Patients with psoriatic arthritis may show differences in their clinical and genetic profiles depending on their age at psoriasis onset

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Abstract

Objectives

The age of psoriasis onset has an important impact on the clinical expression and heritability of psoriasis. Psoriasis characteristics according to the age at disease onset have been extensively studied. However, the impact of the age of psoriasis onset on psoriatic arthritis (PsA) features has not been analysed in depth. The aim of the present paper is to analyse whether the age of psoriasis onset may have an impact on the clinical and genetic characteristics in a cohort of PsA patients.

Methods

The study included 110 PsA patients classified in accordance with the CASPAR criteria. Patients were divided into early (onset age <30 years) and late (onset age >30 years) onset psoriasis, and clinical features were studied in accordance to this stratification. Distribution of several genes within the MHC region were analysed in accordance with the prior stratification, and their frequencies compared to that of 110 healthy matched blood donors.

Results

*Compared to patients with late-onset disease, PsA patients with early-onset psoriasis showed more frequently: a longer psoriasis-arthritis latency period (9.9±6 years vs. 3.8±4 years, p=0.0001), a positive family history of disease (60.3% vs. 20.5%, OR 6.1, 95% CI: 2.5–15.0, p=0.0001), severe psoriasis (PASI 8.2±4 vs. 3.6±2.2, p=0.0001), clinical enthesitis (37.7% vs. 22.4%, OR 2.09, 95% CI: 0.9–4.9, p=0.08), and oligoarthritis (47.5% vs. 28.6%, OR 2.26, 95% CI: 1.02–5.02, p=0.04). MICA-A9 was associated with susceptibility in both early-onset (60.7% vs. 30%, p=0.0002) and late-onset patients (59.2% vs. 30%, p=0.0008). However, HLA-Cw*0602 was significantly increased in patients with early-onset psoriasis (73.8% vs. 17%, p<0.0001), whereas the allele 384 of the microsatellite C1_4_4, located 34 kb telomeric to HLA-C locus, was increased only in late-onset cases (49% vs. 21%, p=0.001).*

Conclusion

Clinical and genetic features of PsA may differ depending on the age at psoriasis onset. This type of stratification should be considered in future genetic and epidemiological studies of PsA.

Key words

psoriasis, psoriatic arthritis, age at disease onset, HLA, MICA

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Received on July 26, 2011; accepted in revised form on November 28, 2011.

Funding: This work was supported by the Spanish grants of Fondo de Investigaciones Sanitarias (Institute Carlos III) PS09/00420.

Competing interests: none declared.

Introduction

Psoriasis is a relatively common T-cell mediated cutaneous disease in which both environmental and genetic factors contribute to its pathogenesis (1). Despite of multiple susceptibility loci for psoriasis that have been identified, the PSORS1 locus located in the MHC region, confers the most risk for psoriasis (1). However, the extensive ranges of polymorphism and the preservation of HLA haplotypes in most populations have made difficult the characterisation of the exact gene responsible for psoriasis susceptibility located in PSORS1. Nevertheless, HLA-Cw*0602 is the strongest association found in psoriasis and it is the only genetic variant repeatedly observed to be associated with psoriasis in most of the populations (1). Additionally, other MHC genes have also been associated with psoriasis independently of HLA-Cw*0602 (2, 3).

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease which affects a significant proportion (10–40%) of psoriatic patients (4, 5). HLA-Cw*0602 has also been associated with PsA susceptibility (6). MICA-A9 polymorphism has been further associated with arthritis susceptibility, but not with psoriasis (7-9). Additionally, HLA-B38, HLA-B39, HLA-B57, HLA-DR7 and TNF-α promoter polymorphisms were associated with PsA susceptibility in the past, even though these alleles are in linkage disequilibrium with HLA-Cw*0602 or MICA-A9. Thus, it has been postulated that there are two different susceptibility loci associated with PsA in the MHC region: HLA-Cw*0602, which is associated with the skin lesions (present in the extended haplotypes, EH13.1, EH37.1, and EH57.1); and another, MICA-A9, associated with susceptibility to arthritis and present in EH38.1, EH39.1, and EH57.1. Therefore, the haplotype EH57.1 (HLA-Cw*0602-B57-DRB1*07-DQA1*02-DQB1*03) is associated with both psoriasis and inflammatory arthropathy.

