

# Usefulness of genetic characterization of narcolepsy and hypersomnia on phenotype definition: a study in Portuguese patients

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**Introduction.** The determination of human leukocyte antigen (HLA) class II genotype is widely used to confirm the diagnosis of narcolepsy with or without cataplexy. The HLA genotyping is reliable, easy to perform and reassures the clinician. It is also less invasive than other methodologies and is in accordance with the autoimmune hypothesis for the origin of narcolepsy.

**Aim.** To assess the usefulness of genetic markers (HLA) in the differential diagnosis between different sleep disorders and their relevance in the context of our population.

**Subjects and methods.** We analyzed a cohort of 113 patients with episodes of daytime sleepiness, 38 patients were classified as narcolepsy with cataplexy, 13 as narcolepsy and 62 as hypersomnia/idiopathic hypersomnia. A control population of 206 reportedly healthy individuals from the same geographic origin was used.

**Results.** The HLA-DQB1\*06:02 allele frequency was overrepresented in patients with narcolepsy and narcolepsy with cataplexy (46% and 71% respectively vs. 16% in control population), with a value of  $p = 4.53 \times 10^{-13}$  for narcolepsy with cataplexy. The HLA-DQB1\*02 frequency was increased in the population with hypersomnia when compared with the control population (55% vs. 34%;  $p = 0.004$ ).

**Conclusions.** Genetic characterization has the potential to enhance the ability to carry out differential diagnosis among diverse excessive daytime sleepiness phenotypes, corresponding to diverse entities with different biological mechanisms.

**Key words.** HLA-DQB1\*06:02. Hypocretin. Idiopathic hypersomnia. Narcolepsy. Narcolepsy with cataplexy. Sleep disorders.

## Introduction

Narcolepsy is a chronic sleep disorder caused by a deficiency in hypothalamic hypocretin neurotransmission, through a selective loss of hypocretin producing neurons [1-3]. This very specific mechanism of neural destruction potentially indicates an autoimmune process.

According to the International Classification of Sleep Disorders—second edition (ICSD2) narcolepsy and idiopathic hypersomnia are neurological disorders characterized by a clinically significant complaint of excessive daytime sleepiness that is neither explained by circadian sleep disorder, sleep-disorder breathing or sleep deprivation, nor is it caused by a medical condition disturbing sleep [4]. The diagnosis of these disorders is based on sleep studies by nocturnal polygraphic sleep recording and consecutive Multiple Sleep Latency Test (MSLT), which objectively quantifies daytime sleepiness.

Concerning these sleep disorders, narcolepsy is a chronic neurological disorder characterized by

excessive daytime sleepiness that may lead to ‘sleep attacks’, hypnagogic hallucinations, sleep paralysis, and in some cases abnormal REM sleep events. Cataplexy—characterized by sudden loss of muscle tone frequently triggered by an emotional stimulus—is a key feature on diagnosis. One of the possible main causes for narcolepsy with cataplexy (NC) is the loss of hypothalamic hypocretin-producing neurons. This specific depletion is present in more than 98% of NC patients carrying HLA-DQB1\*06:02 allele, frequently in linkage disequilibrium with HLA-DRB1\*15. This hypocretin-HLA association supports the hypothesis that narcolepsy has an autoimmune origin [5].

The abnormalities of REM sleep and excessive daytime sleepiness can be the consequence of the loss of hypothalamic neurons, and subsequent deficiency in the hypocretin production [1,2,5-7].

Idiopathic hypersomnia (IH) is a disorder that closely resembles narcolepsy syndrome, and its presumed causes lay in the central nervous system. It is also characterized primarily by severe excessive

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daytime sleepiness, but without cataplexy. Differently to narcolepsy, the sleep naps on hypersomnia are not refreshing [4,5].

Epidemiological studies show that narcolepsy affects approximately 0.02% to 0.05% of the European population [4,5]. Meanwhile, the frequency of hypersomnia in the same population has extreme values of 4% to 26% [8-10].

