OPEN

Citation: Human Genome Variation (2015) 2, 15031; doi:10.1038/hgv.2015.31

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DATA REPORT

An association analysis of *HLA-DQB1* with narcolepsy without cataplexy and idiopathic hypersomnia with/without long sleep time in a Japanese population

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Narcolepsy without cataplexy (NA w/o CA) (narcolepsy type 2) is a lifelong disorder characterized by excessive daytime sleepiness and rapid eye movement (REM) sleep abnormalities, but no cataplexy. In the present study, we examined the human leukocyte antigen *HLA-DQB1* in 160 Japanese patients with NA w/o CA and 1,418 control subjects. Frequencies of *DQB1*06:02* were significantly higher in patients with NA w/o CA compared with controls (allele frequency: 16.6 vs. 7.8%, $P = 1.1 \times 10^{-7}$, odds ratio (OR) = 2.36; carrier frequency: 31.3 vs. 14.7%, $P = 7.6 \times 10^{-8}$, OR = 2.64). Distributions of *HLA-DQB1* alleles other than *DQB1*06:02* were compared between NA w/o CA and narcolepsy with cataplexy (NA-CA) to assess whether the genetic backgrounds of the two diseases have similarities. The distribution of the *HLA-DQB1* alleles in *DQB1*06:02*-negative NA w/o CA was significantly different from that in NA-CA ($P = 5.8 \times 10^{-7}$). On the other hand, the patterns of the *HLA-DQB1* alleles were similar between *DQB1*06:02*-positive NA w/o CA and NA-CA. *HLA-DQB1* analysis was also performed in 186 Japanese patients with idiopathic hypersomnia (IHS) with/without long sleep time, but no significant associations were observed.

Human Genome Variation (2015) **2,** 15031; doi:10.1038/hgv.2015.31; published online 17 September 2015

The 2nd Edition of the International Classification of Sleep Disorders (ICSD-2), in the category of hypersomnia of central origin, subdivides narcolepsy into two groups: narcolepsy with cataplexy (NA-CA) and narcolepsy without cataplexy (NA w/o CA). NA w/o CA is characterized by excessive daytime sleepiness and abnormal manifestations of rapid eye movement (REM) sleep in common with NA-CA, but no cataplexy. Patients with NA w/o CA have frequent sleep-onset REM periods, as do those with NA-CA, as revealed by performance of the multiple sleep latency test. A population-based study suggested that the prevalence of NA w/o CA is 36% of the prevalence of narcolepsy as a whole, corresponding to a point prevalence of 0.02%.[1] NA-CA is tightly associated with *HLA-DQB1*06:02* and orexin (hypocretin) deficiency. Almost all patients with NA-CA in many populations consistently carry *DQB1*06:02*, while approximately 12% of Japanese, 25% of Caucasian and 38% of African American healthy individuals are *DQB1*06:02*-positive.[2–4] Low levels of orexin A in cerebrospinal fluid (CSF) (< 110 pg/ml) are commonly observed in patients with NA-CA.[5,6] Regarding NA w/o CA, positivity of *HLA-DQB1*06:02* (30–50%) is also higher than that in the general population,[7–10] but less than that in NA-CA. However, only approximately 20% of patients with NA w/o CA have low levels of CSF orexin A,[6,10] indicating that the etiology of the majority of NA w/o CA is still unknown.

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Received 2 July 2015; accepted 8 July 2015

There have been a number of studies of *HLA* in NA-CA; results indicated that *HLA-DQB1* alleles other than *DQB1*06:02* modulate susceptibility or resistance to NA-CA. *DQB1*06:01* and *DQB1*05:01* in the Korean and Japanese populations and *DQB1*06:03* in European populations are protective against NA-CA,[2,7,11–14] whereas individuals with *DQB1*03:01* and *DQB1*03:02* are at an increased risk.[2,7,11,13–17] In the present study, to test for associations of *HLA-DQB1* alleles in NA w/o CA, we performed an association study for *HLA-DQB1* in 160 Japanese patients with NA w/o CA and 1,418 control subjects.

