Genetic factors in sleep disorders

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SUMMARY Several sleep disorders have a genetic basis. These conditions include the narcoleptic syndrome, sleep walking, periodic movements in sleep, circadian delay syndromes and familial insomnia. These disorders illustrate different control mechanisms involved in sleep and wakefulness, including those determining the prevalence and timing of NREM and REM activity, somatomotor inhibition and excitation, autonomic discharge, and the circadian framework of sleep. The genetic defect in narcolepsy has been localised to the short arm of chromosome 6, but the chromosomal localisations of the genetic basis for the other disorders are not known. Also, with the possible exception of acetylcholine, no definite neurotransmitter involved in any aspect of sleep regulation has been positively identified and the biochemical defect in narcolepsy is not known.

Several sleep disorders have a familial or genetic component. These conditions include the narcoleptic syndrome, idiopathic hypersomnolence, sleep walking, periodic movements in sleep, various forms of insomnia, and circadian delay syndromes.¹⁻⁸ In addition, genetically determined sleep apnoea may result from a number of neuromuscular and skeletal disorders which cause an anatomically narrow upper airway. Medullary chemoreceptor sensitivity to pCO₂ is an inherited trait important in respiratory control systems during both sleep and wakefulness.⁹ In these conditions, a wide variety of different mechanisms that control the normal sleep-wake cycle are selectively involved, including NREM and REM sleep onset and prevalence systems, autonomic control mechanisms, and somatomotor inhibitory and excitatory systems. In insects and mammals, both the genetic mechanisms of time clocks in drosophila and somatomotor inhibition corresponding to cataplexy in dogs have been explored, although the exact anatomical localisation of the human time clock is not known, and cataplexy has a different genetic basis in dogs and man.¹⁰ Of the human sleep disorders, narcolepsy has been most investigated, and this review deals mainly with the hunt for the narcolepsy gene, localised to the short arm of chromosome 6.¹¹⁻¹³

In contrast to narcolepsy, little is known of exact genetic mechanisms in parasomnias that involve autonomic function or somatomotor inhibitory

mechanisms during sleep. Sleep walking, often accompanied by sleep terrors, and usually arising from deep NREM sleep, is familial in between 10-20% of all cases, with an increased incidence of sleep walking in children when a parent has been a somnambulist.¹⁴ Bakwin showed convincingly that monozygotic twins sleepwalk much more often than dizygotic twins, and identical twins have a very similar sleep structure.³ In the families of children who sleepwalk, other individuals tend to be deep sleepers, with high thresholds for arousal from sleep.⁴ However, there is no convincing evidence for any defect in NREM sleep structure in children who sleepwalk, nor sign of waking autonomic disorder in subjects with sleep terrors, despite the high degree of autonomic release during this parasomnia.

The restless leg syndrome, often accompanied by sleep myoclonus (periodic movements in sleep) is familial in up to a third of cases, usually transmitted as an autosomal-dominant trait.¹⁵ Montagna *et al* described a family with the restless leg syndrome and sleep myoclonus which they followed for over 20 years. The propositus was a 68 year old Italian monk whose symptoms started at the age of 15 and gradually got worse, causing severe insomnia and peculiar sensory disturbances in the legs by the age of 48.⁵

Roth has stressed the importance of familial factors in idiopathic hypersomnia, characterised by a lifelong tendency to excessive daytime drowsiness without accessory symptoms of narcolepsy, and with a family history of the condition in 39% of cases.² However, subsequent studies of similar cases have suggested that in some instances "idiopathic" hypersomnia may

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result from monosymptomatic narcolepsy, as determined by an HLA DR2 incidence as high as 60%.¹⁶

A delayed sleep phase syndrome has been described in a small number of patients who sleep quite normally, awaken spontaneously, but are unable to go to sleep at socially acceptable hours.⁸ These subjects have normal sleep itself, and normal polysomnographic recordings, but abnormal circadian sleep timing. This condition, which may date from childhood or early adolescence, is sometimes familial, although insufficient cases have been described to determine the pattern of inheritance.

