Clinical Associations of the Risk Alleles of HLA-Cw6 and CCHCR1*WWCC in Psoriasis

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INVESTIGATIVE REPORT

The PSORS1 locus is the consistently replicated genetic risk factor for psoriasis. Clinical associations with the main marker allele of PSORS1, HLA-Cw6, have been addressed in a number of studies, but clinical associations have not been used as a way to distinguish the effects of the neighbouring candidate genes in PSORS1. Our results show that HLA-Cw6 and CCHCR1 risk allele associations with clinical features of psoriasis are predictably highly similar in a Finnish nationwide cohort of 379 psoriasis patients. The clinical profiling of a small group of patients (n=34) who were HLA-Cw6− but CCHCR1*WWCC positive suggested that no great differences existed between them and HCR−Cw6− patients. HCR+ genotype (as well as Cw6+ genotype) correlated for the first time positively with female sex and, in contrast with previous studies, negatively with disease severity. Presence of psoriatic arthritis was more pronounced in HCR−psoriasis (as well as in Cw6− psoriasis). Clinical profiling may be a useful approach to distinguishing genetic effects of candidate genes even within a locus in sufficiently large cohorts. Key words: HLA-C antigens; psoriatic arthritis; guttate psoriasis; nail; anti-psoriatic drugs.

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A strong genetic component associates with psoriasis, which is a common chronic skin disorder affecting 2% of Caucasians, males and females equally (1, 2). The overall clinical course of psoriasis may be highly variable: the symptoms may worsen, wane, and occasionally go into spontaneous remission. The sudden, generalized appearance of small, red, scaly lesions is typical for guttate psoriasis, which is the most frequent disease form in children and young adults. Later in life, approximately 70% of these patients develop the chronic plaque form (psoriasis vulgaris), which is the psoriasis subtype affecting 90% of patients (1, 3). Chronic plaque patients may also present with guttate flares. In severe forms, the entire skin becomes inflamed, leading to erythrodermic psoriasis, or generalized sterile pustules arise, leading to pustular psoriasis. About 5–20% of psoriatic patients develop psoriatic arthritis (PsA), a seronegative spondyloarthropathy, which often improves with cutaneous improvement. Arthritis is associated more commonly with nail changes, including pitting, discoloration, subungual hyperkeratosis and onycholysis (4).

Cutaneous trauma can cause the development of a psoriatic plaque in about 40% of psoriatic patients (Koebner’s phenomenon) (5). In addition, psychological stress and several drugs, alcohol and cigarette smoking, as well as bacterial, viral and yeast infections may exacerbate or trigger psoriasis (6–9). In particular, group A beta-haemolytic streptococcal infections are associated with acute guttate psoriasis and exacerbation of chronic plaque psoriasis (10, 11). T-cell-mediated immunity is considered to be the key element in the disease process, but the exact pathogenesis remains unknown (12, 13).

Several candidate genes exist on the basis of either direct evidence or genetic associations with clinical features of psoriasis (earlier HCR, alpha-Helical Coiled-coil Rod homologue C6orf18), which is one of the eight genes in the PSORS1-9 region (14–16). The predicted structure of the risk allele of HCR protein differs from the wild-type allele, affecting possibly also the antigenic properties of the protein (15). We have previously shown that HCR protein is differently expressed in lesional psoriatic skin compared with normal skin (15) and staining for the cell proliferation marker Ki67 shows negative correlation with HCR...
staining, suggesting that HCR has a role in keratinocyte proliferation (15). A regulatory role for CCHCR1 in transcription factor binding has been discovered recently (17). HCR transgenic mice having either the human non-risk HCR allele or the psoriasis risk allele showed altered cutaneous expression profiles for several proteins known to be upregulated in human psoriasis, such as keratins 6, 16, and 17, tenasin C, and certain SPRRs and matrix metalloproteinases (18). All these findings make HCR a plausible candidate gene for psoriasis susceptibility.