Idiopathic hypersomnia (IHS) is a sleep disorder of presumed central nervous system origin that is associated with excessive daytime sleepiness consisting of prolonged non-REM sleep episodes. Daytime naps of IHS patients tend to be longer and less refreshing than those of NA-CA patients. IHS is a rare disease, representing 8:10 to 1:10 patients with NA-CA. This suggests that the prevalence of IHS approximates 0.005%.[18] The ICSD-2 describes two clinical forms of IHS by the difference in nocturnal sleep time: IHS with long sleep time (IHS-LST) and IHS without long sleep time (IHS w/o LST). The nocturnal sleep time of IHS-LST is prolonged to at least 10 h, while that of IHS w/o LST is either normal or slightly prolonged (less than 10 h). CSF orexin A levels in IHS are normal.[6] The cause and pathogenesis of IHS remain largely unknown. NA w/o CA and IHS w/o LST have several common characteristics except for REM-related symptoms. Distinguishing NA w/o CA and IHS w/o LST is impossible without the multiple sleep latency test to identify sleep-onset REM periods. According to the ICSD-2, the diagnosis is based on the number of sleep-onset REM periods, two or more in the former and less than two in the latter. In the present study, we tested whether *HLA-DQB1* alleles have an influence on susceptibility to IHS w/o LST and IHS-LST.

A total of 346 Japanese patients and 1,418 Japanese healthy controls were included in this study. NA w/o CA, IHS w/o LST and IHS-LST were diagnosed according to the ICSD-2 criteria. The patient groups consisted of NA w/o CA ($n=160$), IHS w/o LST ($n=118$) and IHS-LST ($n=68$). We utilized *HLA* data of healthy individuals, who have been previously studied for disease association analyses.[17,19,20] In addition, to assess genetic similarities between the above hypersomnia disorders and NA-CA, *HLA-DQB1* data from 664 patients with NA-CA were utilized.[17] All of the patients and controls were mainland Japanese and gave written informed consent. This study was approved by the local institutional review boards at participating institutions. Typing for the *HLA-DQB1* locus was performed by a Luminex Multi-Analyte Profiling system (xMAP) with WAKFlow HLA typing kits (Wakunaga Pharmaceutical, Wakunaga, Hiroshima, Japan). Comparisons of frequencies were performed using the Chi-square test or Fisher's Exact test as appropriate. To account for multiple testing, the significance level was adjusted by the number of *HLA* alleles with allele frequencies no less than 0.5% in controls (12 for *HLA-DQB1* alleles). The significance level was set to be $P < 4.2\times10^{-3}$ (0.05/12). If any of the four cells was zero, the Woolf-Haldane correction was applied (adding 0.5 to all cells). An association analysis controlling for the effects of *DQB1*06:02* was needed to test the other *HLA-DQB1* alleles. Specifically, the analysis was performed using counts of the other *HLA-DQB1* alleles remaining after excluding allele counts of *DQB1*06:02* from both cases and controls, which is the relative predispositional effects method.[21] Briefly, frequencies and ORs were calculated for the alleles carried by the non-*DQB1*06:02* chromosomes. To determine whether there was a different allelic distribution between two groups, the overall frequency distribution of *HLA-DQB1* alleles in one group was compared with the distribution in another group by using the global Chi-square test with 12 degrees-of-freedom.

HLA-DQB1 allele frequencies of 160 patients with NA w/o CA and 1,418 control subjects were determined, and are shown in Table 1. *DQB1*06:02* was significantly associated with NA w/o CA (allele frequency: 16.6 vs. 7.8% in controls, $P=1.1\times10^{-7}$, OR = 2.36). Regarding carrier frequencies for *HLA-DQB1*, 31.3% of the patients carried *DQB1*06:02*, vs. 14.7% of controls ($P=7.6\times10^{-8}$, OR = 2.64) (Supplementary Table 1). We tested whether there were other independent *HLA-DQB1* associations aside from *DQB1*06:02* using the relative predispositional effect method.[21] *DQB1*06:04* showed a marginal association ($P=5.9\times10^{-3}$, OR = 1.80) (Table 2). However, the *P* value did not reach the threshold corrected for multiple comparisons. NA w/o CA was subdivided into *DQB1*06:02*-positive and -negative groups for further analyses, because previous studies suggested that these two disease groups have different etiology, clinical characteristics and electroencephalographic findings.[10,22–24] The analyses were performed by controlling for the effects of *DQB1*06:02* (Table 2). No significant association with *HLA-DQB1* alleles was found in *DQB1*06:02*-positive NA w/o CA. *DQB1*06:04* was nominally associated with *DQB1*06:02*-negative NA w/o CA patients ($P=5.6\times10^{-3}$, OR = 1.88).