A rare familial form of insomnia with dysautonomia and selective degeneration of thalamic nuclei was described by Lugaresi *et al.*,⁷ and the separate condition of childhood onset primary insomnia is also sometimes familial.⁶

Familial and genetic factors in narcolepsy

Narcolepsy is characterised by a lifelong disorder of REM sleep mechanisms, somatomotor inhibitory mechanisms, and possibly autonomic systems without major circadian disturbance. The main symptoms are REM sleep-related attacks of daytime sleep, the periodic brief triggered attacks of loss of muscle tone and paralysis of cataplexy, sleep paralysis and pre-sleep dreams. In addition, patients suffer from severe daytime sleepiness and episodic automatic behaviour. The evidence for an autonomic nervous system disturbance of central origin is inconclusive, with the occasional description of minor changes in pupillary responses, heart rate and blood pressure, pressor responses and ejaculatory function.^{17,18} The tendency to abnormal sleepiness can be demonstrated by sleep latency testing, with in many cases sleep-onset REM activity. Minnesota Multiphasic Personality Inventory (MMPI) scores in narcoleptics strongly suggest an increased prevalence of psychopathology, although these findings may be due to stimulant drug treatment or the distinctive symptoms of cataplexy, hypnagogic imagery and sleep paralysis.¹⁹

An anatomical basis for narcolepsy has not been established, and no definite pathology has ever been described.²⁰ A variety of minor neuroradiological changes have been described in narcolepsy, including abnormal spin-echo signals in the ventral pons on MR imaging,²¹ but some of these changes appear to be artefactual or have no relevance to the illness. A case for "secondary" narcolepsy (for example, narcolepsy with typical clinical features associated with brain disease, head injury, brain tumour, encephalitis or syphilis) has been made, but there is little or no convincing evidence that this association is real, with the exceptions of encephalitis lethargica and possibly multiple sclerosis. Here a common genetic determinant of narcolepsy and multiple sclerosis, possibly

an epitope of DQ beta may explain the concurrence of both diseases, rather than narcolepsy-cataplexy resulting from brainstem demyelination in multiple sclerosis.²²

The biochemical basis for narcolepsy is unknown, and the very idea of sleep neurotransmitters may be false. Sleep mechanisms are heterogeneous, and it is not possible to explain sleep-wake behaviour in terms of changes in only two or three known neurotransmitters. Drucker-Colin, writing in 1976, observed that there was no solid demonstration of the important regulation of the sleep-wake cycle by any known neurotransmitter,²³ and this is still true today, with the possible exception of acetylcholine, which when injected into pontine areas of the cat has major effects on REM sleep and sleep atonia.²⁴ No conclusions as to the physiological role of the many proposed "sleep peptides" in circadian control or the sleep-wake cycle are possible at present. For example, drowsiness or sleep have been reported following arginine vasotocin, cholecystokinin octapeptide, beta endorphin, alpha MSH and several of the family of interleukins.²⁵ The likely nature of the biochemical defect or defects in the narcoleptic syndrome cannot be deduced from these data. In contrast, the pattern of inheritance may give an important clue. Dominant inheritance tends to be associated with an amino acid abnormality on cell surface proteins, recessive inheritance with intracellular enzymic defects. It is striking that very few of the inborn errors defined at the biochemical level are caused by dominant genes.

Familial narcolepsy

The first case of familial narcolepsy came from Westphal, who described a mother and son with both narcolepsy and sleep paralysis.²⁶ Frequency estimates of familial cases vary from 6–52%.^{27,28} Some of the variation in estimate is due to incomplete case ascertainment in first-degree relatives, or failure of disease recognition. Although controversial, the pattern of inheritance appears to be autosomal-dominant rather than multifactorial (table 1).^{29–32}

Twin studies in narcolepsy show unequivocally the importance of environmental as well as genetic factors. Discordance for narcolepsy in presumed monozygotic twins has been reported by Mitchell and Cummins,³³ Schrader *et al.*,³⁴ and Montplaisir and Poirier.³⁵ A further monozygotic pair described by Mamelak *et al.* was possibly concordant,³⁶ as also in the case reported by Imlah of twins who simultaneously developed narcolepsy and cataplexy at the age of 13.³⁷ Atypical features, possibly birth trauma, and variation of disease severity in a twin pair, complicate these reports (table 2).³⁸ The report by Schrader *et al.* is of particular interest, one member only of a monozygotic twin pair having both multiple sclerosis and narcolepsy-cataplexy.³⁴

