HLA-DRB1*04 and DRB1*14 Alleles Are Associated with Susceptibility to Pemphigus Among Japanese

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It has previously been demonstrated that susceptibility to pemphigus vulgaris is associated with human leukocyte antigen (HLA)-DR4 serologic specificity among Ashkenase Jews, and with DR4 as well as DR6 (DR14) in other ethnic groups. We genotyped HLA-DRB1, DQA1, DQB1, and DPB1 alleles in 16 patients with pemphigus by polymerase chain reaction-restriction fragment length polymorphism, to find evidence of potential HLA class II allele associations with pemphigus in Japanese patients who have a relatively homogeneous ethnic background. All nine patients with pemphigus vulgaris and five of seven patients with pemphigus foliaceus carried one or two alleles of HLA-DRB1*04 (*0403, *0406) and HLA-DRB1*14 (*1401, *1405, *1406) subtypes. Sequence analysis of these DRB1*04 and DRB1*14 alleles revealed the amino acid homology of phenylalanine at position 26 and valine at position 86 with the DRB1*0402 allele that reportedly confers a strong susceptibility to pemphigus vulgaris in Ashkenazi Jews. Thus our findings, together with previous HLA studies on pemphigus vulgaris patients of different ethnic groups, suggest that HLA-DRB1*04 and DRB1*14 alleles are commonly associated with pemphigus vulgaris across racial barriers. These HLA-DRB1 alleles are likely to be also associated with pemphigus foliaceus. Further studies on more diverse ethnic populations will be helpful in determining the significance of the association between certain amino acid residues of the class II molecules and disease susceptibility to pemphigus vulgaris as well as pemphigus foliaceus. ***Key words: pemphigus foliaceus/pemphigus vulgaris.***
J Invest Dermatol 109:615–618, 1997

Pemphigus is a chronic acantholytic blistering disease mediated by autoantibodies that bind to the keratinocyte cell surface causing loss of cell adhesion with resultant blister formation (Stanley, 1995). Complementary DNA cloning of pemphigus autoantigens indicated that both pemphigus vulgaris (PV) and pemphigus foliaceus (PF) antigens are members of the cadherin family of cell adhesion molecules (desmoglein 3 and desmoglein 1, respectively) (Amagai *et al*, 1991; Amagai, 1995). PV is strongly associated with the human leukocyte antigen (HLA)-DR4 serologic specificity among Ashkenazi Jews, and with DR4 as well as DR6 specificities in other ethnic groups (Szafer *et al*, 1987). More recent studies utilizing DNA typing have suggested that the HLA-DR4 association with PV largely involves DR4 haplotypes bearing HLA-DRB1*0402, DQA1*0301, and DQB1*03 alleles (Matzner *et al*, 1995). DR6 susceptibility is associated with DRB1*14, DQA1*0101, and DQB1*0503 alleles (Sinha *et al*, 1988).

Thus, class II HLA genes are thought to play a role in predisposition to PV. Few studies, however, have examined polymorphism at the molecular level now recognized for HLA-DR and DQ loci (Marsh and Bodmer, 1995), although Scharf *et al* (1988a, b, 1989) and Wucherpfennig *et al* (1995) reported significant associations of the amino acid residues at positions 67–71 of DRB1 as well as at position 57 of the DQB1 chains with disease susceptibility. There have been no molecular analyses of the polymorphic HLA-DR and DQ chains in PV patients with ethnic backgrounds other than Jewish and non-Jewish Caucasians, and no study has examined the HLA class II polymorphism in PF.

In a related disease, endemic pemphigus foliaceus (*fogo selvagem*), which is an autoimmune bullous disease mediated by antidesmoglein 1 antibodies (Olague-Alcala *et al*, 1994), has been associated with HLA-DRB1*01, *0404, *1402, and *1406 alleles in Brazilian populations. All these alleles share an amino acid sequence at position 67–74 on the third hypervariable region of the DRB1 gene (Moraes *et al*, 1997).

In this study we investigated fine specificities of the HLA class II alleles DRB1, DQA1, and DQB1 in Japanese patients with PV or PF.

PATIENTS AND METHODS

Patient population The subjects in this study were 16 unrelated Japanese patients with pemphigus (nine PV and seven PF). In all patients, histopathologic examination of a biopsy specimen revealed suprabasilar (PV) or superficial (PF) acantholytic cleft within the epidermis. Direct immunofluorescence of perilesional skin showed intercellular deposition of IgG and/or C3. Indirect immunofluorescence using normal human skin as a substrate showed anti-intercellular-substance antibodies at various titers.