The purpose of this study was to investigate whether the clinical phenotype shows a different profile in subjects stratified according to the presence or absence of risk allele at nearby genes within PSORS1. Specifically, we addressed the clinical profiles in type I psoriatic patients (19) identified in the course of our psoriasis gene study (15). Our results suggest that, at least in this population, female psoriatic patients in Finland tend to be HCR+ more often than men and HCR+ disease seems to correlate negatively with severity of the disease and positively with puberty as a trigger. Psoriatic arthritis was associated with the HCR− genotype, especially in men, and correlated more often with nail disease.

MATERIALS AND METHODS

Subjects

Between 1999 and 2001, 399 psoriatic patients (282 probands, 117 family members) were recruited from Helsinki, Turku, Tampere, and Oulu University Central Hospitals and Central Hospital of Päijät-Häme, Lahti, Finland, for a genetic study (15). Of these, 379 had psoriasis onset before or at 40 years of age (type I psoriasis) and were included in the present study. The subgroup of probands was analysed separately, but due to similar findings, only the results comprising the whole group of type I psoriatic patients are reported here. Familial psoriatic patients (n = 172, 45.4%) were affected offspring-parent pairs (n = 46), affected sibling pairs (n = 30) or belonged to large multiplex families (n = 84) and 12 patients had another psoriatic patient distantly related. A slight majority of the patients (n = 216, 57.8%) were men (Table I). The diagnosis of psoriasis was established by physical examination by a dermatologist, with the following inclusion criteria: (i) onset of psoriasis before the age of 40 years; (ii) at least two typical psoriasis plaques present when the patient was examined and interviewed. Patients who had pustulosis palmpoplantaris, lesions only on scalp, or uncertain diagnosis were excluded. All participants donated a blood sample. The clinical assessment was carried out and recorded before patients were genotyped for HCR and HLA-C susceptibility alleles. Psoriatic arthritis was recorded positive if it had been diagnosed by a rheumatologist earlier; mere joint complaints were not recorded. Psoriasis Area and Severity Index (PASI) was calculated at the time of onset, blood sugar and lipid levels, puberty as a contributing factor, possible favourable effect of sunlight or UV therapy and usage of anti-psoriatic systemic medications, was designed and sent to patients from Helsinki and Päijät-Häme districts. In total, 170 psoriatic patients answered.

Genotyping

DNA was extracted from venous blood samples using a standard non-enzymatic method. HCR susceptibility allele was determined by genotyping two SNPs in the HCR gene, HCR−325 (rs130076) and HCR−1723 (rs130079) using polymerase chain reaction (PCR) amplification and altered restriction sites for AvaII and MsII, respectively, as described previously (15). HCR+ patients were defined as those having the alleles HCR−325*T and HCR−1723−*T, and HCR− all the other allele combinations (CG, CT, TG, respectively). Based on our previous results, HCR−325*T and HCR−1723*T are in strong linkage disequilibrium with each other and with the other two SNPs comprising the psoriasis susceptibility haplotype HCR*WWCC (18). HLA-Cw*6 allele was genotyped using SSP-PCR (21).

Statistical analysis

Binary and categorical traits were compared between the sexes and risk allele carriers vs. non-carriers by χ² test and by Fisher’s exact test, when the asymptotical properties for the χ² test were not appropriate.

One-way ANOVA with post hoc tests accompanied by adjusted p-values for normal traits and Mann-Whitney U test for non-normal traits were used to make the between-group-comparisons of continuous variables.

Logistic regression was used for controlling for confounding effects of binary phenotypes, such as differing sex ratio in the risk allele carrier groups. For rare traits, odd’s ratios with 95% confidence intervals (CI) were estimated. Because of the exploratory nature of the study, correction for multiple testing was only applied in the post hoc tests. All statistical analyses were done with the SPSS statistical package.

To create an overall picture of the differences of averages of the continuous variables and occurrence frequencies of categorical variables in genotype classes HCR+Cw6+, HCR+Cw6−, and HCR−Cw6−, a profile of the differences was drawn. Here, the significance was tested by a parameter-free permutation test procedure (22). The number of random permutations was 1000 and the significance threshold was set at p = 0.05.