Table 1 Familial narcolepsy

Number of probands with narcolepsy	Percentage of probands with positive family history	Suggested mode of inheritance
250-300 ²⁹	19	Dominant gene Incomplete penetrance
13 ³⁰	(family study)	Dominant gene Incomplete penetrance
100 ³¹	30	Dominant gene
64 ³²	33	Multifactorial
50 ²⁸	52	Autosomal dominant
232 ¹¹	6	Two-threshold Multifactorial

HLA findings in narcolepsy

DR2 positive narcolepsy to be HLA data on over 500 Caucasian, European, North American, Japanese and Negroid narcoleptics had been reported by 1988. Ninety nine per cent of all white narcoleptics with cataplexy, with both the sporadic and familial form of disease, are DR2 positive. With a single exception, no DR2 negative subject with narcolepsy has been reported from Japan. Almost all of these DR2 positive subjects have also been DQw1 positive.^{11-13, 39-43}

A number of different techniques have been used to identify and classify class II HLA proteins. Not all subtypes are identified by all techniques. Mixed lymphocyte reactions may delineate class II groups not identified by serotyping. Most European and North American white subjects with narcolepsy who are DR2 positive are also Dw2, although in Japan DR2 is more often associated with Dw12 than with Dw2. However, in both groups, narcolepsy is associated with DR2, Dw2/DQw1.

Approximately 25-35% of subjects with narcolepsy are DR2 homozygous, the remainder heterozygous.

There is general agreement that the HLA-DR2 association with narcolepsy is the strongest HLA-disease association known, where patients with an unequivocal diagnosis of narcolepsy with cataplexy are included. If patients with cataplexy are excluded, slightly lower figures obtain, and in some of these examples, the clinical diagnosis of narcolepsy is probably incorrect.⁴³

DR2 negative narcolepsy There are a few unequivocal reports of both white and black subjects

with both narcolepsy and cataplexy, a short sleep latency and REM sleep onset, who are DR2 negative. White Caucasian subjects with unequivocal narcolepsy and cataplexy, DR2 negative, have been identified by Guilleminault,⁴⁴ Andreas Zietz *et al*,⁴¹ and Sachs and Müller.⁴⁵ Nealy *et al* described DR negative narcolepsy in six of 18 Negroid subjects, but not all of these had cataplexy.⁴⁵ Further DR2 negative Negroid subjects with both narcolepsy and cataplexy have been described by Langdon *et al*,⁴⁶ and Confavreux *et al*.⁴² All black, but not all white, subjects with narcolepsy and cataplexy who were DR2 negative in the study of Nealy *et al* were DQw1 positive,⁴⁵ while four of 118 narcoleptics (racial origin not specified: two without cataplexy) who were DR2 negative in the study of Andreas-Zietz were DQw3 positive.

HLA DR2 segregation distortion Initial evidence suggested that in narcoleptic males, but not in females, the transmission of the DR2/DQw1 haplotype deviates from Mendelian expectation, with higher transmission by narcoleptic fathers than by mothers.⁴⁷ This finding has not been confirmed. Similar patterns have been observed in some other HLA linked diseases including type I diabetes.

Restriction fragment length polymorphism studies in narcolepsy The identification of the narcolepsy-HLA linkage led to intensive efforts to identify disease unique or restricted HLA class II allelic variants by serologic, cellular and restriction fragment length polymorphism (RFLP) typing methods, and many workers have now examined RFLPs in the DNA that encodes the DR/DQw1 alleles. Using DQ region probes, a polymorphism has been described in all Japanese narcoleptics studied, only present in 38% of DR2 positive non-narcoleptic controls (a control group was mainly Dw12).⁴⁹⁻⁵¹ The DQ beta RFLP associated with narcolepsy is also that associated with DR2 positive multiple sclerosis and reflects the association with DR2 Dw2 in both diseases. Approximately 45-50% of subjects with multiple sclerosis in the UK are DR2 positive.

