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CLINICAL REPORT

Comparison of Clinical Features of HLA-Cw*0602-Positive and -Negative Psoriasis Patients in a Han Chinese Population

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HLA-Cw6 is strongly associated with psoriasis and has been suggested to be the PSORS1 gene that confers susceptibility to early-onset psoriasis. In this study of the clinical features of HLA-Cw*0602-positive and -negative psoriasis patients in a Han Chinese population, we typed HLA-C in a cohort of 679 patients and compared the two groups. Cw*0602-positive patients (n=345) had an earlier disease onset ($p<1\times10^{-5}$), more severe disease ($p<1\times10^{-3}$), higher frequency of guttate psoriasis ($p<1\times10^{-9}$), more affected legs and trunk ($p<1\times10^{-5}$), higher incidence of Köbner's phenomenon (p=0.005) and of trauma history (p=0.009). Cw*0602-negative patients (n= 334) had more palmoplantar pustulosis (p=0.004), nail changes (p=0.001) and scalp involvement (p=0.007). However, there was no statistically significant difference between the two groups regarding age, gender, incidence of plaque psoriasis, erythrodermic, inverse, psoriatic arthritis, and the precipitation factors stress and infection. The study showed that Cw*0602-positive patients had some obvious clinical differences from Cw*0602-negative patients in a Han Chinese population, which provides evidence for an HLA-Cw*0602-associated phenotype in psoriasis. ***Key words: psoriasis, HLA-Cw*0602, Han Chinese population.***

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Psoriasis is an inflammatory and hyper-proliferative skin disease affecting 0.12% of the Chinese population (1). It has a strong genetic component, but environmental factors, such as infections, can also play an important role in the presentation of disease. It appears to be heterogeneous, with distinct but overlapping phenotypes, including plaque lesions, guttate attacks, pustular lesions, psoriasis arthritis and other rare types. Available evidence shows PSORS1 at 6p21 to be a major susceptibility locus for psoriasis (2). A recent study from the USA implicates HLA-Cw6 as a highly probable disease allele at the PSORS1 locus (3).

The strong association between psoriasis and HLA-Cw6 has been known for many years (3–5). Caucasians with this allele have an approximately 10-fold increased relative risk of developing psoriasis, whereas the Chinese population has an approximately 4-fold increased relative risk (6–7). In particular an association of the HLA-Cw6 with early-onset psoriasis has been reported in various cohorts (7–10).

Studies on correlation between HLA-Cw6 and the clinical features of psoriasis have produced different results. Ikaheimo et al. (8) failed to show any connection between the occurrence of Cw6 and the clinical psoriasis phenotype. Henseler & Christophers (10) have shown that Cw6-positive patients are more likely to have widespread and recurrent psoriasis. A recent study of a large Icelandic population of patients with psoriasis suggested distinct clinical differences between Cw*0602-positive and -negative psoriasis patients and a diverging pattern of disease severity in Cw*0602-positive and -negative patients depending on the age of onset of the disease (11–12).

This study investigated 679 Han Chinese psoriasis patients and observed clinical differences between Cw*0602-positive and -negative patients.

MATERIALS AND METHODS

Recruitment and clinical evaluation of patients and controls

The study population comprised 679 patients, most of whom were recruited from the Department of Dermatology at No. 1 Hospital of Anhui Medical University in China, between 2002 and 2005. A total of 451 patients were the probands belonging to 451 families with an incidence of psoriasis ranging from 2 to 6 patients. A positive family history in our study means at least one relative had psoriasis among first- and second-degree relatives. A further 228 sporadic patients without any affected relatives were randomly recruited. All patients who entered the study were examined clinically by two experienced dermatologists and were diagnosed clinically as psoriasis without a previous diagnosis or a history of skin lesions similar to psoriasis.

Clinical data, including age, gender, age of onset, sites, the pattern and severity of psoriasis lesions on the skin, presence or absence of nail disease, Köbner's phenomenon that had been reported to influence the disease course and joint disease at the time of initial examination, were recorded. All patients with any joint symptoms were examined and diagnosed by an experienced rheumatologist.

Additional information included a history of recent infections, stressful events prior to onset and history of trauma surrounding onset and previous and ongoing medication or systemic therapy.

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A total of 384 controls (198 males and 186 females, mean age 32.4 years) from local unrelated subjects presenting for health examination in our hospital were recruited simultaneously with patients. Controls were screened for a history of psoriasis and other autoimmune diseases.

