep and biological rhythms in man: a twin study. Clin Neuropharmacol 15 Suppl 1 (pt A): 42A–43A
Linkowski P, Van Onderbergen A, Kerkhofs M, Susanne C, Mendlewicz J (1993) Twin study of the 24-h cortisol profile: evidence for genetic control of the human circadian clock. Am J Physiol 264:E173–E181
Lugaresi E (1992) The thalamus and insomnia. Neurology 42 Suppl 6:28–33
Lugaresi E, Medori R, Montagna P, Baruzzi A, Cortelli P, Lugaresi A, Tinuper P, et al (1986) Fatal familial insomnia and dysautonomia with selective degeneration of thalamic nuclei. N Engl J Med 315:997–1003
Maeda AR, Hofstetter JR, Belknap JR, Nurnberger JI Jr (1996) Hypothetical quantitative trait loci (QTL) for circadain period of locomotor activity in C×B recombinant inbred strains of mice. Behav Genet 26(5): 505–511
Mahowald MW, Schenk CH (1994) REM sleep behavior disorder. In: Kryeger M, Roth T, Dement WC (eds) Principles and practice of sleep medicine, 2d ed. WB Saunders, Philadelphia, pp 574–588
Manetto V, Medori R, Cortelli P, Montagna P, Tinuper P, Baruzzi A, Rancurel G, et al (1992) Familial fatal insomnia: clinical and pathological study of five new cases. Neurology 42:312–319
Manni R, Zucca C, Martinetti M, Ottolini A, Lanzi G, Tartara A (1991) Hypersomnia in dystrophia myotonica: a neurophysiological and immunogenetic study. Acta Neurol Scand 84:498–502
Manon-Espaillat R, Gothe B, Adams N, Newman C, Ruff R (1988) Familial "sleep apnea plus" syndrome: report of a family. Neurology 38:190–193
Marini G, Imeri L, Mancia M (1988) Changes in sleep waking

cycle induced by lesions of medialis dorsalis thalamic nuclei in the cat. Neurosci Lett 85:223–227

Markel PD, Fulker DW, Bennet B, Corley RP, DeFries JC, Erwin VG, Johnson TE (1996) Quantitative trait loci for ethanol sensitivity in the LS×SS recombinant inbred strains: interval mapping. Behav Genet 26(4): 447–458

Marley RJ, Freund RK, Whener JM (1988) Differential response to flurazepam in long-sleep and short-sleep mice. Pharmacol Biochem Behav 31:453–458

Matsuki K, Grumet FC, Lin X, Gelb M, Guilleminault C, Dement WC, Mignot E (1992) DQ (rather than DR) gene marks susceptibility to narcolepsy. Lancet 339:1052

Matsuki K, Juji T, Honda Y (1988) HLA and narcolepsy. In: Honda Y, Juji T (eds) Immunological features in Japan. Springer-Verlag, New York, pp 58–76

Mathur R, Douglas NJ (1995) Family study in patients with the sleep Apnea-Hypopnea syndrome. Ann Intern Med 122: 174–178

McClearn GE, Kakihana R (1973) Selective breeding for ethanol sensitivity in mice. Behav Genet 3:409–410

Melberg A, Hetta J, Dahl N, Nennesmo I, Bengtsson M, Wilbom R, Grant C, et al (1995) Autosomal dominant cerebellar ataxia deafness and narcolepsy. J Neurol Sci 124:119–129

Mestel R (1996) Putting prions to the test. Science 273:184–189

Mignot E. Genetic and familial aspects of narcolepsy. Neurology (in press)

Mignot E, Guilleminault C, Dement WC, Grumet FC (1992) Genetically determined animal models of narcolepsy, a disorder of REM sleep. In: Driscoll P (eds) Genetically defined animal models of neurobehavioral dysfunction. Birkhäuser Boston, Cambridge, pp 90–110

Mignot E, Hayduk R, Black J, Grumet FC, Guilleminault C. HLA class II studies in 509 narcoleptic patients. Sleep Res (in press)

Mignot E, Kimura A, Lattermann A, Lin X, Yasunaga S, Mueller-Eckhardt G, Rattazzi C, et al (1997) Extensive HLA class II studies in 58 non DRB1*15 (DR2) narcoleptic patients. Tissue Antigens 49:329–341

Mignot E, Nishino S, Hunt-Sharp L, Arrigoni J, Siegel JM, Reid MS, Edgar DM, et al (1993) Heterozygosity at the canarc-1 locus can confer susceptibility for narcolepsy: induction of cataplexy in heterozygous asymptomatic dogs after administration of a combination of drugs acting on monoamninergic and cholinergic systems. J Neurosci 13(3): 1145–1152

