

# Genetics of narcolepsy and other major sleep disorders

Stéphanie Maret, Mehdi Tafti

Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland

## Summary

One third of the population is affected by a sleep disorder with a major social, medical, and economic impact. Although very little is known about the genetics of normal sleep, familial and twin studies indicate an important influence of genetic factors. Most sleep disorders run in families and in several of them the contribution of genetic factors is increasingly recognised. With recent ad-

vances in the genetics of narcolepsy and the role of the hypocretin/orexin system, the possibility that other gene defects may contribute to the pathophysiology of major sleep disorders is worth in-depth investigation.

*Key words: HLA; narcolepsy; apnea; sleepwalking; Kleine-Levin syndrome*

## Introduction

In the past few years study of the molecular basis of sleep-wakefulness regulation has become a major and productive new field in neuroscience. Starting in 1997 with our first report of mapping genes for the amount and distribution of normal sleep in mice and more recently with the discovery of hypocretin/orexin deficiency by Emmanuel Mignot's laboratory in canine and human narcolepsy, the genetics of sleep and sleep disorders is emerging as one of the most promising avenues in our understanding of the basic mechanisms regulating the complex behaviour sleep. Sleep disorders are highly prevalent in the general population

and have dramatic health, social, and economic impacts. Their treatments remain largely symptomatic owing to our ignorance of their molecular pathophysiology. However familial and twin studies indicate the presence of important genetic factors in a large number of sleep disorders. Any dysfunction in the expression and the regulation of sleep results in a complex sleep disorder that needs integrated clinical and laboratory investigations. The genetic dissection of well-characterised sleep disorders might improve treatments and also provide fundamental insights into the underlying neurobiological bases of normal sleep and wakefulness.

## Can a single gene defect cause a sleep disorder?

In 1986, Lugaresi and colleagues described a 53 year-old man who suffered from progressive insomnia, dysautonomia, dysarthria, tremor, later myoclonus and coma identifying the first sleep disorder for which a gene mutation has been identified: fatal familial insomnia (FFI) [1]. The major features of FFI include a progressive reduction of total sleep time, early disappearance of sleep spindles, loss of slow wave sleep, and disintegration of sleep cyclic organisation. This neurodegenerative disorder is caused by a point mutation at codon 178 of the Prion protein gene (PrP) and is responsible for a degeneration of specific thalamic nuclei. FFI affects both sexes equally in an autosomal dominant manner with high penetrance and is uniformly fatal. The identified mutation at codon

178 results in the substitution of asparagine for aspartate. Familial Creutzfeld-Jacob disease (CJD) is also associated with codon 178 mutation and spongiform neurodegeneration leading to dementia. However the FFI patients have a methionine at codon 129 whereas CJD patients have a valine at this position. Furthermore homozygosity at codon 129 was associated with a more rapid disease course in both FFI and CJD patients and lower age of onset in CJD patients [2].

Familial advanced sleep phase syndrome (FASPS) is a highly penetrant autosomal dominant abnormality of human circadian behaviour, which produces a striking 4 hour advance of the daily sleep-wakefulness rhythm. *hPer2*, a human homolog of the *Drosophila* period gene was found to

be mutated in affected members of one family with FASPS [3]. A mutation at position 2106 (A to G) of the casein kinase I epsilon (CKIε) binding region of hPer2 gene on chromosome 2 leads to a substitution of a serine at amino acid 662 with a glycine (S662G) and is therefore responsible for FASPS. However not all the families tested, and not all the members of the same family are linked with the hPer2 locus, suggesting a genetic heterogeneity in FASPS. A recent study identified a missense mutation (T44A) in the human CKIdelta gene in a family affected by FASPS. An A to G mutation was identified, which causes a threonine-to-alanine alteration at amino acid 44 in the mature protein [4].

Molecular studies of primary insomnias are very rare but a recent study reported a missense mutation in a single patient with chronic insomnia. This mutation is a substitution of the amino

acid arginine for histidine at position 192 (R192H) in the gene coding GABA-A beta3 subunit and alters the GABA-A receptor function in vitro [5]. The Beta-3 subunit is presumed to be implicated in sleep processes by the observation that beta3 Knockout mice do not respond to the hypnotic action of oleamide [6].

Although highly rare, the three above examples together with a single narcolepsy case (see below), clearly indicate that single gene defects can produce substantial alterations of sleep. However sleep is a highly complex behaviour and as such is regulated by the action of many genes, environment, and gene-environment interactions. Sleep is therefore a complex trait where the contribution of susceptibility or protective genetic factors will lead to either its normal variation in the population (eg, short vs long sleepers), or to complex sleep disorders such as narcolepsy.

