HLA-DRB1 and DQB1 genetic susceptibility to pemphigus vulgaris and pemphigus foliaceus in Vietnamese patients

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Abstract

Pemphigus is a group of rare, life-threatening bullous autoimmune diseases that affect the skin and mucous membranes and are associated with high morbidity and morbidity. HLA class II genes, particularly HLA-DRB1 and HLA-DQB1, play roles in pemphigus. The aim of this paper is to investigate the susceptibility of HLA class II DRB1 and DQB1 alleles in Vietnamese patients with pemphigus vulgaris (PV) or pemphigus foliaceus (PF). The study enrolled 31 participants (22 with PV, 9 with PF) with diagnoses confirmed by clinical manifestations, histopathology, and direct immunofluorescence from November 2019 to June 2020. The HLA polymorphisms were determined by Sanger sequencing. The HLA-DRB1 and HLA-DQB1 profiles of the 101 healthy individuals in the control group have been published previously. The frequencies of HLA-DRB1*14, DRB1*13:07, DRB1*04:04, DRB1*03:02, DQB1*02:02, and DQB1*05:03 were significantly higher, whereas those of DRB1*09:01, DRB1*12:02, DQB1*03:03, DQB1*05:01, and DQB1*06:01 were significantly lower, in the PV group than in the controls. The frequencies of DRB1*14:54, DRB1*13:07, and HLA-DQB1*03:02 were significantly higher in the PF group than in the controls. Alleles HLA-DRB1*14:54, DRB1*14:04, DRB1*14:03, DRB1*14:01, DRB1*14:12, DRB1*13:07, DRB1*04:04, DRB1*03:02, DQB1*02:02, and DQB1*05:03 were associated with an increased risk of PV, whereas alleles DRB1*09:01, DRB1*12:02, DQB1*03:03, DQB1*05:01, and DQB1*06:01 might protect against PV. In PF, DRB1*14:54, DRB1*13:07, and HLA-DQB1*03:02 are promising susceptibility alleles.

Introduction

Pemphigus is a group of rare, life-threatening autoimmune diseases affecting the skin and mucous membranes that are associated with high morbidity and characterised by the presence of autoantibodies against desmogleins (Dsg).[1] Based on clinical and histological criteria, the disease is subcategorised into pemphigus vulgaris (PV), pemphigus foliaceus (PF), pemphigus erythematosus, pemphigus vegetans, and paraneoplastic pemphigus.[2] PV and PF are the most common clinical forms. While PF causes only skin lesions via production of anti-Dsg1 antibodies, PV causes painful blistering on both the skin and mucous membranes via production of autoantibodies against Dsg1 and Dsg3.[3] Although the pathogenic mechanisms of pemphigus remain unclear, there is evidence that genetic and environmental factors, including HLA-DR, DQ genes,[4] drug intake,[5] and viral infections,[6] contribute to its onset and progression.

HLA class II genes are highly polymorphic and encode a variety of molecules with different binding affinities to ensure a high capacity of variable antigen peptide binding to CD4+ T cells.[7] HLA class II polymorphisms play an important role in the restriction of Dsg3-reactive T and B cell autoantibody production and contribute to specify Dsg-derived peptides in PV and PF.[8,9] The role of HLA class II genes was confirmed in a humanised HLA DRB1*04:02 transgenic mouse model, in which DRB1*04:02 regulated T-cell recognition of Dsg3 and induced the loss of epidermal keratinocyte adhesion, a key manifestation in PV.[10] Population-based studies have reported the association between HLA class II alleles and PF or PV in various ethnic groups, focusing on HLA-DRB1 and DQB1. In the UK, Saha *et al*. suggested that DQB1*02 is a protective allele for PV.[11] Interestingly, Saha *et al*. found differences in the PF susceptibility alleles between white British and Indo-Asian patients, highlighting the important role of racial variation in the genetic susceptibility to disease development.[12] Studies in Brazil have reported several PF susceptibility alleles, including HLA-DRB1*01:01, DRB1*01:02, DRB1*01:03, DRB1*04:04, DRB1*04:06, DRB1*04:10, DRB1*14:06, and DRB1*16:01,[13,14] as well as the PV-associated alleles HLA-DRB1*04:02, DRB1*08:04, and the DRB1*14 group.[15] A Korean study discovered significant associations of PV with DRB1*01 and of PF with DRB1*01, DQA1*03:02, and DQB1*06:03.[16] HLA class II alleles are considered promising genetic markers of pemphigus and are being investigated globally.[17]

