Distribution Of Jewish And Non-Jewish Haplotypes Among Pemphigus Vulgaris Patients Worldwide

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Citation

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Abstract

Pemphigus Vulgaris (PV) has been reported in most countries of the world. PV is associated with HLA genes, and specifically with class II HLA alleles which have been linked to the disease predisposition. HLA-DRB1*0402, DQB1*0302 haplotype has been found in the Jewish PV patients, while HLA-DRB1*1401/1404, DQB1*0503 haplotype has been reported in the non-Jewish PV patients. The purpose of this communication was to conduct a retrospective review of the literature on the HLA mapping in PV patients and to determine the frequencies of Jewish and non-Jewish haplotypes in the PV patients in different regions of the world. Twenty two studies were reviewed and the data was collected and analyzed. Regardless of the ethnicity or the geographic region, these PV-associated haplotypes were distributed similarly between different populations. Jewish and non-Jewish haplotypes have been reported to occur at increased frequencies among PV patients as compared to control haplotypes. This is a significant observation which might be important for development of novel immunotherapies.

INTRODUCTION

Pemphigus vulgaris (PV) is a potentially fatal autoimmune blistering disease affecting the skin and mucous membranes ([1], [2]). It usually begins in the oral cavity, with areas of the body involvement decreasing from head downwards ([3]). The hallmark of PV is flaccid blisters on the skin that rupture easily and leave denuded, painful surfaces ([1], [4], [5]). PV is characterized by the loss of intercellular adhesion of keratinocytes, resulting in acantholysis ([5],[6],[7],[8]), which refers to the loss of adhesion between epidermal cells, leading to their detachment and floating in the cavity of the blister. Direct immunofluorescence (DIF) studies of perilesional biopsy of skin or mucosal tissues showed deposition of IgG on keratinocyte cell surfaces in almost all patients ([9]). Indeed, a majority of PV patients contain circulating antibodies to one or more keratinocyte cell surface antigens, desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1), which can be detected in an ELISA assay ([10],[11],[12]). The titer of the antibody has been shown to correlate with disease activity ([13],[14],[15]). High titers of these circulating autoantibodies are believed to cause clinical disease by direct binding to and disruption of desmoglein proteins localized in the desmosome, which is essential for maintaining the integrity of the epidermis ([4], [16], [17]).

Current therapies for PV include treatment with systemic corticosteroids which are often used as the main drugs ([1], [5], [18], [19]), along with anti-inflammatory drugs i.e. dapsone, minocycline, or tetracycline with nicotinamide. Immunosuppressive agents have also been used and these include: azathioprine, methotrexate, cyclophosphamide, gold, chlorambucil, and mycophenolate mofetil (reviewed in ref. [19]). However, the prolonged use of these immunosuppressive drugs can cause significant side effects and therefore may necessitate their discontinuation. Moreover, patients who are on long-term immunosuppressive therapy have an increased risk of developing malignancies. Patients with severe disease in whom immunosuppressive agents are not effective, are treated with intravenous corticosteroids, plasmapheresis, extracorporeal photopheresis, or intravenous cyclophosphamide ([19]), however, the mortality and morbidity associated with these approaches is not trivial. An alternative treatment with intravenous immunoglobulins (IVIg), which has increasingly being used for the treatment of autoimmune and systemic inflammatory diseases ([20]) appears to provide an effective control of PV ([21]). Having a demonstrable corticosteroid-sparing effect, IVIg is a safe and effective treatment modality in patients with PV who are dependent on systemic corticosteroids or who develop significant adverse effects as a result of their use ([19], [22],[23],[24]).

PV has been reported among males and females of all ages

in most countries of the world, with the incidence of between 0.1–3.2 cases per 100,000 individuals per year ([19, 26,27,28,29,30,31]). This incidence is higher in patients of Ashkenazi Jewish descent ([32]). The association of HLA antigens with the susceptibility to PV has been demonstrated in numerous studies ([33,34,35,36,37,38]). The etiology of PV is unknown but its direct linkage is attributed to the specific susceptible HLA alleles: HLA-DRB1*0402, DQB1*0302 in Jewish patients and HLA-DRB1*1401/1404, DQB1*0503 in non-Jewish patients. The purpose of this study was to review the literature and analyze the data on HLA typing of PV patients in search for the frequency of occurrence of Jewish and non-Jewish HLA haplotypes in different regions of the world.

MATERIALS AND METHODS

A retrospective review of the English language literature was carried out on reports of HLA typing of PV patients from different regions of the world. Search for articles of interest was conducted using the Pubmed search engine with the following key words:

1. HLA typing in Pemphigus Vulgaris
2. HLA association in Pemphigus Vulgaris
3. HLA in Pemphigus Vulgaris

Thirty reports, published between 1977 and 2006, presenting HLA typing data in PV patients, have been examined. Studies in which the data couldn‘t be correlated with the manifestations of PV, or the ones reporting on HLA typing of less than 15 patients, were excluded from the analysis. Hence, 22 publications were identified and studied ([38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59]). The following information was recorded in each case:

1. Country or region of the world where the PV patients were studied
2. Race or ethnic group representing PV patients
3. Number of patients recruited for the study
4. Number of healthy controls included in the study
5. Data on HLA typing
6. Statistical significance of the allele frequencies

RESULTS

DEMOGRAPHICS AND WORLD DISTRIBUTION OF THE STUDIED GROUPS OF PV PATIENTS

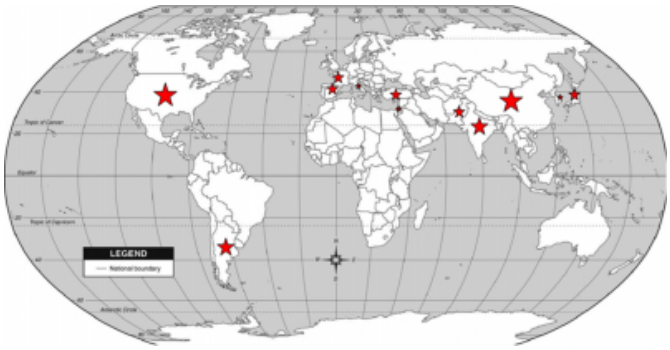
The PV patients were studied in different regions of the world (Fig.1). Details and assessment of the severity and extent of disease were not quantifiable because of variability in reporting. In several reports, the PV patients represented both Jewish and non-Jewish populations in a given country. Five studies reported the HLA typing data on patients living in the US ([38,39,40,41,42]), one from Pakistan ([42]), two from India ([43, 51]), six from Japan ([44,45,46,47,48,49]), one from Israel ([50]), one from Turkey ([52]), 2 from Italy ([53, 54]), one from Spain ([55]), one from Argentina ([56]), one from China ([57]), one from South Korea ([58]), and one from France ([59]). For more precise analysis and for narrowing the population variability, certain regions within the country were studied as opposed to the random distribution over the country.

