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Association of HLA Class I And Class II Genotyping in Autoimmune Vesiculo-Bullous Lesion of Skin

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Abstract:

BACKGROUND: Autoimmune vesiculo-bullous diseases of skin are characterized by autoantibodies against different intra-/extracellular structures within the epidermis and at the basement membrane zone. The human leukocyte antigen (HLA) also known as major histocompatibility complex, are involved in antigen processing and presentation, and usually show highly significant associations with autoimmune diseases

AIM: To study the association of HLA class I and class II alleles with cases of Autoimmune vesiculo-bullous lesion of the skin.

MATERIAL AND METHOD: A case-control observational study comprised of 37 cases of AIBD has been done by punch biopsy followed by histopathological and direct immunofluorescence examination. Furthermore, HLA genotyping study can be done on diagnosed AIBD cases by PCR-SSOP method.

RESULTS: The patients ranged from 3-80 years of age with female preponderance (67.6%). Among 37 cases, pemphigus vulgaris (48.6%) is most common followed by bullous pemphigoid (18.9%), pemphigus foliaceus (13.5%), and dermatitis herpetiformis (10.8%). The HLA genotyping study showed that among HLA class I, HLA-A*03, A*29 and A*31; and B*52 and among HLA class II, HLA-DR*03, DR*11, DR*14 and DR*15; and DRB5* showed stronger association with various AIBD cases.

CONCLUSION: The variable frequency of class I and II showed their respective association with various AIBDs.

INTRODUCTION

AIBDs represent a heterogenous group of dermatoses with protean manifestation, treatment of which greatly depends upon the correct diagnosis.[1] AIBDs of the skin are rare, yet potentially fatal autoimmune disorders. The autoantibodies are directed against distinct molecules expressed in the epidermis and at the DEJ of skin and/or mucous membrane. The binding of these autoantibodies ultimately leads to loss of cell-cell and cell-matrix adhesion in the skin and/or mucous membranes, which results in erosions and/or blister formation.[2] Antigens are presented as a cleaved fragments via the Major histocompatibility complex (MHC). MHC, also known as the human leukocyte antigen (HLA) region in humans, comprises a region of 7.6 megabases (Mb) on chromosome 6p21. The HLA region is furthermore characterized by an extraordinarily high degree of polymorphisms with more than 1000 known alleles for HLA-A and -B. The HLA class I and class II gene clusters comprise the isotypes HLA-A/-B/-C as well as HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1 respectively. They are involved in

antigen processing and presentation, and usually show highly significant associations with autoimmune diseases, representing the strongest predisposing genetic factors.[3]

The development of AIBDs is generally multi-factorial. Factors involved are a genetic predisposition, ethnicity, age, environment, and gender. They are broadly divided into pemphigus vulgaris, pemphigus foliaceus, pemphigus vegetans, bullous pemphigoid, dermatitis herpetiformis and linear IgA disease.

Occasionally, atypical presentation of an AIBDs may pose a diagnostic delay. A diagnosis based solely on clinical and histological findings may not be accurate. DIF is extremely useful in distinguishing closely related groups. The DIF result is based on the site (intercellular, along basement membrane zone or dermal papillae), type (IgG, IgM, IgA or C3), pattern (granular or linear) and intensity of deposition of immune reactants.[5]Furthermore, HLA genotyping can be done on the confirmed diagnosed cases. This technique is different from gene sequencing and serotyping. Here, the PCR primers specific to a variant region of DNA are used, this technique is known as sequence specific primer (SSP-PCR). It works on the principle that the autoimmune responses to Dsg1 or Dsg3 or both are regulated by the hydrophobic amino acid and hydrophilic amino acid residues at specific position on the HLA class I/II chain.[5]

Thus there is significant variation in the HLA allele types that have been reported in association with AIBDs from different ethnic populations around the world. There is, however, a paucity of data in this field from India. Therefore, the primary objective of the study was to determine the HLA class I and class II alleles prevalence in Indian patients with AIBDs. The secondary objective was to assess the correlation between the clinical and histopathological features with respective direct immunofluorescence findings.

MATERIAL & METHOD

The study was a hospital-based case-control observational study of patients with AIBDs either admitted or attending the dermatology outpatient department, Vardhman Mahavir Medical College, New Delhi, India. It was conducted between January 2021 and July 2022 for a period of 18 months.