In the Vietnamese Kinh general population, the characteristics of HLA class II alleles and haplotypes were more closely associated with Southeast Asians (Thai, Malaysians, and Indonesians) than with East Asians (Han Chinese, Japanese, and

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South Koreans).[18] However, except for the study by Saha *et al*. that investigated Indo-Asian patients living in the UK,[12] little is known about the associations of HLA-DRB1 or DQB1 with PF and PV in Southeast Asians and Vietnamese. Therefore, this study investigated the PV and PF susceptibility of HLA class II DRB1 and DQB1 alleles in Vietnamese patients.

Materials and Methods

Study subjects

This cross-sectional study was conducted in Ho Chi Minh City Hospital of Dermato-Venereology from November 2019 to June 2020. Patients with a confirmed diagnosis of pemphigus based on clinical manifestations, histopathology, and direct immunofluorescence showing IgG at intercellular borders in the epidermis were enrolled. Other eligibility criteria were Vietnamese Kinh descent and age of at least 18 years. Exclusion criteria were a history allogeneic stem cell transplantation and other coexisting autoimmune diseases. All subjects underwent a thorough physical and laboratory examination by a research doctor. The control group consisted of 101 healthy Kinh Vietnamese, the HLA-DRB1 and DQB1 profiles of which have been published.[18]

DNA extraction

Venous blood (2 ml) was collected from each patient into an EDTA-K2 anticoagulant tube. Genomic DNA was extracted from whole blood using the GeneJET Whole Blood Genomic DNA Purification Mini Kit (Thermo Scientific, USA), according to the manufacturer's protocol.

Table 1. HLA-DRB1 frequencies in PV patients compared to healthy controls.

HLA-DRB1	PV (n=44)	Healthy individual (n=202)	OR (CI 95%)	p
03:01	2 (4.5)	15 (7.4)	0.63 (0.09-2.39)	0.745
03:02	*3 (6.8)*	*0 (0.0)*		*0.005*
04:01	0 (0.0)	1 (0.5)		1.000
04:03	1 (2.3)	3 (1.5)	1.67 (0.06-14.79)	0.548
04:04	*2 (4.5)*	*0 (0.0)*		*0.031*
04:05	0 (0.0)	13 (6.4)		0.133
04:06	0 (0.0)	2 (1.0)		1.000
07:01	1 (2.3)	6 (3.0)	0.85 (0.03-5.32)	1.000
08:02	1 (2.3)	0 (0.0)		0.179
08:03	2 (4.5)	11 (5.4)	0.88 (0.12-3.48)	1.000
08:08	1 (2.3)	0 (0.0)		0.179
08:12	0 (0.0)	1 (0.5)		1.000
09:01	*0 (0.0)*	*27 (13.4)*		*0.006*
10:01	0 (0.0)	16 (7.9)		0.084
11:01	1 (2.3)	5 (2.5)	1.02 (0.04-6.83)	1.000
11:06	0 (0.0)	3 (1.5)		1.000
11:129	0 (0.0)	1 (0.5)		1.000
12:02	*1 (2.3)*	*45 (22.3)*	*0.09 (0.00-0.44)*	*0.001*
13:01	0 (0.0)	1 (0.5)		1.000
13:02	0 (0.0)	3 (1.5)		1.000
13:03	1 (2.3)	0 (0.0)		0.179
13:07	*2 (4.5)*	*0 (0.0)*		*0.031*
13:12	0 (0.0)	6 (3.0)		0.595
14:01	*2 (4.5)*	*0 (0.0)*		*0.031*
14:03	*2 (4.5)*	*0 (0.0)*		*0.031*
14:04	*3 (6.8)*	*1 (0.5)*	*13.31 (1.51-388.34)*	*0.019*
14:05	1 (2.3)	2 (1.0)	2.46 (0.08-31.03)	0.448
14:06	1 (2.3)	0 (0.0)		0.179
14:10	0 (0.0)	1 (0.5)		1.000
14:12	*2 (4.5)*	*0 (0.0)*		*0.031*
14:18	0 (0.0)	1 (0.5)		1.000
14:54	*9 (20.5)*	*3 (1.5)*	*16.22 (4.49-80.15)*	*<0.001*
15:01	0 (0.0)	5 (2.5)		0.589
15:02	2 (4.5)	21 (10.4)	0.44 (0.06-1.59)	0.389
15:03	1 (2.3)	0 (0.0)		0.179
16:01	1 (2.3)	0 (0.0)		0.179
16:02	2 (4.5)	9 (4.5)	1.08 (0.15-4.48)	1.000

