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ABSTRACT

Background: A common Human Leukocyte Antigen (HLA) class II allele, DQβ1*03:01, seems to be associated with Bullous pemphigoid (BP) in Caucasians whereas previous studies in other ethnic groups showed other HLA class II alleles as genetic predisposing factors for BP. **Objective:** To investigate the association of HLA class II alleles and haplotypes with BP in Iranian population. **Methods:** Fifty patients with Bullous pemphigoid and 180 geographically matched, healthy individuals as control group enrolled into this study. HLA typing of class II (DR and DQ alleles) was carried out using polymerase chain reaction based on sequence-specific primers method. **Results:** Class II DQA1 and DQB1 typing showed a significantly higher frequency of HLA-DQA1*05:01 (45% vs. 33%, p=0.03), HLA-DQB1*03:01 (36% vs. 23.6%, p=0.02) and HLA-DQB1*04:01 (4% vs. 1.6%, p=0.04) in the BP patients compared with controls. For DRB1 allele frequencies, there were no significant disease associations. The frequency of DRB1*08:01/DQA1*05:01/DQB1*03:01 (3% vs. 0%, p=0.02) haplotype showed an increase among patients compared with controls. **Conclusion:** Our data suggest that Iranian patients with BP present the same genetic predisposition linked to HLA-DQB1*03:01 previously reported in Caucasians.

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Keywords: Bullous Pemphgoid, Haplotype, HLA Class II Alleles, Iranian

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INTRODUCTION

Bullous pemphigoid (BP) is an autoimmune blistering skin disease of the elderly patients, who present with generalized tense bullae, frequently in the extremities and lower trunk and, more rarely mucous membrane involvement (1-3). BP is characterized by the presence of circulating antibodies against hemidesmosomal components in the epidermal basement membrane zone, designated as BP230 (BPAG1) and BP180 (BPAG2 or type XVII collagen) (4).

Autoantibodies against BPAG2 are thought to play a key role in the pathogenesis of the disease (5). It is likely that this autoimmunity involves autoreactive T cells that recognize epitopes located in the extracellular region of BP180, mainly NC16A ectodomain. CD4+ T helper cells are crucial for stimulating B cells to produce autoantibodies (6,7). These autoreactive T cells were also found in normal individuals (6,8). There is strong evidence that genetic factors, including HLA alleles may promote activation of potentially autoreactive T cells (9). The MHC Class II genes on human chromosome 6p21 (found only on professional antigen presenting cells, such as dendritic cells, macrophages and B cells) present self- and non-self-antigenic peptides to CD4+ T-lymphocytes (10). Accordingly, correlation between target Basement Membrane Zone (BMZ) antigens and specific alleles or haplotypes may be informative.

Previously, Delgado et al. demonstrated that there is a strong association of HLA-DQB1*03:01with the development of BP in the Caucasian (11). Although another study in the same population confirmed that HLA-DQB1*03:01 is associated with a susceptibility to BP, but only significant in male patients (12). Budinger et al. identified autoreactive T cell response from normal individuals and BP patients to the BP180 extracellular domain are restricted to the expression of DQB1*03:01.

While Japanese found DQB1*03:02, DRB1*11:01 and haplotypes DRB1*04⁄DQA1*03:01⁄DQB1*03:02 and DRB1*11:01⁄DQA1*05:05⁄DQB1*03:02 were associated with BP, which is different from the frequent^{+} allele DQB1*03:01 association among Caucasians (14). Similarly, in a study of Northern Chinese patients with BP, no statistically significant frequency of DQβ1*0301 was observed (15). These findings indicate that different HLA class II alleles and haplotypes can influence on genetic susceptibility to BP between different ethnic groups.

We have already carried out two separate studies in our Autoimmune Bullous Diseases Research Center to evaluate the association of the HLA Class I and HLA-DR and DQ alleles and haplotypes in Iranian patients with pemphigus vulgaris (16,17). Therefore, in the present study we aimed to evaluate the associations of HLA-DR and DQ alleles and haplotype frequencies in Iranian patients with autoimmune bullous pemphigoid, in comparison with healthy controls.