PRIOR FINDINGS ON HLA TYPING OF PV PATIENTS

PV has been shown to strongly associate with the HLA serotypes HLA-DR4 and HLA-DR6 ([60]). Indeed, greater than 95% of PV patients possess one or both of these haplotypes ([61]). By direct nucleotide sequence analysis of DR4 and DR6 subtypes, susceptibility to PV has been linked to several molecular subtypes ([61,62,63,64]). However, population studies of patients with PV have clearly shown that there are differences among the most prevalent alleles in various ethnic groups. Nine DRB1 alleles have been associated with PV (DRB1*0402, *0403, *0406, *0802, *0804, *1401, *1404, *1405, *1408) in 11 distinct populations ([41, 42, 49, 53, 55, 56, 59, 65]). Two DQB1 alleles, DQB1*0302 and DQB1*0503, are associated with PV patients across the world as well ([43, 53, 56, 59, 65]). At the DQA1 locus, four alleles, DQA1*0101, *0104, *0301, and *0401, are associated with PV. In addition, several alleles have been negatively correlated with PV: DQB1*02, DQB1*0601, DQA1*0103, DRB1*03, DRB1*13, and DRB1*07 ([43, 48, 53, 54, 55, 59]) are postulated to have a protective effect; however, no study to date has demonstrated a direct preventive benefit to carrying a negatively associated allele.

Figure 1

Figure 1: Distribution of PV patients around the world.



The countries in which the PV patients have been mapped and reported in the literature searched are marked with red stars.

FREQUENCIES OF JEWISH AND NON-JEWISH ALLELES AMONG PV PATIENTS

The data obtained from the literature on each study is presented in Table 1.

HLA TYPING OF PV PATIENTS RESIDING IN THE US

Park et al. studied 23 Jewish PV patients and 180 normal White controls living in the metropolitan Los Angeles area in 1979 ([40]). The report found HLA-DRW4 in all 11 female and 10 out of 12 male Jewish patients with PV, a frequency of 91% in all, which was significantly higher than the 25% frequency among normal Jewish controls. The relative risk was 31.5. The BW38-DRW4 haplotype occurred in 12 out of 22 patients (55%) but in only 2% of White non-Jews and 11% of normal Jewish people.

In 1987, Ahmed et al. performed HLA typing for the A, B, C, and D locus antigens on 65 patients with PV and on 558 controls from the Los Angeles area ([38]). The patients were divided into several categories, including Jewish and non-Jewish patients, patients with only mucous membrane involvement, only skin or both mucous membrane and skin involvement, and those with a single-episode or recurrent disease. Depending on the highest titer of anti-intercellular cement substance antibody titer, the patients were categorized into those whose titers were 0-80, 160-320, and 640 or greater. A statistically increased incidence of HLA-A25, HLA-B38, and HLA-DR4 antigens was observed in patients compared to controls. Moreover, this incidence was significantly higher in Jewish compared to non-Jewish patients. The correlations were insignificant in the group with an antibody titer of 0-80, but considerable in those with a titer of 160-320, and even more significant in those with titers greater than 640. No major differences were present between patients who had a single-episode or recurrent disease or in those that had only mouth or only skin involvement. In all categories tested, the association was stronger with DR4 than with A26 or B38. Importantly, DR4 was present equally in B38-positive and B38-negative patients. Ahmed et al. concluded that in PV the primary association may be with the DR4 antigen, and it may be a marker for the severity of the disease.

Delgado et al. performed high resolution HLA class II typing in 19 patients with PV from Rawalpindi, Pakistan and of 19 non-Jewish European PV patients from Boston by sequence-specific oligonucleotide probe hybridization ([42]). The results were compared with two separate ethnically matched control populations. PV patients from Pakistan had significantly increased frequencies of DRB1*1404 ($p = 0.01$), DQA1*0101 ($p = 0.02$), and DQB1*0503 ($p = 0.01$). Among the patients of non-Jewish European ancestry, DRB1*1401 ($p < 10(-6)$), DQA1*0101 ($p < 10(-5)$) and DQB1*0503 ($p < 10(-6)$), were increased in PV patients. Formal linkage analysis between the MHC and the PV antibody was performed in 67 relatives of the 19 Pakistani patients. The results showed strong evidence for linkage of HLA-DRB1*1404, DQA1*0101, DQB1*0503, with the presence of PV antibody in relatives' families with a significant logarithm of the odds score of 6.06. Based on the three dimensional structure of class II molecules, the authors proposed that HLA-DQA1*0101 and DQB1*0503, encode a negatively charged P9 peptide binding pocket of the DQ molecule and are significantly associated with susceptibility to PV in non-Jewish populations.

Mobini et al. explored the possibility of the common ancestral origin between non-Jewish Iranian and Ashkenazi Jews by typing HLA alleles of 20 Iranian PV patients ([41]). Among these, 17 were found to carry DRB1*0402, DQB1*0302 haplotypes, similarly to the frequency found among normal Iranian haplotypes and to that of the Jewish PV patients. These findings suggested that the MHC susceptibility to PV gene among Iranians derived from the same ancestor as that in the Ashkenazi Jews. It is well documented that the ancient Jews were under Persian domination from 500 B.C. until 300 B.C. and in the 8th century A.D. Around that time, Tataric people living in the kingdom of Khazar on the Western shore of the Caspian Sea and the Northern shore of the Black Sea, near Persia, converted to Judaism, providing possible opportunities for

gene mixing in two populations that are distinct and separate today.

Lee et al. ([39]) reported genotyping data for the largest sampling of North American Caucasian non-Jewish and Ashkenazi Jewish PV patients studied to date and compared these data with other population studies. To detect true susceptibility of alleles among overrepresented sequences, a step-wise reductionist analysis has been applied through (1) determination of the degree of linkage disequilibrium (LD) between purportedly associated alleles, (2) haplotype frequencies comparisons, and (3) primary sequence comparisons of disease-associated versus non–disease-associated alleles to identify crucial differences in amino acid residues in putative peptide/MHC binding pockets. Taken together, the data provided extended support for the hypothesis that the HLA associations in Caucasian PV patients map to DRB1*0402 and DQB1*0503 alleles alone.

Figure 2

Table 1: Jewish and non-Jewish Alleles/haplotype in PV Patients from Different Regions of the World.

