BMC Medical Genetics

BioMed Central

Research article

ApoE polymorphisms in narcolepsy

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Published: 9 August 2001

BMC Medical Genetics 2001, **2**:9

Received: 13 June 2001
Accepted: 9 August 2001

This article is available from: http://www.biomedcentral.com/1471-2350/2/9

Summary

Background: Narcolepsy is a common neuropsychiatric disorder characterized by increased daytime sleepiness, cataplexy and hypnagogic hallucinations. Deficiency of the hypocretin neurotransmitter system was shown to be involved in the pathogenesis of narcolepsy in animals and men. There are several hints that neurodegeneration of hypocretin producing neurons in the hypothalamus is the pathological correlate of narcolepsy. The *ApoE4* allele is a major contributing factor to early-onset neuronal degeneration in Alzheimer disease and other neurodegenerative diseases as well.

Methods: To clarify whether the ApoE4 phenotype predisposes to narcolepsy or associates with an earlier disease onset, we have genotyped the *ApoE* gene in 103 patients with narcolepsy and 101 healthy controls.

Results: The frequency of the E4 allele of the *ApoE* gene was 11% in the patient and 15% in the control groups. Furthermore, the mean age of onset did not differ between the $ApoE4^+$ and $ApoE4^-$ patient groups.

Conclusion: Our results exclude the *ApoE4* allele as a major risk factor for narcolepsy.

Background

Narcolepsy is a frequent debilitiating neuropsychiatric disorder characterized by increased daytime sleepiness, cataplectic episodes and hypnopompic and hypnagogic hallucinations. The occurence of narcolepsy is sporadic; however, a proportion of cases is familial with an autosomal-dominant type of inheritance. In contrast to the normal population with an *HLA-DR2* allele frequency of ~30%, over 90% of narcoleptics type *HLA-DR2* $^+$ and *HLA-DQB1*0602* $^+$[1,2]. The biological significance of this association remains elusive implicating autoimmune aspects in the ethiology [3]. In two animal models the involvement of the hypocretin (orexin) neurotransmitter system was demonstrated. Murine narcolepsy induced by knocking out the *hypocretin* gene shows symptoms corresponding to human narcolepsy [4]. Dobermann pincher and Labrador breeds with autosomal recessively inherited narcolepsy each share a splice-site mutation in the *hypocretin-receptor 2* gene [5]. Although hypocretin levels in CSF of most narcoleptics is *decresed* or not detectable [6], no causative mutations in both *hypocretin receptor* genes were found in humans. A single patient with atypical early-onset narcolepsy carries a dominant signal peptide mutation in the *prepro-hypocretin* gene [7]. Furthermore a rare sequence variant in the 5'UTR of *preprohypocretin* gene has been

shown to be a risk factor for narcolepsy [8]. Recent reports describe a nearly complete loss of hypocretinergic neurons in brains of narcoleptic patients as well as scar tissue normally occupied by the hypocretin-producing cells [7,9].

Among several neurodegenerative diseases the *E4* allele of the *ApoE* gene has been recognized as a predisposing genetic risk factor mainly influencing the age of manifestation of M. Alzheimer. The ApoE protein is a component of the VLDL particles and chylomicrons and its primary role is lipid transport [10,11]. The pathophysiological effect of *ApoE4* in neurodegeneration is not clarified yet and may possibly involve diminished neuroprotection against amyloid depositions, reactive oxygen species or exitotoxins [12]. We have tested the hypothesis of the involvement of the *E4* allele of ApoE in the etiology of narcolepsy.

Methods

Patients were recruited from the University Hospital in Mainz and St. Josef Hospital in Bochum, Germany. All but two patients suffered from cataplexies. All patients fulfilled diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM IV) and the International Classification of Sleep Disease of the American Sleep Disorders Association for narcolepsy. For further details see Gencik *et al.* 2000 [8]. The control group was composed of neurologically investigated 101 healthy individuals. All participants gave written, informed consent.

ApoE genotyping was performed as described [13]. The HLA-DR2 status of the patients was determined previously. 94 patients typed HLA-$DR2^+$ and 9 patients HLA-$DR2^-$[8]. Genotype and allele frequencies were compared with the X^2-significance test. The age of onset was known in 60 patients with $E4^-$ genotypes and 13 patients with $E4^+$genotypes, these data were compared by the Mann Whitney test.

Results and discussion

Until now, only a few factors were recognized to predispose to narcolepsy. It is the major association with the *HLA-DR2* allele on the one hand. Specific *TNF*α alleles [14] as well as the 3250T allele of the *preprohypocretin* gene [8] are minor contributors to the etiology on the other hand. No exogenous risk factors for narcolepsy have been recognized so far.

Recently, a novel neurotransmitter system was shown to be involved in narcolepsy in the canine disease model and in the orexin knock-out mouse. Autopsy reports of narcoleptic dogs and patients with narcolepsy pointed out possible neurodegenerative processes in areals with hypocretin-producing neurons. Taken together, the pathophysiology of narcolepsy seems to involve an autoimmune driven neurodegeneration of yet unkown cause [3,15].