MATERIALS AND METHODS

Subjects. In this study, a total 50 Iranian patients with BP (22 female and 28 male) who attended to Dermatology Center of Razi Hospital, Tehran, Iran, from August to February 2011, were randomly recruited. Control group consisted of 180 unrelated healthy subjects they were also randomly selected from the same region as the patient group. Diagnosis of BP was based on clinical, histological and direct immunoflorescence of cutaneous biopsies. Patients with blistering disease other than PV or any systemic dis-

ease such as diabetes mellitus and thyroid disorders associated with specific major histocompatibility complex (MHC) alleles were excluded from this study. In the control group, people who had history of autoimmune blistering diseases or family history of such disorders in first-degree relatives or being affected by any other systemic disease were excluded from study. This study was approved by the Ethical Committee of Tehran University of Medical Sciences. Written informed consent was obtained from the subjects before sampling.

HLA Typing. Genomic DNA was extracted from 10 ml peripheral blood in EDTA vacutainers by modified salting out method. HLA-DRB, -DQA1, and -DQB1 typing was performed by polymerase chain reaction based on sequence-specific primers (PCR-SSP) (15) following Olerup and Zetterquist method (16). HLA-DRB, -DQA1, and -DQB1 PCR-SSP kits were supplied by Biotest (Heidelberg, Germany). Taq DNA polymerase was supplied from Roche (Basel, Switzerland). The PCR reactions were carried out in 10 µl volumes. Samples were amplified in Techne genius thermal cyclers, after initial denaturation at 94°C for 2 min, followed by 10 cycles of 94°C denaturation for 10 s, 65°C annealing and extension for 60 s, and finally, 20 cycles of 94°C denaturation for 10 s, 61°C annealing for 50 s, and 72°C extension for 30 s. After amplification, PCR products were run on a 2% agarose gel electrophoresis, and then gel was interpreted for specific bands using a UV trans-illuminator. The haplotypes were calculated according to Iranian population specific linkage disequilibrium pattern among HLA-DRB, -DQA, and -DQB alleles (17).

Statistical Analysis. Chi-Square test and Yates' correction were used for analyzing the differences between frequencies of HLA -DRB, -DQA1 and -DQB1 alleles in BP patients and control group. When it was necessary, Fisher's exact 2-tailed correction was applied. The odd Ratio (OR) and related 95% confidence interval (95% CI) was also calculated. P value of less than 0.05 was considered as significant.

RESULTS

The HLA class II alleles frequencies of BP patients and the control groups are presented in the Tables 1-3.

There were no significant differences in the frequencies of alleles between patients and controls at HLA-DRB1 locus while at the DQA1 locus only the HLA-DQA1*05:01 allele was increased significantly (45% vs. 33%, p=0.03, OR=1.65, 95%CI=1.05-2.6). Higher frequencies of HLA-DQB1*03:01 (36% vs. 23.6%, p=0.02, OR=1.82, 95%CI=1.13-2.92) and HLA-DQB1*04:01 (4%vs. 1.6%, p=0.04, OR=7.45, 95%CI=1.34-41.3)) alleles were found in the patient group, compared to the controls. Regarding linkage disequilibrium between HLA-class II alleles the frequent haplotypes has been depicted in Table 4, the most frequent haplotype in the patient and control groups was DRB1*11:01/DQA1*05:01/DQB1*03:01(30% and 24.7%, respectively). Although there was no significant differences between the two groups (p=0.34). In addition, the haplotype DRB1*08:01/DQA1*05:01/DQB1*03:01was increased significantly in our patients. (3% vs.0%, p=0.02), other DQB1*03:01-carrying haplotypes "DRB1*11:01/DQA1*05:01/DQB1*03:01" and "DRB1*13:03/DQA1*01:03/DQB1*03:01" did not have significant difference between patient and control groups (p=0.34 and 0.77, respectively).

Table 1. HLA-DRB allele frequencies in Iranian patients with Bullous Pemphigoid and healthy control group.