HLA class II genotyping is widely used to confirm the diagnosis of narcolepsy with or without cataplexy. Studies carried out in the 80's and 90's demonstrated that genetic markers, particularly HLA-DR2 (HLA-DRB1\*15) and later DQB1\*06:02 allele, are strongly associated with susceptibility to narcolepsy and NC in non-familial cases [11,12].

The first studies conducted in a cohort of 37 individuals from European descendant, described that all NC patients expressed the HLA-DR2 allele [11]. In 1997, Mignot et al studied a population of 509 patients (421 with NC and 88 with narcolepsy) and reported that DQB1\*06:02 allele was a more sensitive marker for narcolepsy than DRB1\*15, across all ethnic groups [12]. In 2001 a multi-ethnic study comprised by 420 subjects with cataplexy (77 Afro-Americans, 238 Caucasians, and 105 Japanese), demonstrated that HLA-DQB1\*06:02 (but not HLA-DRB1\*15:01) homozygosity increases susceptibility for NC [13]. Mignot et al [12] also reported the contribution of the HLA system to the severity of narcolepsy syndrome. He observed that 76.1% of NC patients were positive for HLA-DQB1\*06:02, but when the severity of cataplectic attacks was considered, the HLA-DQB1\*06:02 frequency was 94.8% in severe cases and 54.2% in the mild ones.

The correlation between HLA-DQB1\*06:02 and cataplexy was elegantly demonstrated by Okun et al [14]. He studied 482 narcoleptic patients and proposed that the presence of this allele correlates with older patients, with earlier onset of symptoms and more severe and typical symptoms of cataplexy (for example triggered by joking or strong emotions) and finally with polysomnographic features. He noted that 2/3 of all HLA-DQB1\*06:02 narcoleptic patients experienced cataplexy triggered by strong emotions. In this context he proposed that determining this allele in narcoleptic patients could be an alternative to invasive methods to validate cataplexy diagnosis [14].

One of the most interesting aspects in this study was indeed the detection of a high correlation between HLA-DQB1\*06:02 positivity and cataplexy. 92-93% of the narcoleptic patients who had their cataplexy attacks triggered by strong emotions were HLA-DQB1\*06:02. This confirmed the allele

in question as a specific marker for defining genuine cataplexy in narcolepsy [14].

More recent studies showed that the frequency of HLA-DQB1\*06:02 was different in children and adults with narcolepsy with and without cataplexy. This difference varied between 93.7% (adults) vs. 92.6% (children) with NC, and 78.6% in adults vs. 52.9% in children with narcolepsy without cataplexy [15].

In 2007, Hong et al studied 163 Korean patients with daytime somnolence (79 with NC; 22 with narcolepsy; 19 IH; 43 complex cases) and 211 controls, and confirmed that hypocretin deficiency correlates with DQB1\*06:02. He observed that 81% of the NC group had simultaneously low/absent levels of hypocretin and DQB1\*06:02 positivity [16], providing an alternative way to the more invasive medical techniques.

In spite of the wide range of frequencies of these alleles observed in populations of diverse origins, it has been considered since then, that their presence add value to the diagnosis of sleep disorders. The increased use of HLA genotyping was the result of three convergent reasons:

- The method is reliable, easy to perform and reassures the clinician.
- The assay is less invasive than other methodologies.
- The wide acceptance of the hypothesis of an autoimmune origin for narcolepsy (a clinical field in which the relevance of the HLA system is generally accepted).

This last reason finds support in the virtually absent levels of hypocretin peptides in the cerebrospinal fluid of patients with NC, as reported by Hong et al [16], which is postulated to be due to the autoimmune destruction of hypocretin producing neurons [2,17]. In fact, it was demonstrated that approximately 90% of the hypocretin producing neurons are lost in human NC [17]. According to Jones et al [18] and Siebold et al [19], this autoimmune process may be the result of the conformation of the P4 pocket (in the 13 $\beta$  and 26 $\beta$  positions) in the tri-dimensional molecular structure of the DQB1\*06:02, that is claimed to be responsible for hypocretin peptide binding.