Table 2 Twins with narcolepsy

Authors	Zygosity	Concordance	Observation
Imlah ³⁷	Monozygous (?)	Yes	Atypical symptoms
Mitchell and Cummins ³³	Monozygous (?)	No	Narcolepsy attributable to birth trauma
Vein ³⁸	Uncertain	No	Atypical symptoms
Mamelak ³⁶	Monozygous (?)	Probable	
Montplaisir and Poirer ³⁵	Monozygous (?)	No	Classic narcolepsy
Schrader <i>et al</i> ³⁴	Monozygous (?)	No	Association multiple sclerosis

Genetic sequence studies in narcolepsy

Gene sequence studies in narcolepsy have examined the two expressed DR2 beta chains along with DQw1 alpha and beta chains.⁵² The coding regions of these four genes are similar to published nucleotide and protein sequences from corresponding healthy non-narcoleptic DR2 positive controls, with some minor exceptions.

The DR beta 2a clone from a narcoleptic subject had an extended 3' end, 42 bases longer than expected. This sequence contained an additional polyadenylation signal, and a sequence characteristic of a retroviral direct terminal repeat.⁵³ The significance of the extended 3' end is uncertain; this may alter message stability or translation. The retroviral sequence is probably not of significance, as this is also present in other DR beta genomic sequences (fig). This extension contained a Bst N1 site.

DQ alpha and beta sequences were identical to normal control sequences at the amino acid level. However, DQ alpha contained a single transversion mutation, GGG-GGC, at amino acid 23. Compared with the DR Dw2 control cell line for PGF, this does not result in an amino acid change, but creates a Bal I restriction site. These differences may be useful as genetic markers for distinguishing the narcoleptic DR2 haplotype and may indicate heterogeneity within DR2 Dw2.

It is still not clear whether the genetic susceptibility to narcolepsy is determined by the DR, DQ, or a linked gene, and there are still large unmapped gaps within the flanking MHC region. Recently identified genes within the MHC include tumour necrosis factor alpha and beta (lymphotoxin) as well as a number of other genes of unknown function including "RD".⁵⁴ It is noteworthy that one of the genes for a nicotinic receptor chain, *Acra*, is in the mouse on chromosome

17. This is the mouse equivalent of the human MHC on chromosome 6 and in view of the conservation of the organisation of the two regions in mouse and man it is possible that a brain specific nicotinic receptor gene is present on the human chromosome 6. As stressed above, of the classic neurotransmitters, acetylcholine is the only compound with definite implications in REM sleep.

Environmental factors and disease associations with narcolepsy

Despite the extremely strong genetic linkage, in addition, environmental factors are of considerable importance in narcolepsy. This may explain the low penetrance observed in families with narcolepsy. Only a small percentage of DR2 positive individuals, about 0.2%, develop narcolepsy.

Menstruation, pregnancy, sudden abrupt changes in the sleep-wake cycle, psychological stress, infectious diseases, influenza, mumps, pneumonia, scarlet fever, hepatitis, malaria, operation, anaesthetic and head injury, have all been described as antecedents to narcolepsy.^{2,55} However, any true relationship between such illnesses and narcolepsy is in doubt. The occurrence of chronic daytime sleepiness and fatigue but not narcolepsy-cataplexy following infectious mononucleosis is well documented.⁵⁶ This post-infective association is of considerable interest, with reports of sleep provoked by interleukin 1 in animals.⁵⁷ However, the incidence of previous infectious mononucleosis in some populations as determined by EBV IgG levels is over 50%, and most postviral fatigue symptoms differ markedly in clinical characteristics from the narcoleptic syndrome. Billiard *et al* have recently described elevated antistreptolysin and antistreptodona beta levels in the majority of narcoleptic

Comparison of narcoleptic DR beta 2a 3' extension with control DR beta genomic sequence (from DR4 haplotype)*

Narcoleptic
DR4 genomic sequence

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AGTTAAAAATCATCTGTCCACCTGGCTCCAAAGACAAAAAATAAAAA
AGTTAAAAATCGTCTGGTCAATTGGCCCCAAGGACAAAAAATAAAAA
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↓ = Bst N1 site (CCTGG); this restriction site is present only in this upper sequence.
 * = Direct terminal repeat of retrovirus-like sequence.
 — = Polyadenylation signal.

