Relationship between human leukocyte antigen DRB1 and psoriasis in Iraqi patients

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ABSTRACT

الأهداف: دراسة دور مستضدات كريات البيض البشرية من النوع الثاني *DRB1* في القابلية على الإصابة بداء الصدفية لدى المرضى العراقيين.

الطريقة: هذه دراسة مقارنة مقطعية شملت 40 مصابا بداء الصدفية تم تقييمهم في قسم الأمراض الجلدية في مستشفى الكندي التعليمي ببغداد للفترة من سبتمبر 2013م إلى سبتمبر2015م وتم مقارنتهم مع تسعين فرد غير مصاب بالمرض كمجموعة ضابطة.

النتائج: هناك زيادة في تكرار الاليلات لمستضد كريات البيض البشرية من النوع الثاني HLA-DRB1*0102, *0306 في المرضى المصابيين بداء الصدفية *p*-values=0.001، فاصل الثقة =2.492-37.487ونسبة الارجحية = 9.666. كما أظهرت الدراسة زيادة في تكرار الأليل لمستضد كريات البيض البشرية من النوع DRB1*1101بشكل كبير مع داء الصدفية اللوحي *p*=0.0434، فاصل الثقة= 1.04-1.69 ونسبة الأرجحية = 4.2 وارتبط الاليل لمستضد كريات البيض البشرية من النوع DRB1*0102 مع الأنواع الأخرى من الصدفية *p*=0.018 وفاصل الثقة=0.0223-0.701 ونسبة الأرجحية = 0.125

الخاتمة: أظهرت الدراسة أن هناك ارتباط بين الأليلات لمستضد كريات البيض البشرية من النوع -0306*, DRB1*0102 مع داء الصدفية. أما الأليل لمستضد كريات البيض البشرية من النوع DRB1*1101 فأنه يرتبط مع داء الصدفية اللوحي والأليل لمستضد كريات البيض البشرية من نوع DRB1*0102 فأنه يرتبط مع الأنواع الأخرى من الصدفية.

Objectives: To investigate the role of Human leukocyte antigen (HLA) Class II *DRB1* in susceptibility to psoriasis in Iraqi patients.

Methods: A cross-sectional comparative study including 40 patients with psoriasis attending the Department of Dermatology, Al-Kindy teaching hospital in Baghdad, Iraq, between September 2013-2015. Patient selection was carried out by the dermatologists. Ninety healthy individuals were included in the study. Human leukocyte antigen genotyping was carried out by the sequence specific oligonucleotide (SSO) method using Auto LiPA 48 (Innogenetics, Belgium) in the HLA typing research unit of the Al-Kindy College of Medicine, Baghdad, Iraq.

Results: There is an increased frequency of HLA-DRB1*0102, *0306 in psoriatic patients with psoriasis *p*-values=0.001, confidence interval(CI)=2.492-37.487 and odds ratio(OR)=9.666. Human leukocyte antigen-DRB1*1101 is significantly associated with plaque-type psoriasis with *p*=0.0434, CI=1.04-1.69, and OR=4.2. Human leukocyte antigen-DRB1*0102 is significantly associated with other types of psoriasis with *p*=0.018, CI=0.0223-0.701, and OR=0.125.

Conclusion: Human leukocyte antigen-DRB1*0102 and *0306 are significantly associated with psoriasis. Human leukocyte antigen-DRB1*1101 is significantly associated with plaque-type psoriasis. Human leukocyte antigen-DRB1*0102 is significantly associated with other types of psoriasis rather than plaque-type psoriasis.

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Psoriasis is a chronic inflammatory skin disorder affecting 1% of the population worldwide, which is clinically characterized by erythematous, sharply demarcated papules and rounded plaques, covered by silvery micaceous scales.[1] It can involve the skin, scalp, nails, and joints. Psoriasis has a bimodal age distribution. In one group, onset typically occurs around 30 years of age, often in individuals with positive family history and severe course of the disease. In the other group, onset occurs around 50-60 years of age, usually with a less severe course and without family history. There is no gender predominance.[2] There are many types of psoriasis, (plaque-type, inverse, guttetate, and pustular), with the plaque-type being the most common. Up to 30% of patients with psoriasis have psoriatic arthritis.[1]

The etiology of psoriasis is not truly understood, but genetic, immune pathological and environmental factors may be involved in its pathogenesis. Children have a 15% chance of having psoriasis if one parent is affected and a 50% chance if both parents are affected.[2,3]