RESULTS

HCR risk allele positive vs. HCR risk allele negative patients

The majority (62.3%) of patients were HCR risk allele positive (HCR+) (Table I). When psoriatic arthritis
patients were excluded, the numbers of HCR+ and Cw6+ patients were even more pronounced: of the 309 patients, 66.3% were HCR+ and 57.4% (159/277) Cw6+. For comparison, only 9% of the normal population is Cw6+ and 19% HCR+, as documented previously (14). A positive family history was more common in the HCR+ group (54.5%), while in the HCR– group, 69.2% were sporadic cases ($p<0.001$) (Fig. 1). The median age at onset was lower (18 years, range 0–40 years) in the HCR+ group compared with 25 years (range 1–40 years) in the HCR– group ($p<0.001$) (Table II). Consequently, the HCR+ disease had lasted longer (24 vs. 23 years, the proportion of those who had no contacts with the healthcare system due to psoriasis was 38.6% in the HCR+ group and 26.7% in the HCR– group ($p<0.045$). During the last 5 years, the proportion of those who had no contacts with the healthcare system was 38.6% in the HCR+ group and 23.7% in the HCR– group ($p<0.002$) (Table II). In addition, all PASI scores over 20 ($n=9$) were reported in the HCR– group. Anti-psoriatic systemic drugs had been used as a treatment in 33.6% of cases in HCR+ patients compared with 51.9% of HCR– patients ($p<0.001$) (Fig. 1). During the last 5 years, the proportion of those who had no contacts with the healthcare system due to psoriasis was 38.6% in the HCR+ group and 23.7% in the HCR– group ($p<0.002$) (Fig. 1). When classified into mean disease severity subgroups “severe”/“moderate”/“mild”, 14.4% of HCR+ psoriatic patients were ranked as having severe psoriasis compared with 24.5% of HCR– patients, and 36.4% of the HCR+ were reported to have mild psoriasis compared with 27.3% of the HCR– group ($p<0.05$). Moreover, the proportion of those who had been hospitalized, was 17.8% in the HCR+ group and 10.6% in the HCR– group ($p<0.045$). UV treatments had been administered just as often in HCR+ as in HCR– groups, but according to query results, UV therapy proved to be more beneficial in HCR+ patients (94% vs. 82%, $p<0.025$). Only 6/223 of the HCR+ patients had ever had the pustular form of psoriasis, compared with 18/127 of HCR– patients.