*DR2 genomic sequence not available

Table 3 Association between "narcolepsy" and other disease

Disease associated with narcolepsy	Notes
Possible immune mechanisms Polycythemia Lymphoma Systemic lupus erythematosus Multiple sclerosis Pernicious anaemia	Occasional association with "narcolepsy", but very uncommon in all instances, and presentation of narcolepsy usually atypical with exception of multiple sclerosis
Probable sleep apnoea Acromegaly Myotonic dystrophy Dysautonomias Thyroid disease	Probably always sleep apnoea
Ocular disorders Extrinsic muscle paralysis Cataract Glaucoma	1-2% of subjects with narcolepsy may have oculomotor disorder unrelated to cataplexy
Metabolic disorders Diabetes mellitus Thyroid disease	Not true narcolepsy. DR2 +ve rare in type 1 diabetes mellitus
Miscellaneous Essential tremor Parkinsonism	Single patient only Two patients

subjects, but not controls: the significance of this finding is at present uncertain.³⁷

With the exception of multiple sclerosis, and possibly encephalitis lethargica, there are no unequivocal associations between narcolepsy and other diseases (table 3). Pituitary and thyroid disease result in daytime drowsiness as a consequence of sleep apnoea, not narcolepsy. Myotonic dystrophy (chromosome 19) is associated in a third of subjects with severe daytime drowsiness (not always attributable to sleep apnoea). Here drowsiness is of unknown cause, but not associated with cataplexy. In Japanese patients with narcolepsy, there is a positive linkage with type 2 diabetes (non-insulin dependent),³⁸ and in Western series, DR2 Dw2 is negatively associated with type 1 diabetes. Interestingly, six Czechoslovakian cases of so-called secondary narcolepsy and cataplexy, initially attributed to previous encephalitis or brain tumour, were all DR2 positive.⁴¹

Autoimmunity in narcolepsy

The extremely high HLA linkage, 99%, of DR2/DQw1 with narcolepsy, is unique for any disease among the 60 or more conditions which show significant HLA associations with class 1 or class 2 antigens. The only conditions to approach narcolepsy in this respect are Goodpasture's syndrome and ankylosing spondylitis, with a reported HLA B27 association of 89%, 85% and 58% respectively in white, orientals and blacks (versus control values of 9%, 15% and 4%).³⁹ Pemphigus vulgaris, a severe autoimmune disease of the skin, characterised by intra-epidermal blistering, is also very strongly HLA-linked, but in contrast to narcolepsy, pemphigus is relatively frequent among Jews, associated with a DR6

DQw1 sub-type in this population, and mediated by autoantibodies to a keratinocyte surface antigen.⁶⁰ Despite the autoimmune association with many HLA-linked diseases, there is no convincing evidence of any immune abnormality in narcolepsy. Minor cerebrospinal fluid abnormalities, including lymphocytosis, protein increase, and oligoclonal bands in one instance have been described in narcolepsy, but these findings are unusual. Estimates of T-cell activation and T-cell subsets as a possible indicator of immune mechanism in narcolepsy have shown no abnormality.⁶¹

Prevalence of narcolepsy and HLA frequency

Accurate surveys of the prevalence of narcolepsy worldwide are not available. However, available reports suggest marked regional variations, from 2-3 cases per 10 000 in Czechoslovakia, to 5-6.7 in the San Francisco area, and 16 in Japan (table 4).^{27 46 48 62-65} Only six subjects with narcolepsy have been identified in the Israeli population.⁶² The condition may be more common in men than women, although sex incidence is equal in UK series. The age of onset varies from early childhood to old age, with a median between 18 and 25. The condition usually starts gradually, and