DRB_1	B. Pemphigoid (N=50) (100 alleles)		Healthy Controls (N=180) (360 alleles)		Odd Ratio (Cl 95%)	P Value Two sided
	N	%	N	%		
01:01	6	6	24	6.6	0.84 (0.33-2.11)	0.88
15	10	10	47	13.1	0.74 (0.35-1.52)	0.51
16	2	2	16	4.4	0.43 (0.09-1.94)	0.42
03:01	7	7	32	8.8	0.77 (0.32-1.8)	0.69
04	14	14	33	9.1	1.61 (0.82-3.14)	0.22
07	4	4	36	10	0.37 (0.13-1.08)	0.09
08	6	6	8	2.2	2.8 (0.78-9.46)	0.12
09:01	1	1	7	1.9	0.5 (0.06-4.18)	0.9
10:01	5	5	12	3.3	1.52 (0.52-4.43)	0.6
11	30	30	89	24.7	1.3 (0.79-2.13)	0.34
12	0	0	3	0.8	------	0.83
13:01	3	3	21	5.8	0.49 (0.14-1.7)	0.38
13:02	5	5	10	2.7	1.84 (0.61-5.51)	0.41
13:03	2	2	4	1.1	1.81 (0.16-12.87)	0.77
14:01	5	5	18	5	1 (0.36-2.76)	0.79
DRB3	50	50	177	49.1	1.03 (0.66-1.61)	0.97
DRB4	19	19	76	21.1	0.87 (0.5-1.53)	0.74
DRB5	12	12	50	13.8	0.84 (0.43-1.65)	0.74

HLA polymorphism between patients and controls was compared using the Chi-square test for two by two Tables. Fisher's exact 2-tailed correction test was used when necessary.

In this study the two haplotypes including DRB1*07 /DQA1*01:02/ DQB1*02:01 (4 vs. 10%, p=0.09) and DRB1*13:01/DQA1*01:03/DQB1*06:02(1 vs. 4.7%, p=0.13) had higher frequency (not significant) in control compared with patients. The possible protective role of these haplotypes needs to be confirmed in a larger population.

Table 2. HLA-DQA$_1$ allele frequencies in Iranian patients with BullousPemphigoid and healthy control group.

DQA$_1$	B. Pemphigoid (N=50) (100 alleles)		Healthy Controls (N=180) (360 alleles)		Odds ratio (Cl 95%)	P Value
	N	%	N	%		
01:01	6	6	35	9.7	0.59(0.24-1.45)	0.33
01:02	10	10	49	13.6	0.7(0.34-1.44)	0.43
01:03	9	9	43	11.9	0.72(0.34-1.55)	0.51
01:04	10	10	34	9.4	1.065(0.5-2.23)	0.98
02:01	4	4	36	10	0.37(0.13-1.08)	0.09
03:01	16	16	38	10.5	1.61(0.85-3.03)	0.18
04:01	0	0	6	1.6	----	0.45
05:01	45	45	119	33	1.65(1.05-2.6)	0.03

HLA polymorphism between patients and controls was compared using the Chi-square test for two by two tables. Fisher's exact 2-tailed correction test was used when necessary.

Table 3. HLA-DQB$_1$ allele frequencies in Iranian patients with BullousPemphigoid and healthy control group.

DQB$_1$	B. Pemphigoid (N=50) (100 alleles)		Healthy Controls (N=180) (360 alleles)		Odds ratio (Cl 95%)	P Value
	N	%	N	%		
02:01	11	11	72	20	0.49 (0.25-0.97)	0.05
02:03	0	0	1	0.3	--------	1
03:01	36	36	85	23.6	1.82 (1.13- 2.92)	0.01
03:02	12	12	21	5.8	2.13 (1.01- 4.51)	0.06
03:03	2	2	15	4.2	0.46 (0.105- 2.08)	0.47
03:05	0	0	2	0.5	-	1
04:01	4	4	6	1.6	7.45 (1.34- 41.3)	0.04
05:01	19	19	79	21.9	0.95 (0.54-1.67)	0.97
06:01	5	5	30	8.3	0.57 (0.21-1.53)	0.36
06:02	6	6	37	10.3	0.55 (0.22-1.36)	0.26
06:03	3	3	2	0.5	5.53 (0.91-33.6)	0.14
06:04	2	2	10	2.7	0.71 (0.07-3.43)	0.99

Table 4. The most frequent HLA class II Haplotype frequencies in Iranian BullousPemphigoid patients and controls.

