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The relationship between human leukocyte antigen-cw6 allele and psoriasis vulgaris

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Abstract

Psoriasis vulgaris is chronic skin disease that is linked to genetics and immune system. The most important predisposing genetic factor is human leukocyte antigen (HLA). This study was performed to determine the relationship between HLA-Cw6 allele and psoriasis vulgaris and the changes of nucleotide base sequences, using observation method with a cross sectional comparative study. Samples were selected using consecutive sampling of 30 patients with psoriasis vulgaris attending the Dermatology and STD polyclinic at DR. M. Djamil Hospital. 30 healthy volunteers were selected as controls. The subjects' medical history was recorded followed by a dermatological examination, collection of samples, DNA isolation, then primers were designed for HLA-Cw6 allele, genes were sequencing and finally analyzed using PCR-SSP. The results were 20% of patients with psoriasis vulgaris carried HLA-Cw6 allele, while it was absent in the control group. This difference is statistically significant at the 5% level ($p = 0.024$). We found the changes of nucleotide base formations of HLA-Cw6. In conclusion, based on these observations, presence of the HLA-Cw6 allele is an important genetic risk factor for developing psoriasis vulgaris.

Introduction

Psoriasis vulgaris is a chronic skin disease that interferes with daily life resulting in high levels of morbidity.¹ It affects a patient's appearance², reducing their quality of life^{1,2}, and impacting both the social and health systems.¹ Globally the incidence is 2-3 % of the population.^{3,4} Amongst patients

at the Dermatology and STD polyclinic at the DR. M. Djamil Hospital in Padang, the prevalence of patients diagnosed with psoriasis is increasing; 2.8% in 2014 and 3.6% in 2016. Psoriasis is an autoimmune disease that is mediated by T cells, characterized by hyperproliferation of keratinocytes and is related to HLA (*human leukocyte antigen*) particularly the HLA-Cw6 allele.⁵ Psoriasis is the result of an interaction between this hyperproliferation of keratinocytes and the infiltration and activation of immune cells.⁴

The human leukocyte antigen (HLA) system is a gene locus that encodes a cell wall protein responsible for the regulation of the human immune system. Human leukocyte antigen-Cw6 is a class one variant of MHC (major histocompatibility complex) related to the early onset of psoriasis vulgaris and primarily responds with a T cell expression of CD-8+. Type I psoriasis occurs in patients before 40 years of age, often reoccurs, runs in families, has a more severe clinical presentation and is primarily related to HLA-Cw6. Type II psoriasis has a later onset, does not occur in family histories and clinical symptoms are less severe. It is related to HLA-Cw2 and -B27, with only a weak correlation with HLA-Cw6.⁶

HLA-Cw6 incidence varies with racial background and geography and also this chronic recidive disease is hard to treat. Hence, this study focused on the role of HLA-Cw6 in psoriasis vulgaris patients and the changes of nucleotide base sequences.

Materials and Methods

Consecutive random sampling was used to select from the subjects fulfilling the criteria. A physical examination was conducted to determine the severity of the psoriasis (PASI score). A 5cc blood sample was taken from the cubital vein of each subject. This was used to check for the presence of HLA-Cw6 using a sequence-specific primer. DNA isolation was conducted using a Vivantis GF-1 Blood/Cultured Cell DNA Genaid Cat.No GB100 kit. Synthesis of the primer was done by Integrated DNA Technologies (IDT) Singapore. The reagent for PCR was KAPATaq Extra Hot Start (Cat. No. KK3606).

Results

Table 1 shows the characteristics of subjects in the two samples. Subject age was 51.0 ± 15.1 with a mode of 46 to 56 years (23.3%). All subjects were 12 years old or above. Males slightly outnumbered females (53.3% compared to 46.7%)

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amongst psoriasis sufferers. 43.0% of psoriasis patients and 43.3% of control subjects had junior high school education and half of each group had a tertiary education. Table 2 shows 76.7% of patients had mild psoriasis, 16.7% moderate psoriasis and 6.6% had severe psoriasis, 76.7% first suffered the disease at or before the age of 40 while only 23.3% first experienced it after this age. 50% had suffered from the disease from between 5 and 15 years, 46.7% for five years or less and only 3.3% had suffered from psoriasis for more than 15 years. Bioinformatic study of the HLA-Cw6 was conducted using primer designed by Bunce & Welsh (1994). The appropriateness of the primer was verified by alignment with the Homo Sapiens HLA-C gene sequence (NCBI Accession NG_029422.2) using the Geneious (version 7.0.6) software. Tables 3 and 4 show the primer for HLA-Cw6. PCR products are 336 bp respectively (adapted from Bunce & Welsh, 1994) (Figures 1-3).

