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Original Article

Evaluating the Role of HLA-DRB1 Alleles in Genetic Predisposition to Psoriatic Arthritis in Patients with Psoriasis

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Abstract *- Psoriasis is considered a chronic disease among the most common inflammatory autoimmune skin diseases. Psoriatic arthritis PsA is the most important systemic manifestation of psoriasis and often appears after the onset of psoriasis. HLA genes are considered the most important predisposing genetic factors associated with psoriasis, especially HLA-C*06, but the association between HLA-DRB1 alleles and psoriasis, in addition to the risk of developing PSA has not been widely studied since this association tends to differ between ethnic groups. The HLA-DRB1 alleles were identified in 50 patients with psoriasis in addition to 30 healthy patients using the sequence-specific primers PCR. Psoriasis patients were classified into two groups according to the presence of arthritis. 40% of patients had arthritis. Susceptibility to psoriasis in this study sample was significantly associated with HLA-DRB1*07, *11 and *10 (odds ratio (OR) 8.5, 4 and 3, p-value= 0.002, 0.02 and 0.01 respectively), While a negative association was found with HLA-DRB1*03 ((OR) 0.1). It was also observed that the presence of alleles *07, *11 and *01 is associated with a high risk of developing PsA in psoriasis patients ((OR) 14, 4.88 and 4.84, respectively). In contrast, alleles *03 and *14 were considered protective alleles against developing PSA in psoriasis patients ((OR) 0.14 and 0.2, respectively). Genetic associations identified in psoriasis have been found to be significantly associated with PsA. It is important to conduct genetic studies to determine the genetic factors involved in the pathogenic mechanism and thus reach a more effective treatment.*

Keywords *- DRB1 alleles, HLA, Psoriasis, Psoriatic arthritis, Genetic predisposition.*

1. Introduction

Human Leukocyte antigens (HLA) are polymorphic membrane proteins encoded by the HLA genes in the Major Histocompatibility Complex (MHC), which is located on the short arm of chromosome 6 (6p21.3).[1] HLA genes are composed of two main classes: the first, HLA-I, located telomerically encoding HLA-A, HLA-B, and HLA-C antigens, while the second, HLA-II, located centromerically encoding HLA-DR, HLA-DP, HLA-DQ.

[2] These proteins play an essential role in protecting against cancers and viruses, but they are also implicated in autoimmune diseases.[2],[3] The observation that some diseases are more common in individuals with a specific HLA allele has allowed studies of the association between HLA and diseases. Hence, the aim of all studies on HLA-associated diseases remains to determine the cellular molecular basis of the disease.[2]

Psoriasis is a chronic, hyperproliferative, inflammatory skin disease with genetic and immunological pathogenesis.[4] The incidence rate of psoriasis ranges between 0.09-11.4% depending on the population and geographic region worldwide.[5] Most psoriatic patients suffer from serious diseases, including psoriatic arthritis PsA, nail injury and others, which cause a decrease in the quality of the patient's life.[6], [7], [8] PsA is known as inflammatory arthritis correlated with psoriasis. The clinical characteristics of psoriasis vary depending on the clinical type of psoriasis (plaque, pustular, guttate, etc.).[9] Most clinical types of psoriasis share three main clinical features: erythema, thickness, and scaling.[10] About 30% of psoriatic patients develop PsA, considered a seronegative form of arthritis with negativity for the Rheumatoid Factor (RF).[11], [12]

The psoriasis and PsA are strongly associated with the MHC region.[1] Susceptibility alleles for psoriasis play an

important role in the pathogenesis.[2], [13] Previously, serogical techniques were used to determine the phenotypes of HLAs, such as HLA-B13, HLA-B14 and HLA-DR7, that were associated with psoriasis[14], [15]. However, with the advent of genotyping techniques using PCR, the risk alleles associated with psoriasis were identified more accurately.

The most common allele was HLA-C*06[16], [17]. In fact, this allele is not the only one involved in the pathogenesis of psoriasis and the risk of developing PsA. These differences in HLA allele distributions are due to racial and geographic differences, as the results reported by Shankarkumar et al. [18] and Al-Fouzan et al.[19], and the conclusion was that the HLA-DR7 has been found in PsA and psoriasis. In addition, some alleles can be negatively associated with the disease, which contributes to protection from it and affects the severity and development of systemic manifestations[2], [13] This is confirmed by the results recorded by Munir et al. in Pakistan 2023[20] and Bejerano et al. 2013.[21] Most studies around the world have focused on the association of HLA-C alleles with psoriasis rather than HLA-DRB1 alleles and their relationship with the development of arthritis. On the other hand, some previous studies have shown that HLA-DRB1 alleles had been seen as associated with PsA susceptibility.[22], [23] Determining and understanding the role of HLA alleles in psoriasis and PsA can lead to better prevention and more effective treatment.[3]

There are no studies on HLA alleles associated with psoriasis or systemic manifestations in the Syrian population. This study aims to provide information about the distribution of HLA-DRB1 alleles in psoriatic patients in Syria, their relationship to psoriasis compared to the control sample, and the risk of developing PsA in these patients.