Psoriatic lesions have been shown to be infiltrated with activated T-cells which is responsible for keratinocyte hyperproliferation through cytokine production. Recently, it has been suggested that there are 2 newly discovered antigens playing a role in psoriasis pathogenesis. The first is cathelicidin (LL37), derived from keratinocyte and may be considered as an autoantigen since it is an antimicrobial peptide. The second antigen is ADAMTS-like protein 5 (ADAMTSL5), which is originated from melanocytes and acts as an antigen for interleukin(IL)-17-production from T-cells.[4,5] These antigens are presented to T-cells by HLAs, suggesting that HLA has a role in the pathogenesis of psoriasis.[6,7] The bimodal age distribution of psoriasis indicates the existence of 2 pathogenically distinct forms of the disease, similar to the model of diabetes. Thus, severe type I is, strongly HLA-associated (particularly, HLA-C:06:02), in contrast to mild Type II which is HLA-unrelated.[3,8,9]

Several studies have reported an increased frequencies of the occurrence of HLA-class I (HLA-A1, A2, B13, B37, B39, B57, Cw1, Cw6) in patients with psoriasis.[10] In addition, psoriatic arthritis has been associated with HLA-B57, although some studies have also reported HLA-Cw6 in more than 50% of all patients with this disease.[11]

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The aim of this study was to investigate the role of HLA Class II DRB1 in susceptibility to psoriasis vulgaris and other forms of psoriasis in Iraqi patients and to contribute to the data related to HLA and psoriasis.

Methods. This is a cross-sectional comparative study carried out through direct interviews with patients attending the Department of Dermatology of the Al-Kindy teaching hospital in Baghdad, Iraq, between September 2013-2015. Inclusion criteria necessitated that all patients have previously or newly diagnosed of psoriasis vulgaris or any other types of psoriasis, included nail, scalp, palmoplantar, flexural, and pustular types.

The sample size was 130 subjects, 40 patients with psoriasis and 90 gender and age matched healthy control groups volunteers among the staff of Al-Kindey College of Medicine, Baghdad, Iraq, who did not have a history of psoriasis. The Sample size was calculated using Epi-tools Epidemiological calculator with a 0.95 confidence level.

Informed written consent was given to the patients. Ethical approval was obtained from the scientific unit of Al-Kindy College Of Medicine, Baghdad, Iraq, and the study was carried out in accordance with Helsinki Declaration.

HLA genotyping. Three milliliter venous blood was drawn by venipuncture from both the patients and control groups and kept at -20°C in an ethylenediamine tetraacetic acid (EDTA) containing tubes until DNA extraction which was carried out by using Qiagen DNA extraction Kit. Polymerase chain reaction (PCR), and SSO technique were used for HLA-DRB1 typing using both amplification and hybridization kits with Auto LiPA 48 automated machine from (Innogenitics, Belgium) according to manufacturer instructions. LIRAS version 5.0 software (Innogenetics, Belgium) was used for results interpretation.

Statistical analysis. Data was introduced in MiniTab version 15 software (Minitab Inc.,State College,PA,USA). Frequency distribution tables were used to describe number and percentage of statistical variables. Chi square test was used to find out the association between related variables and Fishers exact

Table 1 - Number of patients according to psoriasis type.

Type of psoriasis	n (%)
Generalized plaque	22 (55)
Other types	18 (45)
Total	40

Table 2 - Human leukocyte antigen (HLA-DRB1*) allele frequencies, Odds ratio, confidence interval and *p*-value in patients with psoriasis and healthy controls.

HLA Alleles	Psoriasis patient group (n=40)	Healthy control group (n=90)	Odds ratio (95% confidence interval)	*P*-value
	n (%)	n (%)		
0102	10 (25)	3 (3.3)	9.666 (2.492-37.487)	0.001
0203	0	6		NA
0301	0	18		NA
0306	10(25)	3 (3.3)	9.666 (2.492-37.487)	0.001
0311	0	3		NA
0317	0	12		NA
0401	2 (5)	0		NA
0402	4 (10)	0		NA
0701	10 (25)	21 (23.3)	1.09 (0.46-2.605)	0.837
0801	0	6		NA
0802	6 (15)	6 (6.6)	2.471 (0.744-8.200)	0.1395
1001	6 (15)	0		NA
1101	12 (30)	21 (23.3)	1.408 (0.611-3.243)	0.4213
1103	0	18		NA
1122	2 (5)	0		NA
1137	2 (5)	0		NA
1201	2 (5)	0		NA
1305	0	12		NA
1318	0	21		NA
1359	2 (5)	0		NA
1401	4 (10)	6 (6.6)	1.55 (0.4139-5.846)	0.5131
1402	0	24		NA
1507	4 (10)	0		NA
1501	4 (10)	0		NA

HLA - Human leukocyte antigen, NA - not applicable

Table 3 - HLA-DRB1 allele frequency in plaque-type and other types of psoriasis.