All the samples were recruited with informed consent. The study was approved by the ethics committee of Anhui Medical University and was conducted according to the principles of the Declaration of Helsinki.

Skin examination

Diagnosis and classification of psoriasis were made by adopting established terminology (13). Guttate psoriasis was defined as acute onset of scattered small coin-like lesions. In addition to plaque psoriasis, the non-guttate group included palmo-plantar, generalized pustular, erythrodermic and inverse psoriasis. Köbner's phenomenon was defined as the appearance of psoriatic lesions in uninvolved skin of psoriatic patients as a consequence of trauma or other trigger factors between 3 and 20 days after trauma (14).

The severity of the psoriasis was assessed by the Psoriasis Area and Severity Index (PASI) (15). The scoring by the different dermatologists was in good agreement. Psoriatic arthritis and patients receiving systemic treatments were not included in the evaluation of severity score. A PASI score below 3 was defined as mild, between 3 and 15 as moderate, and above 15 as severe disease.

Nail examination

Only fingernails were examined clinically, since clinical evaluation of toenails may be complicated by frequent fungal infections. The evaluation included pitting, defined as a minimum total of two pits on a nail, onycholysis, subungual hyperkeratosis and dystrophy (oil spots). Scoring of nail problems was according to the method of Mallbris et al. (16).

Joint examination

Patients with joint symptoms were evaluated by the same rheumatologist and divided into five groups according to the following patterns: distal predominant pattern, oligoarticular asymmetrical, polyarticular RA-like, spondylitis, and arthritis mutilans (17). All arthritis patients had active psoriasis and were seronegative for rheumatoid factor.

Environmental factors

Associated environmental factors were recorded. Infection history was defined as acute symptoms requiring antibiotics or antiviral treatment occurring up to 10 days before onset or exacerbation of psoriasis (15). Stressful events were defined as a distinct severe events profoundly affecting life occurring within 2 months prior to disease onset, and in the absence of streptococcal pharyngitis. Stressful events included divorce, severe/life-threatening diseases affecting the patient or close family members, serious financial difficulties, being dismissed from work, and harassment at school, etc. (18). Trauma is also referred to as Köbner's phenomenon. Trauma included animal bites, burns, electrodessication, freezing, friction, lacerations, nail manicuring, needle scarification, poor fitting shoes, shaving, surgical incision, thumb sucking, etc.

HLA-C typing and laboratory analysis

All samples were typed for HLA-C alleles. Genomic DNA was extracted from peripheral blood leukocytes using a standard procedure (19). HLA-C was typed using the polymerase chain reaction with sequence-specific primers (PCR-SSP) (20).

Statistical analysis

Data were analysed with the Statistical Package for Social Scientists (SPSS) version 11.5. Allele frequencies for psoriasis and control subjects were estimated by counting alleles and calculating sample proportions. Comparisons of allele frequencies were made using the Pearson's χ^2 test (with Yates' correction) and odds ratios (OR). The Fisher's exact test was used for comparing the frequencies of variables when the expected count was less than 5. Comparison between the Cw*0602-positive and -negative groups in the age of onset and disease severity was made using the Mann-Whitney *U* test. Correlation *p*-values were calculated using the Spearman's rank sum test. A logistic regression was performed to obtain OR and *p*-values to explore predictive ability of variables on the Cw*0602 status. The type of patient was entered as Cw*0602-positive =1, or Cw*0602-negative=0. The level of statistical significance was set at 5% (i.e. $p \leq 0.05$).

RESULTS

*Distribution of HLA-Cw*0602 and age of onset*

A total of 679 patients with psoriasis included 388 males and 291 females (mean age 37.7 years). All patients had a mean age of onset of 22.9 years (range 6 months to 70 years). A total of 577 patients had an onset of psoriasis below the age of 40 years (early-onset psoriasis) and 102 patients had an onset at age 40 years or older (late-onset psoriasis).

The allelic frequency distribution of the HLA-Cw*0602 in the 679 patients and 384 control subjects are shown in Table I. A significant proportion of patients were Cw*0602-positive compared with the control group (OR=4.716, 95% CI (confidence interval): 3.490–6.371). The Cw*0602 allele was present in 32.6% of those with early-onset psoriasis (≤40 years) and 15.9% of late-onset (>40 years) psoriasis, both higher than control subjects. Familial patients had a significantly higher frequency than sporadic patients (36.7% vs. 17.5%, OR=3.226).