Study #	Reference #	Country/ Region	Race/ Ethnic Group	No. of patients	No. of controls	Statistics	Findings
1.	39 Lee (2006)	USA (Michigan)	Caucasians	58			DRB1*0402, 1401, 1404 DQA1*0104, 0301, 0303 DQB1*0303, 0302
2.	38 Ahmed (1987)	USA (California)	Caucasians	54	218	$p=10^{-7}$	HLA-DR4(78%)
3.	40 Park (1979)	USA (California)	Jews	23	100	$p=4.4x10^{-7}$	HLA-DRW4(91%) HLA-Bw38(55%) HLA-A26(41%)
4.	41 Mobini (1997)	USA (Boston)	NJ Iranian	20 (F+F)[1]	37	p<0.0001	**DRB1*0402= DQB1*0302= (17/20)(85%) DRB4*0101= DQA1*03 haplotype** DRB1*1401/04= DQB1*0303= (6/20)(30%) DRB3*02 haplotype
5a.	42 Delgado (1997)	Pakistan (Sweajmi)	Asian	19	26	p<0.01 p=0.02 p=0.02 NS	**DRB1*1404(21/38)(55.3%) DQB1*0503(22/38)(57.9%) DQA1*0101(24/38)(63.2%)** DRB1*04(4/38)(10.5%) DQB1*0302(3/38)(7.9%) DQA1*0301(6/38)(15.8%)
5b.	42 Delgado (1997)	USA (Boston)	Non-Jewish European vs Pakistani	19	496	$p<10^{-7}$ $p<10^{-6}$ $p<10^{-6}$ NS	**DQA1*0101(17/38)(44.7%) DRB1*1401(14/38)(36.8%) DQB1*0503(14/38)(36.8%)** DRB1*0402= DQB1*0302= (9/38)(23.7%) DQA1*0301
6.	43 Delgado (1996)	India	Indian	36 (New Delhi) (F+F) 38 (Ahmedabad) (F+F)	49 40	p=0.04 p=0.04 p=0.04 p=0.01 p=0.004 p=0.02 p=0.04	DRB1*1404(15/36)(41.67%) DQA1*0503(15/36)(41.67%) DRB3*0202(22/36)(61.1%) DQA1*0101(16/36)(44.44%) DRB1*1404(19/38)(50%) DQA1*0503(21/38)(55.26%) DRB3*0202(23/38)(60.52%) DQA1*0101(18/38)(47.36%)NS No data for Jewish alleles.
7.	44 Sakurai (1981)	Japan (Kyoto)	Japanese	17	144		B15(5/17)(47%), Bw35(7/17)(41%), Cw4(4/17)(24%) DRw4(7/17)(41%) All increased but insignificant
8.	45 Nunezki (1991)	Japan (Tokyo, Ieshara)	Japanese	17	100	p<0.005 p<0.05	DRw52(94.1%), DRw6(64.7%) DR5(41.2%), DRw12(35.3%)
9.	46 Miyagawa (2002)	Japan (Hagamchubo)	Japanese	43	60	p<0.025	A10(41.3%) - all belonged to Aw26 group
10.	47 Hashimoto (1977)	Japan (Tokyo)	Japanese	31	117		**DRB1*1401/1405(18.51)(58.06%)** DRB1*0406(9/31)(29.03%)
11.	48 Nunezki (1994)	Japan (Tokyo)	Japanese	32	45	p for DRB1*1405 =0.001 DQB1*0503 =0.001	**DRB1*1401(28%), 1405(28%),** 1406(19%), 1403(16%) DQB1*0503(56%) DQA1*0301+0106(50%) **DRB1*0402(9%),** 0403+0405(9%), 0406(22%) DQB1*0302(38%) DQA1*0301(50%)
12.	49 Matsuyama (1981)	Japan (Osaka)	Japanese	20	73		DR4(55.5%) DR5 increased but not significant
13.	50 Shamov (2003)	Israel (Tel Aviv)	Jews	38	76		**DRB1*04 (29/38)(76.3%)** DRB1*14 (10/38)(26.31%) Both 04 & 14 (7/38)(18.42%)
14.	51 Wilson (1994)	India (New Delhi)	Indian (North Indian Hindu)	43	NA		HLA-DR4(34%) HLA-DR1(26.9%)
15.	52 Birol (2002)	Turkey (Ankara)	Turkish	27	100		DR4, DQ3 (12/27)(44.44%) DR1/4/1, DQ1 (10/27)(37.03%)
16.	53 Lombardi (1999)	Italy (Naples)	Italian	61	128	p<0.0001 p<0.0001 p<0.005 p<0.0001	**DQB1*0303(62.2%) DRB1*1401(44.2%)** DQB1*0302(34.4%) DRB1*0402(32.7%)
17a.	54 Carcassi (1996)	Italy (Rome)	Sardinian	16	91	$p<10^{-6}$ $p=1.2x10^{-5}$ $p=3.5x10^{-5}$ $p=3.5x10^{-5}$ $p=3.5x10^{-5}$ p=0.024	**DRB1*0402= DQB1*0302= (13/16)(81.25%) DQA1*0301** DRB1*1401= DQB1*0303= (5/16)(31.25%) DQA1*0104
17b.	54 Carcassi (1996)	Italy (Rome) (Central/ Southern Italy)	Italian	16	264 (DRB1) 406 (DQB1) 462 (DQA1)	$p>2.8x10^{-5}$ $p<10^{-8}$ $p=4.5x10^{-7}$ $p=1.5x10^{-7}$ $p=4.7x10^{-7}$ $p=7.4x10^{-7}$	**DRB1*1401= DQB1*0503= (12/16)(75%) DQA1*0104** DRB1*0402= DQB1*0302= (7/16)(43.75%) DQA1*0301
18.	55 Gonzales-Escribano (1998)	Spain (Sevilla)	Spanish Caucasians	26	200	$p=1.1x10^{-7}$ $p=4.7x10^{-7}$ $p=3.6x10^{-7}$ $p=5.8x10^{-7}$	**DQB1*0302(23/26)(88.8%)** **DRB1*0402(21/26)(80.8%)** DQB1*0303(8/26)(30.8%) DRB1*1401(7/26)(28%)
19.	56 Olorio (2002)	Argentina (Buenos Aires)	Caucasians European Ancestary	47	199	$p<10^{-8}$ $p<10^{-8}$ $p<10^{-6}$ $p<10^{-2}$	**DRB1*0402(17/47)(63.82%) DQB1*0302(25/47)(53.19%)** DRB1*1401(15/47)(31.91%) DQB1*0303(14/47)(29.78%)
20.	57 Geng (2005)	China (Shanyang)	Chinese	27	105 (Gen 1) 469 (DRB1) 166 (DQB1)	p=<0.05 $p<10^{-5}$ $p<10^{-5}$	A3(13/27)(48.15%), A26(8/27)(29.6%), B60(40)(11/27)(40.7%) **DRB1*1403=(1401.4.5.7. 8)(18/27)(66.7%)** DRB1*0402=(7/27)(25.92%)**NS** **DQB1*0503(11/27)(40.7%)** DQB1*0302(5/27)(18.5%)**NS**
21.	58 Lee (1998)	South Korea (Seoul)	Korean	15	100	p=0.0001	**DRB1*01(9/15)(60%)** DRB1*04(8/15)(53.3%) NS DQB1*0302(3/15)(6.7%)NS DRB1*1402(5/15)(8%)NS DQB1*0503(5/15)(33.3%)NS DQA1*0301(10/15)(66.7%)NS DQA1*0102(6/15)(40%)NS
22.	59 Loiseau (2000)	France (Paris)	French (diverse origin) Caucasian, Asian & North African	37	106	$p=10^{-10}$	**33 out of 37(89.18%)** patients were either DRB1*-1401 or 1404- DQB1*0503 or DRB1*0402 -DQB1*0302 No separate data for the Jewish and non-Jewish alleles/haplotype.