The inclusion criteria for cases were patients with AIBDs diagnosed by clinical features, histopathology and immunofluorescence or serological demonstration of anti-desmoglein antibodies and consenting for the study. Healthy renal transplant donors who were willing to participate in the study were chosen as controls. Sample size was calculated to be 37 cases and 37 controls. Low-resolution HLA class I and II typing was done.

HISTOPATHOLOGICAL EXAMINATION: On skin punch biopsy, the sample was collected in 10% formalin. Following scrutinising the patient details and identity, the specimen of skin bullous lesion was fixed in fresh formalin for 24 hrs. Gross description of all fragments and processed all fragments for microscopic study by using haematoxylin and eosin staining. After overnight fixation of specimen in formalin, dehydration of tissue done with graded alcohol, then it is cleared in chloroform, followed by paraffin embedding and section cutting in rotary microtome. Sections of 3 micrometer thickness would be made & stained with H&E.

DIRECT IMMUNOFLUORESCENCE TECHNIQUE: Skin specimen was obtained by 3-5 mm punch or surgical biopsy. Biopsy specimen was snap frozen, if delayed was kept in cold saline. Frozen 4-6 micron section was cut on cryostat and placed on glass slide before being air dried for 15 minutes. After rinsing in phosphate buffer saline (PBS) pH 7.2 for 15 minutes in 3 cycles. Slides were overlaid in moist chamber with FITC conjugates with following specificities anti IgG, IgA and C3. Each reagent on separate slide for 1 hour. After rinsing in PBS again for 15 minutes in 3 cycles. Slides were mounted on buffered glycerine and examined in fluorescence microscopy.

METHODOLOGY FOR HLA TYPING: Firstly, DNA extraction was done that included - Binding: 200µl blood sample + 20µl RNase + 20µl proteinase K + 20µl binding buffer which was incubated at 55ºC for 10 minutes. Added 20µl 100% ethanol and then added total of 600µl lysate to spin column. Whole prepared sample was centrifuged at 10000g for 1 minute followed by washing which involved adding of 500µl wash buffer 1 to spin column. Centrifuged at 10000g for 1 minute and then added 500µl wash buffer 2 to spin column; again centrifuged at 12000g for 3 minutes. Discarded collection tube and attached 1.5ml eppendorf to column. Elution buffer prepared by adding 200µl elution buffer and incubated at room temperature for 1 minute. Centrifuged at 10000g for 1 minute. Then DNA was extracted in the eppendorf tube. Finally, OD (Optical Density) of DNA on NANODROP (Spectrophotometer) was measured.
HLA automatic evaluation which was done by using FLUOGENE SOFTWARE after PCR processing of extracted DNA.

RESULT

The patient ranged from 3-80 yrs of age, with mean age of presentation at the diagnosis being 40.24 yrs. There was a female preponderance with 67.6% female and 32.4% male. Among 37 cases, PV (48.6%) is most common followed by BP (18.9%), PF (13.5%) and DH (10.8%). Histopathological and DIF testing were done to make a final diagnosis. Furthermore, HLA genotyping was done, the observed results are as follows:

Table 1: Association between HLA and PV

Parameters	PV		p value
	Cases (n = 18)	Controls (n = 37)	
HLA- A*01	**8 (44.4%)**	7 (18.9%)	0.059[2]
HLA- A*11	**6 (33.3%)**	10 (27.0%)	0.629[3]
HLA- A*24	**4 (22.2%)**	8 (21.6%)	1.000[2]
HLA- A*26	**4 (22.2%)**	5 (13.5%)	0.454[2]
HLA-B*15	**6 (33.3%)**	6 (16.2%)	0.177[2]
HLA-B*52	**5 (27.8%)**	7 (18.9%)	0.499[2]
HLA- DR*13	**4 (22.2%)**	3 (8.1%)	0.200[2]
HLA- DR*14	**15 (83.3%)**	8 (21.6%)	<0.001[3]
HLA-DRB3*	**17 (94.4%)**	20 (54.1%)	0.003[3]
HLA-DRB 4*	**6 (33.3%)**	20 (54.1%)	0.149[3]
HLA-DRB 5*	**4 (22.2%)**	14 (37.8%)	0.247[3]

In PV, the alleles of HLA-A*01, A*11, A*24 and A*26; B*15 and B*52; DR*13 and DR*14; DRB3*, DRB4* and DRB5* showed high association.