An important clinical variability of psoriatic patients has been defined according to the age of disease onset (10). Early-onset psoriasis (also referred to as type I) has a peak of age of onset of 16–22 years and comprises 70% of all psoriatic patients. Conversely, late-onset psoriasis (also termed type II psoriasis) shows a peak of age of psoriasis onset at 57–60 years. Clinically, early-onset psoriasis is more extensive, is frequently recurrent and more frequently associated with involvement of nail; while late-onset psoriasis seems to be a milder form of disease. A recent study has reported that HLA-Cw*0602 was present in 85.3% of type I psoriasis patients, but only 14.7% of patients with late-onset psoriasis had HLA-Cw6 and were defined as sporadic (10). In PsA patients with type I psoriasis, Cw*0602 and MICA-A9 have been associated with susceptibility to PsA (7). The potential association of MICA-A9 or other genes of the MHC region with the susceptibility of PsA in patients with late-onset psoriasis has not been elucidated. In the present study, we analysed the distribution of several polymorphic markers and genes located both telomeric and centromeric to HLA-C (Fig. 1) in a well defined population of PsA patients, in order to correlate them with the clinical features as well as with the age of psoriasis onset.

Patients and methods

Patients

One-hundred and ten consecutive patients who fulfilled the classification criteria for psoriatic arthritis (CASPAR criteria) (11) were randomly selected from the rheumatology outpatient clinic of a tertiary care hospital. There were 55 men and 55 women with a mean age of 48±12 years. The mean disease duration for psoriasis was 19±10 years and 13±8 years for arthritis. Psoriasis preceded the arthritis in 75% of the cases and a family history of psoriasis was recorded in 42% of the patients. According to the predominant articular pattern of the last 5 years of follow-up, 38% had oligoarthritis, 26% polyarthritis, and 36% presented a predominantly axial disease. Distal interphalangeal joint disease was seen in 31% of the patients, whereas nail disease was seen in 43.6%. Dactylitis was noted in 30% of the patients. Clinical enthesitis was present in 30% of the subjects. Patients were divided taking

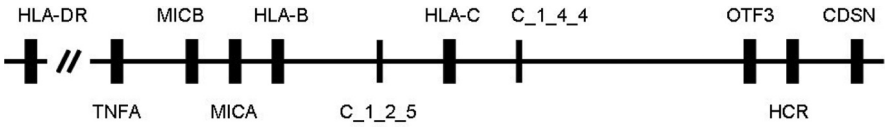

Fig. 1. Map of the MHC region. Polymorphisms in microsatellite C1_4_4, octamer transcription factor 3 gene (OTF3), a-helix coiled-coil rod homologue (HCR), corneodesmosin gene (CDSN), HLA-C, microsatellite C1_2_5, HLA-B, MICA, MICB, TNFA, and HLA-DRB1 were analysed in this study.

into account the age at psoriasis onset with a cut-off at 30 years old. This cut-off point has been found suitable for a better definition of PSORS1 associated psoriasis in PsA populations (12). All patients gave written informed consent before enrolling in the study. The study was carried out with the approval of the ethics committee of our hospital.

HLA typing

Human leukocyte antigen HLA-C was typed using the polymerase chain reaction with sequence-specific primers (PCR-SSP) (8). The polymorphisms of the octamer transcription factor 3 gene (OTF3), the corneodesmosin gene (CDSN), and the *a*-helix coiled-coil rod homologue (HCR) gene were analysed as described previously (8). The microsatellites C1_2_5 and C1_4_4 were amplified using the PCR primers described by Tamiya *et al*. (13). HLA-B typing was carried out using the Dynal RELI™ SSO HLA-B test following the manufacturer's instructions. HLA-DRB1 alleles were typed and subtyped by performing polymerase chain reaction using specific primers (PCR-SSP). For the analysis of microsatellite repeat polymorphism in the MICA gene, PCR was carried out using primers labelled at the 5´ end with the fluorescent reagent Cy5, as previously described **(8).** For MICB typing, a dinucleotide microsatellite polymorphism in the first intron was analysed by PCR analysis and TNF-α polymorphism at positions -238 and -308 were typed by PCR, as previously described (8).

All previous typing was also performed in a control population of 110 random ethnically and geographically matched blood donors.

Statistical analysis

The differences between the frequencies of these allelic markers in patients and controls, as well as the differences found in accordance to age at disease onset, were assessed using the chi-squared test with Yates's correction and the Student *t*-test. The odds ratio (OR) was calculated by the cross-product ratio and the 95% confidence intervals by the Cornfield method. The extent of linkage disequilibrium between the two loci is expressed as the observed disequilibrium value (λs), *i.e*. a proportion of the theoretical maximum disequilibrium value (λ_{max}) achievable for this combination of alleles. The λs were calculated using the formula: $\lambda s = \lambda/\lambda_{max}$ = Pab-(Pa.Pb)/Pa.(1-Pb).