Table I. Epidemiological factors and other characteristics for type I psoriatic patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
<th>Psoriatic arthritis</th>
<th>Only skin lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>379</td>
<td>219</td>
<td>160</td>
<td>66</td>
<td>309</td>
</tr>
<tr>
<td>HCR+ (%)</td>
<td>62.3</td>
<td>54.8</td>
<td>72.5</td>
<td>43.9</td>
<td>66.3</td>
</tr>
<tr>
<td>Cw6+ (%) ($n=338$)</td>
<td>53.8</td>
<td>43.6</td>
<td>67.8 ($n=143$)</td>
<td>35.6 ($n=59$)</td>
<td>57.4 ($n=277$)</td>
</tr>
<tr>
<td>Male/Female (%)</td>
<td>57.8/42.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>46 (5–81)</td>
<td>47 (5–77)</td>
<td>45 (9–81)</td>
<td>49 (5–74)</td>
<td>45 (9–80)</td>
</tr>
<tr>
<td>Median age at onset (range), years</td>
<td>20 (0–40)</td>
<td>24 (1–40)</td>
<td>16 (0–40)</td>
<td>24 (1–40)</td>
<td>20 (0–40)</td>
</tr>
<tr>
<td>Median duration (range), years</td>
<td>22 (1–68)</td>
<td>22 (1–56)</td>
<td>23 (1–68)</td>
<td>26 (3–58)</td>
<td>22 (1–68)</td>
</tr>
<tr>
<td>Median PASI (range)</td>
<td>4.0 (0–32.0)</td>
<td>4.3 (0.4–32.0)</td>
<td>3.3 (0–24.3)</td>
<td>5.8 (0.4–29.1)</td>
<td>3.6 (0–32.0)</td>
</tr>
<tr>
<td>Median BMI (range)</td>
<td>25.98 (15–47)</td>
<td>26.26 (15–41)</td>
<td>25.25 (18–47)</td>
<td>25.94 (18–47)</td>
<td>26.07 (15–41)</td>
</tr>
<tr>
<td>Positive family history (%)</td>
<td>45.5</td>
<td>39.0</td>
<td>54.4</td>
<td>33.3</td>
<td>48.1</td>
</tr>
<tr>
<td>Infection/tonsillitis/stress/trauma</td>
<td>22.2/18.2/31.9/11.1</td>
<td>16.4/11.7/35.2/11.9</td>
<td>30.0/27.4/27.5/10.0</td>
<td>19.7/16.7/28.8/12.1</td>
<td>23.0/18.7/32.7/11.0</td>
</tr>
<tr>
<td>as a trigger (%)</td>
<td>17.6</td>
<td>20.3</td>
<td>13.9</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Psoriatic arthritis (%)</td>
<td>64.9</td>
<td>72.6</td>
<td>54.5</td>
<td>89.4</td>
<td>59.6</td>
</tr>
<tr>
<td>Nail changes (%)</td>
<td>18.2/33.0</td>
<td>20.5/28.8</td>
<td>15.0/38.8</td>
<td>40.9/15.2</td>
<td>13.3/37.2</td>
</tr>
<tr>
<td>Sought for medical advice (%)</td>
<td>66.9</td>
<td>70.2</td>
<td>62.5</td>
<td>88.5</td>
<td>62.3</td>
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<tr>
<td>Inpatient (%)</td>
<td>21.1</td>
<td>24.3</td>
<td>16.7</td>
<td>46.8</td>
<td>15.5</td>
</tr>
<tr>
<td>Anti-psoriatic drugs (%)</td>
<td>40.4</td>
<td>46.6</td>
<td>32.0</td>
<td>75.4</td>
<td>32.2</td>
</tr>
<tr>
<td>Erythrodermic/pustular form (%)</td>
<td>2.5/6.3</td>
<td>3.3/6.4</td>
<td>1.3/6.3</td>
<td>4.9/9.1</td>
<td>2.0/5.8</td>
</tr>
<tr>
<td>Plaque/solely plaque lesions (%)</td>
<td>86.3/60.7</td>
<td>88.7/64.2</td>
<td>82.9/55.9</td>
<td>91.8/34.4</td>
<td>84.9/39.9</td>
</tr>
<tr>
<td>Guttate/solely guttate lesions (%)</td>
<td>27.2/8.8</td>
<td>22.7/1.1</td>
<td>34.2/11.2</td>
<td>18.1/6.5</td>
<td>28.8/10.4</td>
</tr>
<tr>
<td>Scalp/facial lesions (%)</td>
<td>92.2/58.7</td>
<td>93.0/56.9</td>
<td>91.1/61.3</td>
<td>93.8/61.5</td>
<td>92.1/58.6</td>
</tr>
<tr>
<td>Asthma and allergy symptoms (%)</td>
<td>8.7</td>
<td>8.3</td>
<td>9.4</td>
<td>10.6</td>
<td>8.2</td>
</tr>
<tr>
<td>High blood pressure (%)</td>
<td>15.6</td>
<td>17.4</td>
<td>13.1</td>
<td>16.7</td>
<td>15.2</td>
</tr>
</tbody>
</table>

PASI: psoriasis area and severity index; BMI: body mass index.

Fig. 1. Clinical characteristics according to HCR genotype. Female gender and positive family history were more frequently encountered in HCR+ patients (■). Male gender, psoriatic arthritis (PsA), nail changes, contacts with healthcare system (HCS), usage of systemic anti-psoriatic drugs, and pustular disease form were more common in the HCR– group (□).
and 2/225 of HCR+ cases had erythrodermic psoriasis at the time of investigation compared with 7/137 of HCR− cases \((p<0.03)\), further stressing the more severe nature of HCR− psoriasis. The results persist after taking confounding factors (different sex ratio) into account (data not shown).