HLA-DRB/DQA/DQB Haplotype	Patients N=50(%)	Controls N=180(%)	P Value	Odd ratio 95% CI
DRB1*11 / DQA1*05:01/ DQB1*03:01	30 (30)	89 (24.7)	0.34	1.3 (0.79-2.13)
DRB1*04/ DQA1*03:01/ DQB1*03:02	12 (12)	33 (9.2)	0.51	1.35 (0.67-2.72)
DRB1*03:01/ DQA1*05:01/DQB1*02:01	7 (7)	32 (8.8)	0.69	0.77 (0.32-1.8)
DRB1*01:01/DQA1*01:01/ DQB1*05:01	6 (6)	24 (6.6)	0.88	0.84 (0.33-2.11)
DRB1*15/ DQA1*01:03/ DQB1*06:01	5 (5)	28 (6.4)	0.46	0.62 (0.23-1.66)
DRB1*10:01/ DQA1*01:04/ DQB1*05:01	5 (5)	12 (3.3)	0.6	1.52 (0.52- 4.43)
DRB1*14:01/ DQA1*01:04/ DQB1*05;01	5 (5)	18 (5)	0.79	1 (0.36-2.76)
DRB1*15/ DQA1*01:02/ DQB1*06:02	4 (4)	19 (4.7)	0.79	0.74 (0.24-2.25)
DRB1*07 /DQA1*01:02/ DQB1*02:01	4 (4)	36 (10)	0.09	0.37 (0.13-1.08)
DRB1*08 / DQA1*05:01/ DQB1*03:01	3 (3)	0	0.02	----
DRB1*08 / DQA1*04:01/ DQB1*04:01	3 (3)	8 (2.2)	0.88	1.36 (0.22-5.8)
DRB1*13:02/ DQA1*01:02/ DQB1*06:04	2 (2)	8 (2.2)	0.8	0.89 (0.18-4.3)
DRB1*13:02/DQA1*01:03/DQB1*06:02	2 (2)	2 (0.6)	0.41	3.65 (0.5-26.26)
DRB1*13:03/DQA1*01:03/DQB1*03:01	2 (2)	4 (1.2)	0.77	1.81 (0.32-10.06)
DRB1*16/ DQA1*01:02/ DQB1*05:01	2 (2)	16 (4.4)	0.42	0.43 (0.048-1.92)
DRB1*15/ DQA1*01:02/ DQB1*05:01	1 (1)	0	0.49	----
DRB1*04/ DQA1*0301/ DQB1*0303	1 (1%)	0	0.49	----
DRB1*04/ DQA1*0401/ DQB1*0401	1 (1%)	0	0.49	----
DRB1*0901/ DQA1*0301/ DQB1*0201	1 (1%)	0	0.49	----
DRB1*13:01/ DQA1*01:03/ DQB1*06:02	1 (1)	16 (4.7)	0.13	0.2 (0.02-1.55)
DRB1*13:01/ DQA1*01:03/ DQB1*06:03	1 (1)	2 (0.6)	1	1.8 (0.03-35.01)
DRB1*13:01/ DQA1*05:01/ DQB1*06:03	1 (1)	3 (0.9)	1	1.8 (0.03- 35.01)
DRB1*1302/DQA1*0103/DQB1*0603	1 (1%)	0	0.49	------
DRB1*09:01/ DQA1*03:01/ DQB1*03:03	0	7 (1.9)	0.35	-----
DRB1*12 / DQA1*05:01/ DQB1*03:01	0	3 (0.9)	0.83	----

DISCUSSION

Bullous pemphigoid is a well-characterized model of autoantibody-mediated blistering disease, in which autoreactive T cell helping in the pathogenic autoantibody production (7). It is assumed that autoreactive T cell responses to BPAG2 are elicited upon the recognition of this antigen bound to HLA class II region of DQB1 molecule (9,11). In this study, HLA class II (DRB, DQA1 and DQB1) was investigated in the Iranian patients with BP compared to a group of healthy controls with the same ethnic origin.