Of all the patients, 345 were Cw*0602-positive and the remaining 334 patients were Cw*0602-negative. The gender distribution showed an approximately

Table I. *Allele frequency distribution of HLA-Cw*0602 in patients and controls*

	Cw*0602 allele (AF %)	OR	95% CI for OR
Psoriasis (*n*=679)	29.8	4.716	3.490–6.371
Early-onset psoriasis (*n*=577)	32.6	5.489	4.035−7.467
Late-onset psoriasis (*n*=102)	15.9	1.902	1.155−3.134
Familial psoriasis (*n*=451)	36.7	6.937	5.029−9.569
Sporadic psoriasis (*n*=228)	17.5	2.150	1.469−3.148
Controls (*n*=384)	9.4		

AF: allelic frequencies; OR: odds ratio, comparing patients with controls; 95% CI: 95% confidence interval.

equal proportion in the two groups (p=0.245). Females had earlier disease onset than males among Cw*0602-positive patients (19.0 vs. 23.0 years, p <0.001), but there was no gender difference in Cw*0602-negative group (25.9 vs. 27.0 years, p >0.05). In this cohort Cw*0602-positive patients have an earlier disease onset than negative patients, although there was a very marked overlap between the two groups, the mean age of onset being 23.7 (range 0.5–70) years vs. 27.3 (range 3–66) years for the Cw*0602-positive and -negative patients, respectively (p=0.004) (Fig. 1).

Phenotypes

Plaque psoriasis (n=509) was the most frequent clinical type of psoriasis (74.9%), but there was no difference between the Cw*0602-positive and -negative groups (p >0.05). Guttate psoriasis were found in 104 (15.3%) of the patients, it was more common in the Cw*0602-positive group (p <1×10^{-9}). Palmoplantar pustulosis was diagnosed in only 34 patients (5%) of the study cohort, and was observed more frequently in patients of Cw*0602-negative (p=0.004). No significant differences were observed between the two groups in other different clinical forms of psoriasis (p >0.05) (Table II).

Fingernail involvement was detected in 121 patients (17.8%). The majority were estimated as mild. However, 1.6% (n=11) had severe nail involvement, all of whom were Cw*0602-negative. Nail changes were also more frequent in Cw*0602-negative patients (22.7% negative vs. 13% positive, p=0.001) and patients with arthropathic psoriasis (66.7% vs. 15.1%; p <1×10^{-5}). There was no significant correlation between nail changes and PASI score in this study. The Köbner's phenomenon was observed in 14% of all patients (n=95) and more commonly reported in the Cw*0602-positive patients (p=0.001). And we observed significant association within the Cw*0602-positive group between early-onset and the occurrence of the Köbner's phenomenon (p=0.005).

Table II. *Clinical comparison of HLA-Cw*0602-positive and -negative patients*

Clinical characteristics	Type of patients: Cw*0602-positive (%) (n=345)	Cw*0602-negative (%) (n=334)	p-value
Gender (female)	40.6	45.2	0.245
Onset			
Mean age of onset (years)	23.7	27.3	0.004
Early-onset (≤ 40 years)	91.3	78.4	< 1×10^{-5}
Late-onset (> 40 years)	8.7	21.6	< 1×10^{-5}
PASI score			< 1×10^{-3}
ND	9.3	11	
Mild (0–3)	15.4	24.6	
Moderate (>3–15)	40.3	44.6	
Severe (>15)	35	19.8	
Phenotype			
Guttate	21.1	9.3	< 1×10^{-9}
Plaques	72.8	77.2	0.185
Pustular (palms and soles)	2.6	7.5	0.004
Pustular (generalized)	1.2	2.4	0.256
Erythrodermic	0.9	1.8	0.333[b]
Inverse	1.4	1.8	0.769
Arthritis	4.9	5.7	0.733
Nail involvement	13	22.7	0.001
Köbner's phenomenon	18.5	9.3	0.001
Precipitating factors			
Infections	14.5	11.7	0.307
Stressful events	22.9	19.5	0.302
Trauma	15.1	8.4	0.009

ND: no data available; PASI: Psoriasis Area and Severity Index. [a]Fisher's exact p-value (two-tailed), otherwise Yates' continuity corrected p-value is given.