Mignot E, Tafti M, Dement WC, Grumet FC (1995) Narcolepsy and immunity. Adv Neuroimmunol 5:23–37

Mignot E, Wang C, Rattazzi C, Gaiser C, Lovett M, Guilleminault C, Dement WC, et al (1991) Genetic linkage of autosomal recessive canine narcolepsy with an immunoglobulin μ chain switch like segment. Proc Natl Acad Sci USA 88: 3475–3478

Millar AJ, Carré IA, Strayer CA, Chua NH, Kay SA (1995) Circadian Clock mutants in Arabidopsis identified by luciferase imaging. Science 267:1161–1166

Montagna P, Coccagna G, Cirignotta F, Lugaresi E (1983) Familial restless leg syndrome. In: Guilleminault C, Lugaresi E (eds) Sleep/wake disorders: natural history, epidemiology and long term evolution. Raven Press, New York, pp 231–235

Montplaisir J, Godbout R, Boghden D, Poirier G (1985) Familial restless legs with periodic movements in sleep: electrophysiological, biochemical, and pharmacological study. Neurology 35:130–134

Montplaisir J, Godbout R, Pellettier G, Warnes H (1994) Restless legs syndrome and periodic movements during sleep. In: Kryeger M, Roth T, Dement WC (eds) Principles and practice of sleep medicine, 2d ed. WB Saunders, Philadelphia, pp 589–597

Morzorati S, Lamishaw B, Lumeng L, Li TK, Bemis K, Clemens J (1988) Effects of low dose ethanol on the EEG of alcohol-preferring and nonpreferring rats. Brain Res Bull 21:101–104

National Institute of Mental Health (1984) Consensus Development Conference: drugs and insomnia: the use of medications to promote sleep. JAMA 251:2410–2414

Nevsimalova-Bruhova (1973) On the problem of heredity in hypersomnia, narcolepsy and related disturbance. Acta Univ Carol [Med] (Praha) 18:109–160

Nolan P, Sollars PJ, Bohne BA, Ewens, WJ, Pickard GE, Bucan M (1995) Heterozygosity mapping of partially congenic lines: mapping of a semi dominant neurological mutation, wheels, on mouse chromosome 4. Genetics 140:L245–L254

O'Hare JP, O'Brien IA, Arendt J, Astley P, Ratcliffe W, Andrews H, Walters R, et al (1986) Does melatonin deficiency cause the enlarged genitalia of the fragile-X syndrome? Clin Endocrinol 24(3): 327–333

Oren J, Kelly DH, Shannon DC (1987) Familial occurrence of sudden infant death syndrome and apnea of infancy. Pediatrics 80:355–358

Overstreet DH, Rezvani AH, Janowsky DS (1990) Increased hypothermic responses to ethanol in rats selectively bred for cholinergic supersensitivity. Alcohol Alcohol 25(1): 59–65

Oyahon MM, Priest R, Caulet M, Guilleminault C (1996) Hypnagogic and hypnopompic hallucinations: pathological phenomena? Br J Psychiatry 169:459–467

Partinen M, Kaprio J, Koskenvuo M, Putkonen P, Langinvainio H (1983) Genetic and environmental determination of human sleep. Sleep 6:179–185

Petersen RB, Parchi P, Richardson SL, Urig CB, Gambetti P (1996) Effect of the D178N mutation and the codon 129 polymorphism on the prion protein. J Biol Chem 271(21): 12661–12668

Phillips TJ, Dudek BC (1991) Locomotor activity responses to ethanol in selectively bred long- and short-sleep mice, two inbred mouse strains, and their F1 hybrids. Alcohol Clin Exp Res 15(2): 255–261

Phillips TJ, Feller DJ, Crabbe JC (1989) Selected mouse lines, alcohol and behavior. Experientia 45:805–827

Pillar G, Lavie P (1995) Assessment of the role of inherence in sleep apnea syndrome. Am J Respir Crit Care Med 151: 688–691

Poirier G, Montplaisir J, Decary F, Momege D, Lebrun A (1986) HLA antigens in narcolepsy and idiopathic central nervous system hypersomnolence. Sleep 9:153–158

Prusiner SB (1991) Molecular biology of prion diseases. Science 252:1515–1522

Ralph MR, Menaker M (1988) A mutation of the circadian system in golden hamsters. Science 241:1225–1227

Rechtschaffen A, Gilliland MA, Bergmann BM, Winter JB (1983) Physiological correlates of prolonged sleep deprivation in rats. Science 221:182–184

Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K (1997) Racial differences in sleep-disordered breathing in African-Americans and Caucasians. Am J Respir Crit Care Med 155:186–192