Next, we tested whether *HLA-DQB1* allele distributions (except for *DQB1*06:02*) in *DQB1*06:02*-positive and -negative NA w/o CA patients showed similarities with those of NA-CA patients (Table 2 and Supplementary Figure 1). The allele distribution of *DQB1*06:02*-negative NA w/o CA was significantly different from that of NA-CA ($P=5.8\times10^{-7}$). On the other hand, no significant difference was observed in the distribution between *DQB1*06:02*-positive NA w/o CA and NA-CA ($P=0.97$). When we focused on *HLA-DQB1* alleles with frequencies no less than 5% in *DQB1*06:02*-positive NA w/o CA, all the ORs of the alleles were found in the same direction as those of NA-CA (Table 2). These results suggest that a common etiological pathway might exist for *DQB1*06:02*-positive NA w/o CA and NA-CA, whereas *DQB1*06:02*-negative NA w/o CA has a different etiological pathway from NA-CA. Orexin A in the CSF of typical NA-CA patients is known to be reduced or undetectable.[5,6] A minority of NA w/o CA patients have low concentrations of CSF orexin A levels, although a majority of NA w/o CA patients have normal concentrations;[6,10] thus, an etiologic heterogeneity in NA w/o CA is suggested. In addition, most of the NA w/o CA patients with low CSF orexin A are *DQB1*06:02*-positive, as in NA-CA.[6,10] In contrast, *DQB1*06:02* positivity of patients with normal CSF orexin A is not higher than that seen in the general population.[10] Therefore, the heterogeneity in NA w/o CA might be divided by *DQB1*06:02* positivity, and *DQB1*06:02*-positive NA w/o CA might have the same etiology as NA-CA from the view point of orexin deficiency. In addition, clinical characteristics and electroencephalographic findings have been

Table 1. *HLA-DQB1* allele frequencies of patients with NA w/o CA

DQB1	*NA w/o CA*	*(2n = 320)*	*Control*	*(2n = 2836)*	*OR*	P
	No.	*%*	*No.*	*%*		
02:01	1	0.3	11	0.4	0.81	1.00
03:01	29	9.1	334	11.8	0.75	0.15
03:02	27	8.4	264	9.3	0.90	0.61
03:03	46	14.4	450	15.9	0.89	0.49
04:01	42	13.1	374	13.2	0.99	0.97
04:02	12	3.8	118	4.2	0.90	0.73
05:01	22	6.9	191	6.7	1.02	0.92
05:02	3	0.9	63	2.2	0.42	0.13
05:03	10	3.1	106	3.7	0.83	0.58
06:01	45	14.1	515	18.2	0.74	0.07
06:02	53	16.6	220	7.8	2.36	1.1.E − 07
06:03	1	0.3	16	0.6	0.55	1.00
06:04	28	8.8	160	5.6	1.60	0.03
06:09	1	0.3	14	0.5	0.91	1.00

Abbreviations: NA w/o CA, narcolepsy without cataplexy; OR, odds ratio.

