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TCRA, *P2RY11*, and *CPT1B/CHKB* associations in Chinese narcolepsy

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Abstract

Objectives—Polymorphisms in the *TCRA* and *P2RY11*, two immune related genes, are associated with narcolepsy in Caucasians and Asians. In contrast, *CPT1B/CHKB* polymorphisms have only been shown to be associated with narcolepsy in Japanese, with replication in a small group of Koreans. Our aim was to study whether these polymorphisms are associated with narcolepsy and its clinical characteristics in Chinese patients with narcolepsy.

Methods—We collected clinical data on 510 Chinese patients presenting with narcolepsy/hypocretin deficiency. Patients were included either when hypocretin deficiency was documented (CSF hypocretin-1 ≤110 pg/ml, n=91) or on the basis of the presence of clear cataplexy and HLA-DQB1*0602 positivity (n=419). Genetic data was compared to typing obtained in 452 controls matched for geographic origin within China. Clinical evaluations included demographics, the Stanford Sleep Inventory (presence and age of onset of each symptom), and Multiple Sleep Latency Test (MSLT) data.

Results—Chinese narcolepsy was strongly and dose dependently associated with *TCRA* (rs1154155C) and *P2RY11* (rs2305795A) but not *CPT1B/CHKB* (rs5770917C) polymorphisms. *CPT1B/CHKB* polymorphisms were not associated with any specific clinical characteristics. *TCRA* rs1154155A homozygotes (58 subjects) had a later disease onset, but this was not significant when corrected for multiple comparisons, thus replication is needed. *CPT1B/CHKB* or *P2RY11* polymorphisms were not associated with any specific clinical characteristics.

Conclusion—The study extends on the observation of a strong multiethnic association of polymorphisms in the *TCRA* and *P2RY11* with narcolepsy, but does not confirm the association of *CPT1B/CHKB* (rs5770917) in the Chinese population.

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Keywords

narcolepsy; TCR alpha; *P2RY11*; *CPT1B/CHKB*; hypocretin; orexin; MSLT; HLADQB1*0602

INTRODUCTION

Narcolepsy-cataplexy results from the loss of ~70,000 hypothalamic neurons producing the neuropeptide hypocretin, also called orexin [1–3]. Since 1984, it has been known that narcolepsy is associated with the Human Leukocyte Antigen (HLA) [4], most specifically HLA Class II allele DQB1*06:02 [5–7] across all ethnic groups. As most strongly HLA associated diseases are autoimmune, these discoveries have led to the hypothesis that narcolepsy is caused by an autoimmune destruction of hypocretin-containing cells. This finding was recently strengthened by the discovery that narcolepsy/hypocretin deficiency is also associated with T-cell receptor (TCR) alpha rs1154155C [8] and *P2RY11* purinergic receptor rs2305795A polymorphisms [9]. TCR is the only currently known natural receptor for MHC class II, and is integral to the development of adaptive immune responses. *P2RY11* is a poorly understood ATP receptor known to have immune modulatory effects, such as effects on immune cell chemotaxis, maturation, and regulated cell death [9,10]. The hypothesis of autoimmunity in narcolepsy has also been strengthened by reports of anti *TRIB2* antibodies [11–13] and potential association with infectious triggers such as H1N1 (including vaccination) [14,15] and Streptococcus infections [15–17].

In addition to these, an association with rs5770917C, a polymorphism located between the *CPT1B* and *CHKB* loci and modulating expression of these genes, has been reported in a Japanese sample [18]. The finding was replicated in a smaller group of Korean patients, where significance was nominal, but not in Caucasians where allele frequency for the disease associated allele is low [8,18]. *CPT1B* is an enzyme involved in the carnitine shuttle and regulation of fatty acid beta-oxidation, a pathway known to be involved in regulating theta frequency during REM sleep in mice [19]. *CHKB* phosphorylates choline, the precursor of acetylcholine, a regulator of REM sleep and wakefulness [20], suggesting that either of these two genes could be involved in sleep regulation. In this study, we extended work on these loci to the study of a large sample of Chinese narcolepsy patients and also examined whether these polymorphisms affect MSLT characteristics, age of onset, and the presence of ancillary symptoms

METHODS

Chinese patients and controls

Patients included 510 patients (70.0% male, 18.41±0.38 years old, 97% Han Chinese (3% from other ethnicities), and 89.8% from North China presenting with narcolepsy/hypocretin deficiency. Patients were included either when hypocretin deficiency was documented (CSF hypocretin-1 ≤110 pg/ml, n=91) or on the basis of the presence of clear cataplexy and HLA-DQB1*0602 positivity (n=419). The 91 patients with low CSF hypocretin-1 all had typical cataplexy and DQB1*0602 except for four subjects: one was DQB1*0602 negative with clear cataplexy, one was DQB1*0602 positive without cataplexy, and two were DQB1*0602 positive with atypical cataplexy.

