

Allele frequency and the associations of HLA-DRB1 and HLA-DQB1 polymorphisms with pemphigus subtypes and disease severity

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Abstract

Pemphigus is a rare, devastating, bullous autoimmune disease that damages the skin and mucous membranes, and has high morbidity and mortality. Studies have shown associations of pemphigus vulgaris (PV) and pemphigus foliaceus (PF) with human leukocyte antigen (HLA) class II polymorphisms.

This study examined the frequency of Major Histocompatibility Complex, Class II, DR Beta 1, a Protein Coding gene (HLA-DRB1) and Major Histocompatibility Complex, Class II, DQ Beta 1 (HLA-DQB1) alleles in Vietnamese PV and PF patients, and the association of these polymorphisms with pemphigus subtypes and disease severity.

The study enrolled 31 unrelated Vietnamese who underwent HLA typing using Sanger sequencing.

HLA-DRB1*14:54 was the most frequent allele in both PV (20.5%) and PF (33.3%) patients. The percentage of HLA-DQB1*03:02 was significantly higher in PF than PV patients, while the percentage of HLA-DQB1*05:03 was approximately 10 times higher in PV patients. Pemphigus patients who have the HLA-DRB1*04 alleles are more likely to have mild or moderate disease.

The HLA-DRB1 and DQB1 alleles may influence susceptibility to pemphigus subtypes, with DQB1*05:03 being specific for PV and DQB1*03:02 for PF. Our findings suggest that the DRB1*04 alleles are likely to be associated with mild and moderate disease.

Abbreviations: HLA = human leukocyte antigen, PDAI = pemphigus disease area index, PF = pemphigus foliaceus, PV = pemphigus vulgaris.

Keywords: HLA-DQB1, HLA-DRB1, pemphigus foliaceus, pemphigus severity, pemphigus vulgaris

1. Introduction

Pemphigus is a rare, potentially devastating autoimmune disease targeting the skin and mucous membranes that has high morbidity and mortality.^[1] Its pathological mechanism is

attributed to the direct effect of autoantibodies on desmoglein antigens on the surface of keratinocytes, which disrupts cell–cell adhesion and causes the formation of intraepithelial blisters on the skin and mucosa.^[2] Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the 2 most common major clinical forms. The main target of antibodies in PV patients is desmoglein 3, while PF patients mostly possess autoantibodies against desmoglein 1.^[3] It has been suggested that the diseases result from genotype–environment interactions that regulate the autoimmune response to desmoglein antigens. Therefore, genetic susceptibility to pemphigus has been investigated worldwide.^[4]

Most genetic research on pemphigus has focused on the association between the disease and human leukocyte antigens (HLAs), especially HLA class II genes. Studies have shown that HLA class II polymorphisms make a significant contribution to the identification of desmoglein-derived peptides in PV and PF patients.^[5] Approximately 95% of pemphigus patients possess specific HLA-DRB1 or DQB1 alleles, which highlights the important role of these gene polymorphisms in the pathogenesis and invasion of the disease.^[4] While some HLA class II polymorphisms are population-specific, others have been reported to be universally associated with the pemphigus subtype. The 2 alleles most commonly associated with PV are DRB1*04:02 and DQB1*05:03.^[4] Associations of PV with DRB1*04:02 and DQB1*03:02 have been recorded in Jewish populations, whereas DQB1*05:03 was found to be more common in non-Jewish PV patients.^[2,6] Because of the heterogeneity in disease manifestations and progression among individual patients, HLA alleles are considered promising genetic markers of susceptibility to pemphigus.^[7]

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Due to privacy and ethical concerns, neither the data nor the source of the data can be made available.

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Due to the rarity of the disease, little is known about the genotypic characteristics of Vietnamese pemphigus patients. This study examined the frequency of HLA class II DRB1 and DQB1 alleles in Vietnamese PV and PF patients, and investigated the associations of these polymorphisms with pemphigus subtypes and disease severity.