Table 2: Association between HLA and PF

Parameters	PF		p value
	Cases (n = 5)	Controls (n = 37)	
HLA- A*03	**2 (40.0%)**	4 (10.8%)	0.141[2]
HLA- A*11	**3 (60.0%)**	10 (27.0%)	0.162[2]
HLA-B*52	**2 (40.0%)**	7 (18.9%)	0.288[2]
HLA- DR*04	**3 (60.0%)**	6 (16.2%)	0.057[2]
HLA- DR*12	**2 (40.0%)**	0 (0.0%)	0.012[2]
HLA- DR*14	**2 (40.0%)**	8 (21.6%)	0.577[2]
HLA-DRB 3*	**3 (60.0%)**	20 (54.1%)	1.000[2]
HLA-DRB 4*	**4 (80.0%)**	20 (54.1%)	0.371[2]

In PF cases, the alleles of HLA-A*03 and A*11; B*52; DR*04, DR*12 and DR*14; DRB3* and DRB4* showed significantly association.

Table 3: Association between HLA and P.vegetans

Parameters	P. vegetans		p value
	Cases (n = 2)	Controls (n = 37)	
HLA- A*11	**1 (50.0%)**	10 (27.0%)	0.490[2]
HLA- A*24	**1 (50.0%)**	8 (21.6%)	0.413[2]
HLA- A*33	**1 (50.0%)**	6 (16.2%)	0.331[2]
HLA-B*44 (Yes)	**1 (50.0%)**	2 (5.4%)	0.150[2]
HLA-B*52	**2 (100.0%)**	7 (18.9%)	0.049[2]
HLA- DR*07	**1 (50.0%)**	12 (32.4%)	1.000[2]
HLA- DR*13	**1 (50.0%)**	3 (8.1%)	0.197[2]
HLA- DR*14	**2 (100.0%)**	8 (21.6%)	0.061[2]
HLA-DRB 3*	**2 (100.0%)**	20 (54.1%)	0.495[2]
HLA-DRB 4*	**1 (50.0%)**	20 (54.1%)	1.000[2]

In P.vegetan cases, the alleles of HLA-A*11, A*24 and A*33; B*44 and B*52; DR*07, DR*13 and DR*14; DRB3* and DRB4* significantly showed high association.

Table 4: Association between HLA and BP

Parameters	BP		p value
	Cases (n = 7)	Controls (n = 37)	
HLA- A*01	**2 (28.6%)**	7 (18.9%)	0.619[2]
HLA- A*03	**3 (42.9%)**	4 (10.8%)	0.068[2]
HLA- A*11	**3 (42.9%)**	10 (27.0%)	0.404[2]
HLA- A*24	**2 (28.6%)**	8 (21.6%)	0.649[2]
HLA-B*15	**2 (28.6%)**	6 (16.2%)	0.593[2]
HLA-B*35	**3 (42.9%)**	10 (27.0%)	0.404[2]

Parameters	BP		p value
	Cases (n = 7)	Controls (n = 37)	
HLA-B*44	**3 (42.9%)**	2 (5.4%)	0.023[2]
HLA- DR*11	**4 (57.1%)**	8 (21.6%)	0.075[2]
HLA- DR*13	**3 (42.9%)**	3 (8.1%)	0.042[2]
HLA- DR*14	**2 (28.6%)**	8 (21.6%)	0.649[2]
HLA-DRB 3*	**7 (100.0%)**	20 (54.1%)	0.032[2]
HLA-DRB 4*	**2 (28.6%)**	20 (54.1%)	0.412[2]

In BP cases, the alleles of HLA-A*01, A*03, A*11 and A*24; B*15, B*35 and B*44; DR*11, DR*13 and DR*14; -DRB3*, and -DRB4* significantly increased.

Table 5: Association between HLA and Linear IgA Diseases

Parameters	Linear IgA Disease		p value
	Cases (n = 1)	Controls (n = 37)	
HLA- A*26	**1 (100.0%)**	5 (13.5%)	0.158[2]
HLA- A*29	**1 (100.0%)**	0 (0.0%)	0.026[2]
HLA-B*08	**1 (100.0%)**	2 (5.4%)	0.079[2]
HLA- DR*03	**1 (100.0%)**	8 (21.6%)	0.237[2]
HLA- DR*15	**1 (100.0%)**	12 (32.4%)	0.342[2]
HLA-DRB 3*	**1 (100.0%)**	20 (54.1%)	1.000[2]
HLA-DRB 5*	**1 (100.0%)**	14 (37.8%)	0.395[2]

In LAD cases, the alleles of HLA-A*26 and A*29; B*08; DR*03 and DR*15; DRB3* and DRB5* showed high association.

