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EVALUATION OF THE RELATIONSHIP BETWEEN HUMAN LEUKOCYTE ANTIGEN-C (HLA-C) ALLELES AND CLINICAL PHENOTYPES OF PSORIASIS

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ABSTRACT

Background: Psoriasis is a chronic inflammatory skin disease with an immune genetic background and a close correlation to the major histocompatibility complex (MHC) because of containing the psoriasis susceptibility gene PSORS1. **Objective**: To evaluate the relationship between human leukocyte antigen C alleles and different clinical phenotypes of psoriasis. **Materials and methods**: This study included 50 patients with psoriasis. Patients were divided into three subgroups based on the clinical phenotype of psoriasis. Their HLA-C alleles were determined by PCR using sequence-specific primers PCR-SSP. **Results**: The most common clinical phenotype was plaque psoriasis diagnosed in 40 of 50 patients (80%), followed by pustular psoriasis and guttate psoriasis; 12% and 8%, respectively. The alleles were not associated with the clinical phenotype of psoriasis ($P > 0.05$), except for the HLA-C*17 allele with pustular psoriasis ($P = 0.05$). The alleles HLA-C*02, HLA-C*08, HLA-C*14 were only found in plaque psoriasis. **Conclusion**: Due to racial and geographic differences in the distribution of alleles and their relationship with psoriasis types. It is important to conduct more studies in larger populations to identify more risk alleles involved in the pathogenesis of psoriasis.

KEYWORDS: HLA-C, PCR-SSP, psoriasis, plaque psoriasis, pustular, guttate.

INTRODUCTION

Psoriasis PsO is a common chronic inflammatory immune-mediated skin disease, which has a significant effect on the quality of life of the patients and is associated with high morbidity.[1] The most common clinical type is chronic plaque psoriasis, which is present in 85-90% of patients and is characterized by raised, red patches of skin that are covered by silvery-white scales. These lesions result from epidermal hyperproliferation, incomplete differentiation of keratinocytes, and infiltration of the epidermis and papillary dermis with activated immune cells. Plaques can appear anywhere on the body, but are most commonly found on the scalp, trunk, knees, elbows, and extremities.[2] Other forms include guttate psoriasis, pustular psoriasis, psoriatic erythroderma, and palmar psoriasis.[3]

The human leukocyte antigen (HLA) gene region carries the most important genetic factors of psoriasis susceptibility PSORS1. HLA genes (the major histocompatibility complex (MHC)) are located on the short arm of chromosome 6 (6p21.3).[4] and encoding polymorphic proteins on the surfaces of cells, named the Human leukocyte antigens (HLA). HLA genes are composed of two main classes, the first; HLA-I, encoding HLA-A, HLA-B, HLA-C antigens, while the second; HLA-Ⅱ, encoding HLA-DR, HLA-DP, HLA-DQ.[5] These proteins play a major role in protection against some cancers and viruses, but they have also implicated in autoimmune diseases.[6],[7] The observation that some diseases are more common in individuals with a specific HLA allele has allowed studies of association between HLA and diseases, so all studies focused on HLA genes to determine the cellular molecular basis of the disease.

There is no Syrian study of the association between HLA-C alleles and the clinical phenotype of psoriasis. The current study aims to identify these alleles in patients and evaluate the relationship between HLA-C alleles and the clinical phenotype of psoriasis

MATERIALS AND METHODS

The Study Sample

The present study included (50) psoriasis patients who were randomly selected from dermatology clinics at Tishreen University Hospital - Latakia, and the Dermatology and Venereal Diseases Hospital - Damascus, during the period from June 2022 until

September 2023. Detailed demographic and clinical information was obtained (gender, age, age of disease onset, presence of family history, presence of psoriatic arthritis, type of psoriasis), the severity of the disease were 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. psoriasis is classified based on age of onset into early type I, age of onset less than 40 years, and late type II: age of onset more than 40 years. Written informed consent was taken from patients to participate in the research after receiving sufficient information. The questionnaire form for each patient was filled out with the assistance of a dermatologist.