These patients were identified and studied over a period of over 10 years (1998–2010) at the sleep lab of People's Hospital, Peking University, Beijing. Clinical evaluation included recordings of symptoms (cataplexy, age of onset if present). The sleep laboratory is part of the adult pulmonary medicine department and evaluates both child and adult patients with various sleep disorders, receiving referrals from all over China. In prior studies, we

estimated that around 70% of all diagnosed narcolepsy patients in China have been evaluated at Beijing University in our laboratory [21]. A description of these subjects and evaluation procedures are reported in Han et al. [22]. Age of onset of disease was defined as the earliest of cataplexy or sleepiness. Presence or absence of cataplexy, sleepiness, sleep paralysis, hypnagogic hallucination and disturbed nocturnal sleep was noted, and Multiple Sleep Latency Testing (MSLT) was conducted in all cases. Chinese controls (n=452) were healthy controls matched for subethnicity (95% Han Chinese, 90.2% from North China) drawn from the Beijing University student population and from Beijing University Hospital employees. Patients gave written assent and parents consented for inclusion into this study. The local institutional review boards of Beijing and Stanford Universities approved the study.

Genetic Typing

Genetic typing of DQB1*06:02 was performed using a Sequence specific PCR while typing of rs1154155, rs2305795, and rs5770917 used Taqman assays, as described [8,10]. Genotypic groups in controls met Hardy Weinberg equilibrium predicted values ($p>0.5$).

Statistics

Genetic associations between controls and narcolepsy patients were conducted using χ squares. Both allelic Odds Ratios (OR) and genotypic OR are reported; Bonferroni correction for three loci was applied for a single tailed test ($p<0.033$) to determine statistical significance but nominal p values are reported. We next studied the effect of genotypes on the severity of daytime sleepiness, as reflected by the MSLT and on age of onset in (untreated) Chinese patients. To do so, we compared clinical variables across the three genotypes using general linear regression or Cochran–Armitage trend test. As severity variables (and onset age variables for various symptoms) are not independent and correlate with each other, Bonferroni correction for two comparisons (severity, onset) was applied (nominal p value reported). Post hoc comparisons between individual genotype groups across genotype groups (e.g., TT versus CT plus CC) were only applied in variables where the three genotype group comparison was significant. All comparisons were controlled for age, sex, or DQB1*0602 status whenever necessary (significant covariate) or to confirm significance in the presence of these cofactors.

RESULTS

Chinese narcolepsy is associated with TCRA rs1154155C and P2RY11 rs2305795A, but not CPT1B/CHKB rs5770917C

As in other ethnic groups, we found a strong dose dependent increase in risk with *TCRA* rs1154155C and *P2RY11* rs2305795A (Table 1). Data obtained for *TCRA* rs1154155C constitute an independent replication, while data obtained with *P2RY11* rs2305795A largely overlap with data published across ethnic groups by Kornum et al. [10]. Allelic risk and genotypic risk for rs1154155C and rs2305795A in this ethnic group were similar to those reported among other ethnicities. These associations were independent of HLA status (or sex), as expected since these loci are both autosomal and unlinked (data not shown). In contrast, no effect of *CPT1B/CHKB* rs5770917C was found in these subjects (Table 1), unlike previously reported data in Japanese and Koreans [18].

TCRA rs1154155A homozygosity is associated with a later onset of narcolepsy

We next explored whether these polymorphisms were associated with age of onset, or the severity of objective sleepiness in these subjects (Table 2). *CPT1B/CHKB* rs5770917 genotype had no effect on any clinical characteristics (Table 2). We found a nominally

significant effect of rs1154155A homozygosity in the *TCRA* gene on the onset of all symptoms ($p<0.05$), but no effect on severity of sleepiness as measured with the MSLT or the occurrence of individual symptoms (Table 2). Surprisingly, however, the effect on age of onset effect was not additive for the increase in risk for developing narcolepsy, as rs1154155 CA and CC did not show any difference in these parameters. This effect was independent of sex, which has no effect on age of onset in this sample. The effect of rs1154155 status on age of onset was not significant after Bonferoni correction for multiple comparisons.

DISCUSSION

Our study extends genetic association studies for two previously reported loci in a large number of Chinese patients with narcolepsy/hypocretin deficiency. We also took advantage of the fact that most patients with narcolepsy diagnosed at Beijing are diagnosed rapidly after disease onset (most frequently as children, see Han et al. [22]), and are untreated at the time of evaluation and diagnosis, allowing for a baseline measure of severity to compare the effects of genotypes at three loci on disease severity and age of onset.