At the time of investigation, no significant differences were observed in the presence of plaque-type lesions in HCR− vs. HCR+ groups (84.7% vs. 87.2%), but HCR+ patients had more of the guttate-type lesions (31.7% vs. 19.7%) \((p<0.025)\), data not shown). When HCR+ and HCR− patients were compared, no statistically significant differences were observed in the number of scalp or facial lesions or presence of pure guttate form.

Puberty was reported to have modified psoriasis symptoms more often in the HCR+ group according to the query (33% vs. 11%, \(p<0.01\)). The BMI was, on average, lower in both HCR+ men and women, as well as PsA and skin psoriasis patients. With pure skin psoriasis, the BMI was, on average, lower in both HCR+ men and women, as well as PsA and skin psoriasis patients. With pure skin psoriasis, the BMI was over 30 in 13.9% of cases in HCR+ group vs. 20.6% in HCR− group, though the \(p\)-value remained non-significant. The age of onset was higher in the obese group (BMI >25.5): 18 vs. 24 years \((p<0.006)\), and the obese were also older at the time of investigation, 50 vs. 42 years \((p<0.001)\).

Possible genotype-wise differences in susceptibility to rare traits were evaluated by odds ratios (OR). They give relative risk of developing the condition given exposure class, e.g. the risk ratio for developing pustular psoriasis in HCR− compared with the risk for developing pustular psoriasis in HCR+. Erythrodermic psoriasis seemed to be more common in HCR− vs. HCR+; the OR was 5.75 (with CI 1.21–27.27). The same applied to pustular psoriasis: 4.88 (CI 1.99–12.00), and asthma and allergy symptoms (HCR− vs. HCR+): 2.02 (CI 1.05–3.86).

Women vs. men

Women were more often HCR+ than men: 72.5% of female psoriatic patients had HCR risk allele compared with 54.8% of men \((p<0.001)\) (Table I, Fig. 1). Women had earlier disease onset than men (16 vs. 24 years, \(p<0.001\)) (Fig. 2).
and HCR+ women had been younger than HCR– women at the time of onset (15 vs. 20 years; p<0.03) and HCR+ men even more so (21 vs. 27 years, p<0.001) (Fig. 2). Of the HCR+ patients, however, 50.2% were men and 49.8% were women (Table II). Many other characteristics that differed significantly in HCR+ vs. HCR– comparison differed also according to sex (Table I). However, most characteristics remained significant in HCR+ vs. HCR– comparisons independently in both sexes.

Both HCR+ men and women had positive family history more frequently than HCR– men and women (men: 46% vs. 33%, p=0.016; women: 63% vs. 32%, p<0.001). Nail changes and pustular form were more common in female (69% vs. 49%, p=0.027; 16% vs. 3%, p=0.004, respectively) and male (79% vs. 67%, p=0.049; 11% vs. 3%, p=0.026, respectively) HCR– groups.

HCR– men had higher PASI values (5.7 vs. 3.6, p<0.002), more frequent visits to the dermatologist (126 contacts vs. 48 contacts during the last 5 years, p<0.004), more frequently had psoriatic arthritis (29% vs. 13%, p<0.005), more frequently used anti-psoriatic drugs (57% vs. 38%, p<0.007), had asthma or allergy symptoms more often (13% vs. 4%, p<0.026), and puberty influenced their symptoms less (3% vs. 25%, p<0.004) than HCR+ men. No significant difference was seen among women in these characteristics, probably because of the low number of HCR– women (n=44). HCR+ women more often had guttate lesions, and stress less frequently influenced the onset of their psoriasis (44% vs. 21%, p<0.05; and 45% vs. 24%, p<0.025, respectively).