HLA studies Genomic DNA was isolated from peripheral blood leukocytes and typed for HLA class II (DRB1, DQA1, DQB1, and DPB1) alleles using the polymerase chain reaction-restriction fragment length polymorphism method as previously described (Maeda *et al*, 1989; Fukumori *et al*, 1992; Kaneshige *et al*, 1994; Senger and Goldstein, 1994) with the addition of several endonucleases to detect the class II alleles officially updated by the WHO Nomenclature Committee (Bodmer *et al*, 1995). Normal controls for HLA typing consisted of 525 unrelated race matched subjects (Yasunaga *et al*, 1996). DRB1-DQA1-DQB1 haplotypes were assigned on the basis of known linkage disequilibria in Japanese (Hashimoto *et al*, 1994; Yasunaga *et al*, 1996). The HLA class II region sequences included in this study were taken from a previous publication (Marsh and Bodmer, 1995).

Manuscript received December 27, 1996; revised July 8, 1997; accepted for publication July 18, 1997.

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Abbreviations: HLA, human leukocyte antigen; MHC, major histocompatibility complex; PF, pemphigus foliaceus; PV, pemphigus vulgaris.

Table I. HLA class II DRB1*04- and DRB1*14-associated haplotypes are increased in Japanese patients with pemphigus

Class II HLA genotype	Patients with pemphigus: PV (n = 9)[a]	PF (n = 7)	Total (%) (n = 16)[b]	Normal control (%) (n = 525)
DRB1*-DQA1*-DQB1*				
0403–0301–0302	1	1	2 (12.5)	3.8
0406–0301–0302	5	2	7 (43.8)[c]	6.7
1401–0104–0502	0	1	1 (6.3)	2.1
1401 (or 1405)-0104–05031	4	1	5 (31.2)[d]	4.7
1406–0503–0301	1	0	1 (6.3)	4.8[f]
DRB1 *0406	5	2	7 (43.8)[c]	6.7
*1401	1	2	3 (18.8)[e]	3.6
*1405	3	0	3 (18.8)[e]	3.2
DQA1 *0104	4	2	6 (37.5)[c]	7.2
*0301	5	3	8 (50.0)[d]	15.2
DQB1*05031	4	1	5 (31.2)[d]	4.8
*0302	5	3	8 (50.0)[d]	17.1

[a] n is the number of patients and controls examined.
[b] The p values were determined by Fisher's exact test comparing percentages of patients and controls positive for a haplotype or an allele. The respective numbers of patients with PV or PF were too small for meaningful statistical analysis.
[c] $p < 0.001$ with corrected $p < 0.05$.
[d] $p < 0.01$ with corrected $p < 0.05$.
[e] $p < 0.05$.
[f] Frequency of DRB1*14 (*1402, *1403, or *1406)-DQA1*0503-DQB1*0301.

Statistical analysis Allele and haplotype frequencies were compared between pemphigus patients and control subjects. Fisher's exact test was employed for statistical comparisons; p values were corrected for the number of alleles tested for each locus (DRB1 = 38, DQA1 = 14, DQB1 = 15, DPB1 = 60) or for the number of haplotypes found in Japanese populations (DRB1-DQA1-DQB1 = 40) (Hashimoto *et al*, 1994; Yasunaga *et al*, 1996).

RESULTS

Increase of DRB1*0406-DQA1*0301-DQB1*0302 and DRB1*-14DQA1*0104-DQB1*05031 haplotypes in Japanese patients with pemphigus Sixteen patients with pemphigus (nine PV and seven PF) were typed for major histocompatibility complex (MHC) class II HLA alleles by the polymerase chain reaction-restriction fragment length polymorphism method. Results of a survey of pemphigus patients and controls for the presence of DRB1*04- and DRB1*14-associated haplotypes and alleles are summarized in **Table I**. The respective numbers of patients with PV or PF were too small for meaningful statistical analysis. The data for PV and PF were therefore combined. The DRB1*0403-DQA1*0301-DQB1*0302 haplotype showed an increased incidence (12.5%) in pemphigus patients compared with that in the normal control population (3.8%), but did not reach statistical significance. DRB1*0406-DQA1*0301-DQB1*0302 and DRB1*14 (*1401 or *1405)-DQA1*0104-DQB1*05031 as well as HLA class II alleles comprising these haplotypes were significantly increased among pemphigus patients as a whole.