Library preparation

PCR amplification and target gene sequencing were performed using primers complementary to HLA-DRB1 (acc. no. NG_002392) and HLA-DQB1 (acc. no. NG_02922) sequences, obtained from NCBI or Lazaro *et al.*[19]

Sequencing

Sanger sequencing was performed using POP-7™ Polymer and a 50 cm capillary array on the ABI 3500 Genetic Analyser (Applied Biosystems, USA). The sequences were subsequently analysed using the CLC Main Workbench and compared using BLAST in EBI software to identify the HLA-DRB1 and DQB1 alleles of the participants.

Statistical analysis

Continuous data are presented as the mean ± standard deviation or median with interquartile range according to the normality of the data. Categorical data are described as the frequency and percentage. Quantitative variables were analysed using Student's *t*-test. Fisher's exact test was used to compare allele frequencies between the pemphigus subtypes. A two-sided $p<0.05$ was considered statistically significant. All analyses were conducted using R ver. 4.0.2 (Vienna, Austria).

Ethics

This study was approved by the Biomedical Research Ethics Review Committee of the University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam (approval number: 593/DHYD-HDDD, November 4, 2019). Informed consent was received from all participants.

Results

In the 22 PV and 9 PF patients enrolled in this study, 23 and 10 HLA-DRB1 alleles and 9 and 7 HLA-DQB1 alleles were detected, respectively.

HLA-DRB1 profile in the PV group

HLA-DRB1*14:54 and DRB1*14:04 were the two alleles most strongly associated with PV susceptibility [OR = 16.22 (4.49–80.15) and OR = 13.31 (1.51–388.34), respectively]. Other susceptibility alleles detected in the PV patients, but not in healthy controls, were DRB1*03:02 (p=0.005), DRB1*04:04 (p=0.031), DRB1*13:07 (p=0.031), DRB1*14:01 (p=0.031), DRB1*14:03 (p=0.031), and DRB1*14:12 (p=0.031). The frequencies of DRB1*09:01 (p=0.006) and DRB1*12:02 (p=0.001) were significantly higher in the control group (Table 1).

HLA-DQB1 profile in the PV group

Regarding HLA-DQB1 polymorphisms, the DQB1*02:02 (p=0.011) and DQB1*05:03 (p<0.001) alleles were more frequent [OR = 6.23 (1.52–27.34) and 12.65 (4.81–36.36), respectively], whereas DQB1*03:03 (p=0.036), DQB1*05:01 (p=0.011), and DQB1*06:01 (p=0.048) were less frequent, in the PV patients than healthy controls (Table 2).

HLA-DRB1 profile in the PF group

In the HLA-DRB1 region, the frequencies of DRB1*14:54 [OR = 30.99 (7.05–172.21), p<0.001] and DRB1*13:07 (p=0.006) were significantly higher in the PF group than controls (Table 3).