2. Methods

2.1. Study subjects

The study was performed at Ho Chi Minh City Hospital of Dermato-Venereology from November 2019 to June 2020. The study was designed to find any associations between HLA-DRB1 or DQB1 alleles and the pemphigus subtypes (PV and PF) and the disease severity in both subtypes. Thirty-one unrelated Vietnamese aged 18 years or older were confirmed diagnosis of PV or PF based on clinical manifestations, histopathological results with superficial epidermal blistering formation within the stratum granulosum for PF or intraepidermal acantholysis within the suprabasal epidermis for PV, and a direct immunofluorescence test proving the presence of immunoglobulin G (IgG) at the intercellular borders of the epidermis within the superficial layers of the epidermis for PF and within the lower suprabasal epidermis for PV before enrolled in the study. Patients were excluded if they had previously undergone allogeneic stem cell transplantation or had other coexisting autoimmune diseases. All patients did not receive specific treatment for pemphigus before enrollment in the study.

Eligible patients were invited to participate in the study and underwent clinical evaluation by a research doctor. Their baseline characteristics, including age, age of onset, and sex, were recorded during an interview. Disease activity was assessed using the Pemphigus Disease Area Index (PDAI) score which representing for disease activity and disease damage. The PDAI score is ranging from 0 to 263 points (120, 10, 120 points for skin, scalp, and mucosal activity respectively and 13 points for postinflammatory hyperpigmentation).^[8] The disease severity was categorized to 3 levels: mild as PDAI scores were less than 15, moderate as PDAI scores were range from 15 to 44, and severe as PDAI scores were from 45 to 263.^[9]

2.2. DNA extraction

Two milliliters of peripheral blood was collected from each patient in an EDTA-K2 anticoagulant tube. Genomic DNA was extracted by using a GeneJET Whole Blood Genomic DNA Purification Mini Kit (Thermo Scientific, Waltham, MA, USA).

2.3. Sequencing

PCR amplification and target gene sequencing were performed using primers designed based on the DNA sequences of HLA-DRB1 (acc. no. NG_002392) and HLA-DQB1 (acc. no. NG_02922), according to the National Center for Biotechnology Information and Lazaro et al.^[10]

Sanger sequencing was performed using POP-7 Polymer and a 50-cm capillary array on an ABI 3500 Genetic Analyser (Applied Biosystems, USA). The sequences were analyzed using CLC Main Workbench software, and Basic Local Alignment Search Tool software (European Bioinformatics Institute) was used to identify HLA-DRB1 and HLA-DQB1 alleles.

2.4. Statistical analysis

Continuous data are presented as the mean \pm standard deviation or median with interquartile range depending on the normality of the distribution. Categorical data are described as the frequency and percentage. Quantitative variables were analyzed with Student *t* test. Fisher exact test was used to compare allele frequencies between pemphigus subtypes. Findings were considered significant at a 2-sided *P* value $< .05$. All statistical analyses were performed using R software (ver. 4.0.2; R Development Core Team, Austria).

2.5. Ethical issues

This study was approved by the Biomedical Research Ethics Review Committee of the University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam (Approval no. 593/DHYD-HDDD, November 4, 2019). Informed consent was obtained from all participants.

3. Results

3.1. Participant epidemiological characteristics

Thirty-one pemphigus patients, 22 PV and 9 PF, were enrolled in the study. Table 1 showed the patient's epidemiological data, including age, gender, age of onset, PDAI score, and disease severity classification. The average age of the patients was 51.55 ± 15.40 years (range: 23–83 years). Most participants had been diagnosed around 1 year before this study, with a mean age of onset of 50.19 ± 15.67 years. Most patients were female (74.2%). Participants with PV had more severe disease than PF patients (91.0% vs. 55.6% classified as severe).

3.2. Allele frequencies

The frequencies of HLA-DRB1 and HLA-DQB1 alleles were summarized in Table 2. HLA-DRB1*14:54 was the most frequent allele in both PV (20.5%) and PF patients (33.3%). Regarding HLA-DQB1, DQB1*05:03 (31.8%) was the most frequent allele in PV patients, while DQB1*03:01 and DQB1*03:02 (27.8% each) were the most prevalent among PF patients. The second-most frequent HLA-DQB1 allele was DQB1*03:01 (29.5%) among PV patients and DQB1*05:02 (22.2%) among PF patients.