It should be noted that all nine PV patients had at least one HLA-DP2 subtypes DPB1*0201 and *0202, although the increased phenotypic frequency of DPB1*02 alleles ($p < 0.02$; 100% in PV patients compared with 57.4% in the normal population; Hashimoto *et al*, 1994) proved to be insignificant after correction of the p value for the number of HLA-DPB1 alleles tested. This association was not observed in the group of PF patients.

Patients with pemphigus vulgaris carried one or two alleles of the DRB1*04 and DRB1*14 subtypes As shown in **Table II**, all nine PV patients had one or two alleles of the DRB1*04 and *DRB1*14 subtypes. The DRB1*0403 or *0406 allele carried by five PV patients (cases 1–5) was linked to the DQA1*0301-DQB1*0302 haplotype. The DRB1*1401 or *1405 allele, carried by four PV patients (cases 5–8), was linked to the rare HLA-DQ haplotype DQA1*0104-DQB1*05031. These HLA class II haplotypes are virtually those HLA-DR4-DQ8 and DR6 (DR14)-DQ5 haplotypes that were assumed earlier to be the dominantly expressed susceptibility haplotypes to PV in other ethnic groups (Ahmed *et al*, 1990, 1991). In one patient (case 9), the DRB1*1406 was linked to DQA1*0503-DQB1*0301. Two patients (cases 1 and 2) were homozygous for the DRB1*04-DQA1*0301-DQB1*0302, and one (case 5) was heterozygous for the DRB1*04-DQA1*0301-DQB1*0302 and DRB1*14-DQA1*0104-DQB1*05031.

Table II. The majority of pemphigus patients carry one or two alleles of HLA-DRB1*04 and DRB1*14 subtypes

No	Age/sex	DRB1	DQA1	DQB1	DPB1
Pemphigus vulgaris					
1	21/M	0406	0301	0302	0201
		0406	0301	0302	0501
2	71/F	0403	0301	0302	0501
		0406	0301	0302	0201
3	61/F	0406	0301	0302	0201
		0802	0401	0402	0201
4	54/M	0406	0301	0302	0201
		1101	0501	0301	0201
5	64/F	0406	0301	0302	4701
		1401	0104	05031	0202
6	39/M	1405	0104	05031	0201
		1302	0102	0604	0501
7	61/F	1405	0104	05031	0202
		08032	0103	0601	0501
8	64/F	1405	0104	05031	0201
		0802	0401	0402	0501
9	45/F	1406	0503	0301	0202
		08032	0103	0601	0501
Pemphigus foliaceus					
10	56/F	0403	0301	0302	0501
		1501	0501	0301	0201
11	85/F	0406	0301	0302	0201
		1502	0103	0601	0901
12	65/F	0406	0301	0302	0901
		1401	0104	05031	0501
13	73/M	1405	0104	05031	0501
		1602	0102	0502	0501
14	68/M	1401	0104	0502	0201
		0901	0302	0303	0501
15	72/M	1202	0601	0301	0501
		08032	0103	0601	0201
16	88/F	0901	0302	0303	0501
		0901	0302	0303	0501

The majority of patients with pemphigus foliaceus also carried one or two alleles of the DRB1*04 and DRB1*14

Table III. Fine specificities of DRB1*04, DRB1*14, and other selected DRB1 alleles found in patients with pemphigus[a]

DRB1*	Polymorphic DRB1 residue								Associated DQA1*-DQB1*
	26	37	57	67	70	71	74	86	
PV and PF patients									
0403	F	Y	D	L	Q	R	E	V	0301–0302
0406	F	S	D	L	Q	R	E	V	0301–0302
1401	F	F	A	L	R	R	E	V	0104–05031 (or 0104–0502)
1405	F	F	D	L	R	R	E	V	0104–05031
1406	F	N	D	L	Q	R	A	V	0503–0301
*PF patients negative for DRB1*04 and DRB1*14 alleles*									
08032	F	Y	S	I	D	R	L	G	0301–0302
0901	Y	N	V	F	R	R	E	G	0302–0303
1202	L	L	V	F	D	R	A	V	0601–0301
Associated with PV among Ashkenazi Jews									
0402	F	Y	D	I	D	E	A	V	0301–0302 (or 0301–0301)