HLA-DQB1 profile in the PF group

HLA-DQB1*03:02 was significantly more frequent in the PF patients than controls [OR = 14.68 (3.55–61.44), p<0.001] (Table 4).

Discussion

HLA genes are reported to be associated with the occurrence and development of pemphigus.[20] HLA class II antigens are typically expressed on the surface of active T cells, which are believed to play a major role in T cell activation and antigen recognition.[21] Importantly, studies have highlighted the importance of racial variation in the genetic susceptibility to pemphigus,[12] indicating the need for profiling and investigation of the genetic factors of the disease among different ethnic groups and populations. However, few studies have examined pemphigus patients living in Southeast Asia. This is the first study to identify HLA-DRB1 and HLA-DQB1 susceptibility alle-

Table 2. HLA-DQB1 frequencies in PV patients compared to healthy controls.

HLA-DQB1	PV (n=44)	Healthy individual (n=202)	OR (CI 95%)	p
02:01	1 (2.3)	14 (6.9)	0.35 (0.01-1.85)	0.483
02:02	*5 (11.4)*	*4 (2.0)*	*6.23 (1.52-27.34)*	*0.011*
03:01	13 (29.5)	58 (28.7)	1.05 (0.49-2.11)	1.000
03:02	2 (4.5)	5 (2.5)	1.95 (0.24-9.83)	0.612
03:03	1 (2.3)	27 (13.4)	0.17 (0.01-0.84)	0.036
03:05	0 (0.0)	1 (0.5)		1.000
04:01	0 (0.0)	10 (5.0)		0.216
04:02	0 (0.0)	2 (1.0)		1.000
05:01	0 (0.0)	25 (12.4)		0.011
05:02	8 (18.2)	23 (11.4)	1.74 (0.68-4.10)	0.217
05:03	*14 (31.8)*	*7 (3.5)*	*12.65 (4.81-36.36)*	*<0.001*
05:10	0 (0.0)	1 (0.5)		1.000
05:18	0 (0.0)	2 (1.0)		1.000
06:01	*0 (0.0)*	*17 (8.4)*		*0.048*
06:02	0 (0.0)	2 (1.0)		1.000
06:03	0 (0.0)	1 (0.5)		1.000
06:04	0 (0.0)	1 (0.5)		1.000
06:09	0 (0.0)	2 (1.0)		1.000

Table 3. HLA-DRB1 frequencies in PF patients compared to healthy controls.

HLA-DRB1	PF (n=18)	Healthy individual (n=202)	OR (CI 95%)	p
03:01	2 (11.1)	15 (7.4)	1.64 (0.22-6.68)	0.636
03:02	1 (5.6)	0 (0.0)		0.082
04:01	0 (0.0)	1 (0.5)		1.000
04:03	2 (11.1)	3 (1.5)	8.30 (0.91-58.38)	0.055
04:05	1 (5.6)	13 (6.4)	0.96 (0.04-5.38)	1.000
04:06	1 (5.6)	2 (1.0)	6.14 (0.19-79.40)	0.227
04:07	1 (5.6)	0 (0.0)		0.082
07:01	1 (5.6)	6 (3.0)	2.12 (0.08-14.00)	0.455
08:03	0 (0.0)	11 (5.4)		0.606
08:12	0 (0.0)	1 (0.5)		1.000
09:01	0 (0.0)	27 (13.4)		0.138
10:01	0 (0.0)	16 (7.9)		0.373
11:01	0 (0.0)	5 (2.5)		1.000
11:06	0 (0.0)	3 (1.5)		1.000
11:129	0 (0.0)	1 (0.5)		1.000
12:02	1 (5.6)	45 (22.3)	0.23 (0.01-1.19)	0.131
13:01	0 (0.0)	1 (0.5)		1.000
13:02	0 (0.0)	3 (1.5)		1.000
13:07	*2 (11.1)*	*0 (0.0)*		*0.006*
13:12	0 (0.0)	6 (3.0)		1.000
14:04	0 (0.0)	1 (0.5)		1.000
14:05	0 (0.0)	2 (1.0)		1.000
14:10	0 (0.0)	1 (0.5)		1.000
14:18	0 (0.0)	1 (0.5)		1.000
14:54	*6 (33.3)*	*3 (1.5)*	*30.99 (7.05-172.21)*	*<0.001*
15:01	0 (0.0)	5 (2.5)		1.000
15:02	0 (0.0)	21 (10.4)		0.229
16:02	0 (0.0)	9 (4.5)		1.000

Table 4. HLA-DQB1 frequencies in PF patients compared to healthy controls.