2. Materials and Methods

An Analytic Case-Control Study to determine the incidence of psoriatic arthritis in psoriasis patients and the HLA-DRB1 alleles in patients and healthy people and to determine the association between the allele and the disease.

The study was conducted in two phases: a phase of collecting samples from skin disease clinics and divisions at the Department of Joint Diseases and Rheumatology at Tishreen University Hospital- Latakia, Syria and the Dermatology and Venereal Diseases Hospital- Damascus, Syria, and a phase of laboratory work in the molecular biology laboratory at Al-Assad University Hospital in Damascus during the period from June 2022 to September 2023.

The study included 50 chronic psoriasis patients who were randomly selected. Detailed demographic and clinical information were obtained (sex, age, habits, age of disease onset, presence of family history, presence of PsA, psoriasis phenotype, treatment), and disease severity was estimated using the Psoriasis Area and Severity Index (PASI), the family history was considered positive if at least one first- or second-degree relative had psoriasis.

Patients were divided into two subgroups based on the age of onset of the disease, and thus psoriasis was typed into the Early type I: age of onset is less than 40 years, and Late type II: age of onset is greater than 40 years.[12] The study also included **30** control samples, who were healthy people who did not suffer from psoriasis and had no family history of the disease.

This study adhered to the guidelines of the Declaration of Helsinki and was approved by the Research Ethics Committee of Tishreen University Hospital. Written informed consent was taken from the patients or from their relatives to participate in the research after receiving sufficient information. All information and data remained confidential.

2.5 ml venous blood samples were collected into tubes containing anticoagulant EDTA. According to the manufacturer's instructions, DNA was extracted under sterile conditions using a Ready DNA Spin Kit, Inno-train, Germany.

Genotyping and HLA-DRB1 alleles identification were performed using the PCR-SSP technique by HLA-Ready Gene Kit, Inno-train, Germany, Taq DNA Polymerase (recombinant), (DNA Amplification Product, Vivantis Technologies Sdn. Bhd., Malaysia), according to the manufacturer's instructions. Amplification products were examined using electrophoresis on an agarose gel 2% (Bio-Rad Laboratories, Inc. Spain) for 16 min at 150 V. (See Figure 1)

The descriptive statistics were conducted using measures of central tendency and measures of dispersion for quantitative variables, frequencies, and percentage values for qualitative variables. The chi-square test was adopted to evaluate the relationships between qualitative variables. The risk of association of certain alleles with psoriasis and the risk of developing arthritis in psoriasis patients were expressed as Odds Ratios (OR) odd ratios with 95% Confidence Intervals (CI) calculated according to Wolff's formula and were considered to have a value starting from 2 and more.

The statistical significance of these correlations was evaluated using P values determined by Fisher's test, and the results are considered statistically significant at p-value <0.05. The IBM SPSS statistics (Version25) program was adopted to calculate statistical coefficients and analyze the results.

3. Results

The sample of this study included 50 chronic psoriasis patients (13 males and 37 females) who were randomly selected from the clinics and divisions of skin diseases, Joint diseases and Rheumatology in Tishreen University Hospital- Latakia and the Dermatology and Venereal Diseases Hospital- Damascus, and 30 controls (12 males and 18 females) who did not suffer from psoriasis and did not have a family history of psoriasis during the period from June 2022 until September 2023.

The age of patients in this study ranged from 8 to 73 years old, with a mean age of 40.42 ± 17.62 years old, and the age of controls ranged from 7 to 72 years old, with a mean age of 34.03 ± 15.99 years old. Positive family history was recorded in 15 psoriatic patients (18.7%). 40% of psoriasis patients had arthritis, while 60% did not. 74% (37/50) of psoriasis cases were of the early type, and 26% (13/50) were of the late type. The age of onset of the disease ranged from 3 to 63 years, with an average of 29.04±15.6 years. 66% of the psoriatic patients had an old disease with an age of five years or more, with an average of 11.08±10.1 years.