Affected sites

The mean numbers of affected sites at the time of examination in Cw*0602-positive and -negative patients were 4.09±2.12 and 1.33±0.47, respectively. Cw*0602-positive patients affected more sites than negative patients (p =0.002). More Cw*0602-positive patients affected legs (p<1×10^{-5}) and trunk (p<1×10^{-6}), whereas more Cw*0602-negative patients affected scalp (p=0.007) and nail (p=0.001). Patients had no significant differences in other affected sites that we analysed (Fig. 2).

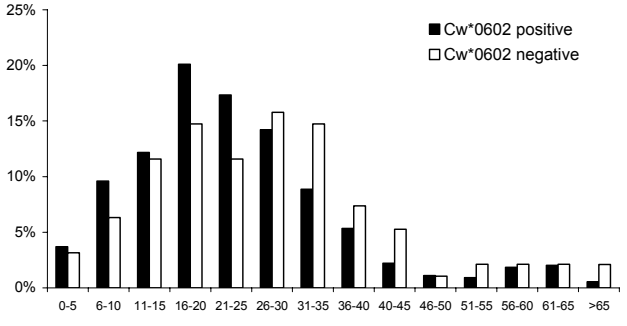

Fig. 1. Age of onset distribution for the HLA-Cw*0602-positive and -negative patients.

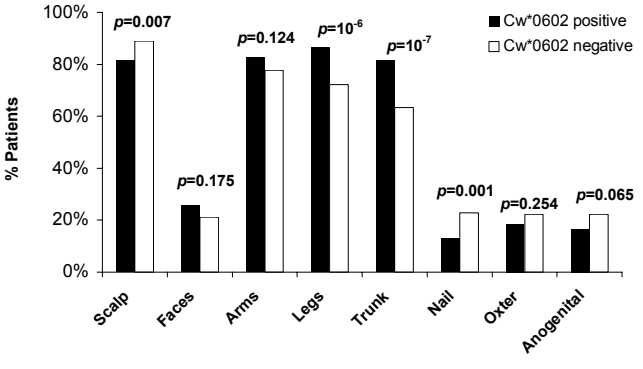

Fig. 2. Sites of disease involvement at examination in the HLA-Cw*0602-positive and -negative patients.

Disease severity

The mean time from disease onset to skin examination was 5 months. Five percent of patients (n=33) had received systemic treatment before examination and 5% had psoriasis arthritis. Of the remaining patients 42.4% were evaluated as having moderate disease, whereas 19.9% had mild and 27.5% had severe psoriasis at examination. Patients who were Cw*0602-positive had a higher frequency of severe psoriasis than the negative patients ($p < 1 \times 10^{-3}$).

Associated environmental factors

In total, 89 patients (13%) had a positive history of infection preceding psoriasis onset. The most frequent infection was verified pharyngitis. Overall, 74% of patients with guttate psoriasis (n=77) had a history of infection prior to occurrence of skin lesions, and the majority of these patients (n=67) had a verified pharyngitis. No differences were either observed between Cw*0602-positive and -negative patients in relation to infection (p=0.307).

Patients who were Cw*0602-positive reported a significantly higher frequency of trauma history (p=0.009). Trauma lesions correlated strongly with Köbner's phenomenon (p <0.0001). A total of 144 patients (21.2%) had a positive history of different types of stressful events prior to disease onset, however, no statistical differences were observed between the two groups in relation to stressful events (Table II).

Logistic regression analysis

In a logistic regression analysis, we entered Cw*0602 status as dependent variable and 6 items (age, gender, age of onset, PASI score, phenotype and precipitating factors) as the independent variables. Based on the measure of agreement between the observed and the predicted outcomes (Hosmer and Lemeshow test), the model fit the data well (χ^2=3.926, df=8, p=0.864). Table III shows the results of the analyses. The predictive ability of variables revealed that three items had significant effect on Cw*0602 status: phenotype (OR: 2.241, 95% CI: 1.284–3.911, p=0.004); PASI score (OR: 1.436, 95% CI: 1.078–1.913, p=0.013), and age of onset (OR: 0.968, 95% CI: 0.943–0.994, p=0.018).

Table III. *Logistic regression analysis of HLA-Cw*0602 status and clinical variables*

Variable	Wald	p-value	Odds ratio	95% CI
Age	0.790	0.374	1.011	0.986–1.037
Gender	0.231	0.631	1.139	0.669–1.938
Age of onset	5.613	0.018	0.968	0.943–0.994
PASI score	6.124	0.013	1.436	1.078–1.913
Phenotype	8.072	0.004	2.241	1.284–3.911
Precipitating factors	0.248	0.618	1.166	0.638–2.129

95% CI: 95% confidence interval.