HLA-DRB1	PF (n=18)	Healthy individual (n=202)	OR (CI 95%)	p
02:01	1 (5.6)	14 (6.9)	0.89 (0.04-4.92)	1.000
02:02	0 (0.0)	4 (2.0)		1.000
03:01	5 (27.8)	58 (28.7)	0.97 (0.29-2.74)	1.000
03:02	*5 (27.8)*	*5 (2.5)*	*14.68 (3.55-61.44)*	*<0.001*
03:03	0 (0.0)	27 (13.4)		0.138
03:05	0 (0.0)	1 (0.5)		1.000
03:09	1 (5.6)	0 (0.0)		0.082
04:01	0 (0.0)	10 (5.0)		1.000
04:02	0 (0.0)	2 (1.0)		1.000
05:01	1 (5.6)	25 (12.4)	0.47 (0.02-2.47)	0.703
05:02	4 (22.2)	23 (11.4)	2.27 (0.58-7.06)	0.249
05:03	1 (5.6)	7 (3.5)	1.82 (0.07-11.47)	0.501
05:10	0 (0.0)	1 (0.5)		1.000
05:18	0 (0.0)	2 (1.0)		1.000
06:01	0 (0.0)	17 (8.4)		0.372
06:02	0 (0.0)	2 (1.0)		1.000
06:03	0 (0.0)	1 (0.5)		1.000
06:04	0 (0.0)	1 (0.5)		1.000
06:09	0 (0.0)	2 (1.0)		1.000

les in Kinh Vietnamese PV and PF patients and should contribute to the knowledge on pemphigus genetic factors in Vietnamese and Southeast Asians.

The frequencies of the HLA-DRB1*14:54, DRB1*14:04, DRB1*14:03, DRB1*14:01, DRB1*14:12, DRB1*13:07, DRB1*04:04, and DRB1*03:02 alleles were significantly higher in the PV group than healthy controls among Kinh Vietnamese. Overall, the DRB1*14 allele group is associated with susceptibility to PV, which is similar to the findings of Saha *et al.* in the UK,[22] Glorio *et al*. in Argentina,[21] Gil *et al*. in Brazil,[23] Párnická *et al*. in Slovakia,[24] and Porro *et al.* in India.[25] In China, Geng *et al*. reported several PV-associated alleles similar to our findings, specifically the DRB1*14 allele group (DRB1*14:01, DRB1*14:04, DRB1*14:05, DRB1*14:07, and DRB1*14:08).[26] Concordant results from multiple genetic analyses worldwide, including ours, suggest that the DRB1*14 allele group is a promising biomarker of PV that is independent of race or ethnicity.

The association between the DRB1*14:01 allele and PV has been reported worldwide, such as by Lombardi *et al.* in Italy,[27] Loiseau *et al*. in France,[9] and Glorio *et al.* in Argentina.[21] This association is supported by molecular evidence that the DRB1*14:01 allele restricts the T-cell responses to Dsg3, the specific PV antigen that plays an essential role in cell–cell adhesion among keratinocytes.[4] Note that DRB1*14:54 was previously considered to be DRB1*14:01 and was only identified as a new allele in 2005 by the World Health Organisation Nomenclature Committee.[28] It is possible that the susceptibility allele DRB1*14:01 evaluated in studies conducted before 2005 is actually DRB1*14:54.[17,22] Consistent with our findings, many studies worldwide have suggested that DRB1*14:54 is a susceptibility allele for PV, such as Saha *et al.* in the UK and Párnická *et al.* in Slovakia.[11,24] Other studies reported a relationship of the DRB1*04:04 and DRB1*14:04 alleles with PV. Párnická *et al*. showed that DRB1*04:04 [OR = 30.57 (1.67–559.40)] and DRB1*14:04 [OR = 24.71 (1.32–464.28)] significantly increase the risk of PV.[24] In China, Zhang *et al*. confirmed the association between DRB1*14:04 and PV using an Affymetrix array.[29]