Table I. Clinical characteristics of patients stratified by the age at psoriasis onset (cut-off at 30 years old).

Variables	Psoriasis before 30 yr. n: 61	Psoriasis after 30 yr. n: 49	*p*-values
Age (yr)	41±13	53± 12	0.0001
Gender (M:F)	1.03:1	1.04:1	NS
Psoriasis duration (yr)	22± 10	14± 8	0.002
Arthritis duration (yr)	12±7	11± 8	NS
Psoriasis onset age (yr)	18± 6.9	38± 8.6	0.0001
Arthritis onset age (yr)	29± 9.07	42± 9.5	0.0001
Psoriasis-arthritis latency (yr)	9.9±6	3.8±4	0.0001
Family history	60%	20%	0.0001*
Oligoarthritis	47.5%	28.6%	0.04**
Polyarthritis	21.3%	38.8%	NS
Spondylitis	31%	32.7%	NS
DIP disease	31%	32.7%	NS
Nail disease	41%	43%	NS
Enthesitis	37.7%	22.4%	NS
Dactylitis	34.4%	36.7%	NS
PASI	8.2±4	3.6±2.2	0.0001

*OR 6.1 (95% CI: 2.5–15.0). **OR 2.26 (95% CI: 1.02–5.02). NS: non significant.

Results

Clinical features according to the age at psoriasis onset (cut-off at 30 years old)

Patients with psoriasis onset before 30 years old were more likely to have a positive family history of the disease (60.3% *vs*. 20.5%, OR 6.1, 95% CI: 2.5–15.0, *p*=0.0001). In this group, oligoarthritis was the most common articular pattern of PsA (47.5% *vs*. 28.6%, OR 2.26, 95% CI: 1.02–5.02, *p*=0.04). These patients also tended to have more frequently clinical enthesitis (Achilles enthesitis) than patients with disease onset over 30 years old (37.7% *vs*. 22.4%, OR 2.09, 95% CI: 0.9–4.9, *p*=0.08). The extent and severity of psoriasis was also more pronounced in subjects with psoriasis onset before 30 years old (PASI: 8.2±4 *vs*. 3.6±2.2, *p*=0.0001). The psoriasis-arthritis latency period was markedly longer in this group than in patients with late-onset psoriasis (9.9±6 years *vs*. 3.8±4 years, *p*=0.0001). There were no additional differences in the other parameters analysed in the study. Table I reflects these features.

*HLA-Cw*0602 and MICA-A9 were associated with PsA susceptibility*

The distribution of several polymorphic markers and genes located around the HLA-C locus were analysed in the present report (Fig. 1). HLA-Cw*0602 (56.4% *vs*. 17%, OR 6.18, 95% CI: 3.32–11.5, *p*<0.00001) and MICA-A9 (60% *vs*. 30%, OR 3.5, 95% CI: 2.0–6.12, *p*<0.0001) were significantly increased in PsA patients (Table II). MICB-CA22 allele, located centromeric to HLA-C, was also significantly associated with PsA susceptibility (25.4% *vs*. 7%, OR 4.35, 95% CI: 1.88–10.06, *p*=0.0004); however, MICB-C22 allele was in linkage disequilibrium with MICA-A9 (λs=0.6). We did not

find association with PsA susceptibility of other genes located centromeric (the microsatellite C_1_2_5, HLA-B, TNFA promoter polymorphisms and HLA-DR) or telomeric to HLA-C (the microsatellite C1_4_4, OTF3, HCR and CDSN) (data not shown).

*The susceptibility effect of HLA-Cw*0602 declined with increasing age*

HLA-Cw*0602 was significantly increased in PsA patients with early-onset of psoriasis (73.8% *vs*. 17%, OR 13.5, 95% CI: 6.33–28.65, $p<0.0001$), but it was not significantly associated with susceptibility in late-onset of psoriasis (Table III). In fact, the effect of HLA-Cw*0602 on the susceptibility of PsA significantly decreased with the increase of the onset of psoriasis (data not shown). MICA-A9 was significantly associated with both early-onset (60.7% *vs*. 30%, OR 3.59, 95% CI: 1.86–6.93, $p=0.0002$) and late-onset disease (59.2% *vs*. 30%, OR 3.38, 95% CI: 1.67–6.81, $p=0.0008$).