Redline S, Tishler PV, Tosteson TD (1995) The familial aggregation of obstructive sleep apnea. Am J Respir Crit Care Med 151:682–687

Roehrs T, Zwyghuizen-Doorenbos A, Timms V, Zorick F, Roth T (1989) Sleep extension, enhanced alertness and the sedating effects of ethanol. Pharmacol Biochem Behav 34: 321–324

Roemer K, Johnson PA, Friedmann T (1991) Knock-in and knock-out: transgenes, development and disease. N Biol 3(4): 331–335

Rogers AE, Meehan J, Guilleminault C, Grumet FC, Mignot E (1997) HLA DR15(DR2) and DQB1*0602 typing studies in 188 narcoleptic patients with cataplexy. Neurology 48: 1550–1556

Rosenberg RS, Bergmann BM, Son HJ, Arnason BGW, Rechtschaffen A (1987) Strain differences in the sleep of rats. Sleep 10(6): 537–541

Roth B, Bruhova S, Berkova L (1968) Familial sleep paralysis. Arch Suisse Neurol Neurochir Psychiatry 102:321–330

Rubin RL, Hajdukovic RM, Mitler MM (1988) HLA DR2 association with excessive somnolence in narcolepsy does not generalize to sleep apnea and is not accompanied by systemic autoimmune abnormalities. Clin Immun Immunopathol 49:149–158

Schenck CH, Garcia-Rill E, Segall M, Mahowald MW (1996) HLA class II genes associated with REM sleep behavior disorder. Ann Neurol 39:261–263

Schwartz WJ, Zimmerman P (1990) Circadian time keeping in BALB/c and C57BL/6 inbred mouse strains. J Neurosci 10(1): 3685–3694

Sehgal A, Ousley A, Hunter-Ensor M (1996) Control of circadian rhythms by a two component clock. Mol Cell Neurosci 7:165–172

Shiromani PJ, Velazquez-Moctezuma J, Overstreet D, Shalauta M, Lucero S, Floyd C (1991) Effects of sleep deprivation on sleepiness and increased REM sleep in rats selectively bred for cholinergic hyperactivity. Sleep 14(2): 116–120

Singh S, George CFP, Kryger MH, Jung JH (1990) Genetic heterogeneity in narcolepsy. Lancet 335:726–727

Solomon P (1965) Narcolepsy in Negroes. Dis Nerv Syst 6: 179–183

Staley-Gane MS, Holloway RJ, Hagerman MD (1996) Temporal sleep characteristics of young fragile X boys. Am J Hum Genet Suppl 59:A105

Steinlein O, Anokhin A, Yping M, Schlat E, Vogel F (1992) Localization of a gene for low-voltage EEG on 20q and genetic heterogenity. Genomics 12(1): 69–73

Stériade M (1992) Basic mechanisms of sleep generation. Neurology 42 Suppl 6:9–18

Stino FKR (1992) Divergent selection for pentobarbital-induced sleeping times in mice. Pharmacology 44:257–259

Strang PG (1967) The symptom of restless legs. Med J Aust 1:1211–1213

Strohl KP, Saunders NA, Feldman NT, Hallett M (1978) Obstructive sleep apnea in family members. N Engl J Med 229(18): 969–972

Summers JA, Lynch PS, Harris JC, Burke JC, Allison DB, Sandler L (1992) A combined behavioral/pharmacological treatment in sleep-wake schedule disorder in Angelman syndrome. Dev Behav Pediatr 13(4): 284–287

Tafti M, Nishino S, Aldrich MS, Dement WC, Mignot E (1996) Narcolepsy is associated with increased microglia expression of MHC class II molecules. J Neurosc 16(15): 4588–4595

Takahashi JS (1995) Molecular neurobiology and genetics of circadian rhythms in mammals. Annu Rev Neurosci 18: 531–553

Takahashi JS, Pinto LH, Vitaterna MH (1994) Forward and reverse genetic approaches to behavior in the mosue. Science 264:1724–1733

Thomas DA, Swaminathan S, Beardsmore CS, McArdle EK, MacFayden UM, Goodenough PC, Carpenter R, et al (1993) Comparison of peripheral chemoreceptor responses monozygotic and dizygotic twin infants. Am Rev Respir Dis 148(6): 1605–1609

Thorpy MJ (1994) Classification of sleep disorders. In: Kryeger M, Roth T, Dement WC (eds) Principles and practice of sleep medicine, 2d ed. WB Saunders, Philadelphia, pp 426–436

Thorpy MJ, Glovinsky PB (1989) Headbanging (jactatio capitis nocturna). In: Kryeger M, Roth T, Dement WC (eds) Principles and practice of sleep medicine. WB Saunders, Philadelphia, pp 648–654