Regarding HLA-DQB1, the frequency of the DQB1*05:03 allele was significantly higher in our PV patients compared with the controls, suggesting that DQB1*05:03 is a susceptibility allele. This is consistent with Saha *et al*., who reported that DQB1*05:03 significantly increased the risk of PV among British Indonesians [OR = 6.93 (3.03–16.48)] and white British [OR = 6.18 (3.07–12.57)].[11] Glorio *et al*. in Argentina [RR = 8.02 (3.03–21.48)] and Párnická et al. in Slovakia [OR = 10.40 (3.99–27.10); p<0.0001] reported a similar association between DQB1*05:03 and PV compared with controls.[21,24] A meta-analysis by Li *et al.* pooled data from 18 studies and confirmed the association between the DQB1*05:03 allele and PV [OR = 10.02 (5.41–18.55)].[8] Due to the consistent association of this allele with PV in studies worldwide, we suggest that the DQB1*05:03 allele should be regarded as a global genetic factor for PV. Interestingly, none of our PV patients carried the HLA-DQB1*06 allele, while the healthy controls had several HLA-DQB1*06 alleles, including DQB1*06:01 (8.4%), DQB1*06:02 (1.0%), DQB1*06:03 (0.5%), DQB1*06:04 (0.5%), and DQB1*06:09 (1.0%). This implies that DQB1*06:01 protects against PV. Recently, Dere *et al.* derived the same conclusion about the HLA-DQB1*06 allele as a protective factor against PV in Turkey.[30]

Similar to findings in the PV group, DRB1*14:54 was a susceptibility allele for PF [OR = 30.99 (7.05–172.21)]. There was no difference in the frequency of this allele between the PV and PF groups (p=0.334), implying that it is not specific to any subtype. This is in contrast to the study of Saha *et al.,* who found that the DRB1*14:54 allele was associated with PV in Caucasians,[11] but not with PF in either ethnic group (British and Indo-Asian patients).[12] However, Rovesti *et al*. recently reported a 19-year-old European female who carried the DRB1*14:54 allele and presented with both PV and PF.[30] Transitions from PV to PF and vice versa have been reported. However, according to Rovesti *et al*., this might be an extremely rare situation in which both conditions present simultaneously; only four such cases have been reported since 1998.[31] The case supports our findings that the DRB1*14:54 allele is not specific to either PV or PF. Vietnamese patients with PF had a significantly higher DQB1*03:02 allele frequency compared with the controls. This result is similar to that of Zhang et al., confirming that the DQB1*03:02 allele is specific to PF in Chinese patients.[29] Abida *et al*. investigated 90 Tunisian PF patients and found that the DQB1*03:02 allele was statistically associated with PF.[32]

Limitations

Due to the rarity of this disease, we could only recruit a relatively small number of participants, and this our study might be subject to selection bias. Multicentre studies with larger samples are needed to confirm our results and obtain more comprehensive data on pemphigus patients.

Conclusions

The HLA-DRB1*14:54, DRB1*14:04, DRB1*14:03, DRB1*14:01, DRB1*14:12, DRB1*13:07, DRB1*04:04, DRB1*03:02, DQB1*02:02, and DQB1*05:03 alleles were associated with an increased risk of PV, while DRB1*09:01, DRB1*12:02, DQB1*03:03, DQB1*05:01, and DQB1*06:01 appeared to have protective effects on PV. For PF, DRB1*14:54, DRB1*13:07, and HLA-DQB1*03:02 were found to be promising susceptibility alleles.

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