[a]DRB1*1501, *1101, *1302, and *0802 that were found in heterozygosity with one of the HLA-DRB1*04 or DRB1*14 alleles are not listed in the table.

subtypes Three patients (cases 10–12) carried DRB1*04 (*0403 or *0406)-DQA1*0301-DQB1*0302 haplotype, respectively. Three patients carried DRB1*14-DQA1*0104, which was linked to DQB1*05031 (cases 12 and 13) or to DQB1*0502 (case 14). One patient (case 12) was heterozygous for the two PV-associated HLA class II haplotypes DRB1*04-DQA1*0301-DQB1*0302 and DRB1*14-DQA1*0104-DQB1*05031. There were two exceptions: one patient (case 15) carried the DRB1*1202-DQA1*0601-DQB1*0301 and DRB1*08032-DQA1*0103-DQB1*0601, and another (case 16) was homozygous for HLA-DRB1*0901-DQA1*0302-DQB1*0303, making identification of the susceptible class II haplotype ambiguous.

Importance of class II HLA-DR and -DQ polymorphic amino acid residues The presence of HLA-DRB1*04 (*0403, *0406), DRB1*14 (*1401, *1405, *1406), or both alleles in all nine PV patients suggests that amino acid sequences shared by these HLA-DRB1 molecules represent the primary MHC class II association with anti-PV antigen response. Four polymorphic amino acid residues are shared by the HLA-DRB1*0403 and *0406 alleles, including phenylalanine at position 26 (Phe^{26}), leucine at position 67 (Leu^{67}), arginine at position 71 (Arg^{71}), and valine at position 86 (Val^{86}). All of these amino acid residues are also shared by DRB1*1401, *1405, and *1406 (**Table III**), and 14 (nine PV and five PF) of 16 pemphigus patients shared these four polymorphic amino acid residues in the hypervariable regions of their respective DRB1 chain.

There was no sharing of polymorphic amino acid residues among DQA1 (*0104, *0301, *0503) or among DQB1 (*05031, *0502, *0301, *0302) alleles that were in linkage disequilibrium with the DRB1*04 or DRB1*14 alleles.

DISCUSSION

It is well known that some alleles of the MHC complex confer a strong susceptibility to PV (Hameed and Ahmed, 1993). Among Ashkenazi Jews, the alleles commonly associated with PV are DR4 and DQ8 (DQB1*0302) (Szafer *et al*, 1987; Scharf *et al*, 1988a, b; Ahmed *et al*, 1990. In other ethnic groups, including non-Ashkenazi Jews, Caucasians and Japanese, susceptibility to PV is linked to DR4 as well as DR6 and DQ5 (Szafer *et al*, 1987, 1988a, b, 1989; Ahmed *et al*, 1991; Niizeki *et al*, 1994). Reohr *et al* (1992) studied the MHC of two sisters with PV by restriction fragment length polymorphism and found that the sisters shared DR4 and DQw3.2 (DQB1*0302) alleles. Revenga-Arranz *et al* (1996) also reported two brothers with PV who shared homozygous DR4/DQ3 haplotypes. Ahmed *et al* (1993) found that the presence of antibodies to PV antigens at low antibody levels in asymptomatic relatives of PV patients was linked to DR4 or DR6 haplotypes. They postulated that these class II HLA alleles would confer a predisposition to PV, but that a second trigger would be necessary to develop the disease.

Although the number of patients was small and additional studies are warranted, our data supported these previous studies showing that all nine Japanese PV patients carried one or two of the HLA-DR4 or DR6 (DR14) haplotypes. Five patients (56%) carried the HLA-DRB1*04-DQA1*0301-DQB1*0302 (DR4/DQ8), and two were homozygous for this haplotype. Five patients (56%) carried HLA-DRB1*1401, *1405, or *1406, which all constitute HLA-DR6 specificity. One patient had the class II haplotype DRB1*0406-DQA1*0301-DQB1*0302 in heterozygosity with DRB1*1401-DQA1*0104-DQB1*05031.