Psoriatic arthritis

PsA was diagnosed in 66 patients (17%), who were significantly older than other patients (median age 49 vs. 45 years, p<0.002). This form of disease was more common in the HCR– group: 26.2% of HCR– patients had been diagnosed with PsA, compared with only 12.4% of HCR+ patients (p<0.001) (Table I, Fig. 1). Only 33.3% of the psoriatic arthritis patients were women (Table I). Psoriatic arthritis patients also resembled HCR– patients in other characteristics: only 33.3% had another psoriatic patient in the family and they rarely had pure guttate form (1 out of 66 vs. 31 out of 299 skin psoriatic patients, p<0.04) (Table I). The median PASI score was highest in this subgroup, 5.8 compared with 3.6 in psoriasis confined to skin (p<0.039), and the patients had had contact with the healthcare system, been inpatients, received systemic anti-psoriatic drugs and PUVA therapy more frequently (p<0.001 with all these characteristics) compared with skin psoriasis patients (Table I). Dermatologists categorized these patients as having “severe” psoriasis in 40.9% of cases vs. 13.3% with pure skin psoriasis (p<0.001). Nail changes were reported in 89.4% of cases, equally in HCR+ and HCR– patients (85.7% vs. 91.4%), but clearly more often than in skin psoriasis (59.6%, p<0.001). Subdividing PsA patients into HCR+ and HCR– groups revealed the HCR– patients to have more often scalp and facial lesions (scalp: 92% vs. 69%, p<0.047; facial: 76% vs. 43%, p<0.007) and additionally to have higher PASI values (p<0.001).

Comparison between HCR+Cw6+, HCR+Cw6–, and HCR–Cw6– psoriasis

Cw6 status was determined in 338 cases; 53.8% were Cw6+ (57.4% when psoriatic arthritis patients were excluded) (Tables I and II). All Cw6+ cases were also HCR+ (n=182), but 10% of all patients (n=34) were HCR+Cw6– (Table II). This offered a valuable point of comparison for the combinations of genotypes. The differences are depicted as averages and occurrence frequencies of the different variables in the groups HCR+Cw6+, HCR+Cw6–, and HCR–Cw6– (Fig. 3). Number of random permutations was 1000 and the significance threshold was set at p=0.05; thus it is not corrected for

Acta Derm Venereol 87
overall number of tests made in the study, and should be interpreted with that in mind, as suggestive evidence.

All three groups were similar with respect to age at the time of investigation. HCR–Cw6– patients differed from HCR+Cw6+ patients in the same way as HCR– patients differed from HCR+ patients (Figs 1 and 3; Table II). HCR+Cw6+/– patients had significantly less high blood pressure than HCR–Cw6– patients, though, and contacts with the healthcare system did not reach significance in HCR+Cw6+ vs. HCR–Cw6– comparisons. Guttae form and infection and puberty as triggers were significantly related to HCR+Cw6+ genotype and pustular form and stress as a trigger to HCR–Cw6– genotype. Also HCR+Cw6– patients differed from HCR+Cw6+ patients, largely in the same clinical characteristics as HCR–Cw6– patients (Fig. 3). In contrast, presence of PsA (11.7% vs. 14.7%, \( p = 0.01 \)) was more frequent in HCR–Cw6– patients. In a study (19) also reported more extensive and frequently recurrent symptoms in a HLA-Cw6+ group. In a study (23) high familial penetrance (23). Henseler & Christophers (8, 23, 24), longer duration of disease, infection as a trigger (especially throat infection) (8, 23, 24), guttate type lesions (8, 23–25) and HLA-Cw6 were linked together. In this study, these characteristics also associated with HCR positivity. As a new finding, puberty had influenced the symptoms more often in the HCR+ group (as well as in Cw6+ group) than in the HCR– group, especially in men, reflecting either the earlier onset or possible hormonal effects. However, trigger factors represent retrospective and putatively uncertain data and thus those results should be interpreted with caution.