Tishler PV, Redline S, Ferrette V, Hans MG, Altose MD (1996) The association of sudden unexpected infant death with obstructive sleep apnea. Am J Respir Crit Care Med 153(6): 1857–1863

Tobler I, Gauss SE, Deboer T, Ackermann P, Fischer M, Rulicke T, Moser M, et al (1996) Altered circadian activity rhythms and sleep in mice devoid of prion protein. Nature 380:639–642

Todd JA, Aitman TJ, Cornall RJ, Hall JRS, Hearne CM, Knight AM, Love JM, et al (1991) Genetic analysis of autoimmune type 1 diabetes mellitus in mice. Nature 351:542–547

Travis J (1992) Scoring a technical knockout in mice. Science 256:1392–1394

Trenkwalder C, Colladoso-Seidel V, Gasser T, Oertel WH (1996) Clinical symtoms and possible anticipation in a large kindred of familial restless legs syndrome. Mov Disord 11: 389–394

Valatx JL (1984) Genetics as a model for studying the sleep-waking cycle. Exp Brain Res Suppl 8:135–145

Valatx JL, Buget R (1974) Facteurs génétiques dans le détérminisme du cycle veille-sommeil chez la souris. Brain Res 69: 315–330

Valatx JL, Buget R, Jouvet M (1972) Genetic studies of sleep in mice. Nature 238:226–227

Van Beijsterveldt CEM, Molenaar PCM, De Geus EJC, Boomsma DI (1996) Heritability of human brain functioning as

assessed by electroencephalography. Am J Hum Genet 58: 562–573

Van Twyver H, Webb WB, Dube M, Zackheim M (1973) Effects of environment and strain differences on EEG and behavioral measurement of sleep. Behav Biol 9:105–110

Vela Bueno A, Campos Castello JC, Baos RJ (1978) Hereditary cataplexy: is it primary cataplexy? Waking Sleeping 2:125–126

Vitaterna MH, King DP, Chang AM, Kornhauser JM, Lowrey JD, McDonald JD, Dove WF, et al (1994) Mutagenesis and mapping of a mouse gene clock, essential for circadian behavior. Science 264:719–725

Vgontzas An, Kales A, Seip J, Mascari MJ, Bixler EO, Myers DC, Vela Bueno AV, et al (1996) Relationship of sleep abnormaities in Prader-Willi syndrome. Am J Med Genet 67: 478–482

Vogel F (1986) Brain physiology: genetics of the EEG. In: Vogel F, Motulsky AG (eds) Human genetics. Springer-Verlag, New York, pp 590–593

Vossler DG, Wyler AR, Wilkus RJ, Gardner-Walker G, Vleck BW (1996) Cataplexy and monoamine oxidase deficiency in Norrie disease. Neurology 46:1258–1261

Walters AS, International RLS study group (1995) Mov Disord 10:634–642

Walters AS, Picchietti Dl, Ehrenberg BL, Lazzarini A (1994) Restless legs syndrome in childhood and adolescence. Pediatr Neurol 1193:241–245

Walters A, Picchieti D, Hening W, Lazzarini A (1990) Variable expressivity in familial restless legs syndrome. Arch Neurol 47:1219–1220

Webb WB, Campbel SS (1983) Relationship in sleep characteristics of identical and fraternal twins. Arch Gen Psychiatry 40:1093–1095

Webb WB, Friedmann JK (1971) Attempts to modify the sleep patterns of the rats. Physiol Behav 6:459–460

Wehner JM, Pounders JI, Bowers BJ (1991) The use of recombinant inbred strains to study mechanisms of drug action. In: George FR, Clouet DH, Stimmel B (eds) Behavioral and biochemical issues in substance abuse. Haworth Press, New York, pp 80–107

Wehner JM, Pounders JI, Parham C, Collins A (1992) A recombinant inbred strain analysis of sleep-time responses to several sedative-hypnotics. Alcohol Clin Exp Res 16(3): 522–528

Weissman C (1991) A "unified theory" of prion propagation. Nature 352:679–682

Wittig RM, Zorick FJ, Roehrs TA, Sicklestell JM, Roth T (1988) Familial childhood sleep apnea. Henry Ford Hosp Med J 36(1): 13–15

Yoshizawa T, Akashiba T, Kurashina K (1993) Genetics and obstructive sleep apnea syndrome. Intern Med 32(2): 94–97

Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993) The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328:1230–1235

Zwyghuizen-Doorenbos A, Rohers T, Timms V, Roth T (1990) Individual differences in the sedating effects of ethanol. Alcohol Clin Exp Res 14(3): 400–404