[1] Patients with their family members were HLA typed, in the rest of the cases only patients have been typed

STUDIES OF HLA HAPLOTYPES IN PV PATIENTS FROM INDIA

Delgado et al. compared high resolution MHC class II alleles and haplotype frequencies (HLA-DRB, DQA1 and DQB1) in 37 patients with PV to 89 haplotypes of normal relatives from New Delhi and Ahmedabad ([43]). The study showed that PV patients had significantly increased frequencies of DRB1*1404 ($P < 0.0001$), DQA1*0101 ($P = 0.001$), and DQB1*0503 ($P < 0.0001$). These associations were due to the increased frequencies of the haplotype HLA-DRB1*1404, DRB3*0202, DQA1*0101, DQB1*0503 in patients compared to control haplotypes ($p < 0.0001$). Also, patients from Ahmedabad had a significant increase in HLA-DQB1*0302 ($p = 0.03$). The authors further speculate on the genetic basis of autoantibody response in PV patients carrying DR14 alleles. Since an identical amino acid sequence (Leu-Leu-Glu-Arg-Arg-Arg-Ala-Glu), in positions 67-74 of the beta domain of DRB alleles is restricted to some DR14 alleles, there might be three possible scenarios. First, class II alleles could correspond to an unidentified susceptibility gene found in linkage disequilibrium. Second, the primary association could be with DQB1*0503 and the association with HLA-DR14 alleles would be the result of linkage disequilibrium. Third, the HLA-DRB1 locus susceptibility could involve a specific amino acid sequence in the third hypervariable region shared by several HLA-DR14 alleles.

Wilson et al. reported on clinical and histological subtypes and socio-economic data, and HLA typing of 50 PV patients in New Delhi, India, and 20 patients in Oxford, UK ([51]). Interestingly, PV predominated in New Dehli, but in Oxford, PV and pemphigus foliaceus (PF) have equal prevalence. Disease distribution with gender was the same, but age at onset was significantly lower in New Delhi ($p = 0.0019$). HLA typing in PV patients revealed a significant reduction in HLA-DR2 in New Delhi ($p = 0.0008$) and Oxford ($p = 0.09$). A small increase in HLA-DR1 and -DR4 was found in both groups and, in males only, a subtle increase in HLA-DR6 and reduction in HLA-DR3. No differences were found in the class I antigens. Thus, in spite of the striking differences in the types of PV between the two populations, the genetic predisposition appears to be the same.

HLA TYPING IN JAPANESE PV PATIENTS

Sakurai et al. examined 17 Japanese patients with PV by HLA typing ([44]). HLA-DRW2 was found in none of them as compared to 56 (39%) of 144 Japanese controls ($p = 0.02$). The association of HLA-DRW4 with PV was not found in this study. HLA-A, B and C typings were also performed, showing relatively high frequencies of the B15, BW35 and CW4. However, the occurrence of these specificities was not statistically significant. It was suggested that DRW2 plays an important role in the susceptibility to PV.

Niizeki et al. ([45]) investigated the HLA class II antigens in 30 Japanese cases of pemphigus, 17 cases of PV and 13 cases of PF, by both serologic and restriction fragment length polymorphism (RFLP) analyses. Two major haplotypes susceptible to PV were detected, i.e., DRw12-DQw7 and DRw6-DQw5. In contrast, DR2 was absent in PV. RFLP analyses showed that DRw6 PV patients had a disease-associated restriction fragment representing DQw5, the same association as that found in DRw6 Jewish PV patients. However, DRw12 Japanese PV patients had DQw7, whereas DR4 Jewish PV patients had DQw8. On the other hand, all 13 PF patients were serologically typed for DQw1, which could not be further subdivided into DQw5 by RFLP analyses. These results suggested that Japanese and Jewish PV patients may be immunogenetically closely related to each other, but Japanese PV patients appear to be immunogenetically different from Japanese PF patients.

In view of the limited reports on MHC class I antigens in PV, Miyagawa et al. conducted characterization of HLA-A, B and C class I alleles by genotyping of Japanese PV patients, and analyzed the possible association of class I alleles with disease susceptibility within a relatively homogeneous ethnic population ([46]). Alleles of HLA-A, B and C, and DRB1 and DQB1 loci were fully determined in 51 Japanese patients with PV. Asian alleles of the HLA-B15 family, including the allele B*1507, which was significantly increased in comparison with normal controls, were prevalent in PV patients. The prevalence of B*15 alleles in patients with PV was not due to linkage disequilibrium with HLA-DR4 or DR14 alleles, which have been shown to confer strong susceptibility to PV across racial barriers. In contrast to the unique distribution of the HLA-B alleles, HLA-A and C alleles were unremarkable in patients with PV when compared with normal control subjects. These results suggested that there may be differences in the ethnic concentrations of different HLA-B alleles in patients with PV.

The study by Hashimoto et al. ([47]) was carried out to determine whether HLA-A10 or HLA-Aw30 antigens are increased in Japanese PV patients. The frequency of the MHC antigen, HLA-A10, was significantly increased

(corrected P < .025) in 43 unrelated patients with PV (41.9%) and in 25 patients with PF (48.0%), when compared with 60 unrelated healthy controls (16.7%). No significant correlations with other HLA or differences between PV and PF were observed. Both forms of pemphigus were considered to associate with the HLA-A10.