Discussion

The literature suggests that the onset of psoriasis vulgaris can occur at any age from infancy until the seventies. There are two peaks for onset age, between 20-30 and 50-60.^{7,8} Henseler and Christopher (1985)⁹ divided psoriasis into two types. Type 1 usually has an onset before the age of 40 and is coincident with the HLA-Cw6 allele in 85% of the cases so runs in families. Type II has a later onset and is unrelated to HLA.

Bologna *et al.* (2004) found that 75% of all psoriasis vulgaris cases in their study were early onset.⁸ Sommer *et al.* (2006) also found that psoriasis type I (60.2%) was more common than type II (36.9%).¹⁰ Similarly, over three quarters (76.7%) of the patients in our study first contracted psoriasis vulgaris before they were 40 years old.

Psoriasis vulgaris afflicts males and females equally. Most psoriasis patients in this study were aged between 46 and 56 and the number of males and females was almost the same (53.3% and 46.7%). A dis-

proportionate number of patients had higher levels of education and the majority had mild cases of the disease. This maybe because more educated and social aware sufferers feel embarrassed about this disease so seek early treatment. More than half the patients in our study had suffered from the disease for more than 5 years. This is in line with the chronic recidive nature of psoriasis vulgaris reported in the literature.

The presence of HLA-Cw6 in 20% of the psoriasis vulgaris patients and not in the control group compares with the findings of

Amr *et al.*, (2010) that amongst Egyptians. HLA-Cw6 was more common (86%) in psoriasis patients than in the control group (40%). Gudjonsson *et al.*, (2001) reported that of 369 Icelandic psoriasis vulgaris patients (66.9%) were HLA-Cw6 positive and 122 were HLA-Cw6 negative. Atasoy *et al.*, (2006) found that 48 of 72 (66.9%) Turkish patients were HLA-Cw6 positive but only 9 of 104 (8.7%) of control subjects.¹¹

High resolution PCR studies have shown that HLA-Cw*0602 is the primary

Table 1. Age, gender, and level of education of subjects with psoriasis vulgaris and control.

Characteristics	Psoriasis Vulgaris		Non-Psoriasis Vulgaris	
	n	%	n	%
Age				
12-<17	1	3.3	0	0
>17-<26	5	16.7	6	20
>26-<36	5	16.7	5	16.7
>36-<46	6	20	6	20
>46-<56	7	23.3	7	23.3
>56-<65	6	20	6	20
>65	0	0	0	0
Sum	30	100	30	100
Gender				
Male	16	53.3	16	53.3
Female	14	46.7	14	46.7
Sum	30	100	30	100
Level of Education				
Elementary School	4	13.3	0	0
Junior High School	5	16.7	0	0
Senior High School	13	43.3	15	50
Tertiary Education	8	26.6	15	50
Sum	30	100	30	100

Table 2. Degree of severity, onset and duration of psoriasis vulgaris in each patient.

Characteristic	Psoriasis Vulgaris	
Severity		
Mild (PASI <8)	23	76.7
Moderate (PASI >8-<12)	5	16.7
Severe (PASI >12)	2	6.6
Sum	30	100
Onset of disease		
Before age 40	23	76.7
After age 40	7	23.3
Sum	30	100
Duration		
<5years	14	46.7
between >5 and <15years	15	50
>15years	1	3.3
Sum	30	100