Extraction and genotyping

DNA was extracted from whole blood with EDTA anticoagulant using a kit (Inno-train's Ready DNA Spin Kit, Germany) according to the manufacturer's instructions, to which lysis was added after proteinase K application, then incubation, washing and centrifugation stages to obtain DNA. The purity and concentration of the extracted DNA were determined using the Nano Drop method.

Genotyping was performed using the PCR-SSP technique using Inno-train's HLA-Ready Gene C Kit, Germany. The master mix was prepared according to the manufacturer's instructions. After mixing well, 10 µL were taken from the negative control tube before adding DNA and placing it in the first well. After that, DNA was added and 10 µL were distributed in the remaining wells in preparation for the amplification process in the Eppendorf™ MasterCycler Nexus Gradient Thermal Cycler according to the program (an initial cycle of 96°C for 2 minutes, then 10 cycles: 96°C for 15 seconds and 65°C for 60 seconds. sec, followed by 20 cycles: 96°C for 15 s, 61°C for 50 s, then 72°C for 30 s, the final temperature being 4°C. Bands were evaluated by electrophoresis on a 150 V agarose gel for all 16 min Laboratory procedures were carried out in the Molecular Biology Laboratory at Al-Assad University Hospital in Damascus.

STATISTICAL ANALYSIS

The Descriptive statistics were conducted using: measures of central tendency and measures of dispersion for quantitative variables, and frequencies, and percentage values for qualitative variables. The chi-square test was adopted to evaluate the relationships between qualitative variables. 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.

RESULTS

The research sample included 50 chronic psoriasis patients (13 males and 37 females) who were randomly selected from dermatology clinics and departments at Tishreen University Hospital - Latakia, and the Dermatology and Venereal Diseases Hospital - Damascus, during the period from June 2022 to September 2023. The ages of the psoriasis patients in this study ranged from 8 to 73 years, with a mean age of 40.42 ± 17.62 years. A positive family history was recorded in 15 patients (18.7%). Also, 40% of psoriasis patients had arthritis. 74% (37/50) of psoriasis cases were of the early type and 26% (13/50) were of the late type, where the age of disease onset ranged from 3 to 63 years, with a mean of 29.04±15.6 years. The most common clinical phenotype was plaque psoriasis diagnosed in 40 of 50 patients (80%), followed by pustular psoriasis and guttate psoriasis; 12% and 8%, respectively. Regarding disease severity, 24 of 50 patients (48%) had mild disease according to a PASI score of less than 5, 14 patients (28%) had moderate disease, and 12 patients (24%) had severe disease. The demographic and clinical characteristics of the patients in this study are presented in Table 1 and Table 2. Regarding the distribution of HLA-C alleles shown in Table 3; there are no statistically significant differences between HLA-C alleles and the clinical phenotype of psoriasis. The alleles were not associated with the clinical phenotype of psoriasis (P > 0.05), except for the HLA-C*17 allele with pustular psoriasis (P = 0.05) and the HLA-C*04 allele with plaque psoriasis (It approached the statistically significant limit; P = 0.07). The alleles HLA-C*02, HLA-C*08, HLA-C*14 were only found in plaque psoriasis.

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	30

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
Severity of disease		
Mild (PASI <5)	24	48
Moderate (PASI 5-10)	14	28
Severe (PASI >10)	12	24
Concomitant psoriasis arthritis	20	40

Table 3: Distribution of HLA-C alleles among the research groups.

alleles HLA-C	Guttate	Plaque	Pustular	p-value
***02**	0(0%)	6(12%)	0(0%)	0.4
***03**	0(0%)	4(8%)	1(2%)	0.6
***04**	**1(2%)**	**19(38%)**	**0(0%)**	**0.07**
***06**	3(6%)	16(32%)	2(4%)	0.3
***07**	2(4%)	7(14%)	1(2%)	0.2
***08**	0(0%)	6(12%)	0(0%)	0.4
***12**	0(0%)	7(14%)	3(6%)	0.1
***14**	0(0%)	4(8%)	0(0%)	0.5
***15**	1(2%)	3(6%)	0(0%)	0.3
***16**	1(2%)	3(6%)	1(2%)	0.4
***17**	**0(0%)**	**1(2%)**	**2(4%)**	**0.05**

