HLA-B Allele Associations with Certain Drugs are not Confirmed in Japanese Patients with Severe Cutaneous Drug Reactions

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Accepted May 9, 2008.

Sir,

Although it is not known which factors induce the variability seen in cutaneous adverse reactions, special attention has focused recently on genetic susceptibility. For instance, a strong association has been demonstrated between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome (SJS) in Han Chinese patients (1, 2), suggesting a role of the HLA-B*1502 allele in the pathogenesis of anti-epileptic drug-induced severe cutaneous reactions, including SJS and toxic epidermal necrolysis (TEN) (1–3). Moreover, Hung et al. (4) have reported a strong association between the HLA-B*5801 allele and allopurinol-induced severe cutaneous reactions. In support of this association, Dainichi et al. (5) have demonstrated that Japanese patients with different clinical types of severe cutaneous reactions caused by allopurinol, including SJS, TEN and drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms (DIHS/DRESS), had the same HLA-B*5801 allele. However, Lonjou et al. (6) have pointed out that the HLA-B*1502 allele is not a universal genetic marker for SJS, based on the results of a European study (RegiSCAR) of 12 patients with carbamazepine-induced SJS/TEN, who are known to have greater ethnic heterogeneity than the Han Chinese population, and stressed that ethnicity plays a role, because 4 patients with Asian ancestors had the HLA-B*1502 allele.

We have determined the HLA-B alleles in Japanese patients with severe cutaneous drug reactions, including SJS, TEN and DIHS/DRESS, caused by various drugs.

MATERIALS AND METHODS

Twenty-one patients with SJS (2 patients), TEN (3 patients), and DIHS/DRESS (16 patients) were enrolled in the study. All patients examined met full criteria for SJS, TEN and DIHS/DRESS, respectively (7, 8). The causative drugs were identified by a temporal correlation between drug introduction and onset of symptoms, and lymphocyte transformation tests: they include allopurinol, carbamazepine, phenobarbital and phenytoin. The study was approved by the Institutional Review Board at Kyorin University School of Medicine. HLA-B alleles were determined by PCR amplification and subsequent hybridization with sequence-specific oligonucleotide probes, using commercial typing kits (9).

RESULTS

The HLA-B*1502 allele was not observed in any patients with SJS or DIHS/DRESS caused by anti-epileptic drugs, but the HLA-B*5801 allele was detected in one out of the 3 patients with allopurinol-induced DIHS/DRESS. On the other hand, the HLA-B*4801 allele was found in 6 out of the 16 patients with DIHS/DRESS (37.5%) and one out of the 3 patients with TEN. The causative drugs in 6 patients with DIHS/DRESS were carbamazepine ($n=4$) and allopurinol ($n=2$). The frequencies of the HLA-B*4801 allele in patients with DIHS/DRESS was considerably higher than the reported frequencies in the Japanese population (4.3%) (10), although the difference is not statistically significant after correction for multiple comparisons. Four out of the 6 patients with HLA-B*4801 allele showed severe liver dysfunction (alanine aminotransferase (ALT) > 300 IU/l) during the course of DIHS/DRESS; 2 out of the 6 patients were infected with hepatitis C virus because of blood transfusion and one of these was infected with human T-lymphotropic virus type 1. In addition, 4 out of the 16 patients with DIHS/DRESS had the HLA-B*1301 allele (25.0%), independently of drugs given; the frequency of the HLA-B*1301 allele in those patients was much higher than that reported for the Japanese population (1.3%) (10), although the difference is not statistically significant after correction for multiple comparisons. Interestingly, in 3 out of the 4 patients with HLA-B*1301, not only HHV-6 but also cytomegalovirus was reactivated in association with severe liver dysfunction during the course of DIHS/DRESS (Table I).