## Narcolepsy and genetic susceptibility to sleep disorders

Among highly prevalent sleep disorders the contribution of genetic factors to parasomnias, enuresis, restless legs syndrome and periodic limb movements in sleep, and sleep apnoea syndromes is now well demonstrated [see table 1]. Most of the available evidence comes from twin studies where the relative contribution of genetic and environmental factors can be assessed. In the case of simple disorders the concordance rate in monozygotic twins (probability of same phenotype in co-twins) is usually high (close to 100%), while in complex disorders the concordance rate is usually low (usually less than 50%). Therefore the concordance rate in monozygotic twins reflects a direct measure of respective contribution of genetic and environmental factors. In some disorders the possibility of a single autosomal dominant gene effect cannot be ruled out. However even in these disorders (eg, enuresis, restless legs syndrome), ge-

netic heterogeneity, phenocopy, incomplete penetrance, and variable expressivity may complicate the discovery of the underlying genes. Only a few sleep disorders have so far been investigated at the molecular genetic level but narcolepsy represents a unique model of a complex sleep disorder for which substantial genetic evidence is available. As discussed below even if the recently discovered hypocretin-orexin deficiency is the best biological marker of narcolepsy, the condition remains complex in terms of its molecular basis.

Narcolepsy-cataplexy is a rare but a highly disabling disorder of vigilance affecting 0.02–0.06% of the general population. The onset of the disease is generally between 15 and 30 years old and affects both sexes equally. Excessive daytime sleepiness leads characteristically to irresistible and daily repeated sleep periods while cataplexy is defined as a “sudden bilateral loss of postural muscle tone

**Table 1.**  
Genetic contribution to sleep disorders.

Disorder	family history	twin studies	linkage evidence	candidate gene	mode of transmission*
Sleepwalking	Familial in up to 80%, higher risk in 1 <sup>st</sup> degree relatives	5 fold increased concordance in MZ	none	HLA-DQB1*05 HLA-DQB1*04	autosomal dominant or unknown [19–20]
Obstructive Sleep Apnoea	Higher risk in 1 <sup>st</sup> degree relatives	Higher concordance in MZ for snoring	QTL on 1p, 2p, 12p, 19p, 4q, 8q (in African-Americans)	ApoE4	autosomal dominant or unknown [21–22]
Enuresis	Over 75% in 1 <sup>st</sup> degree relatives	Higher concordance in MZ	8q, 13q, 12q, 22q11	None	Autosomal dominant [23]
RLS, PLMS	63–92% familial history	Higher concordance in MZ	12q	MAO-A	Autosomal dominant or recessive [24–25]
Kleine-Levin Syndrome	Very few Familial cases	No studies	None	HLA-DQB1*0201	Unknown [26]
RBD	No studies	Higher concordance in MZ	None	HLA-DQB1*05 HLA-DQB1*06	Unknown [27]
DSPS	50% have relatives with similar symptoms	No studies	None	HLA-DR1 hPER3, AA-NAT	Autosomal dominant or unknown [28–29]

\* based on pattern of transmission in families where the effect of a single gene is evident. MZ: monozygotic twins; QTL: quantitative trait loci; RLS: restless legs syndrome; PLMS: periodic limb movements in sleep; RBD: REM sleep behaviour disorder; DSPS: delayed sleep phase syndrome; AA-NAT: arylalkylamine N-acetyltransferase

in association with intense emotion” but the patient remains totally conscious.

Up to 10% of narcolepsies are familial. Different studies have shown that besides the typical phenotype, attenuated forms of the condition characterised by isolated excessive daytime sleepiness do exist at much higher rates; 10–40% of first degree relatives of narcoleptics may be affected. However twins studies report 25–31% of concordance suggesting a major contribution of environmental factors.

Narcolepsy has one of the tightest associations with a specific HLA allele. A first study reported 100% association between narcolepsy and the HLA-DR2/DQw1 haplotype in Japanese patients [7], a finding quickly confirmed in Caucasians. Four alleles corresponding to DRB1\*1501, DRB5\*0101, DQA1\*0102, and DQB1\*0602 are associated with narcolepsy but DQB1\*0602 constitute the major HLA susceptibility allele across all ethnic groups. The more striking fact is that 88–98% of patients affected by narcolepsy with clear cataplexy are HLA DQB1\*0602 positive. This allele strongly increases the susceptibility for cataplexy although 41% of patients without cataplexy are carriers. DRB1 and DQB1 genes have been sequenced in narcolepsy patients but no mutation was identified suggesting that they strongly confer susceptibility to development of the disease without their function being defective. Therefore non-HLA genes such as monoamine oxidase-A (MAO-A) [8], tumour necrosis factor alpha (TNF-A) [9], TNFR2 (in Japanese) [10], and catechol-O-methyltransferase (COMT) [11] may in addition or independent of HLA also be involved in susceptibility to narcolepsy. Familial forms of narcolepsy with several members of a family affected are rare. A first study, however, reported a suggestive linkage to chromosome 4p13-q21 [12] in 8 small Japanese families. In a second study, from our laboratory, significant evidence for linkage with a locus in a 5 Mb region of chromosome 21q could be established [13].