The genetic susceptibility factors underlying sleep disorders (narcolepsy, NC and IH) might be useful tools in a clinical setting. With this work we evaluated the contribution of genetic markers (HLA) to the differential diagnosis between NC, narcolepsy without cataplexy and IH, in a sleep patient population from the north of Portugal.

**Table I.** HLA-DQB1\* frequencies in Portuguese patients with sleep disorders.

	Control population (n = 206)		Idiopathic hypersomnia (n = 62)				Narcolepsy (n = 13)				Narcolepsy-cataplexy (n = 38)			
	n	%	n	%	p	Odds ratio	n	%	p	Odds ratio	n	%	p	Odds ratio
HLA-DQB1*02	71	34	34	55	0.00396	2.309	5	38	0.769	1.1883	8	21	0.1044	0.5070
HLA-DQB1*03	116	56	32	52	0.514	0.827	9	69	0.361	1.7456	13	34	0.01215	0.4034
HLA-DQB1*06	86	42	22	35	0.378	0.767	9	69	0.052	3.1395	34	89	6.40 <sup>-8</sup>	11.860
HLA-DQB1*06:02	33	16	5	8	0.115	0.276	6	46	0.0058	4.4935	27	71	4.53 <sup>-13</sup>	12.867
HLA-DQB1*06:03	47	23	9	15	0.158	0.574	2	15	0.532	0.6150	4	13	0.18162	0.5125

## Patients and methods

A cohort of 113 patients complaining of periods of excessive daytime somnolence was observed at the Sleep Outpatient Clinic of Hospital Santo António/CHP. Patients were evaluated in a standard protocol of clinical, night sleep polygraphic recording, MSLT on the following day, and blood sampling.

Peripheral blood samples (10 mL) from sleep patients and controls were collected in EDTA. The genomic DNA was obtained from proteinase-K treated peripheral blood leukocytes with a salting-out procedure [20]. DNA was amplified by PCR with sequence-specific primers (PCR-SSP) for the *HLA-DQB1* gene, based on methods and primer sequence previously described [21]. PCR products were visualized under ultra violet light after electrophoretic separation on 1.5% agarose gel containing ethidium bromide. Genotypes were deduced from the amplification patterns.

The medical records of all patients were reviewed by the participating clinicians and confirmed by the study coordinator, clinical reevaluation of the patients was considered if necessary. The patients were then classified as NC, narcolepsy or IH (according to ICSD2): 38 had NC (age at testing: mean, 32.8 years; median, 30 years); 13 had narcolepsy (age at testing: mean, 34.2 years; median, 36 years); 62 patients had IH (age at testing: mean, 38.2 years; median, 40 years). A control population (CP) of 206 reportedly healthy individuals from the same geographic origin was used.

HLA-DQB1 phenotype frequencies were determined by direct counting. HLA frequencies in patients and controls were compared using the Pearson chi-square test or the Fisher's exact test as ap-

propriate. Mean values were compared using the Student's *t* distribution.

## Results

The HLA-DQB1\*06:02 allele was overrepresented in narcolepsy and NC patients (46% and 71% respectively vs. 16% in control population), and the *p* value was extremely significant for NC (Table I). HLA-DQB1\*02 was also increased in the population with IH when compared with CP (55% vs. 34%; *p* = 0.00396). Interestingly the frequency of the HLA-DQB1\*03 allele was decreased in the NC vs. CP group (34% vs. 56%; *p* = 0.012153). No differences were found in the HLA-DQB1\*06:03 frequency between the cohort of patients and the CP (Table I).

The allele frequencies of the CP (*n* = 206) were in accordance with a larger cohort of 2500 individual's representatives from the central and south regions of Portugal.

## Discussion

The significant association found in this study between HLA-DQB1\*02 with hypersomnia, not observed in other sleep disorders, allows us to consider this allele a risk factor to this entity, which may be useful for the differential diagnosis between hypersomnia and narcolepsy.