Niizeki et al. performed HLA-DQA1, -DQB1 and -DRB1 genotyping using the PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) method for 32 Japanese PV patients ([48]). There was a significant association of either DQB1*0503 or DRB1*1405 with PV, and a negative association with PV of either DQA1*0103 or DQB1*0601 alleles. Since the DQB1*0503-positive patients had various DR14-related alleles, the authors concluded that the association with DQB1 is primary and that the association with DRB1 is simply due to linkage disequilibrium between the DQ and DR genes. These results may indicate that specific HLA class II antigens confer the susceptibility to PV among Japanese.

Matsuyama et al. carried out the study in order to find out whether the frequency of HLA-DR4 allele associated with PV in Jewish patients is also increased among Japanese PV patients ([49]). The report showed that the frequency of HLA-DR4 was significantly increased at p<0.02 in 37 unrelated PV patients (62.2%), when compared with unrelated 73 healthy controls (30.1%). Interestingly, this antigen was more frequently found in PF (70.6%) than PV (55.8%).

TYPING OF PV PATIENTS IN ISRAEL

It has been reported that HLA B38, DRB1*0402, DQB1*0302 haplotype is associated with PV in Jews. Significant associations with HLA were also observed in non-Jewish population. The observation that Dsg3-specific T-cell responses were detected in PV patients but also in healthy individuals who were either carriers of the PV-associated DRB1*0402 allele or alleles that share similar or identical peptide binding motifs to DRB1*0402, suggested that genes other than those of classical MHC are associated with the development of the autoimmune response. Slomov et al. used 16 microsatellite probes that span the entire MHC region to screen DNA samples from 38 PV patients and 76 healthy controls ([50]). The study demonstrated that some markers were associated with class II region including a TAP associated marker. However, four probes, D6S265, C_527, D6S510, and MOGC, which are all mapped to the region of HLA-A, were also highly associated with PV. These results suggested that a gene, or genes in the class I region might be important for the initiation of the autoimmune cascade.

HLA SPECIFICITIES IN TURKISH PV PATIENTS

Birol et al. investigated the antigen frequencies of HLA-A, B, C, HLA-DR and DQ in Turkish patients with PV by typing of HLA class I and II antigens in 33 patients with PV and 100 healthy individuals by microdroplet lymphocyte cytotoxicity test ([52]). Occurrence of HLA-B35, B44, CW4, DR4, DR14, DQ8 and DQ4 antigens was significantly higher in the study group, whereas HLA-DR11, DQ7 and DQ2 antigens were elevated among the controls. The most striking differences were observed in HLA class II antigens. HLA DR14-DQ8 and HLA B35-DR14 haplotypes were most frequently observed in the study group. Thus, HLA-B35, B44, CW4, DR4, DR14, DQ4 and DQ8 antigens may be responsible for susceptibility to PV, while HLA-DR11, DQ7 and DQ2 antigens may have a protective role in the Turkish population. On the other hand, it can not be excluded that that the exogenous factors might induce PV in genetically predisposed individuals.

HLA TYPING OF PV PATIENTS IN ITALY

Lombardi et al. reported on HLA molecular typing of 87 patients, 61 with PV and 26 with PF, versus 128 healthy matched controls ([53]). Generic typing showed an increase of DRB1*04 and DRB1*14 and a decrease of DRB1*07 in both PV and PF patients. Molecular subtyping of DR4+ and DR14+ subjects showed a highly significant association between the DRB1*1401 and both PV ($p < 0.0001$) and PF patients ($p < 0.0001$) together with a significant increase of the linked DQB1*0503 (PV, $p < 0.0001$; PF, $p < 0.0001$). Moreover, whereas the association between DRB1*0402 and PV ($p < 0.0001$) has been confirmed, no significant association between a specific allele of the DR4 group and PF, has been found. Therefore, at least in Italian patients, PV and PF share DRB1*1401 and DQB1*0503 as susceptible HLA alleles, whereas DRB1*0402 is only found associated with PV. The observation that both diseases carry the same susceptible HLA alleles has been interpreted on the basis of a common genetic background predisposing to pemphigus, similarly to other autoimmune disorders, in which the onset of the disease is determined not only by these susceptible alleles, but also by presence of other linked genes and/or environmental factors.

Carcassi et al. studied HLA class II antigens and DRB1, DQA1, DQB1 alleles in 16 Italian and in 16 Sardinian patients with PV ([54]). In the last group, the complete HLA A-

DQ haplotypes, including the complotypes, were defined by family studies. As in other populations, two PV susceptibility haplotypes were found: HLA-DRB1*0402, DQA1*0301, DQB1*0302 and HLA-DRB1*1401, DQA1*0104, DQB1*0503. The first haplotype was largely prevalent in the Sardinian patients and was a part of the extended haplotype HLA-A2, Cw4, B35, S31, DR4, DQ8. The strength of the allele associations to PV was in agreement with the view that the main PV susceptibility genes are the DRB1*0402 and DQB1*0503 alleles. A genetic resistance to PV in the Sardinian population was conferred by the HLA-DR3, DQ2 haplotype.

PV-RELATED ALLELES IN SPAIN

Gonzalez-Escribano et al. HLA typed twenty-six unrelated Spanish Caucasian individuals affected by PV and compared frequencies with those of 200 ethnically matched healthy controls ([55]). Twenty-three out of 26 patients were HLA-DR4. The frequency of HLA-DR14 was also increased (31%; controls: 4%). Of the 23 patients positive for HLA-DR4, 21 carried the DRB1*0402 allele. Therefore, the frequency of HLA-DRB1*0402 among patients was 81% (4% in controls; P=4.7x10(-27), OR=100.8). Interestingly, HLA-DR13, a frequent HLA-DR specificity in the Spanish general population (27%), was absent among the PV patients (P=0.009; Pc=0.1; OR=0.05). Taking together, these data suggested that in the Spanish population PV is preferentially and strongly associated with HLA-DRB1*0402, whereas DRB1*13 seems to confer a protective effect in this population.

HLA TYPING OF PV PATIENTS IN ARGENTINA

Glorio et al. attempted to determine the relative risk and the frequency of class I and class II HLA antigens and the allelic variants of the class II HLA antigens, DR and DQ, in patients with PV ([56]). An observational, prospective, transverse, and controlled study was carried out between 1995 and 1999. Forty-seven patients with a diagnosis of PV and a control sampling of 199 unselected individuals from the same ethnic group were included. The HLA alleles were determined by polymerase chain reaction. The study detected no significant associations between HLA A, B, or C and the PV patients. The DR and DQ molecular alleles positively associated with PV were of the two different haplotypes: DRB1*0402/DQB1*0302 and DRB1*1401/DQB1*0503. In patients with the haplotype DRB1*0402/DQb1*0302 the affectation of 10%-30% of the corporal surface prevailed (ACS). In patients with DRB1* 1401/DRQB1*0503, involvement of <10% of the ACS prevailed.