In order to specify the role of ApoE isoforms in narcolepsy, we have determined the allele and genotype frequencies of the *E2*, *E3* and *E4* alleles in patients with narcolepsy and healthy controls. Allelic and genotypic frequencies are shown in table 1. No statistically significant differences were detected between nacoleptics, the DR2 subgroups and the controls. Although not significant, a tendentially increased E3 frequency was seen among the $DR2^+$ subgroup of narcoleptics. Furthermore, in 73 narcoleptics exact age of onset could be determined. 60 patients had an non-E4, 13 patients had an E4 phenotype. The manifestation ages were 19.6 ± 9.9 years (mean ± SD) and 21.4 ± 8.6 years for the non-E4 group and E4 group, respectively. The mean difference of 1.8 years were not statistically signifcant (p = 0.44).

Table 1: Allele and genotype frequencies of the *ApoE* gene in narcolespy patients and controls.

	Patients (n = 103)	$DR2^+$ (n = 94)	$DR2^-$ (n = 9)	Controls (n = 91)
Alleles				
E2	8%(16)	7.5% (14)	11% (2)	10%(18)
E3	82%(168)	83%(155)	72%(13)	75%(136)
E4	11%(22)	10%(19)	17%(3)	15%(28)
Genotypes				
E2/E3	14%(14)	14%(13)	11%(1)	18%(16)
E2/E4	2%(2)	1%(1)	11%(1)	2%(2)
E3/E3	66%(68)	67%(63)	56%(5)	55%(50)
E3/E4	18%(18)	17%(16)	22%(2)	22%(20)
E4/E4	1%(1)	1%(1)	/	3%(3)

Conclusion

The presented results indicate, that the E4 isotype of the ApoE protein, which is an important risk factor for complex traits like alzheimer disease, parkinsonism and other neurodegenerative disorders is not involved in pathophosiological processes in narcolepsy.

Declaration of competing interests

None declared.

References

1. **OMIM 161400**
2. Mignot E, Lin L, Rogers W, Honda Y, Qiu X, Lin X, Okun M, Hohjoh H, Miki T, Hsu S, Leffell M, Grumet F, Fernandez-Vina M, Honda M, Risch N: **Complex HLA-DR and – DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups.** *Am J Hum Genet* 2001, **68**:686-699
3. Mignot E, Thorsby E: **Narcolepsy and the HLA system.** *N Engl J Med* 2001, **344**:692
4. Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato M, Hammer RE, CB Staper, Yanagisawa M: **Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation.** *Cell* 1999, **98**:437-451
5. Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, de Jong PJ, Nishino S, Mignot E: **The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene.** *Cell* 1999, **98**:365-376
6. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E: **Hypocretin (orexin) deficiency in human narcolepsy.** *Lancet* 2000, **355**:39-40
7. Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, Nevsimalova S, Aldrich M, Reynolds D, Albin R, Li R, Hungs M, Pedrazzoli M, Padigaru M, Kucherlapati M, Fan J, Maki R, Lammers GJ, Bouras C, Kucherlapati R, Nishino S, Mignot E: **A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains.** *Nat Med* 2000, **6**:991-997
8. Gencik M, Dahmen N, Wieczorek S, Kasten M, Bierbrauer J, Anghelescu II, Szegedi A, Menezes Saecker AM, Epplen JT: **A prepro-orexin gene polymorphism is associated with narcolepsy.** *Neurology* 2000, **56**:115-117
9. Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, Cornford M, Siegel JM: **Reduced number of hypocretin neurons in human narcolepsy.** *Neuron* 2000, **27**:469-474
10. Mahley RW, Rall SC: **Apolipoprotein E: Far more than a lipid transport protein.** *Annu Rev Genomics Hum Genet* 2000, **01**:507-537
11. **OMIM 107741**
12. Mahley RW, Huanng Y: **Apolipoprotein E: from atherosclerosis to Alzheimer's disease and beyond.** *Curr Opin Lipol* 1999, **10**:207-217
13. Kruger R, Vieira-Saecker AM, Kuhn W, Berg D, Muller T, Kuhnl N, Fuchs GA, Storch A, Hungs M, Woitalla D, Przuntek H, Epplen JT, Schols L, Riess O: **Increased susceptibility to sporadic Parkinson's disease by a certain combined alpha-synuclein/apolipoprotein E genotype.** *Ann Neurol* 1999, **45**:611-617
14. Hohjoh H, Nakayama T, Ohashi J, Miyagawa T, Tanaka H, Akaza T, Honda Y, Juji T, Tokunaga K: **Significant association of a single nucleotide polymorphism in the tumor necrosis factor-alpha (TNF-alpha) gene promoter with human narcolepsy.** *Tissue Antigens* 1999, **54**:138-145
15. Hinze-Selch D, Wetter TC, Zhang Y, Lu HC, Albert ED, Mullington J, Wekerle H, Holsboer F, Pollmacher T: **In vivo and in vitro variables in patients with narcolepsy and HLA-DR2 matched controls.** *Neurology* 1998, **50**:1149-1152

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/content/backmatter/1471-2350-2-9-b1.pdf