Narcolepsy is also found in Dobermans and Labradors and is clinically and electro-physiologically similar to the human disease. Canine narcolepsy is transmitted as a single autosomal recessive trait with full penetrance and is not linked to

the Dog Leukocyte Antigen. After intensive work over the past 15 years on the genetics of canine narcolepsy at Stanford University, Mignot's group identified, through linkage analysis and positional cloning, mutations in the hypocretin-2 receptor as the cause of narcolepsy [14]. Simultaneously, Yanagisawa's group discovered in the mouse a phenotype similar to canine and human narcolepsy after a targeted deletion of the prepro-hypocretin gene [15]. The human prepro-hypocretin gene located on chromosome 17q21 consists of two exons and one intron. Hypocretin-1 and -2 are hypothalamic neuropeptides and act through hypocretin receptor-1 and -2 first identified to be implicated in feeding behaviour. Recently it was discovered that narcolepsy patients have low or undetectable hypocretin-1 levels in their CSF [16] and that there is a dramatic reduction in the number of hypothalamic hypocretin-containing neurons in a small number of post-mortem narcolepsy cases [17]. Also transgenic mice carrying the promoter of the human prepro-hypocretin gene ligated to truncated human ataxin-3, a gene that induces apoptosis of hypocretin containing neurons, present symptoms similar to human narcolepsy [18]. A single presumably pathogenic mutation has been found in an atypical narcolepsy child [17] but despite the compelling evidence for a causal implication of the hypocretin system none of the three genes involved is found mutated in narcolepsy patients and there is no evidence for any association between polymorphisms identified in genes encoding the prepro-hypocretin and its receptors and human narcolepsy. Since 90% of human cases of narcolepsy are sporadic and monozygotic twins show only partial concordance (25–31%), the development of this disease could involve environmental factors interacting with specific genetic susceptibility factors. Therefore together with the tight association with the HLA antigens, the most likely cause of hypocretin deficiency in narcolepsy might be an autoimmune process resulting in acute or progressive degeneration of hypocretin-containing neurons in the hypothalamus. The environmental factor(s) might trigger narcolepsy by inducing an autoimmune reaction that targets hypocretin neurons.

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## Conclusions

The list of sleep disorders with a genetic contribution is rapidly expanding and those reviewed here constitute significant examples only. Other common sleep disorders such as insomnia and nightmares and rare disorders such as idiopathic hypersomnia might well be controlled by genetic factors. The most striking finding remains the HLA association found in narcolepsy, sleepwalking, Kleine-Levin syndrome, and REM sleep behaviour disorder. Although not a single common feature can be proposed in these disorders, this

finding suggests a fundamental relationship between sleep and the immune system, which remains to be discovered. The immune system may modulate brain activity and sleep or at least these two systems seem to influence each other and interact intimately. Because sleep and sleep disorders are complex both in their manifestations and regulation, several approaches are needed to further our understanding of their molecular basis. Studies in animal models like drosophila, zebrafish, and mice could be complemented with genetic linkage

studies, association studies, and genome-wide association studies in humans. This could lead to a better understanding of sleep mechanisms and ultimately help the development of appropriate treatments for sleep disorders.

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### Correspondence:

Prof. M. Tafti  
Faculty of Biology and Medicine  
Center for Integrative Genomics  
University of Lausanne  
CH-1015 Lausanne  
Mebdi.Tafti@unil.ch

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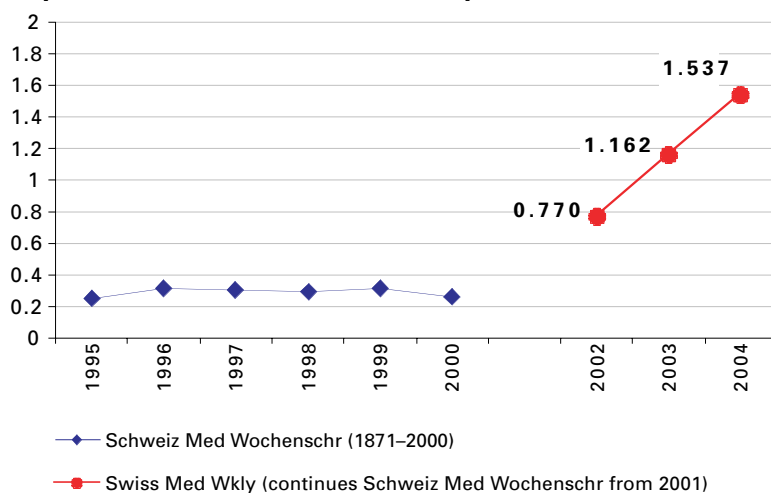
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