There were some discrepancies, however, regarding the DR4 and DR6 (DR14) subtypes between our findings and those of other groups. Jewish and non-Jewish Caucasian PV patients so far studied have the HLA-DR4 subtype DRB1*0402 (Matzner *et al*, 1995; Wucherpfennig *et al*, 1995), whereas in our study PV was associated with DRB1*0406 and to a much lesser extent DRB1*0403. Similary, previous studies show that the DR6 (DR14) association with PV is due to linkage with DQB1*0503 (Sinha *et al*, 1988; Niizeki *et al*, 1994). In our patients, DRB1*1401 and *1405 alleles were in linkage disequilibrium with the rare allele DQB1*05031, whereas the DRB1*1406 was linked to DQB1*0301.

In Jewish as well as non-Jewish Caucasian patients, sequence analyses of the alleles conferring susceptibility to PV revealed amino acid changes at positions 67–71 of the DRB1, and at position 57 of the DQB1 chain (Sinha *et al*, 1988; Scharf *et al*, 1988b, 1989; Wucherpfennig *et al*, 1995). It is speculated that a change in amino acid charge at these positions of the MHC class II β chain, which are thought to come in contact with peptides and T-cell receptors during antigen presentation, may affect the structure of the MHC peptide-binding groove and alter recognition of the MHC peptide complex by the T cells.

The amino acid changes (Leu^{67}, Arg^{70} or Gln^{70}, and Arg^{71}) on DRB1*04 as well as DRB1*14 alleles in the Japanese PV patients as shown in this study (**Table III**) suggest different associations of the HLA class II polymorphism with PV among different ethnic groups. Scharf *et al* (1988b), in a study involving DR4-positive Jewish PV patients, suggested that three amino acid residues (Ile^{67}, Asp^{70}, and Glu^{71}, which were originally described as Ile^{68}, Asp^{71}, and Glu^{72} but were corrected according to recently published data on HLA class II region nucleotide sequences; Marsh and Bodmer, 1995) on the DRB1 chain may be responsible for the association of HLA-DR4 and disease susceptibility. Similarly, according to Wucherpfennig *et al* (1995), the negatively charged Asp^{70} and Glu^{71} on the DRB1*0402 chain appears to be a critical determinant of MHC-linked susceptibility to PV among Ashkenazi Jews.

Correlation of disease susceptibility to PV with aspartic acid at amino acid residue 57 of DQB1*05031 has also been proposed (Sinha *et al*, 1988; Scharf *et al*, 1988a). As shown in **Table I**, four of our nine PV patients (44%) had the rare DQB1*05031 allele in linkage disequilibrium with DRB1*14. Thus, our results may reflect the importance of DQB1-Asp^{57} in the function of the DQ molecule. This model, however, was insufficient to explain the genetic predisposition to PV in our patients: two PV patients were homozygous for DQB1*0302 which carry Ala^{57} instead of Asp^{57}.

Finally our data, together with previous studies on Jewish and non-Jewish Caucasian patients, suggest that DRB1*04 as well as DRB1*14 alleles are commonly associated with PV across racial barriers. These alleles are also carried by the majority, but not all, of patients with PF including *fogo selvagem*. Similar HLA class II distributions between PV and PF patients might be explained by the fact that the PV antigen (desmoglein 3) has marked immunochemical homology with the PF antigen (desmoglein 1): ≈50% of PV sera recognize both PV and PF antigens at the same time, although clinical manifestation reflects one expression (Eyre and Stanley, 1988; Hashimoto *et al*, 1990; Olague-Alcala *et al*, 1994); and cDNA cloning has demonstrated that the autoantigens of PV and PF show significant amino acid sequence homology, both belonging to the cadherin family of cell adhesion

molecules (Amagai *et al*, 1991; Amagai, 1995). Furthermore, certain PV sera as well as PF sera recognize desmocollins I and II, other members of transmembrane components of desmosomal cadherins (Dmochowski *et al*, 1993; North *et al*, 1996).

Sequence analysis of the DRB1*04 and DRB1*14 alleles that were carried by Japanese PV patients revealed the amino acid homology of Phe^{26} and Val^{86} with the DRB1*0402 allele that reportedly confers a strong susceptibility to PV in other ethnic groups including Ashkenazi Jews and Caucasians (Ahmed *et al*, 1990; Hameed and Ahmed, 1993). Additional direct evidence that these class II alleles mediate the autoimmune responses is needed, such as the demonstration of a portion of the desmogleins in the antigen binding cleft of these HLA-DR chains.

We thank Drs Katsushi Tokunaga (University of Tokyo) and Toshihiko Kaneshige (Shionogi Biomedical Laboratories) for critical discussion.

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