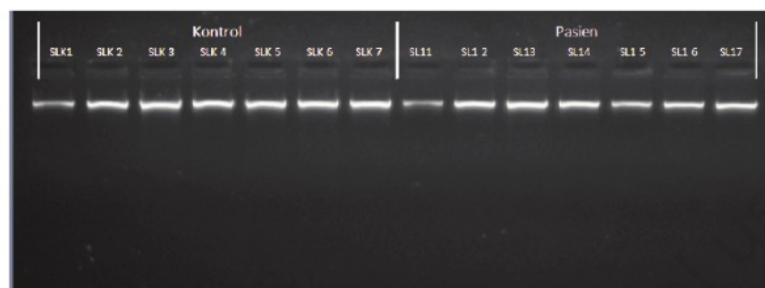
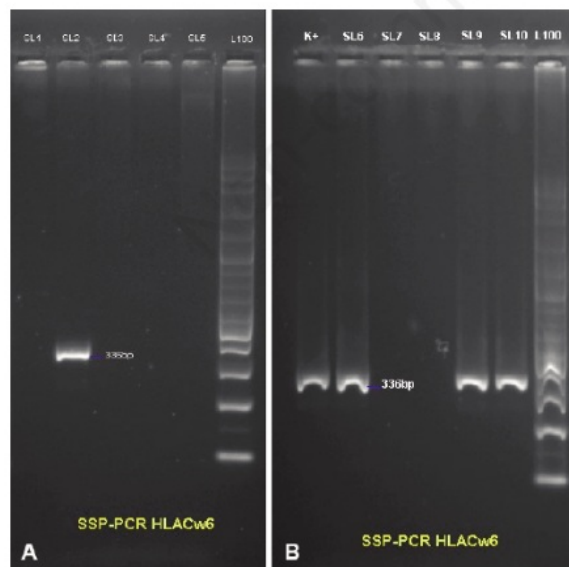
Figure 1. Result of HLA-Cw6 allele primer design. HLA-C (NG_029422.2) gene sequence and HLA-Cw6 attachment position, forward and reverse. HLA-Cw6-F primer attaches from the 5,484th to the 5,502th nucleotide bases. The HLA-Cw6-R primer attaches from the 5,801th to the 5,581th nucleotide bases. Amplification used this primer pair to produce a 336 bp PCR product.

Table 3. Results from primer for HLA-Cw6 allele

HLA Allele	Primer Name	Nucleotide Sequence	Size of PCR product
Cw*0601,0602, CL10v	HLA-Cw6-F	5'-CCGAGTGAACCTGCGGAAA-3'	336 bp
	HLA-Cw6-R	5'-GGTCGCAGCCATACATCCA-3'	

Table 4. Relationship of presence of HLA-Cw6 in patients with psoriasis vulgaris and control subjects. HLA-Cw6 was present in 6 of the 30 patients with psoriasis (20%) and absent in the control group. There is a statistically significant relationship between the presence of HLA-Cw6 with psoriasis vulgaris ($p < 0.05$) so it can be concluded that HLA-Cw6 plays a role and resulting incidence of psoriasis vulgaris.

Subject	Positive		HLA-Cw6 Negative		Sum	P
	N	%	N	%		
Patient	6	20	24	80	30	0.024
Control	0	0	30	100	30	0.024
Sum	6	10	54	90	60	0.024

**Figure 2. Result of DNA isolation from all subjects using electrophoresis. The genomic DNA electrophoresis of 5 μ L samples after electrophoresis in 1.5% agarose gel stained with DNA GelRed. The DNA band is visible on each sample. This shows the genomic DNA has been successfully isolated.****Figure 3. HLA-Cw6 PCR electrophoresis. Isolated genomic DNA forms the template in the reaction. DNA band is visible at ± 336 bp compared to the DNA size marker or the 100 bp (L100) DNA Ladder, then the sample can be said to be positive for HLA-Cw6, for example samples coded SL2, SL6, SL9, and SL10. Conversely, an absence of a band in that position corresponds to an absence of the allele as in SL1, SL3, SL4, SL5, SL7, and SL8.**

allele for susceptibility to psoriasis vulgaris in West India.⁵ Human leucocyte antigen-Cw6 has the ability to produce peptides and trigger a CD8+ T cell response.¹² HLA-Cw6 is a highly significant marker for the predicting risk of developing psoriasis vulgaris.¹³ A study amongst the Chinese population reported that a HLA-Cw6 positive individual has an 8.33 x greater risk of developing psoriasis compared to individuals who are HLA-Cw6 negative.¹⁴ Chandra *et al.*, found a significant relationship between HLA-Cw6 and psoriasis vulgaris. From 705 cases of psoriasis, 61.74% had type I (early onset). 53% of these and 34% of those with type II were HLA-Cw6 positive but only 14.85% of the control group. This last result differs from previous work that showed a significant relationship between HLA-Cw6 and both types of psoriasis vulgaris compared to the control even though the risk associated with HLA-Cw6 for Type I is twice that of Type II.¹⁵

Conclusions

In this research HLA-Cw6 was only found in psoriasis vulgaris patients, not in the control group. We also found some changes of nucleotide base sequences. More research is needed to investigate the other genetic and immunological factors that play a role in clinical psoriasis vulgaris.

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