3.3. HLA-DRB1 and HLA-DQB1 polymorphisms and pemphigus subtypes

Table 3 compared the HLA-DRB1 and HLA-DQB1 polymorphisms between the 2 groups of pemphigus subtypes. Our study indicated no significant difference in the percentage of HLA-DRB1 alleles between the 2 pemphigus subtypes. The percentage of HLA-DQB1*03:02 was significantly ($P = .01$) higher in PF patients (55.6%) than PV patients (9.1%). Patients with DQB1*03:02 were less likely to develop PV than PF [odds ratio (OR) = 0.09; 95% confidence interval (CI): 0.01–0.61]. Conversely, the percentage of HLA-DQB1*05:03 in PV patients (59.1%) was approximately 10 times higher than in PF patients (11.1%) (OR = 9.73; 95% CI: 1.38–276.20; $P = .02$).

Table 1
Participants' epidemiological characteristics.

Characteristics	PV (N=22)	PF (N=9)	Total (N=31)
Age	49.73 ± 13.78 (30.00–83.00)	56.00 ± 18.97 (23.00–80.00)	51.55 ± 15.40 (23.00–83.00)
Age of onset	48.27 ± 13.63 (28.00–81.00)	54.89 ± 19.95 (22.00–79.00)	50.19 ± 15.67 (22.00–81.00)
Sex			
Male	6 (27.3)	2 (22.2)	8 (25.8)
Female	16 (72.7)	7 (77.8)	23 (74.2)
PDAI score	76.14 ± 25.91 (14.00–121.00)	54.11 ± 35.37 (12.00–135.00)	69.74 ± 30.11 (12.00–135.00)
Disease severity classification			
Mild	1 (4.5)	1 (11.1)	2 (6.5)
Moderate	1 (4.5)	3 (33.3)	4 (12.9)
Severe	20 (91.0)	5 (55.6)	25 (80.6)

N=number of patients, PDAI score=Pemphigus Disease Area Index score, PF=pemphigus foliaceus, PV=pemphigus vulgaris.

3.4. Association between HLA-DRB1 and HLA-DQB1 polymorphisms and disease severity

The relationship of the PDAI score and the presently studied HLA alleles was demonstrated in Table 4. For convenience of

identification, we called the group of patients having at least 1 specific allele of DRB1 or DQB1 the “with allele” group, and group of patients without that specific DRB1 or DQB1 allele the “without allele” group. In both DRB1 and DQB1 phenotypes,

Table 2
Frequencies of HLA-DRB1 and HLA-DQB1.

	PV (n=44)	PF (n=18)	Total (n=62)
HLA-DRB1			
14:54	9 (20.5)	6 (33.3)	15 (24.2)
03:02	3 (6.8)	1 (5.6)	4 (6.5)
14:04	2 (4.5)	2 (11.1)	4 (6.5)
03:01	2 (4.5)	2 (11.1)	4 (6.5)
04:04	3 (6.8)	0 (0.0)	3 (4.8)
08:03	1 (2.3)	2 (11.1)	3 (4.8)
13:07	2 (4.5)	0 (0.0)	2 (3.2)
14:01	2 (4.5)	0 (0.0)	2 (3.2)
14:03	2 (4.5)	0 (0.0)	2 (3.2)
14:12	2 (4.5)	0 (0.0)	2 (3.2)
15:02	2 (4.5)	0 (0.0)	2 (3.2)
16:02	2 (4.5)	0 (0.0)	2 (3.2)
04:03	2 (4.5)	0 (0.0)	2 (3.2)
07:01	1 (2.3)	1 (5.6)	2 (3.2)
08:02	1 (2.3)	1 (5.6)	2 (3.2)
08:08	1 (2.3)	0 (0.0)	1 (1.6)
11:01	1 (2.3)	0 (0.0)	1 (1.6)
12:02	1 (2.3)	0 (0.0)	1 (1.6)
13:03	1 (2.3)	0 (0.0)	1 (1.6)
14:05	1 (2.3)	0 (0.0)	1 (1.6)
14:06	1 (2.3)	0 (0.0)	1 (1.6)
15:03	1 (2.3)	0 (0.0)	1 (1.6)
16:01	1 (2.3)	0 (0.0)	1 (1.6)
04:05	0 (0.0)	1 (5.6)	1 (1.6)
04:06	0 (0.0)	1 (5.6)	1 (1.6)
04:07	0 (0.0)	1 (5.6)	1 (1.6)
HLA-DQB1			
03:01	13 (29.5)	5 (27.8)	18 (29.0)
05:03	14 (31.8)	1 (5.6)	15 (24.2)
05:02	8 (18.2)	4 (22.2)	12 (19.4)
03:02	2 (4.5)	5 (27.8)	7 (11.3)
02:02	5 (11.4)	0 (0.0)	5 (8.1)
02:01	1 (2.3)	1 (5.6)	2 (3.2)
03:03	1 (2.3)	0 (0.0)	1 (1.6)
03:09	0 (0.0)	1 (5.6)	1 (1.6)
05:01	0 (0.0)	1 (5.6)	1 (1.6)