DISCUSSION

These results indicate that Japanese patients with carbamazepine-induced DIHS/DRESS were more likely to carry the HLA-B*4801 allele; the strong association between allopurinol and HLA-B*5801 was not found in Japanese patients with DIHS/DRESS (Table II). Although these results and those of Lonjou et al. (6) were derived from small samples, they suggest that the ethnicity beyond HLA-B alleles plays a role in the development of severe drug eruptions and it is still premature to conclude that these alleles, such as HLA-B*1502 and -B*5801, are universal genetic markers for the disease. In fact, the HLA-A*0206 allele has been reported to be strongly associated with SJS/TEN with ocular complications in the Japanese population (11). In view of possible associations between the HLA-B*1301 allele and particular virus reactivations in our study, the effect of certain HLA-B alleles on the occur-

 ISSN 0001-5555
doi: 10.2340/00015555-0528

Table I. *HLA-B alleles in patients with severe cutaneous drug eruptions*

Pat. no.	Clinical type of drug eruption	Previous infection	Severe liver dysfunction	Viral reactivations	Causative drug				
					Allopurinol	Carbamazepine	Phenobarbital	Phenytoin	Other or unknown drug
1	SJS	Nd	–	Nd			B*15010101, B*5401		
2	SJS	Nd	–	Nd					B*3901, B*400201
3	TEN	Mycoplasma	–	Nd					B*5401, B*5502
4	TEN	Nd	–	Nd					B*440301
5	TEN	Nd	–	Nd					B*350101, B*4801
6	DIHS/DRESS	HTLV-1	+	HHV-6	B*4801, B*5801				
7	DIHS/DRESS	HCV	–	HHV-6, CMV	B*4801				
8	DIHS/DRESS	Nd	+	HHV-6	B*15010101, B*520101				
9	DIHS/DRESS	Nd	–	HHV-6, CMV		B*3901, B*400201			
10	DIHS/DRESS	Nd	–	HHV-6		B*4801, B*5401			
11	DIHS/DRESS	Nd	–	HHV-6, CMV		B*510101, B*5901			
12	DIHS/DRESS	Nd	+	HHV-6		B*350101, B*510101			
13	DIHS/DRESS	Nd	–	VZV, HHV-6		B*390201, B*5601			
14	DIHS/DRESS	Nd	+	HHV-6		B*400201, B*4801			
15	DIHS/DRESS	Nd	–	HHV-6		B*5401, B*5502			
16	DIHS/DRESS	Nd	–	HHV-6		B*1301, B*5502			
17	DIHS/DRESS	HCV	+	HHV-6		B*15010101, B*4801			
18	DIHS/DRESS	Nd	+	HHV-6		B*4001, B*4801			
19	DIHS/DRESS	HTLV-1	+	HHV-6, CMV			B*1301, B*4601		
20	DIHS/DRESS	Nd	+	HHV-6, CMV			B*1301, B*15010101		
21	DIHS/DRESS	HBV	+	HHV-6, CMV				B*1301, B*400201	

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; DIHS/DRESS: drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms; Nd: not detected; Sever liver dysfunction: alanine aminotransferase > 300 IU/ l.: HCV: hepatitis C virus; HBV: hepatitis B virus; HTLV-1: human T-lymphotropic virus type 1; HHV-6. human herpesvirus 6; CMV: cytomegalovirus; VZV: varicella-zoster virus.

rence of virus reactivations may contribute, in part, to the HLA-B allele association with the disease. Further large-scale work is required to confirm the significance of these alleles in a variety of severe drug reactions.

ACKNOWLEDGEMENTS

This work was supported in part by grants from the Ministry of Education, Sports, Science and Culture of Japan (to Y. K. and T. S.) and the Ministry of Health, Labor and Welfare of Japan (to T. S.).

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Table II. *Fequencies of HLA-B*1502 and HLA-B*5801 in patients with cutaneous drug eruptions: a literature review*

Ethnicity (ref)	HLA B allele	Causative drug	Type of cutaneous drug eruption	
			SJS/TEN (detected numbers/ examined numbers)	DIHS/DRESS (detected numbers/ examined numbers)
Han Chinese (2)	1502	Carbamazepine	59/60	0/13
Caucasian (6)	1502	Carbamazepine	4[a]/12	ND
Han Chinese (3)	1502	Carbamazepine	4/4	ND
	1502	Phenytoin	1/1	0/1
	1502	Lamotrigine	1/1	0/1
Han Chinese (4)	5801	Allopurinol	21/21	30/30
Japanese (5)	5801	Allopurinol	2/2	1/1
Japanese (present study)	1502	Carbamazepine	ND	0/10
	1502	Phenytoin	0/1	ND
	5801	Allopurinol	ND	1/3

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; DIHS/DRESS: drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms; ND: not done.
[a]Asian ancestor.

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