Table 2. Frequencies of *HLA-DQB1* alleles after removal of *DQB1*06:02* effects

DQB1 alleles	*NA w/o CA*				*DQB1*06:02 (+) NA w/o CA*				*DQB1*06:02 (−) NA w/o CA*				*Control*		*NA-CA*			
	No.	*%*	*OR*	P[a]	*No.*	*%*	*OR*	P[a]	*No.*	*%*	*OR*	P[a]	*No.*	*%*	*No.*	*%*	*OR*	P[a]
02:01	1	0.4	0.89	1.00	0	0.0	2.38	1.00	1	0.5	1.08	1.00	11	0.4	5	0.9	1.78	0.22
03:01	29	10.9	0.83	0.37	9	19.1	1.62	0.20	20	9.1	0.68	0.11	334	12.8	98	16.9	1.38	5.7.E−03
03:02	27	10.1	1.00	0.99	6	12.8	1.30	0.47	21	9.5	0.94	0.80	264	10.1	107	18.4	1.97	2.5.E−09
03:03	46	17.2	1.00	0.99	8	17.0	0.99	0.97	38	17.3	1.00	0.98	450	17.2	74	12.8	0.73	0.02
04:01	42	15.7	1.12	0.53	9	19.1	1.42	0.35	33	15.0	1.06	0.78	374	14.3	112	19.3	1.43	1.2.E−03
04:02	12	4.5	1.00	0.99	1	2.1	0.46	0.72	11	5.0	1.11	0.74	118	4.5	20	3.4	0.77	0.27
05:01	22	8.2	1.14	0.58	2	4.3	0.56	0.58	20	9.1	1.27	0.33	191	7.3	20	3.4	0.48	1.5.E−03
05:02	3	1.1	0.46	0.18	1	2.1	0.88	1.00	2	0.9	0.37	0.15	63	2.4	28	4.8	1.80	4.4.E−03
05:03	10	3.7	0.92	0.81	1	2.1	0.51	1.00	9	4.1	1.01	0.98	106	4.1	21	3.6	0.79	0.31
06:01	45	16.9	0.83	0.27	6	12.8	0.60	0.24	39	17.7	0.88	0.48	515	19.7	49	8.4	0.39	1.4.E−10
06:03	1	0.4	0.61	1.00	0	0.0	1.66	1.00	1	0.5	0.74	1.00	16	0.6	1	0.2	0.25	0.26
06:04	28	10.5	1.80	5.9.E−03	4	8.5	1.43	0.50	24	10.9	1.88	5.6.E−03	160	6.1	42	7.2	1.10	0.58
06:09	1	0.4	0.70	1.00	0	0.0	1.89	1.00	1	0.5	0.85	1.00	14	0.5	3	0.5	1.50	0.46
Global *P* value versus NA-CA[b]	4.3.E−06				0.97				5.8E−07				1.2.E−17					

Abbreviations: NA-CA, narcolepsy with cataplexy; NA w/o CA, narcolepsy without cataplexy; OR, odds ratio. NA w/o CA: $n=267$, *DQB1*06:02* (+) NA w/o CA: $n=47$, *DQB1*06:02* (−) NA w/o CA: $n=220$, Control: $n=2616$, NA-CA: $n=580$. [a]*P* values were calculated for comparisons between disease and control groups. [b]The overall frequency distribution of *HLA-DQB1* alleles in NA-CA group was compared with that in another group using the global Chi-square test.

Table 3. *HLA-DQB1* allele frequencies of patients with IHS w/o LST and IHS-LST

DQB1	*IHS w/o LST*	*(2n = 236)*			*IHS-LST*	*(2n = 136)*			*Control*	*(2n = 2836)*
	No.	*%*	*OR*	P	*No.*	*%*	*OR*	P	*No.*	*%*
02:01	0	0.0	0.52	1.00	0	0.0	0.90	1.00	11	0.4
03:01	33	14.0	1.22	0.32	8	5.9	0.47	0.04	334	11.8
03:02	26	11.0	1.21	0.39	10	7.4	0.77	0.44	264	9.3
03:03	34	14.4	0.89	0.55	19	14.0	0.86	0.55	450	15.9
04:01	35	14.8	1.15	0.48	13	9.6	0.70	0.22	374	13.2
04:02	9	3.8	0.91	0.80	4	2.9	0.70	0.48	118	4.2
05:01	19	8.1	1.21	0.44	11	8.1	1.22	0.54	191	6.7
05:02	5	2.1	0.95	0.92	8	5.9	2.75	6.3.E−03	63	2.2
05:03	8	3.4	0.90	0.79	8	5.9	1.61	0.20	106	3.7
06:01	39	16.5	0.89	0.53	33	24.3	1.44	0.07	515	18.2
06:02	16	6.8	0.86	0.59	12	8.8	1.15	0.65	220	7.8
06:03	2	0.8	1.51	0.64	1	0.7	1.31	0.55	16	0.6
06:04	9	3.8	0.66	0.24	8	5.9	1.05	0.91	160	5.6
06:09	1	0.4	0.86	1.00	1	0.7	1.49	0.51	14	0.5