Females have been reported to have an earlier onset than men (19, 23, 26). To our knowledge, this is, however, the first study to show clear over-representation of HCR+ (as well as Cw6+) female psoriatic patients. In fact, only a little more than 25% of female psoriatic patients proved to be HCR–, and the reason for this is unclear. Of the attended patients, men represented the majority. A smaller proportion of men than women (39% vs. 54.4%) had another psoriatic patient in the family. One explanation for this could be that women were more interested in attending if they had psoriasis in the family and as a result, women were more often related than men. In the subgroup of probands \( n = 282 \), 71% of the attended psoriatic patients, were also more often HCR+ than men( \( p < 0.001 \).

The severity of the disease was measured with several parameters: the PASI score, dermatologist’s evaluation, number of admissions to hospital, frequency of systemic medications, and presence of severe forms of psoriasis (pustular/erythrodermic). Due to the genetic nature of the original study protocol, the PASI value was determined at the time of investigation. Many patients (especially the probands, \( n = 282 \)) had already received therapies by this time, which probably lowered the recorded PASI values. Assuming the impact of therapies would have been the same in both HCR+ and HCR– groups, the possible bias would also have been the same in both groups. The results of HCR– patients having received anti-psoriatic drugs, been hospitalized, having more severe forms of psoriasis and more severe disease from the dermatologist’s point of view, and having contacted the healthcare system more often than HCR+ patients indicated HCR– psoriasis to be more severe in nature than HCR+ psoriasis. The PASI data may be less accurate to compare between patients. It has been shown that HLA-Cw6+ patients have a higher mean disease severity score, at least in a material with high familial penetrance (23). Henseler & Christophers (19) also reported more extensive and frequently recurrent symptoms in a HLA-Cw6+ group. In a study

**DISCUSSION**

Previous studies have proved HLA-Cw6 to be the most highly associated allele in psoriasis: it is found in approximatel 40–60% of psoriatic patients. Also, in the current study comprising both familial and sporadic psoriasis cases, 62.3% of attended psoriatic patients were HCR+ and 53.8% Cw6+. Like in other studies, positive family history (8, 19), earlier age at onset (19, 23, 24), longer duration of disease, infection as a trigger (especially throat infection) (8, 23, 24), guttate type lesions (8, 23–25) and HLA-Cw6 were linked together. In this study, these characteristics also associated with HCR positivity. As a new finding, puberty had influenced the symptoms more often in the HCR+ group (as well as in Cw6+ group) than in the HCR– group, especially in men, reflecting either the earlier onset or possible hormonal effects. However, trigger factors represent retrospective and putatively uncertain data and thus those results should be interpreted with caution.

Females have been reported to have an earlier onset than men (19, 23, 26). To our knowledge, this is, however, the first study to show clear over-representation of HCR+ (as well as Cw6+) female psoriatic patients. In fact, only a little more than 25% of female psoriatic patients proved to be HCR–, and the reason for this is unclear. Of the attended patients, men represented the majority. A smaller proportion of men than women (39% vs. 54.4%) had another psoriatic patient in the family. One explanation for this could be that women were more interested in attending if they had psoriasis in the family and as a result, women were more often related than men. In the subgroup of probands \( n = 282 \), 71% of the attended psoriatic patients, were also more often HCR+ than men( \( p < 0.001 \).

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Psoriasis is a disease with a complex genetic background requiring environmental triggers and complicated by heterogeneity. The PSORS1 region on chromosome 6p21.3 has demonstrated the strongest association with psoriasis in various studies and is therefore believed to contain a major predisposing factor for psoriasis. The HLA-Cw6 allele has shown the strongest association, but whether this allele is “the psoriasis gene” or simply a marker in strong linkage disequilibrium with the true disease gene is not known (37, 38). This epidemiological study shows that HLA-Cw6 and CCHCR1 risk alleles have largely the same clinical associations. As reported for HLA-Cw6+ patients (23, 29), HCR risk allele carriers had lower age of onset, throat infection as a trigger, positive family history, more beneficial response to UV therapy, and more guttate lesions. However, erythrodermic and pustular forms were more common in HCR– patients, agreeing with previous data showing that these subtypes are perhaps not related to PSORS1 (25, 39, 40). HCR and Cw6 generally associate with the same clinical features. However, there still exist type I psoriatic patients who have neither alleles.

REFERENCES