HLA=human leukocyte antigen, n=number of alleles, PF=pemphigus foliaceus, PV=pemphigus vulgaris.

Table 3
Associations of HLA-DRB1 and HLA-DQB1 polymorphisms with pemphigus subtypes.

	PV (N=22)	PF (N=9)	OR (CI 95%)	P
HLA-DRB1				
03:01	2 (9.1)	2 (22.2)	0.36 (0.03–4.05)	.56
03:02	3 (13.6)	1 (11.1)	1.17 (0.11–37.20)	1.0
04:03	1 (4.5)	2 (22.2)	0.19 (0.01–2.65)	.19
04:04	2 (9.1)	0 (0.0)		1.0
04:05	0 (0.0)	1 (11.1)		.29
04:06	0 (0.0)	1 (11.1)		.29
04:07	0 (0.0)	1 (11.1)		.29
07:01	1 (4.5)	1 (11.1)	0.39 (0.01–16.65)	.50
08:02	1 (4.5)	0 (0.0)		1.0
08:03	2 (9.1)	0 (0.0)		1.0
08:08	1 (4.5)	0 (0.0)		1.0
11:01	1 (4.5)	0 (0.0)		1.0
12:02	1 (4.5)	1 (11.1)	0.39 (0.01–16.65)	.50
13:03	1 (4.5)	0 (0.0)		1.0
13:07	2 (9.1)	1 (11.1)	0.77 (0.05–26.41)	1.0
14:01	2 (9.1)	0 (0.0)		1.0
14:03	2 (9.1)	0 (0.0)		1.0
14:04	3 (13.6)	0 (0.0)		.53
14:05	1 (4.5)	0 (0.0)		1.0
14:06	1 (4.5)	0 (0.0)		1.0
14:12	2 (9.1)	0 (0.0)		1.0
14:54	8 (36.4)	5 (55.6)	0.47 (0.09–2.38)	.32
15:02	2 (9.1)	0 (0.0)		1.0
15:03	1 (4.5)	0 (0.0)		1.0
16:01	1 (4.5)	0 (0.0)		1.0
16:02	2 (9.1)	0 (0.0)	0.36 (0.03–4.05)	1.0
HLA-DQB1				
02:01	1 (4.5)	1 (11.1)	0.39 (0.01–16.65)	.50
02:02	4 (18.2)	0 (0.0)		.29
03:01	9 (40.9)	4 (44.4)	0.87 (0.17–4.58)	1.0
03:02	2 (9.1)	5 (55.6)	0.09 (0.01–0.61)	.01
03:03	1 (4.5)	0 (0.0)		1.0
03:09	0 (0.0)	1 (11.1)		.29
05:01	0 (0.0)	1 (11.1)		.29
05:02	6 (27.3)	4 (44.4)	0.48 (0.09–2.64)	.41
05:03	13 (59.1)	1 (11.1)	9.73 (1.38–276.20)	.02

CI=confidence interval, HLA=human leukocyte antigen, N=number of patients, OR=odds ratio, P=P value, PF=pemphigus foliaceus, PV=pemphigus vulgaris. Bold values are statistically significant.

Table 4
Associations of HLA-DRB1 and HLA-DQB1 polymorphisms with PDAI score.