The HLA-DQB1\*06:02 allele, a susceptibility factor for several autoimmune disorders (e.g.: multiple sclerosis, systemic lupus erythematosus, sarcoidosis, sclerosing cholangitis), was confirmed as a susceptibility allele for NC in our population. The

**Table II.** Data comparison of referred studies on genetics of sleep disorders.

	Studied population	Results
Langdon et al [11]	37 patients (European descendants)	37 patients (100%) are HLA-DR2 and DQw1
Mignot et al [12]	509 patients: 421 NC; 88 N (different ethnic groups)	Patients positive for DQB1*06:02. NC: 76.1% (54.2-94.8%); N: 40.9%
Mignot et al [13]	3 ethnics groups: Japanese, Afro-American, European descendants. 1,087 CP; 420 NC	'Almost all' narcoleptics are DQA1*01:02 and DQB1*06:02
Okun et al [14]	64 Afro-Americans, 353 European descendants, 32 Asian, 26 Latinos, 9 mix ethnic	NC: 92% DQB1*06:02 independently of ethnics
Jeong et al [22]	Koreans: 56 NC; 16 N	HLA-DQB1*06:02 in 89.3% NC vs. 50.0% N ( $p = 0.003$ )
Hong et al [16]	Koreans: 163 patients with diurnal somnolence (100 N); 211 CP	DQB1*06:02 associated with hypocretin deficiency (100% vs. 13%)
Nevsimalova et al [15]	Czech Republic: 148 narcoleptic patients (117 adults, 31 children). 109 NC; 39 N	HLA-DQB1*06:02 in NC = 93.7% adults vs. 92.6% children, and N = 78.6% adults vs. 52.9% children
Present study	Portugal (North): 13 N; 38 NC; 62 IH; 206 CP	HLA-DQB1*06:02 in 46% N ( $p = 0.0058$ ), 71% NC ( $p = 0.000$ ), 8% IH, 16% CP

CP: control population; IH: idiopathic hypersomnia; N: narcolepsy without cataplexy; NC: narcolepsy with cataplexy.

frequency of this allele in our cohort of NC patients (71%) is in range with those observed in other studies (Table II). When the three patients with familial history of NC are excluded the DQB1\*06:02 frequency increase to 77%. However, this frequency is lower than expected when compared with studies that considered only patients with severe cataplexy, in which frequencies typically vary between 85-95%. In narcolepsy without cataplexy we also found an association with this allele, with a frequency of 46%, in concordance with previous studies from Jeong et al (50.5%) [22] and Mignot et al (40.9%) [12]. Still, this frequency is lower than the 78.6% reported in Czech patients [15].

The discrepancies reported of HLA-DQB1\*06:02 prevalence in NC patients in diverse studies, can be explained by different population backgrounds or disease heterogeneity. In a detailed analysis of the study of Okun et al [14], in which this group investigate a cohort of 484 NC patients from different ethnic backgrounds, the authors found the HLA DQB1\*06:02 allele in 380 (78.5%) out of them. This value is lower than the frequently reported 'more than 90% of positive HLA DQB1\*06:02 in NC patients'. A possible explanation of these differences is also the presence of diverse elements accompanying the NC phenotype characterization. As stated by these authors, the association of the NC popula-

tions with HLA DQB1\*06:02 allele increases from 77.4% to 97.4% in the presence of different cataplexy triggers [14]. Concerning the HLA susceptibility alleles, if an individual is homozygous for HLA-DQB1\*06:02 it has a greater risk than a heterozygous individual to develop narcolepsy [23]. Furthermore, HLA-DQB1\*03:01 has been proposed as a second allele for susceptibility to NC [13,24]. Our study showed an association between NC and HLA-DQB1\*03 allele ( $p = 0.01215$ ) but with a protective effect.