HLA STUDIES OF PV PATIENTS IN CHINA

Geng et al. investigated the relationship between PV and HLA in Han nation of northeast China ([57]). Standard microcytotoxicity test and PCR-sequence specific primers method were used to detect the HLA class I antigens and HLA-DRB1 and DQB1 alleles in 27 patients with PV, and results were compared with control group. Gene and phenotype frequencies of HLA-A3, A26(10), B60(40), and B13 (27.99%, 48%; 16.11%, 30%; 23.02%, 41%; 16.11%, 30%, respectively) increased significantly in PV group compared with control (1.01%, 2%; 0.5%, 1%; 4.61%, 9%; 5.13%, 10%, respectively). After P value correction, the difference of A3, A26 (10), and B60 (40) between the two groups was still significant. The gene frequencies of HLA-DRB1*140x (1401, 1404, 1405, 1407, 1408), DRB1*120x, and DQB1*0503 alleles in PV group (42.26%, 25.46%, and 23.02%) were significantly higher than control group (5.09%, 7.74%, and 1.89%). After P value correction, the difference was still significant between the two groups. Thus, PV was found to strongly associate with the HLA in Han nation of northeast China.

TYPING OF KOREAN PV PATIENTS

Lee et al. examined the distribution/frequency pattern of HLA class II alleles (DRB1, DQA1 and DQB1) from a group of 30 Korean patients with pemphigus (15 PV and 15 PF) by PCR amplification with sequence-specific primers ([58]). They found that the frequency of DRB1*01 allele in PV was significantly higher (pc = 0.0014); in PF, DRB1*01, DQA1*0302 and DQB1*0603 alleles showed positive associations with statistical significances (pc = 0.0002, 0.0007 and 0.0067, respectively), when compared with those found in Korean controls. In conclusion, in this small-sample study the findings of allelic frequencies among Korean patients with pemphigus were somewhat different from those found in other populations.

HLA TYPING OF PV PATIENTS IN FRANCE

Loiseau et al. ([59]) conducted molecular typing of 57 French patients suffering from PV (37 patients) and from PF (20 patients), confirming previous results on PV association with HLA and showing that DRB1*0102 and 0404 are PF-susceptible molecules in France. The characteristics of the 'pockets' of the PV and PF susceptibility-associated molecules have been analyzed, resulting in the following observations: (i) in PV, two kinds of Dsg3 derived peptides may be presented by HLA-DR according to HLA

polymorphism (DRB1*0402 or DRB1*14/0406); (ii) the same Dsg1 peptides may be presented by DRB1*0102, DQB1*0404 or DRB1*14 in PF; and (iii) the DRB1*14/0406 PV-related molecules may be able to present Dsg1 and Dsg3 peptides thereby providing an explanation for the cases of PV with combined responses to Dsg1 and to Dsg3, which are manifested by a muco-cutaneous clinical phenotype.

DISCUSSION

The goal of the present study was to review the English language literature on the HLA mapping in PV patients and to determine the frequencies of PV-associated Jewish and non-Jewish haplotypes in different regions of the world. The data reviewed in twenty two studies suggests that Ashkenazi Jewish (HLA-DRB1*0402, DQB1*0302) haplotype occurs at similar frequencies in PV patients from different ethnic populations, regardless of the geographic region. On the other hand, non-Jewish PV patients exhibit HLA-DRB1*1401/1404, DQB1*0503 haplotype at varying frequencies. This observation brings on speculations regarding the possible connection or common origin of PV-susceptible alleles in Jews and other ethnicities.

Previous work has failed to precisely define the genetic links responsible for HLA associations with disease susceptibility in PV. In particular, there has been difficulty in determining whether HLA class II loci alone or in haplotypic combinations influence disease. Multiple, ambiguous associations and a lack of consensus autoantigenic epitopes relegate our knowledge of autoimmune induction to hypothesis at this stage. Assignment of substantiated susceptibility loci within the HLA region is a requisite for understanding MHC-mediated control of autoimmunity and may facilitate the formulation of antigen-specific and individualized therapies. The identification of susceptibility loci, however, relies on continued HLA genotyping of patients and controls.

PV-ASSOCIATED ALLELES IN THE WORLD

Multiple alleles have been reported to be overrepresented in PV patients of different ethnicities. At the DRB1 locus, the frequencies of three alleles, DRB1*0402, 1401, and 1404, were significantly overrepresented in non-Jewish patients. DRB1*0402 was the most significantly associated allele (50%), while 36% of PV patients carried *1401, and 11% carried *1404 ([39]). Similar observations were reported for Iranian ([41]), Italian ([53]), Sardinian ([54]), Spanish ([55]), Argentinean ([56]) and French ([59]) populations. Frequency of DRB1*1401 has been increased in Japanese ([46]) and Mediterranean patients ([53, 54, 59]), as well as the higher occurrence of DRB1*1404 allele in Chinese ([65]), Pakistani ([43]) and French ([59]) PV patients. In contrast, only DRB1*0402 was significantly overrepresented at the DRB1 locus in Ashkenazi Jewish patients ([39]).

At the DQA1 locus, three alleles *0104, *0301, and *0505, were significantly overrepresented in non-Jewish patients ([39]). DQA1*0104 and *0301 have been associated with PV in previous studies; *0301 was found at increased frequencies in Japanese patients ([46]) and *0104 has been associated with PV in Indian, Pakistani, and various European patient populations ([42, 43, 54, 59]). However, DQA1*0505 has not been previously associated with PV. DQA1*0501 allele was underrepresented ([39]) and found to be negatively associated with PV in one study of Iranian patients ([41]), but has not been directly linked to any protective role in PV. DQA1*0505 and DQA1*03 were also significantly overrepresented in the Ashkenazi Jewish PV group ([39]). The DQA1*03 association with PV has been reported in Japanese and Sardinian patients ([46, 54]). DQA1*0501, *0101, *0102, and *0201 were negatively associated in this population.

The frequencies of two alleles at the DQB1 locus, DQB1*0503 and *0302, differed significantly in non-Jewish Caucasian patients from controls ([39]). DQB1*0302 has been reported in studies of other non-Jewish Europeans (French, Italian, Sardinian) ([54]) and DQB1*0503 has been reported to be overrepresented in patients of who are non-Ashkenazi Jews of Mediterranean descent ([41, 42]) as well as several other ethnic groups ([43, 48, 53, 56, 59, 65]). In Ashkenazi Jews, the only significantly elevated allele at the DQB1 locus was *0302 ([39]), consistent with previous reports, while DQB1*0201 and *0301 were found to be underrepresented in these patients.