DISCUSSION

Over the past decade, several genome-wide scans have confirmed that PSORS1 at 6p21 is the major susceptibility locus for psoriasis. The interval containing PSORS1 has been narrowed down to a ~300-kb region containing HLA-Cw6. Many studies have reported an association between psoriasis and HLA-Cw6. Estimates of the carrier frequency of this allele in Caucasian psoriasis patients range from 55% to 80%, leading to risk ratios of between 4 and 15 (3–4). The HLA-Cw*0602 allele explains a portion of the genetic contribution to psoriasis and implicates genetic heterogeneity of psoriasis. Cw*0602-positive patients also have obvious clinical differences from Cw*0602-negative patients, such as early-onset, more active and severe disease, familial psoriasis, and more close association with acute guttate attacks, etc. (9–12, 21).

Our study found that Cw*0602-positive psoriasis patients had some obvious clinical differences from Cw*0602-negative patients. The strong correlation of the Cw*0602 allele with early-onset, familial psoriasis or more severe psoriasis was proved in our population, is in agreement with the results of other cohorts (8–11, 22).

A close association with acute guttate-type psoriasis was also observed in Cw*0602-positive patients; however, we did not find differences in infection of the pharynx in the Cw*0602-positive and -negative groups. Streptococcal throat infections and HLA-Cw*0602 have been implicated in the pathogenesis of guttate psoriasis, particularly in the infections by group A β-haemolytic streptococci (21), and streptococcal infections may also cause exacerbation of chronic psoriasis (23). However, a recent UK study has shown that not all patients with guttate psoriasis who showed evidence of streptococcal-related infection were carrying Cw*06 (24), which indicated that Cw*0602 is not essential only for psoriasis triggered by streptococcal-related infections.

A much higher frequency of palmoplantar pustulosis was observed in the Cw*0602-negative patients in our cohort. A previous study of Caucasians has shown that patients with palmoplantar pustulosis do not show any association with the PSORS1 haplotype (25). The results of our study add to the evidence that Cw*0602 has little role in the clinical variants of palmoplantar pustulosis and that the subtype of psoriasis is distinct from psoriasis vulgaris.

Erythrodermic, inverse and psoriatic arthritis were also more common in Cw*0602-negative patients, although there were no significant differences between the two groups, perhaps due to the small samples in the cohort, and low statistical power. The low prevalence of psoriatic arthritis in our study may be due to the strict

definitions used and large proportion of family samples diagnosed as plaque psoriasis.

In sites affected by psoriasis there were also some differences between the two groups. The legs and trunk were more often affected in Cw*0602-positive patients, whereas the scalp was more often affected in Cw*0602-negative patients, in contrast to the results for Caucasians. In addition, Köbner's phenomenon was also observed more commonly in the Cw*0602-positive patients and was associated with earlier onset patients and trauma history, in agreement with other reports (14). It is well-accepted that stressful events associate with a worsening of psoriasis, however, no differences were observed between the two groups in relation to stress or infections, other than trauma history, in our study.

In order to explore predictive ability of variables on the Cw*0602 status, a logistic regression was performed, which revealed that three items had a significant effect on Cw*0602 status. PASI score and age of onset seem to be important predictors of Cw*0602 status; patients with younger age of onset and higher disease severity score had a higher tendency to be Cw*0602-positive, which agreed with the above clinical comparisons. Phenotype does not seem to be a good predictor because there was a marked overlap between the two groups except for the subtype of palmoplantar pustulosis. Knowledge of the distribution of Cw*0602 in different clinical characteristics of psoriasis may help us to understand the genetic heterogeneity of psoriasis, but it is not sufficient to be a good classification for psoriasis.

Overall, the results showed that Cw*0602-positive patients had a significantly higher likelihood of having an earlier disease onset, more severe disease, higher frequency of guttate, the Köbner's phenomenon and trauma history, whereas nail and scalp involvement were observed in Cw*0602-negative patients. However, there was no statistically significant difference between the two patient groups regarding age, gender, incidence of plaque psoriasis, erythrodermic, inverse, psoriatic arthritis, and stress or infections as precipitating factors.

Our study showed some distinct clinical differences between Cw*0602-positive and -negative psoriasis patients in a Han Chinese population, providing evidence that HLA-Cw*0602 is associated with some clinical features of psoriasis.

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