Abbreviations: IHS-LST, idiopathic hypersomnia with long sleep time; IHS w/o LST, idiopathic hypersomnia without long sleep time; OR, odds ratio.

reported to be different between *DQB1*06:02*-positive and -negative NA w/o CA groups.[23,24] These findings correspond well to our result.

Patients with IHS w/o LST and IHS-LST were also typed for *HLA-DQB1* in the present study. *HLA-DQB1* allele and carrier frequencies are shown in Table 3 and Supplementary Table 2, respectively. *DQB1*06:02*, known to be associated with NA-CA and NA w/o CA, was not associated with IHS w/o LST or IHS-LST. Although *DQB1*05:02* ($P=6.3\times10^{-3}$) and *DQB1*03:01* ($P=0.04$) showed nominally significant associations with IHS-LST, there were no *HLA-DQB1* alleles that reached the threshold after correction for multiple comparisons. The similarity of *HLA-DQB1* allele distribution between NA-CA and IHS w/o LST or IHS-LST was tested after controlling for the effects of *DQB1*06:02*, and significant differences were found: for IHS w/o LST: $P=2.1\times10^{-4}$ and for IHS-LST: $P=2.2\times10^{-8}$. Taken together, these results indicate that IHS w/o LST and IHS-LST are caused by different etiological genetic factors than those that give rise to NA-CA.

The International Classification of Sleep Disorders was recently revised for the 3rd Edition (ICSD-3). When we had recruited patient samples, the 2nd edition (ICSD-2) was used. Main differences between the ICSD-2 and ICSD-3 regarding NA w/o CA, IHS w/o LST and IHS-LST are as follows. The terminology has been changed from 'narcolepsy without cataplexy (NA w/o CA)' to 'narcolepsy type 2'. The concept of NA w/o CA and narcolepsy type 2 is almost the same. IHS w/o LST and IHS-LST were unified to 'idiopathic hypersomnia (IHS)' regardless of the extension of the sleep time. Therefore, we combined our IHS w/o LST and IHS-LST data to analyze the *HLA-DQB1* data as IHS (Supplementary Tables 3 and 4). As a result, no significant association was observed between each *HLA-DQB1* allele and IHS. Distribution of *HLA-DQB1*

alleles in IHS was also significantly different from that of NA-CA, even after the effect of *DQB1-06:02* was controlled ($P = 8.6 \times 10^{-9}$).

To conclude, the association of *DQB1*06:02* in NA w/o CA was confirmed. Our results also suggested an immunological pathogenesis of *DQB1*06:02*-positive NA w/o CA, which is similar to that of NA-CA. *DQB1*06:02*-negative NA w/o CA, IHS w/o LST and IHS-LST may have a different etiology, which is not well understood.

HGV DATABASE

The relevant data from this Data Report are hosted at the Human Genome Variation Database at http://dx.doi.org/10.6084/m9.figshare.hgv.688.

ACKNOWLEDGEMENTS

The authors are deeply grateful to all participants in this study. This study was supported by Grants-in-Aid for Young Scientists (A) (23689022), Scientific Research (B) (15H04709) and Scientific Research on Innovative Areas (22133008) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Grants-in-Aid from the Takeda Science Foundation and the SENSHIN Medical Research Foundation.

COMPETING INTERESTS

Y.I. has a commercial research grant from Alfresa Pharma Corporation. The other authors declare no conflict of interest.

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Supplementary Information for this article can be found on the *Human Genome Variation* website (http://www.nature.com/hgv).