Allele	PDAI score		P
	With allele	Without allele	
HLA-DRB1			
03	65.00 ± 38.34	71.39 ± 27.53	.67
04	49.00 ± 20.89	73.73 ± 30.26	.06
13	71.25 ± 16.54	69.52 ± 31.85	.87
14	70.68 ± 30.92	67.44 ± 29.70	.78
HLA-DQB1			
02	75.17 ± 24.60	68.44 ± 31.59	.58
03	63.10 ± 31.30	81.82 ± 24.70	.07
05	69.05 ± 32.53	71.44 ± 24.87	.82

HLA=human leukocyte antigen, P=P value, PDAI score=Pemphigus Disease Area Index score.

there was no difference in the PDAI score between 2 groups with allele and without allele.

However, when disease severity was categorized according to the PDAI score, the percentage of the HLA-DRB1*04 allele was higher in mild/moderate patients (50.0%) than in the severe group (8.0%). Pemphigus patients with the HLA-DRB1*04 allele were more likely to have mild or moderate disease (OR=9.91; 95% CI: 1.11–116.78; P=.04; Table 5).

4. Discussion

This is the first study to compare HLA-DRB1 and DQB1 polymorphisms between the 2 main pemphigus subtypes (PV and PF) in Vietnamese patients. The mean age of our patients (51.55 ± 15.40 years) was similar to other cohort studies of genetic polymorphisms in HLA associated with pemphigus subtypes, such as Zhang et al^[11] (49.3 ± 13.5 years) in China and Aboobaker et al^[12] in South Africa (43 years; range: 12–93 years). A female predominance of pemphigus, reflected in our study by a 3:1 female-to-male ratio, has been reported worldwide.^[13,14]

The most frequent HLA-DRB1 allele in both pemphigus subtypes was DRB1*14:54. DRB1*14 alleles were found in

43.5% of the participants. This was similar to Dere et al,^[15] who reported that the 2 most prevalent alleles in Turkish pemphigus patients were DRB1*04 (41.7%) and DRB1*14 (25.0%). Studies in other Asian countries have provided inconsistent results. A Korean study reported that the most common HLA-DRB1 allele was DRB1*01 in PV patients (60.0%) and DRB1*04 (73.3%) in PF patients.^[16] Niizeki et al^[17] examined HLA polymorphisms in Japanese patients and found that the most common alleles were DRB1*14:01, DRB1*14:05, DRB1*04:06, DRB1*14:06, and DRB1*14:08. In Europe, the DRB1*14:54 allele was reported to be prevalent. Svecova et al^[7] found that the most common HLA-DRB1 alleles in Slovaks were DRB1*04:02, DRB1*04:04, DRB1*14:54, DRB1*14:04, and DRB1*14:05. A study of White British and Indo-Asian pemphigus patients reported that the most prevalent HLA-DRB1 alleles were DRB1*04:02 and DRB1*14:54.^[18] Note that DRB1*14:54 was included in DRB1*14:01 until it was acknowledged as a distinct allele in 2005 by the World Health Organization Nomenclature Committee, due to a difference in exon 3 of gene DRB1. Concerns have been raised that the DRB1*14:01 characterized in studies conducted before 2005 may actually be DRB1*14:54.^[7,18]

The most frequent HLA-DQB1 allele in the PV patients in our study was DQB1*05:03, while in PF patients the most common allele was DQB1*03:02. This is in line with a Japanese study in which the DQB1*05:03 allele also accounted for the largest proportion (27.5%) among PV patients.^[17] Loiseau et al^[5] reported a high percentage of the DQB1*05:03 allele (25.7%), which was the second-most common allele in French PV patients, and found that DQB1*03:02 was the most frequent allele in their PF patients. Abida et al^[19] concluded that DQB1*03:02 might be a common susceptibility allele for pemphigus worldwide.

In our study, the percentage of the DQB1*03:02 allele in the PF group was significantly higher than in the PV group; this is consistent with Zhang et al,^[11] who also concluded that DQB1*03:02 is specific for the PF subtype among Chinese. This characteristic is stable across ethnicities. In a study of white British patients, Saha et al^[20] found that DQB1*03:02 was a susceptibility allele for PF (OR=5.35; 95% CI: 2.38–12.1). In Tunisia, Abida et al^[19] found a specific association between DQB1*03:02 and PF, while DQB1*05:03 was possibly specific

Table 5
Associations of HLA-DRB1 and HLA-DQB1 polymorphisms with disease severity.