Table 4 Reported prevalence of narcolepsy and HLA-DR frequency

	Prevalence of narcolepsy (per 10 000)	Frequency of HLA-DR2 (%)
Israel ^{62 65}	0.2	11-12
Czechoslovakia ⁶³	2	—
USA ⁶⁴	5-6	22-25
Japan ⁴⁸	16	34

Table 5 Types of narcolepsy

	Familial* (n = 35)	Nonfamilial (n = 78)
DR2 status	All positive except 2 subjects	All positive
RFLP-DR2 status† (restriction enzyme Bgl _{II} DQ: probe-band at 3 kb)	Similar HLA-DQ + DQa restriction fragments in familial and nonfamilial cases (also in individual DR2-negative subjects)	
Onset		
Age (mean: range)	21.5 (7–48) years	23 (3–70) years
Sudden or slow	Sudden onset in 14%	Sudden onset in 15%
Previous infection	History of infection in 10%	History of infection in 8%
Recovery	Nil	Single instance
Blood/CSF abnormalities		
Antibodies in blood?	Not found	Not found
T-cell abnormality?	Not demonstrated	Not demonstrated
α-1-Trypsin phenotype	Association unremarkable	Association unremarkable
Immunoglobulin allotype	Association unremarkable	Association unremarkable
CSF abnormality	Occasional increased cell count, minor increase in protein	Minor abnormalities in about 20% of cases
"Sleep factors" present in blood/CSF?	Not detected	Not detected
Benzodiazepine receptor-binding activity in CSF	Not excessive	Not excessive

*Familial: definite narcolepsy, cataplexy, or both, present in first-degree relative (parent, sib or child).

†DR2 RFLP status: similar RFLP present in DR2-positive subjects with multiple sclerosis.

correct diagnosis may take several years. However, 10–15% of cases have an abrupt onset. Spontaneous remission is very rare.⁶⁶ Yoss and Daly,⁶⁷ and Billiard *et al.*,⁶⁸ could find no evidence of complete recovery. Age of onset, sex distribution and severity of symptoms do not appear to vary between populations, and in our experience are similar in both DR2 positive and DR2 negative subjects.

Familial factors in narcolepsy

Clinical factors, age of onset, severity of illness, presence or absence of precipitating factors at disease onset are similar in familial (n = 35) and non-familial (n = 78) subjects with narcolepsy in our clinical experience (table 5). Analysis of paternal and maternal age at birth of index cases, family size and birth month also showed no major differences in the two groups, in contrast to what might be expected if genetic new mutation or seasonally determined environmental factors accounted for non-familial narcolepsy.

The HLA association with narcolepsy remains mysterious. Narcolepsy is unique amongst HLA-linked diseases with possible dominant inheritance, and also by virtue of the negative rather than positive autoimmune associations. It seems likely that the narcolepsy gene is not DR2/DQw1, but a linked non-HLA gene encoding a product affecting sleep, and possibly altered in the DR2 haplotype. Candidate genes here might include that encoding vasoactive intestinal peptide, located on chromosome 6,⁶⁹ although this gene is probably at a very considerable distance from the HLA locus. VIP is present in high concentration in the animal suprachiasmatic nucleus,⁷⁰ a possible candidate time clock, although

the evidence for this in primates and man is uncertain. VIP is a potent hypnogen, but if the autosomal-dominant pattern of inheritance of narcolepsy is correct, it is unlikely that the VIP gene is primarily involved in the disease, since this is not a cell surface protein. It seems probable that the genetic determinant of narcolepsy will prove to be a DR/DQ linked gene, the genetic product being a neurotransmitter receptor involved in sleep-wake systems. A possible candidate for such a linked gene product would be a brain specific nicotinic receptor. Alternatively, since the DR and DQ molecules in narcolepsy are identical with those in normal individuals at a protein level, narcolepsy may depend on the functional properties of the normal DR2 or DQw1 molecules. Muramyl peptides, possibly involved in normal sleep mechanisms, show selective binding to specific DR haplotypes.⁷¹ Whatever the outcome in the search for a narcolepsy gene this is likely to reveal brain neurotransmitter mechanism in REM sleep.

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