Unlike results reported for a Japanese sample, we could not replicate the *CPT1B/CHKB* rs5770917C association in this Chinese sample. In fact, the effect found in this sample was opposite to that reported in Miyagawa, although not significantly. Miyagawa et al. (2008) [18], used a GWA design in 222 Japanese individuals with narcolepsy and 389 Japanese controls, with replication of top hits in 159 Japanese individuals with narcolepsy and 190 Japanese controls, and found a strong association of rs5770917C in this sample, although not reaching the $5x10^{-8}$ p value generally accepted as genome wide significant (allele frequency 0.24 versus 0.14, OR = 1.79, combined $P = 4.4\times10^{-7}$). Interestingly, the polymorphism replicated weakly in a small sample of 115 cases versus 309 controls of Korean descent (0.25 versus 0.19, OR= 1.40, p=0.03) and showed non-significant trends in small samples of African Americans and Caucasians [8]. The testing of two larger Caucasian samples [8], however, did not confirm this association, although allele frequency in this ethnic group is low (0.04–0.05) and thus power is limited.

CPT1B/CHKB rs5770917 was particularly interesting in the context of this study for two reasons. First, rs5770917C has a similar allele frequency in Japanese and Chinese populations (Table 1, see also Miyagawa [18]), and, thus, we had sufficient power to replicate this association. The lack of replication was thus disappointing. Differences between Japanese and Chinese populations (mostly northern Chinese in this sample) could be involved. Second, rs5770917 has been shown to be associated with changes in *CPT1B/CHKB* expression and a recent Japanese study extended the rs5770917C association to patients with essential Hypersomnia Syndrome (sleepiness but no cataplexy), both with and without DQB1*0602 [23]. As DQB1*0602 negative patients with essential Hypersomnia are known to have normal hypocretin levels [24], these cases are likely not to have the same pathophysiological basis as narcolepsy/cataplexy, a finding that could suggest that maybe rs5770917C increases sleepiness across a large range of pathologies, thus explaining the broad association. As noted in Table 2, however, we found no association of this polymorphism with any measure of severity in these patients. Additional replication and studies in Japanese will be needed to clarify this association.

In contrast to the above, the association with *TCRA* rs1154155C was evident in the Chinese sample. This, together with the fact that Hor et al. [25] also replicated this association robustly in a new Caucasian sample (0.21 versus 0.15, OR=1.54 $P = 5\times10^{-7}$), indicates the TCR association is strong across multiple ethnic groups and replicates across investigators. We next assessed whether this polymorphism was also associated with daytime sleepiness or changes in age of onset within narcoleptic patients. Indeed, many disease-associated

polymorphisms are also associated with clinical presentation such as earlier onset or increased disease severity. The unique situation of the Chinese population and its diagnosis close to disease onset and evaluation without treatment allowed us to test this hypothesis in an ideal sample.

As shown in Table 2, we found no effect of *TCRA* rs1154155 on severity of daytime sleepiness, but a possible slight effect on age of onset, to be confirmed by additional studies. This parallels what has been reported with HLA-DQB1*0602 homozygosity, a genotype that increases risk of developing the disorder by 2–4 fold, and has been suggested to affect disease severity and age of onset in some but not all studies [26,27]. Differences in HLA-DQ and *TCRA* frequencies across populations may thus contribute to differences in age of onset, or disease presentation. For example, our recent finding that disease onset has been reported to be younger in Chinese versus Caucasian children [22], where the AA genotype is the most frequent in the general population (58% in Caucasians see Hallmayer et al[8]., versus 21% in Chinese, see Table 1) and DQB1*0602 frequency is as high as in Caucasians. Several authors have also pointed out that in Caucasians the distribution of age of onset is bimodal, with a second peak of onset after age 30, a phenomenon not reported in Japan, another population with low rs1154155A frequency [28,29]. Additional studies of onset age across multiple ethnic groups per rs1154155 and HLA genotypes are warranted. Most likely, however, younger age of onset in the Chinese population could result from ascertainment issues plus genetic and environmental differences between these populations.

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Table 1

Association of rs1154155, rs2305795, and rs5770917 with narcolepsy in Chinese

	Marker	Gene	Allele/Genotype	Freq Cases (n)	Freq Controls (n)	χ_2	OR(95% CI)	*p*
Allelic Association								
	rs1154155	TCRA	C	0.62 (988)	0.53(872)	16.63	1.47(1.22–1.77)	<0.0001
	rs2305795*	P2RY11	A	0.73(1016)	0.68(902)	6.46	1.29(1.06–1.57)	0.0111
	rs5770917	CPT1B/CHKB	C	0.23(1012)	0.24(900)	0.97	0.90(0.73–1.11)	0.3239
Genotypic Association				n=494	n=436			
	rs1154155	TCRA	AA	0.12(58)	0.21(92)		ref	
			AC	0.52(255)	0.52(225)	9.06	1.77(1.22–2.56)	0.0026
			CC	0.37(181)	0.27(119)	18.20	2.37(1.59–3.53)	<0.0001
				n=508	n=451			
	rs2305795*	P2RY11	CC	0.08(39)	0.11(49)		ref	
			CT	0.39(197)	0.43(194)	1.06	1.28(0.80–2.03)	0.3043
			TT	0.54(272)	0.46(208)	4.57	1.64(1.04–2.59)	0.0326
				n=506	n=450			
	rs5770917	CPT1B/CHKB	TT	0.60(302)	0.57(258)		ref	
			CT	0.36(180)	0.36(164)	0.22	0.94(0.72–1.23)	0.6392
			CC	0.05(24)	0.06(28)	1.15	0.73(0.41–1.29)	0.2828