Table 6: Association between HLA and DH

Parameters	DH		p value
	Cases (n = 4)	Controls (n = 37)	
HLA- A: *24	**3 (75.0%)**	8 (21.6%)	0.052[2]
HLA- A: *31	**2 (50.0%)**	0 (0.0%)	0.007[2]
HLA-B: *15	**2 (50.0%)**	6 (16.2%)	0.165[2]
HLA- DR: *03	**2 (50.0%)**	8 (21.6%)	0.245[2]
HLA- DR: *07	**2 (50.0%)**	12 (32.4%)	0.596[2]
HLA- DR: *14	**2 (50.0%)**	8 (21.6%)	0.245[2]
HLA-DRB: 3*	**4 (100.0%)**	20 (54.1%)	0.128[2]
HLA-DRB: 4*	**2 (50.0%)**	20 (54.1%)	1.000[2]

The alleles of HLA-A*24 and A*31; B*15; DR*03, DR*07 and DR*14; DRB3* and DRB4* showed high association in DH patients.

DISCUSSION

A total of 37 cases of AIBDs presenting with fresh lesions were analysed on the basis of frequency of cases and demographic distribution; and observed further histopathological and DIF findings.

In the present study, PV constituted the most common vesiculo-bullous disorder followed by BP and PF. The age of patients ranged from 3-70 yrs with mean age 40.24 yrs. PV and PF were most common in 4th decade with mean age ~38.22 years and ~34.80 years respectively while BP was most common in 7th decade with mean age ~53.57 years. There was female preponderance with 67.6% female and 32.4% male; with F:M ratio is 2.08. PV and LAD showed female predominance; while PF and DH showed male predominance; P.vegetan showed equal gender distribution. On comparing with previous literature studies, no significant dissimilarity has been found in this study.

Level of blister was suprabasal in majority of PV cases and P.vegetans while subepidermal in all BP cases and LAD. Subcorneal blisters were seen in majority of PF cases. In DH cases, subepidermal and intraepidermal blisters were seen. Inflammatory infiltration were seen in all cases of AIBDs. In DH cases, neutrophilic papillary microabscesses along with lymphocytic infiltration were seen. In PV, acanthosis and tombstone basal layer were predominant epidermal changes seen while in PF, acanthosis was seen predominantly. All cases of P.vegetans showed acanthosis.

DIF showed intercellular deposition of IgG in a fish-net pattern in PV and linear pattern in PF. Linear deposition of IgG and C3 along the basement membrane in BP cases. ALL DH cases showed deposition of IgA in papillary pattern in dermo-epidermal junction. Single case of LAD showed linear deposition of IgA along the basement membrane.

Here we compare observed results of the present study with the previous studies on HLA haplotypes association with AIBDs from the literature.

In the present study, the alleles of HLA-A*01, A*02, A*11, A*24 and A*26; B*15, B*35 and B*52; DR*13 and DR*14; DRB3*, DRB4* and DRB5* showed high association in PV patients. While a previous study by Priyadarshini A et al showed association between HLA-DRB1*14, -DQB1*05 alleles and PV in Indian population.[6] The difference in HLA alleles association with PV patients in both studies may be due to ethnicity of study population in respective studies. As in the present study, most of the patients belongs to North Indian region while Priyadarshni A et al study was done in most of the patients that belonged to South Indian population. Yan L et al (2012) revealed that HLA-DRB1*04 was associated with PV in Japanese. Likewise, HLA-DRB1*1404 was correlated with PV in Eastern Indian and Pakistani subjects while -DRB1*1401 was correlated with PV in French, Italian, Japanese and Spanish population.[7] Haase O et al (2015) showed an association with HLA-DRB1*04 and -DRB1*14 in both Egyptian and in German PV patients. In addition, a significant association of HLA-DRB*08 was seen in Egyptian patients but not in Germans.[8]

This study showed that in PF cases, frequency of HLA-A*03 and A*11; B*52; DR*04, DR*12 and DR*14; DRB3* and DRB4* showed significantly increased in Indian population while Pavoni DP et al, case control study showed DRB1 and its subtypes association with PF cases in Brazilian population.[9] The difference in HLA association with PF patients in both individual studies due to difference in origin of study population in respective studies.

In the present study, HLA alleles which showed high association with P.vegetan cases were HLA-A*11, A*24 and A*33; HLA-B*44 and *52; HLA-DR*07, DR*13 and DR*14; HLA-DRB3* and DRB4*. No previous study has been done in literature.