The most common phenotype was plaque psoriasis, diagnosed in 40 of 50 patients (80%), followed by pustular and guttate psoriasis 12% and 8%, respectively. Regarding the severity of the disease, 24 of 50 patients (48%) had mild disease according to PASI score <5, 14 patients (28%) had moderate disease, while 12 patients (24%) had severe disease. The risk factors reported in our study included smoking (25/50, 50%) and alcohol intake (6/50, 12%). The demographic and clinical characteristics of the patients in this study are shown in Table 1 and Table 2.

On the other hand, Table 3 shows a comparison between two groups of psoriasis patients (group A: psoriatic patients with PsA, and group B: psoriatic patients without PsA) according to all demographic and clinical findings. Statistically significant difference between the two study groups according to the patient's age, as the mean age in group A was 44.9±15.9, and they were older; p-value=0.04.

The distribution of females was greater than that of males in the two groups and was not statistically significant. A positive family history was found in 35% of group A patients and 26.7% of group B patients; the difference was statistically significant, as it was higher in group A patients with p-value= 0.003. As for the psoriasis type, most of the patients in both groups were of the early type, and the mean age of disease onset was 31.65±15.07 in group A and 27.3±15.9 in group B without a statistically significant difference; p-value= 0.3. There was a statistically significant difference between the two groups of psoriasis patients depending on the duration of the disease, as we found that psoriasis patients with PsA had a higher duration p-value= 0.02.

The average severity of disease recorded in the patients of this study according to PASI score was 7.55±5.2 and 8.67±9.3 in group A and group B patients, respectively; this did not give a statistically significant difference between the study groups. Our results about risk factors are also not statistically significant.

Regarding the distribution of HLA-DRB1 alleles shown in Table 4, the HLA-DRB1*11 allele was the most frequent in psoriasis patients compared to controls, where the percentage reached 46% in group A and 55% in group B patients. In comparison, it was 20% in controls, followed by HLA-DRB1*07 with a percentage of 30%, 50% and 6.7% in group A, group B and control, respectively.

Statistically significant differences between the research groups were recorded with HLA-DRB1*01, HLA-DRB1*07 and HLA-DRB1*11 alleles, which were higher in psoriasis patients and the HLA-DRB1*03 allele, which was higher in the control group, and HLA-DRB1*10 that was in control only (p-value= 0.01, 0.002, 0.02, 0.03 and 0.01 respectively).

The presence of HLA-DRB1*07, HLA-DRB1*11 and HLA-DRB1*10 alleles was also associated with a higher risk of psoriasis with odd ratios OR [CI 95%] = 8.5 [1.8-40.1], 4[1.3-11.4] and 3[2.1-4.1] respectively. In contrast, the presence of HLA-DRB1*03, HLA-DRB1*04, HLA-DRB1*14 and HLA-DRB1*15 was associated with a lower risk of psoriasis, as they are considered protective alleles against psoriasis.

In addition, the presence of HLA-DRB1*01, HLA-DRB1*07 and HLA-DRB1*11 was associated with a higher risk of developing PSA in psoriatic patients, while HLA-DRB1*03 and HLA-DRB1*14 were considered protective alleles against developing PSA (OR= 4.84, 14, 4.88, 0.14 and 0.2 respectively).

Table 1. Demographic features of 50 psoriatic patients

Demographic features		
Mean age ±SD (years old)	40.42±17.62	
Gender	**The number**	**%**
Male	13	26
Female	37	74
Positive family history	15	18.7

Table 2. Clinical features of 50 psoriatic patients

Clinical features	The number	%
Type of psoriasis		
Early type (disease onset ≤40 Years)	37	74
Late type (disease onset >40 Years)	13	26
Clinical phenotype of psoriasis		
Plaque	40	80
Pustular	6	12
Guttate	4	8
Severity of disease		
Mild (PASI <5)	24	48
Moderate (PASI 5-10)	14	28
Severe (PASI >10)	12	24
Concomitant psoriasis arthritis	20	40
Risk factors		
Smoking	25	50
Alcohol intake	6	12

Table 3. Demographic and clinical characteristics in psoriatic patients with PsA and without PsA.