Collectively, DRB1*0402, *1401; DQA1*0104, *0301, *0505; and DQB1*0503 and *0302 were overrepresented in non-Jewish PV patients, whereas DQA1*0501 was the sole underrepresented allele. In Ashkenazi Jewish PV patients, DRB1*0402, DQA1*03, 0505, and DQB1*0302 were overrepresented, whereas DRB1*0301, *07, *1104; DQA1*0101, *0201, *0501; and DQB1*0202 and *0301 were negatively associated with PV. Since strong linkage disequilibrium (LD) is known to exist across DR-DQ loci, it is unlikely that all overexpressed/underrepresented alleles represent a true association with disease. Therefore, degrees of LD between candidate alleles were quantified to identify

significantly deviated alleles that may be over/underrepresented solely because of linkage with a true PV-associated allele ([39]). In the non-Jewish Caucasian group, DRB1*1401 and DQA1*0104 were found to be in LD with DQB1*0503 ([39]). DQB1*0302 and DQA1*0301 were found to be in LD with DRB1*0402. DQA1*0505 was the only significantly overrepresented allele that did not demonstrate LD with either DRB1*0402 or DQB1*0503 alleles. In the Ashkenazi Jewish population, the three overrepresented alleles, DQA1*0505, DQA1*03, and DQB1*0302 were all found to be in LD with DRB1*0402 ([39]).

Analysis of the allelic pair DRB1*0402- DQB1*0302 revealed that DRB1*0402 is the most likely disease-conferring allele in non-Jewish Caucasian PV patients, whereas DQB1*0302 is more prevalent in patients because it is in LD with DRB1*0402. Likewise, analysis of the allelic pair DRB1*0402-DQA1*0301, demonstrates a similar pattern. Both haplotypes {DRB1*0402; DQA1*0301} and {DRB1*0402; not DQA1*0301} are significantly elevated in PV patients versus controls. Examination of the pair DQB1*0503 - DRB1*1401 reveals that both {DQB1*0503; DRB1*1401} and {DQB1*0503, not DRB1*1401} are significantly elevated in patients. However, when DQB1*0503 is excluded from the haplotype (not DQB1*0503; DRB1*1401), the frequency ceases to be significantly different in patients versus controls. Thus, DQB1*0503, rather than DRB1*1401, is more likely to be the disease-conferring allele in non-Jewish Caucasian PV patients.

In order to assess whether a preventative benefit is conferred by carrying a negatively associated allele, a haplotypic analysis was applied to respective control populations. The data showed no significant differences in frequency of the eight negatively associated alleles. Therefore, none of these underrepresented alleles demonstrates a protective role in DRB1*0402-linked susceptibility in Ashkenazi Jewish controls. In the non-Jewish Caucasian population, the frequency of underrepresented DQA1*0501 allele was compared in controls who were carriers of the PV-associated allele, DQB1*0503 versus non-carriers. No significant differences in the frequency of DQA*0501 was detected, suggesting that there was no protective effect of DQA1*0501 allele in PV.

POLYMORPHISMS IN HLA POCKET RESIDUES

To further detect the functional relevance of candidate loci, primary sequence comparisons between reported PV associated and PV non-associated HLA alleles have been undertaken. Since disease-associated alleles can be expected to share common features within their antigen-binding clefts required for peptide binding and T-cell activation as a requisite for disease induction, specific residues within critical pockets (P1, 4, 6, 7 and 9) of relevant DRB1, DQB1, and DQA1 molecules were compared to segregate disease-relevant sequences among overrepresented alleles and haplotypes.

DRB1 POCKET POLYMORPHISMS

Two negatively charged amino acid residues within the DRB1 binding pocket have been postulated as critical to the binding of positively charged self-peptides in PV patients ([59, 66,67,68]). Negatively charged residues within pocket 4 (P4), Asp and Glu at positions 70 and 71, respectively, are found in the PV-associated allele, DRB1*0402. Although DRB1*1401 has been associated with PV in several populations ([41, 43, 46, 53,54,55,56, 59, 65]), sequence comparison with other DR*04 and DR*14 non–PV-associated alleles reveals that DRB1*1401 is more similar to disease-unrelated alleles. In contrast to DRB1*0402, DRB1*1401 has a positively charged amino acid at residues 70 and 71 (Arg), as do two non–PV-associated alleles, DRB1*1405 and *1406. These data support our analysis of LD relationships and haplotypic comparisons indicating that the DRB1*1401 molecule does not directly confer risk, but is overrepresented in patients because of LD with DQB1*0503. In fact, of the 59 DR*04 alleles that have been sequenced to date, only two other non–disease-associated alleles, *0414 and *0437, carry negative charges at position 70 and 71 in P4—all other alleles possess at least one positive charge at either of these positions (Arg or Lys). Although it appears that negatively charged amino acids may be required at position 70 and 71 in pocket P4 for the DRB1 allele to confer disease susceptibility, the presence of these polymorphisms alone are not sufficient—in addition to DRB1*0414 and *0437 other DRB1 alleles, such as *1301 and *1302, also carry D/E at position 70 and 71 but are not associated with PV. Thus the conformation conferred by other residues within or outside the P4 pocket are likely to contribute to the immunogenicity of DRB1*0402.

Analysis of the primary sequence of the underrepresented alleles in the AJ population (DRB1*07, DRB1*0301, and DRB1*1104) did not reveal significant charge differences to distinguish these potentially protective alleles from either PV-associated or non–PV-associated alleles. Both DRB1*1104 and *0701 carry a negative charge at position

70 (Asp) and a positive charge at 71 (Arg), whereas DRB1*0301 has an essentially positively charged P4 pocket (Arg, Thr at positions 70 and 71, respectively).

DQB1 POCKET POLYMORPHISMS

Comparison of primary sequences of reported DQB1 PV-associated and non–PV-associated alleles reveals a noticeable polymorphism at residue 57 of P9 ([61], [62], [63], [68]). DQB1*0302 molecules carry the uncharged amino acid Ala at position 57, as do several non–PV-associated alleles. DQB1*0301, which is minimally associated with disease by allele frequency, as reported by a single study from Japan ([46]), has a positive Asp residue at position 57, similar to the strongly disease-associated DQB1*0503. However, DQB1*0301 differs at multiple other sites within the binding pockets (residue 86 of pocket 1, residues 13, 70, 71, 74 of pocket 4, and residues 30 and 71 of pocket 7) from DQB1*0503. In the Ashkenazi Jewish PV population, DQB1*0301 was underrepresented, thus highlighting DQB1*0503 as the true disease susceptibility allele at the DQB1 locus ([39]).