Allele	Mild/moderate (N=6)	Severe (N=25)	OR (CI 95%)	P
HLA-DRB1				
03	2 (33.3)	6 (24.0)	1.59 (0.16–11.28)	.63
04	3 (50.0)	2 (8.0)	9.91 (1.11–116.78)	.04
07	0 (0.0)	2 (8.0)		1.0
08	1 (16.7)	2 (8.0)	2.34 (0.07–34.51)	.49
11	0 (0.0)	1 (4.0)		1.0
12	0 (0.0)	2 (8.0)		1.0
13	0 (0.0)	4 (16.0)		.56
14	4 (66.7)	18 (72.0)	0.77 (0.11–7.31)	.79
15	0 (0.0)	2 (8.0)		1.0
16	0 (0.0)	2 (8.0)		1.0
HLA-DQB1				
02	0 (0.0)	6 (24.0)		.31
03	6 (100.0)	14 (56.0)		.06
05	5 (83.3)	17 (68.0)	2.11 (0.26–62.57)	.64

CI=confidence interval, HLA=human leukocyte antigen, N=number of patients, OR=odds ratio, P=P value. Bold values are statistically significant.

for PV, as the proportion of this allele in the PV group (31.8%) was significantly higher than in the PF group (5.6; OR=6.91; 95% CI: 1.20–178.61). However, Zhang et al^[11] showed that allele DQB1*05:03 is shared by both pemphigus subtypes in Chinese patients.

Since the natural history of pemphigus is frequently unpredictable, it is desirable to identify biomarkers that can predict the clinical outcome and thus improve treatment. Our study showed that the HLA phenotype was not relevant to the PDAI score. However, a study was conducted on 54 Indian PV patients by Priyadarshini, demonstrated that HLA-DQB1* 03 was significantly associated with higher PDAI scores ($P=.02$).^[12] In Slovakia, Svecova et al^[7] examined 44 PV patients and proposed that the DRB1*04:02 and DQB1*03:02 alleles were common in severe patients ($P=.001$), contrary to our finding that DRB1*04 alleles were relative to mild/moderate level. These results suggest that HLA class II polymorphisms are promising predictors of prognosis. However, the findings are not fully consistent, probably due to differences in research populations, since ethnicity influences susceptibility or resistance to PV via direct involvement of HLA molecules, which act as antigen presenters or neighbour a linked gene.^[22,23]

The main limitation of this study was the relatively small number of participants, due to the rarity of the disease. As the majority of participants had severe disease, the association between alleles and disease severity may be biased. Multicentre studies with more subjects are needed to confirm our findings and obtain more comprehensive data on pemphigus patients.

5. Conclusions

The HLA-DRB1 and DQB1 alleles may influence the susceptibility to pemphigus subtypes. We found that DRB1*14:54, DQB1*05:03, DQB1*03:01, and DQB1*03:02 were the most frequent alleles in Vietnamese PV and PF patients, of which DQB1*05:03 was specific for PV and DQB1*03:02 was specific for PF. The findings suggest that the DRB1*04 alleles might be associated with mild and moderate disease.