Variables	psoriatic patients with PsA	psoriatic patients without PsA	p-value
Demographic features			
Mean age ±SD (years old)	44.90±15.90	36.36±18.50	**0.04**
Gender			
Male	5(25%)	8(26.7%)	0.4
Female	15(75%)	22(73.3%)	
Positive family history	7(35%)	8(26.7%)	**0.003**
Clinical features			
Type of psoriasis			
Early type (disease onset ≤40 Years)	15(75%)	22(73.3%)	
Late type (disease onset >40 Years)	5(25%)	8(26.7%)	0.8
Age of disease onset (Mean ± SD)	31.65±15.07	27.30±15.9	0.3
Duration of the disease (Mean ± SD)	13.35±11.08	9.56±9.3	**0.02**
Clinical phenotype of psoriasis			
Plaque	18(90%)	22(73.3%)	
Pustular	2(10%)	4(13.3%)	0.2
Guttate	0(0%)	4(13.3%)	
Severity of disease			
Mild (PASI <5)	8(40%)	16(53.3%)	
Moderate (PASI 5-10)	7(35%)	7(23.3%)	0.5
Severe (PASI >10)	5(25%)	7(23.3%)	
Mean ± SD	7.55±5.2	8.67±9.3	0.6
Risk factors			
Smoking	9(45%)	16(53.3%)	0.4
Alcohol intake	3(15%)	3(10%)	0.6

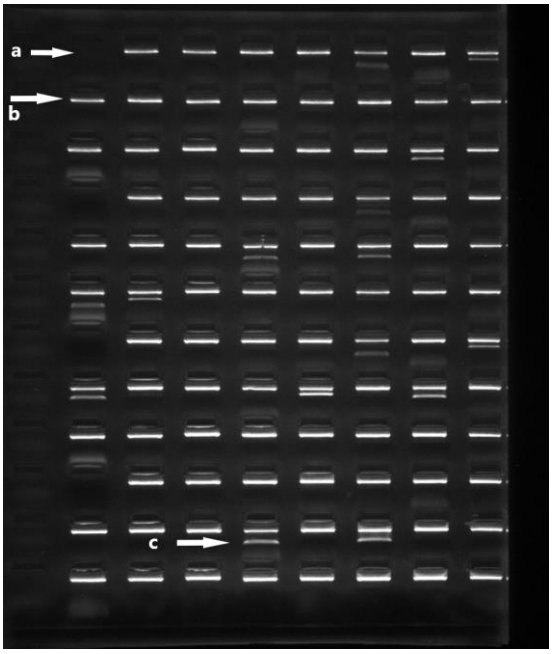

Fig. 1 Electrophoresis results and appearance of bands after imaging in three psoriatic patients (a: negative control (no band), b: positive control, c: electrically migration band; positive result)

Table 4. Distribution of HLA-DRB1 alleles among the research groups

HLA-DRB1 alleles	psoriatic patients with PsA	psoriatic patients without PsA	control	OR [CI 95%] Psoriasis and control	OR [CI 95%] Psoriasis with PsA and control	p-value
***01**	**2(6.7%)**	**7(35%)**	**3(10%)**	1.97[0.4-7.9]	**4.84[1.07-21.8]**	**0.01**
***03**	2(6.7%)	1(5%)	8(26.7%)	0.1[0.04-0.7]	0.14[0.01-1.2]	**0.03**
***04**	9(30%)	3(15%)	9(30%)	0.7[0.2-2.03]	0.4[0.09-1.7]	0.4
***07**	**9(30%)**	**10(50%)**	**2(6.7%)**	**8.5[1.8-40.1]**	**14[2.6-35.2]**	**0.002**
***10**	0(0%)	0(0%)	5(16.7%)	**3[2.1-4.1]**	1.8[1.3-2.3]	0.01
***11**	**14(46.7%)**	**11(55%)**	**6(20%)**	**4[1.3-11.4]**	**4.88[1.3-17.1]**	**0.02**
***12**	1(3.3%)	0(0%)	0(0%)	1.6[1.3-1.9]	———	0.4
***13**	7(23.3%)	4(20%)	5(16.7%)	1.4[0.4-4.5]	1.25[0.2-5.3]	0.8
***14**	4(13.3%)	1(5%)	5(16.7%)	0.5[0.1-2.1]	0.2[0.02-2.4]	0.4
***15**	3(10%)	2(10%)	5(16.7%)	0.5[0.1-2.1]	0.5[0.09-3.1]	0.6
***16**	4(13.3%)	1(5%)	3(10%)	1[0.2-4.5]	0.4[0.04-4.9]	0.6

OR: odds ratio, CI: confidence interval

4. Discussion

It is known that psoriasis is a chronic skin disease immunologically linked to MHC.[24] The genes involved in the pathogenesis of psoriasis are placed within the PSORS1 locus of the HLA region on the short arm of chromosome 6.[24] Studies also indicate that people with certain HLA alleles may be more susceptible to developing PSA.[2] The percentage of arthritis in the present study was 40%, which is compatible with other studies and international rates[1]