DISCUSSION

Psoriasis can manifest different clinical phenotypes and can affect different areas of the body.[8] The sample of psoriasis patients included in the study was clinically heterogeneous, with 80% of patients suffering from plaque psoriasis, 12% pustular psoriasis, and only 8% of patients suffering from guttate psoriasis. This is consistent with the results of previous studies; Chronic plaque psoriasis was the most common clinical type among patients in the study conducted by Benlabsir et al. 2023 in Morocco, at a rate of 62.97%. In Benlabsir study, three phenotypes were diagnosed: chronic plaque psoriasis, psoriatic erythroderma, and pustular psoriasis.[9] It also agreed with the results of the study of Fatema et al. 2021, which also recorded the predominance of chronic plaque psoriasis at a rate of 72.8%, followed by palmoplantar psoriasis at a rate of 17.2%, in addition to the presence of guttate psoriasis in patients.[10] This is also similar to the results reached by Fan et al. in China in 2007 (74.9 % for plaque psoriasis, 15.3% for guttate psoriasis).[11]

The association of the HLA-C*04 allele with plaque psoriasis was recorded at a rate of 38%, which is the highest percentage. It was noted that 19 patients out of 50 psoriasis patients carried this allele and suffered from plaque psoriasis, while the presence of this allele was recorded at a rate of only 2% with guttate psoriasis and was absent from patients with pustular psoriasis with a difference approaching the statistical edge (P value = 0.07), followed by the HLA-C*06 allele, which is the most important allele in patients with psoriasis, as it was present in 32% of patients with plaque psoriasis, 6% of patients with guttate psoriasis, and 4% of patients with pustular psoriasis.

As for the rest of the alleles, they were associated in varying proportions with plaque psoriasis, while most of them were absent with guttate and pustular psoriasis. The allele most associated with pustular psoriasis is HLA-C*12 (6%), and the allele most associated with guttate psoriasis is HLA-C*06 (6%), but without statistically significant significance. The association of the HLA-C*17 allele with pustular psoriasis was at the important statistical level (P value = 0.05).

On the other hand, when carriers of the HLA-C*06 allele were studied, plaque psoriasis was found in 76.1% of carriers of the allele, and guttate psoriasis was found in 14.2%, while pustular psoriasis was found in 9.7% of carriers. This is consistent with what Fan et al. found in their study in 2007; They recorded the presence of plaque psoriasis in 72.8% of carriers of the HLA-C*06 allele, without a statistically significant difference between carriers of the allele and non-carriers, guttate psoriasis was also found in 21.1% of carriers of this allele with significant statistical significance.[11] The presence of the HLA-C*06 allele was observed in 64.2% of patients with chronic plaque psoriasis in the study of Gudjonsson et al. in 2006.[12] Other studies also agreed with the results of the present study, which confirmed that guttate psoriasis is associated with the presence of the HLA-C*06 allele at a high rate, and not just plaque psoriasis, as the percentage of the presence of this allele in guttate psoriasis reached 86% in Ireland in 2006, while the percentage reached 73% in plaque psoriasis[13], and all guttate psoriasis patients included in the study conducted in the United Kingdom in 2000 carried the HLA-C*06 allele[14], which confirmed the association between this allele and the pathogenesis of guttate psoriasis.[14],[15] On the other hand, the results of our study were consistent with the results of the Chinese study in 2007, which observed a greater recurrence in pustular psoriasis patients who did not carry the HLA-C*06 allele.[11] None of the patients in the present study had the HLA-C*01 allele. In contrast, Japanese patients with generalized pustular psoriasis had a significantly higher frequency of this allele (46.2%), and a lower frequency in Chinese patients with chronic plaque psoriasis.[1] These differences may be due to the different clinical phenotypes of the patients included in each study, racial and geographic differences in the distribution of alleles, in addition to the difference in the sample size.

CONCLUSION

The results of this study indicate that the HLA-C*17 allele Associates with pustular psoriasis, with a tendency for the HLA-C*04 allele to be associated with plaque psoriasis, the HLA-C*12 allele with pustular psoriasis, and the HLA-C*06 allele with guttate psoriasis in Syrian population. It is important to conduct more studies in

larger populations to identify more risk alleles involved in the pathogenesis of psoriasis.

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