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References

- [1] Pollmann R, Schmidt T, Eming R, Hertl M. Pemphigus: a comprehensive review on pathogenesis, clinical presentation and novel therapeutic approaches. *Clin Rev Allergy Immunol* 2018;54:1–25.
- [2] Vodo D, Sarig O, Sprecher E. The genetics of pemphigus vulgaris. *Front Med* 2018;5:226.
- [3] Walter E, Vielmuth F, Wanuske M-T, et al. Role of Dsg1- and Dsg3-mediated signaling in pemphigus autoantibody-induced loss of keratinocyte cohesion. *Front Immunol* 2019;10:1128.
- [4] Sinha AA. The genetics of pemphigus. *Dermatol Clin* 2011;29:381–91.
- [5] Loiseau P, Leclach L, Prost C, et al. HLA class II polymorphism contributes to specify desmoglein derived peptides in pemphigus vulgaris and pemphigus foliaceus. *J Autoimmun* 2000;15:67–73.
- [6] Ahmed AR, Wagner R, Khatri K, et al. Major histocompatibility complex haplotypes and class II genes in non-Jewish patients with pemphigus vulgaris. *Proc Natl Acad Sci U S A* 1991;88:5056–2060.
- [7] Svecova D, Parnicka Z, Pastyrikova L, Urbancek S, Luha J, Buc M. HLA DRB1* and DQB1* alleles are associated with disease severity in patients with pemphigus vulgaris. *Int J Dermatol* 2015;54:168–73.
- [8] Rosenbach M, Murrell DF, Bystry J-C, et al. Reliability and convergent validity of two outcome instruments for pemphigus. *J Invest Dermatol* 2009;129:2404–10.
- [9] Boulard C, Duvert Lehemre S, Picard-Dahan C, et al. Calculation of cut-off values based on the ABSIS and PDAI pemphigus scoring systems for defining moderate, significant and extensive types of pemphigus. *Br J Dermatol* 2016;175:142–9.
- [10] Lazaro A, Tu B, Yang R, Xiao Y, Kariyawasam K, Ng J. Human leukocyte antigen (HLA) typing by DNA sequencing. *Methods Mol Biol* 2013;1034:161–95.
- [11] Zhang SY, Zhou XY, Zhou XL, et al. Subtype-specific inherited predisposition to pemphigus in the Chinese population. *Br J Dermatol* 2019;180:828–35.
- [12] Aboobaker J, Morar N, Ramdial PK, Hammond MG. Pemphigus in South Africa. *Int J Dermatol* 2001;40:115–9.
- [13] Alpsyoy E, Akman-Karakas A, Uzun S. Geographic variations in epidemiology of two autoimmune bullous diseases: pemphigus and bullous pemphigoid. *Arch Dermatol Res* 2015;307:291–8.
- [14] Gupta VK, Kelbel TE, Nguyen D, et al. A globally available internet-based patient survey of pemphigus vulgaris: epidemiology and disease characteristics. *Dermatol Clin* 2011;29:393–404.
- [15] Dere G, Yavuz IH, Ozaydin Yavuz G, Bayram Y, Gunes Bilgili S, Ozturk M. Assessment of HLA-A, HLA-DR, and HLA-DQ alleles in patients with pemphigus vulgaris from eastern of Turkey. *J Cosmet Dermatol* 2020;19:2432–7.
- [16] Lee CW, Yang HY, Kim SC, Jung JH, Hwang JJ. HLA class II allele associations in Korean patients with pemphigus. *Dermatology* 1998;197:349–52.
- [17] Niizeki H, Inoko H, Mizuki N, et al. HLA-DQA1, -DQB1 and -DRB1 genotyping in Japanese pemphigus vulgaris patients by the PCR-RFLP method. *Tissue Antigens* 1994;44:248–51.
- [18] Saha M, Bhogal B, Black MM, Cooper D, Vaughan RW, Groves RW. Prognostic factors in pemphigus vulgaris and pemphigus foliaceus. *Br J Dermatol* 2014;170:116–22.
- [19] Abida O, Zitouni M, Kallel-Sellami M, et al. Tunisian endemic pemphigus foliaceus is associated with the HLA-DR3 gene: anti-desmoglein 1 antibody-positive healthy subjects bear protective alleles. *Br J Dermatol* 2009;161:522–7.
- [20] Saha M, Harman K, Mortimer NJ, et al. Sporadic pemphigus foliaceus and class II human leukocyte antigen allele associations in the white British and Indo-Asian populations in the UK. *Clin Exp Dermatol* 2019;44:290–4.
- [21] Priyadarshini A, George R, Daniel D, Varughese S, Jayaseelan V. Association between human leukocyte antigen-DRB1 and human leukocyte antigen-DQB1 alleles and pemphigus vulgaris in Indian patients: a case-control study. *Indian J Dermatol Venereol Leprol* 2018;84:280–4.
- [22] Yan L, Wang JM, Zeng K. Association between HLA-DRB1 polymorphisms and pemphigus vulgaris: a meta-analysis. *Br J Dermatol* 2012;167:768–77.
- [23] Liu C, Cheng B. Association of polymorphisms of human leukocyte antigen-DQA1 and DQB1 alleles with chronic hepatitis B virus infection, liver cirrhosis and hepatocellular carcinoma in Chinese. *Int J Immunogenet* 2007;34:373–8.