*Data provided as reference for Table 2. In contrast to rs1154155 and rs5770917, the rs2305795 data provided here was already reported in Kornum et al.[10]

Table 2

Association between clinical characteristics and SNP genotypes

	rs1154155			rs5770917			rs2305795		
	AA	AC	CC	CC	CT	TT	CC	CT	TT
	n=59	n=255	n=181	n=24	n=180	n=302	n=39	n=197	n=272
Age (yrs)	20.34±1.77(58)	17.88±0.85(254)	18.80±1.00	19.54±2.74	18.31±1.00(179)	18.39±0.77	18.30±2.15	19.18±0.96(1196)	17.92±0.81
Sex (%male)	74.1%	69.7%	68.3%	75.0%	69.7%	68.5%	71.8%	66.0%	71.1%
Body Mass Index	24.82±0.73(58)	23.51±0.35(254)	22.97±0.41	24.18±1.13	23.14±0.41(179)	23.51±0.32	24.17±0.89	23.36±0.40(196)	23.34±0.34
Age of onset[#] (yrs)	14.98±1.11(57)*††	11.53±0.53(249)	11.48±0.64(175)	14.46±1.71	12.00±0.63(176)	11.61±0.49(293)	10.72±1.34	12.73±0.60(192)	11.39±0.52(264)
% with cataplexy	100%	100%	99%	100%	100%	99%	100%	100%	99%
Severity of Catapelxy									
Age of onset (cataplexy)	16.11±1.21(56)*††	12.55±0.58(244)	12.85±0.70(168)	16.09±1.89(23)	12.72±0.69(172)	12.96±0.54(286)	11.92±1.45(23)	13.91±0.66(185)	12.58±0.56(258)
% with sleepiness (EDS)	100%	100%	100%	100%	100%	100%	100%	100%	100%
Epworth Slepiness Scale									
Age of onset (EDS)	15.02±1.11(57)*††	11.71±0.53(249)	11.52±0.64(175)	14.54±1.71	12.13±0.63(176)	11.71±0.49(293)	10.97±1.34	12.89±0.60(192)	11.45±0.51(264)
% with sleep paralysis	50.9%	41.1%	38.7%	50.0%	41.9%	40.6%	41.7%	45.7%	38.4%
Severity of sleep paralysis									
Age of onset (sleep paralysis)	21.93±2.08(27)	17.24±1.11(95)	16.10±1.37(62)	21.75±3.13(12)	18.37±1.34(65)	16.59±1.03(111)	15.79±2.92(14)	17.56±1.22(80)	17.60±1.12(95)
% with hypnagogic hallucinations	69.0%	59.3%	57.8%	62.5%	65.7%	56.4%	52.6%	60.2%	61.6%
Severity of hypnagogic halucinations									
Age of onset (hallucinations)	18.05±1.65(37)*†	12.57±0.85(139)	14.64±1.02(96)	17.85±2.83(13)	14.03±1.96(112)	13.68±0.83(153)	12.45±2.28(20)	14.51±1.00(105)	13.83±0.82(154)
% with disturbed nocturnal sleep	74.1%	75.3%	67.4%	79.2%	71.7%	72.5%	76.9%	72.6%	72.4%
MSLT mean Sleep latency	3.06±0.30(57)	3.39±0.15(242)	3.48±0.17(176)	3.30±0.45(23)	3.36±0.17(174)	3.41±0.13(290)	3.39±0.36(23)	3.62±0.16(187)	3.23±0.14(263)
MSLT number of SOREMP	4.10±0.14(58)	4.29±0.07(248)	4.11±0.08(176)	4.22±0.23(23)	4.18±0.08(176)	4.21±0.06(295)	4.21±0.17(23)	4.15±0.08(190)	4.15±0.07(267)

[#]=sleepiness or cataplexy, whichever came first; MSLT: Mutiple Sleep Latency Test; SOREMP: Sleep Onset REM Period

* $p<0.05$, three group ANOVA;

† $p< 0.01$;

†† $p<0.05$, post hoc comparisons between AA verse AC or AA verse CC