This study showed that in BP cases, haplotypes of HLA-A*01, A*03, A*11 and A*24; B*15, B*35 and

B*44; DR*11, DR*13 and DR*14 significantly increased in study population while HLA class II alleles such as DQA1, DQB1 and DRB1 and their respective subtypes showed their association in worldwide population. The difference in HLA association with BP patients in the present study and previous studies due to difference in the origin of study population. .Esmaili N et al demonstrated that HLA-DQA1 and -DQB1 typing showed a significant higher frequencies of HLA-DQA1*05:01, -DQB1*03:01, -DQB1*04:01; and -DRB1*08 as well in BP cases among Iranian population.[10] Chagury AA et al showed that HLA-C*17, -DQB1*03:01, -DQA1*01:03 and -DQA1*05:05 were associated with BP patients in Brazilian population.[11] Sun Y et al found that HLA-DQB1*03:01 as the only significant risk allele associated with BP patients in Chinese population.[12] Fang H et al concluded that significant association existed between HLA-A*11:01; B*01:01; and G*01:06; HLA-DQA1*05:08, -DQB1*03:01 and BP patients in Chinese population. Even a new risk variants HLA-DRB1*10:01 and -DQB1*05:01 showed association with BP cases in Chinese population. Haplotypes HLA-DQB1*03:02 and -DQB1*04:01 were associated with BP patients in Asian population such as Japanese and Iranian.[13]

This study showed that in LAD cases, haplotypes of HLA-A*26 and A*29; B*08; DR*03 and DR*15; DRB3* and DRB5* showing high association in study population while Patsatsi A reported association of HLA-B*08, DR*03 and Cw*07 alleles in Tunisian children more frequently than in adults.[14] **Here, we observed that HLA-B*08 and -DR*03 alleles showing association in both studies irrespective of difference in origin of study population.**

The present study showing increase trend of alleles of HLA-A*24 and A*31; B*15; DR*03, DR*07 and DR*14; DRB3* and DRB4* in DH patients while Hall MA et al, case control study showed strong association between HLA-DR3 and DQw2 and DH cases in Chinese population.[15] **Only HLA-DR*03 allele showing association with DH patients in both studies irrespective of difference in origin of study population.** Marietta E et al concluded that DH as well as celiac disease is strongly associated with HLA-DQ2 and -DQ8.[16] Sun Y et al showed the strong association of risk variants HLA-B*0801 and DRB1*0301 alleles with DH cases in Chinese population.[17]

In the study, we also observed the high association of specific HLA haplotype with various AIBDs. HLA-A*29 showing high associated with PV and LAD cases (as bias corrected cramer's V =0.61). HLA-DR*15 showing high association with PV and LAD cases (as bias corrected cramer's V= 0.61). HLA-DR*03 showing high association in PV, DH and LAD cases (as bias corrected cramer's V= 0.57).

Here, some HLA alleles that showed moderate association with various groups of AIBDs. HLA-DR*11 showing moderate association in PV, BP and DH cases (as bias corrected cramer's V= 0.43). HLA-DR*14 showing moderate association in PV, BP, PF, DH and P. vegetan cases (as bias corrected cramer's V= 0.4). HLA-DR*13 showing moderate association with PV, BP and P.vegetan cases (as bias corrected cramer's V= 0.39). HLA-DRB5* showing moderate association with PV and LAD cases (as bias corrected cramer's V= 0.38). HLA-A*03 showing moderate association with BP, PF and DH cases (as bias corrected cramer's V= 0.37). HLA-B*52 showing moderate association with PV, PF, DH and P.vegetan cases (as bias corrected cramer's V= 0.32).

CONCLUSION

The present study concluded that AIBDs develop in any age groups; occur predominantly in females. The development of AIBDs is generally multi-factorial. Factors involved are a genetic predisposition, ethnicity, age, environment and gender. On comparing with controls, HLA-DR*14 and DR*15; DRB3* and DRB5* showed stronger association with AIBDs. Overall, among HLA class I, HLA-A*03, A*29

and A*31; and B*52 and among HLA class II, HLA-DR*03, DR*11, DR*14 and DR*15; and DRB5* showed stronger association with various AIBDs cases. However, adequate comparison could not be done with literature as there is extreme paucity of data in HLA profile in these lesions. So, significance of HLA profile in AIBDs patients cannot be properly evaluated. As there is still paucity in the present study due to small sample size and was not performed on all HLA class II haplotypes adequately. So in future, the study should be done on all HLA class I and class II haplotypes including HLA-DP and HLA-DQ profile in AIBDs patients in a large sample size to achieve the accuracy of the result.

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