In hypothetical computer-based model study by Zakka et al., in order to determine a molecular basis of HLA-DQB1*03:01 allele in the pathogenesis of pemphigoid, 21 patients with BP, 100 patients with mucous membrane pemphigoid and ocular cicatricial pemphigoid, and 22 patients with oral pemphigoid were selected for HLA association study, they showed that all the above mentioned pemphigoid patients had a highly statistically significant association with the HLA-DQB1*03:01 allele. This model demonstrated that the relevant epitopes in BPAG1 and BPAG2 can be presented by HLA-DQB1*0301 allele B to autoreactive T cell receptors (18). Then these T cells will interact with B cells to produce specific anti-basement membrane zone antibodies. Many investigators have reported the HLA-DQB1*03:01 allele to be associated with increased susceptibility to BP in Caucasians population (11,12,13). However, the results of the HLA class II typing were different in others ethnic groups especially in the far east ethnic groups (14,15).

The study by Delgado and colleagues showed that clinical variants of pemphigoid (Bullous pemphigoid, Ocular cicatricial pemphigoid and oral pemphigoid) have significant association with HLA-DQB1*03:01 allele (11). Similarly, in our study, this allele was significantly found in higher frequency in the patients compared to the controls.

Although Banfield et al. confirmed that HLA-DQB1*03:01 is associated with a susceptibility in male patients to BP (12). Similarly, in present study, 24 of the men with BP (67%) and 12 of female patients (33%) had DQA1*03:01 allele (p=0.03) and there was significant difference in HLA-DQβ1*03:01 association between two genders with BP.

In the study by Okazaki et al., HLA-DQB1*03:02, DRB1*11:01 and haplotypes DRB1*04⁄DQA1*03:01⁄DQB1*03:02 and DRB1*11:01⁄DQA1*05:05⁄DQB1*03:02 showed higher frequencies in the Japanese patients with BP, although they did not find any association between HLA-DQB1*03:01 allele and BP (14). In our study, no significant difference in frequency of HLA-DQB1*03:02 allele between the patient and control groups (p=0.06) was found but we cannot completely rule out that this allele may be a risk allele for BP (OR=2.13). In addition, the related haplotype DRB1*04/DQA1*0301/DQB1*0302 showed an increase relative risk (OR=1.35).

In the present study no statistically significant association was found between HLA-DRB1 alleles and BP. Razzaque et al. also did not find an increased frequency of HLA-DR antigen in patients with BP (20).

In the study of 25 northern Chinese patients with BP, no statistically significant increased frequency of HLA-DQB1*03:01 has been observed between patients and controls. However, they observed lower frequencies of HLA–DRB1*08 and DRB1*08⁄DQB1*06 haplotypes in BP patients than in controls, suggesting the protective role of this allele in their BP patients (15). The results of HLA-DR and DQ association study in Japanese and Chinese populations with BP in comparison with the Caucasian population showed that difference in genetic background and ethnicity may influence the genetic susceptibility to BP.

HLA-DRB, DQA1, DQB1 haplotype frequencies in our BP patients showed an increased frequency in DRB1*08:01/DQA1*05:01/DQB1*03:01 (3% vs. 0%, p=0.02) among patients compared with controls, since none of the subjects in the control group had this haplotype, this difference is not reliable and the reproducibility of this haplotype should be confirmed in larger group of BP patients. Although DQB1*0301 is known to be in linkage disequilibrium with both DRB1*04 and DRB1*11, the extended haplotype did not have significant difference between patient and control groups. (p=0.51 and 0.34, respectively), however these haplotypes had positive association with disease (OR=1.3).

Finally, while the phenotypic presentation of Pemphigoid may be influenced by different genetic factors, non-genetic factors, and soluble and insoluble mediators of immune and inflammatory processes, HLA-DQB1*0301 allele in Iranian population and other Caucasoid populations may play an important role in the pathogenesis of the clinical variants of pemphigoid. In conclusion, regarding the results of the present study, it is suggested that HLA-DQB1*03:01, HLA-DQA1*05:01 and HLA-DQB1*04:01 alleles are genetic factors which increase susceptibility to BP in Iranian population. However, further studies with larger sample size are required to confirm the results of this study in the Iranian population.

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