In 2007 HLA-DQB1\*06:01 has been described as a protective allele in a Korean population [16,22]. More recently the HLA-DQB1\*06:03 allele was also considered as a protective factor against NC [25,26], but this assumption needs to be explored. In our study, the HLA-DQB1\*06:03 allele had a lower frequency in the sleep disorders analyzed when compared with our control population, however, we found no sign that pointed to a protective role in sleep disorders.

The issue of susceptibility/protection alleles on narcolepsy and NC should be considered on a structural basis of the HLA-DQB1\*06 molecule. The P4 pocket volume of this molecule appears to be central to the positive or negative association with narcolepsy [18,19]. The volume of this pocket differs significantly between DQB1\*06:02 (suscepti-

bility) and DQB1\*06:01 (protection) molecules, and this restricts the peptide repertoire that these molecules can accommodate and present to T cells. The HLA-DQB1\*06:02 molecule will be responsible for hypocretin peptide binding and for the autoimmune attack on the hypocretin secreting neurons. The HLA-DQB1\*06:01 has a significantly smaller volume in its P4 pocket, and can't accommodate such peptides. It is possible that the peptide-binding differences between these two allelic products determine whether they confer risk to or protect against narcolepsy. Concerning the DQB1\*06:03 allele, the configuration of this P4 pocket is exactly the same of the DQB1\*06:02 allele, so if a protective role of this allele exists, some other reason for that must be sought [18,19].

Finally, some of the differences found in this study and in reported studies (HLA and sleep disorders) could also be due to phenotypic ambiguity. As stressed by other authors [14], the clinical picture of narcolepsy could be different in different age groups, which complicates the clinical diagnosis that could often be delayed for several years. If this is due to a modification of hypocretin levels, by circadian oscillations or environmental factors (infections, head trauma, immunization), or to differences in the regenerative potential of central nervous system tissue, is a theme of current research. These agents can trigger different clinical responses changing the phenotype expression. Given those uncertainties, genetic characterization has the potential to improve the ability to carry out differential diagnosis among diverse excessive daytime sleepiness phenotypes, helping in the distinction of diverse entities corresponding to fundamentally different biological processes.

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### Utilidad de la caracterización genética de la narcolepsia y la hipersomnia en la definición del fenotipo: estudio en pacientes portugueses

**Introducción.** La determinación del genotipo de los antígenos leucocitarios humanos (HLA) de clase II es un método muy difundido para confirmar el diagnóstico de la narcolepsia, con y sin cataplejía. El genotipado del HLA es fiable, sencillo y proporciona seguridad al médico. También es menos invasivo que otros métodos y entronca con la hipótesis autoinmunitaria sobre el origen de la narcolepsia.

**Objetivo.** Evaluar la utilidad de los marcadores genéticos (HLA) en el diagnóstico diferencial de diferentes trastornos del sueño y su relevancia en el contexto de nuestra población.

**Sujetos y métodos.** Se analizó una cohorte de 113 pacientes con episodios de somnolencia diurna, 38 de los cuales fueron clasificados como afectados por narcolepsia con cataplejía, 13 con narcolepsia y 62 con hipersomnia/hipersomnia idiopática. La población de control estaba integrada por 206 individuos sanos del mismo origen geográfico.

**Resultados.** La frecuencia del alelo HLA-DQB1\*06:02 era superior a la habitual en los pacientes con narcolepsia y narcolepsia con cataplejía (46% y 71%, respectivamente, frente al 16% en la población control), con un valor de  $p = 4,53^{-13}$  en el caso de la narcolepsia con cataplejía. La frecuencia del alelo HLA-DQB1\*02 era más elevada en la población con hipersomnia en comparación con la población control (55% frente a 34%;  $p = 0,004$ ).

**Conclusiones.** La caracterización genética tiene posibilidades de mejorar el diagnóstico diferencial entre varios fenotipos de somnolencia diurna excesiva, que corresponden a diversas entidades con diferentes mecanismos biológicos.

**Palabras clave.** Hipocretina. Hipersomnia idiopática. HLA-DQB1\*06:02. Narcolepsia. Narcolepsia con cataplejía. Trastornos del sueño.