HLA-DRB1*Alleles	Plaque-type (22)	Other types (18)	Odds ratio (CI)	*P*-value
0102	2	8	0.125 (0.0223-0.701)	0.018
0306	6	4	1.31 (0.306-5.61)	0.714
0402	4	2	1.777(0.286-11.039)	0.5369
0701	6	4	1.3125(0.3065-5.6198)	0.714
0802	2	4	0.35 (0.0562-2.181)	0.2608
1001	2	4	0.35 (0.0562-2.181)	0.2608
1101	12	4	4.2 (1.04-16.9)	0.0434
1201	2	0		NA
1359	0	2		NA
1401	2	2	0.800 (0.1012-6.3228)	0.832
1501	4	0		NA
1507	2	2	0.800 (0.1012-6.3228)	0.832

HLA - Human leukocyte antigen, CI - confidence interval, NA - not applicable.

test when needed. Odds ratio (OR) 95% confidence interval was calculated. A *p*-value<0.05 was considered significant.

Results. Forty Iraqi arab Muslim patients with psoriasis were included in the study. Ten of the 40 patients had a family history of psoriasis. The age of the patients ranged from 12-52 years old, with 18 males and 22 females.

Patients with psoriasis were divided into 2 groups: plaque-type and other types of psoriasis as shown in **Table 1**. Other types of psoriasis included nail, scalp,

palmoplantar, flexural, and pustular types.

The frequencies for significantly elevated HLA-DRB1 alleles identified by PCR-SSO in 40 patients with psoriasis compared to controls are shown in **Table 2**. Human leukocyte antigen-DRB1*0102 and *0306 were the most common allele frequencies in patients with psoriasis as compared to the healthy control group. In contrast, HLA-DRB1*0701, *0802, *1101, and *1401 showed no significant association with plaque psoriasis, while other HLA-DRB1 alleles that were tested failed to show any statistically significant association.

Table 3 shows that the most common allele associated with plaque psoriasis as compared to other forms of psoriasis is HLA-DRB1*1101. On the other hand, HLA-DRB1*0102 was significantly associated with other types of psoriasis.

From **Table 1**, HLA-DRB1* 0306 was significantly associated with all types of psoriasis in comparison with control groups, but the allele is not associated with plaque-type or other types of psoriasis when we compare both groups as shown in **Table 3**.

Discussion. Psoriasis is a disease with multiple etiological factors, both environmental and genetic factors can determine the clinical and susceptibility patterns of the disease.[12,13] Part of the genetic predisposition is due to genes within the major histocompatibility complex (MHC).[14,15]

Studies in different parts of the world have shown that there is an association between Class I and II (MHC) and psoriasis. A Turkish study found that HLA-B*57, Cw6, and DRB1*07 alleles are associated with the disease.[7] Human leukocyte antigen-DR13 was found to be significantly associated with plaque psoriasis in an Omani patient.[16]

This study showed that HLA-DRB1*1101 was significantly associated with plaque-type psoriasis, and DRB1*0102 was significantly associated with other types of psoriasis, while DRB1*0306 was significantly associated with all types of psoriasis. These findings are different from other findings mentioned previously from different parts of the world. Two published Iraqi studies on the association of HLA-DRB1* with vitiligo and alopecia areata, showed that HLA-DRB1*1101 was significantly associated with these diseases.[17,18] It has been proposed that there was an association between class II HLA and the occurrence of autoimmune disease.[19,20,21] Vitiligo, alopecia areata, and psoriasis are considered autoimmune diseases, this sheds light on the possibility that the HLA-DRB1*1101 allele may be a risk factor for autoimmune diseases in the Iraqi population.

In our study, psoriasis was significantly associated with HLA-DRB1*01 and *03, while the HLA-DRB1*07 allele had no significant association with the disease as compared to a Turkish study,[7] although DR*07 allele carriers in patients with psoriasis is 25% compared to the control group, which was 23%. This can be explained by either low sample size or different ethnic groups.

What is well known is that there is an association between psoriasis and HLA especially Cw0602 which is considered as psoriatic risk gene. With the advent of new therapeutic modalities for psoriasis and the introduction of biological therapy for the treatment of psoriasis, several newly published studies showed that there is no association between HLA-Cw06 genetic status and response to treatment especially ustekinumab and Secukinumab.[22,23] Other study showed that the presence of HLA-A Bw4-80I could result in reduction in the response to treatment with Etanercept.[24] So HLA alleles play an important role in psoriasis pathogenesis with controversial role in response to biological therapy.

The limitations of this study are low sample size and lack of correlation between the severity of the disease and the significant alleles in patients with plaque-type and other types of psoriasis.

In conclusion, HLA-DRB1*0102, *0306 alleles are risky psoriatic genes for all types of psoriasis while HLA-DRB1*1101, *0102 are risk genes in plaque-type and other types of psoriasis. There is a need for more studies to show the effect of these significant alleles to biological therapy response in Iraqi psoriatic patients and to correlate the observations with other studies.

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