DQB1*0201 allele has been shown to negatively associate with PV in several studies ([39], [43], [54], [59]). DQB1*0201/0202 alleles have a negatively charged Glu ([86]), a positively charged Lys ([71]) and a hydrophobic Ala ([57]) in pockets P1, P4, and P9, respectively. By comparison, DQB1*0503 carries Ala ([86]), Ala ([71]), and a negatively charged Asp ([57]). The functional relevance of these polymorphisms to the structure and function of positively and negatively disease associated molecules must await a fuller elucidation of DQ-associated T-cell epitopes.

DQA POCKET POLYMORPHISMS

DQA1*0301 allele is elevated in both non-Jewish Caucasian and Ashkenazi Jewish patients and DQA1*0104 is additionally elevated in non-Jewish Caucasian patients ([39]). DQA1*0101 was underrepresented in Ashkenazi Jewish patients in one study ([39]), however, it has been positively associated with disease in Indian, Pakistani, and non-Jewish Europeans PV patients ([42], [43]).

The overrepresentation of DQA1*0505 and under-representation of DQA1*0501 detected in both non-Jewish Caucasian and Ashkenazi Jewish patients have not been previously described in other PV populations. Multiple differences are detected when the sequences of DQA1*0505 and DQA1*0501 are compared to both PV- and non–PV-associated alleles. Furthermore, DQA1*0505 and DQA1*0501 are identical across key pocket-forming residues within the peptide-binding groove. It is unlikely that DQA1*0505 functions as a disease-susceptibility allele whereas DQA1*0501 functions as a protective allele when they share such significant sequence homology at critical peptide-binding sites, diminishing the likelihood that these sequences are directly relevant in PV. Without direct sequencing data, it is difficult to confidently conclude that a valid positive or negative association of either DQA1*05 allele exists.

Thus, susceptibility to PV appears to be viable by at least two primary MHC-mediated pathways. Worldwide, DR4-associated PV maps predominantly to the DRB1*0402 allele, whereas responsibility for DR6-associated disease can be narrowed to DQB1*0503. It remains to be determined if the phenotypic spectrum and fine specificity of autoreactive T-cell populations in DR4 and DR6 individuals is overlapping or entirely distinct. Differences in the regulation of cytokines that induce the expression of MHC molecules or polymorphisms in antigen-processing enzymes may also contribute to the existence of two modes of PV induction. Similarly, the molecular basis for the persistent association in the Asian population with DRB1*0403 and *0406, alleles that are structurally distinct from *0402, awaits further elucidation through the development of allele-specific T-cell lines and associated self-epitopes. The functional consequences of HLA sequence polymorphisms may be best revealed by examining site-specific mutations within peptide binding pockets to determine if critical charge differences at relevant residues can alter the selection of self-epitopes and T-cell response.

The existence of protective alleles has been explored in several autoimmune diseases including type 1 diabetes mellitus ([69], [70], [71]), multiple sclerosis ([72]), lupus nephritis ([73]), and rheumatoid arthritis ([74],[75],[76],[77]). In PV, multiple studies have reported alleles present at significantly lower frequencies, but there has been no direct demonstration that these sequences downgrade risk. Eight underrepresented alleles in Ashkenazi Jewish patients have been observed ([39]). Two of these alleles, DQA1*0101 and DQB1*0301, have been linked to disease development in prior studies. DRB1*1104, underrepresented in Ashkenazi Jewish population, was also negatively associated with disease in Iranian patients ([41]). However, Dsg-responsive, DRB1*1104-restricted T-cell clones have been reported in one study ([67]). The remaining five negatively associated alleles, DQB1*02, DRB1*0301, DRB1*07, DQA1*0501, and DQA1*0201, do

not possess sequence polymorphisms that distinguishes them from either PV-associated or non–PV associated alleles. However, the negative associations of DQB1*02, DRB1*0301, DRB1*07, and DQA1*0501 have been reported in previous studies ([41, 53, 54, 59]). Of note, DRB1*0301 and DRB1*07 are known to be in linkage disequilibrium with DQB1*02 ([59]).

To further evaluate negatively associated alleles, a haplotypic comparison in healthy individuals has been performed ([39]), however, this analysis did not yield an elevation in any of the potentially protective alleles in susceptible controls. In the future, a more direct measure of protective allele function may be ascertained by genotyping healthy relatives of PV patients and correlating autoantibody titers with the presence of susceptibility alleles in combination with potentially protective alleles. Ahmed et al. have observed low levels of autoantibody in 48% of healthy relatives of PV patients, and the inheritance of this trend was linked to the DR4 and DR6 haplotype; however, the absence/presence of protective alleles in this context was not directly assessed ([78]). Three dimensional models of negatively associated MHC class II alleles allowing an examination of the pocket surface electrostatic potential conferred by the primary amino acid sequence may also yield insight as to how protective alleles could alter the presentation of self-peptides to ultimately prevent the activation of autoreactive T cells ([79]).

Of interest is the study showing that the majority of Iranian PV patients carry the DRB1*0402, DRB4*0101, DQB1*0301, DQA1*03 haplotype identical to that of Ashkenazi Jewish PV patients ([41]). This observation leads to the speculation on the possible common origin of these two ethnic populations. In the historical perspective, Jews were under Persian rule in ancient Palestine for 2 centuries from 500 to 322 B.C. Moreover, the conversion of the Kingdom of Khazaria, which spread over the area between Caspian and Black seas, into Judaism around 740 A.D. ([80]), followed by the migration of Khazar people to the West due to the Mongol invasion from the East, might have been the source of Ashkenazi Jews of eastern Europe ([81,82,83,84]). Since there is a common MHC susceptibility gene in Ashkenazi Jewish and Iranian PV patients, it is likely that this trend arose before the separation of the two populations more than a millennium ago.

The high frequency of the Jewish haplotype in PV patients worldwide is a significant observation which might be important for development of novel immunotherapies. In view of the emerging role of T cells in the pathogenesis of PV ([85]), and in spite of the unambiguous function of B cells and anti-Dsg autoantibodies in breakage of tolerance and induction of autoimmune responses, it might be feasible to treat PV patients carrying HLA-DRB1*0402, DQB1*0302 alleles with the immunological approaches aimed at intervention of the structural modalities of HLA-peptide/T cell recognition processes.

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