A significant convergence was observed in the percentage of the presence of the early type in the patients of group A, which was recorded at 75% and 73.3% in the patients of group B. Moreover, the onset age of the disease was lower among patients of group B, with an average age of onset 27.3±15.9 years compared to 31.65±15.07 years, without a statistical difference. Previous studies have shown conflicting results in this idea. Woodrow et al.[25] observed a tendency for a younger age of onset of psoriasis in group B patients, which is consistent with the results of this study. Arthritis with early psoriasis has also been observed in many studies [11], [26], [27], [28] While others reported no significant statistical differences.[29] As for the duration of the disease, the majority of psoriasis patients (66%) were

suffering from an old disease (more than 5 years ago), with the average duration being 11.08±10.1 years in the present study. This result was consistent with the results reached by the studies conducted by Cassia et al.[16], Pham et al.[30] and Lin et al.[31] (16.9, 12.22±10.22, 11.2±7.2 years, respectively)

On the other hand, a correlation was found between the duration and the presence of PsA [9.56±9.3 years in patients with psoriasis alone compared to 13.35±11.08 years (P value = 0.02)]. This confirms that most cases of PsA occur in psoriasis patients at an average time of approximately 10 years after the appearance of psoriasis[32], [33]. Therefore, the dermatologist must not neglect to examine the joints periodically and regularly.

In the current study, it was recorded that HLA-DRB1*11 and HLA-DRB1*07 are the most frequent in psoriasis patients and PsA and are associated with a higher risk of developing PsA; this is coordinated with some studies that have evaluated allele-disease association such as the study that conducted by Ngo Minh V. et al, 2019 (27.3% in psoriasis and 32.5% in PsA).[34] Liao H-Z et al., 2008 in China[35], and Atasoy M. et al., 2006 in Turkey [36] found HLA-DRB1*07 in psoriatic patients compared with controls. It is also consistent with the results reached by Cassia FF et al., 2007[37] in their review article. However, it contradicts the results recorded by Sin C-Z et al., 2019[38] as the most frequent HLA-DRB1 allele was HLA-DRB1*04 (20.2%) followed by HLA-DRB1*08 (16.0%), but in PSA patients there was increased frequency of HLA-DRB1*07 compared with controls. The results of Sin C-Z et al. study indicated that HLA-DRB1*08 is a risk factor for psoriatic polyarthritis.

Some previous studies on patients with psoriasis have shown that HLA-DRB1*07 and HLA-DRB1*04 have been associated with PSA susceptibility[22], [23]. The frequency of the HLA-DRB1*07 allele was the highest compared to the rest of the alleles in the study conducted by Queiro R. et al. in Spain in 2011[39]. While HLA-DRB1*07 and HLA-DRB1*13 were more common in psoriasis patients and PSA compared to controls (42.9%, 17.2% respectively) with a statistically significant difference p-value <0.05 in the study performed by Bejerano C. et al. 2013[21], in addition, the HLA-DRB1*17 was the highest risk allele (OR=31.2).

The study performed by Cardoso et al., 2005[40] detected the HLA-DRB1*13 as a protective allele, while the study by Cassia et al. in Brazil 2021 recorded the HLA-DRB1*07 as the most frequent in psoriasis patients (38.2%), and the HLA-DRB1*14 as high-risk allele (OR=2.02).[16] The results of the Shawkatova I. et al. study in Slovakia 2012[1] were similar to the results of this study, where the susceptibility of psoriasis is significantly associated with HLA-DRB1*07 (OR=2.56) as a risk allele. However, they were the opposite in that HLA-DRB1*01 and HLA-DRB1*11 are associated negatively (OR=0.05). Likewise, the study conducted by Munir S. et al. 2023 in Pakistan[20]. Both HLA-DRB1*07 and HLA-DRB1*13 were considered high-risk alleles, while HLA-DRB1*03 and HLA-DRB1*11 as protective alleles.

These differences in results may be due to the fact that many of the associated alleles tend to differ among patients of different racial and ethnic backgrounds. To date, the allele involved in susceptibility to psoriasis and PsA is still not precisely known and requires more studies, especially linkage disequilibrium within the region.

5. Conclusion

The results of this study indicate that HLA-DRB1*07 and HLA-DRB1*11 are major genetic risks for psoriasis and the development of PsA in the Syrian population. It is important to conduct more family genetic studies to identify alleles in relatives of people with the disease and determine the genetic factors involved in the pathogenic mechanism. It thus can lead to better prevention and more effective treatment.

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