No other marker analysed was associated with PsA susceptibility in patients with early-onset of psoriasis. Analysis of markers telomeric to HLA-C in patients with late-onset psoriasis showed a higher frequency of allele 384 of the microsatellite C1_4_4 (49% *vs*. 21%, OR 3.44, 95% CI: 1.67–7.06, $p=0.001$). We did not observe a significant linkage disequilibrium between this allele and HLA-Cw*0602 or MICA-A9 in these patients. No association of other genetic marker analysed was observed in patients with late-onset of psoriasis.

Table II. Distribution of most significant polymorphic markers in patients and controls.

MHC alleles	Patients n. 110 (%)	Controls n. 110 (%)	OR (95% IC)	*p*-value
Cw*0602	62 (56.4%)	19 (17%)	6.18 (3.32–11.51)	<0.00001
MICA-A9	66 (60%)	33 (30%)	3.5 (2.0–6.12)	<0.00001
MICB22	28 (25.4%)	8 (7%)	4.35 (1.88–10.06)	0.0004
C1_4_4 (384)	33 (30%)	24 (21%)	1.53 (0.83–2.82)	0.22
TNFA-238A	19 (17.3%)	14 (12%)	1.43 (0.68–3.02)	0.45
TNFA-308A	32 (29.1%)	24 (21%)	1.47 (0.8–2.71)	0.28
HLA-DRB1*07	43 (39.1%)	33 (30%)	1.49 (0.85–2.62)	0.2

Table III. Distribution of polymorphic markers that were found differentially distributed between early-onset and late-onset psoriasis in PsA patients.

Marker	Controls n. 110	Age <30 n. 61	OR (95% IC)	Age >30 n. 49	OR (95% IC)
HLA-Cw*0602	19 (17%)	45 (73.8%)	13.5 (6.33–28.65) $p<0.0001$	17 (34.7%)	2.54 (1.18–5.48) $p=0.02$*
MICA-A9	33 (30%)	37 (60.7%)	3.59 (1.86–6.93) $p=0.0002$	29 (59.2%)	3.38 (1.67–6.81) $p=0.0008$
C1_4_4 (384)	24 (21%)	9 (14.8%)	0.62 (0.26–1.43) $p=0.31$	24 (49%)	3.44 (1.67–7.06) $p=0.001$

*Non significant after correction for multiple testing at the HLA-C locus.

Discussion

The characterisation of the exact MHC gene, or genes, involved in psoriasis susceptibility has been controversial. This is due to the high density of polymorphic genes located in this region, the extensive ranges of polymorphism and the preservation of HLA haplotypes (14-20). Additionally, genetic studies in psoriasis are complicated by the clinical heterogeneity of the disease. Based on the age of disease onset, psoriasis has been classified in two distinct forms, an early-onset disease with a peak of ~20 years which is associated to HLA-Cw6, and a late-onset disease with a peak of ~60 years which is not associated to HLA-Cw6 (10).

In this study, we analysed if the age of psoriasis onset may act as a key stratification point for a better knowledge of the clinical and genetic characteristics of PsA. Patients with type I psoriasis had more frequently a positive family history of disease as well as a psoriasis-arthritis latency period 3 times longer than in late-onset psoriatic patients. This is in agreement with our prior observation that HLA-Cw6-positive PsA patients had longer psoriasis-arthritis latency than HLA-Cw6 negative-ones (21). However, PsA patients with type I psoriasis showed a more severe form of psoriasis, as evaluated by PASI values. Nevertheless, these cases had the least aggressive pattern of joint involvement, thus confirming the loose connection between both conditions in terms of disease severity. Taken together, these data show that features of type I psoriasis are quite similar in both psoriasis alone and PsA, though arthritis characteristics may differ.

Our study also confirmed the association of HLA-Cw*0602 and MICA-A9 with PsA susceptibility (7-9). However, significant differences were observed in the distribution of these alleles in patients stratified by the age of psoriasis onset. On one hand, HLA-Cw*0602 was associated with PsA susceptibility in patients with early-onset of psoriasis, but not in patients with late-onset. These data are in agreement with previous studies (10, 16, 17) and suggest that HLA-Cw*0602 play a role in the development of skin lesions rather than in the arthritis (1, 8, 9). On the other hand, MICA-A9 was associated with PsA susceptibility independently of the age of psoriasis onset, suggesting that MICA-A9 is associated with the development of arthritis rather than with the skin lesions (18). MICA is a polymorphic gene capable of activating NK and T-cells via NKG2D. Deregulation of the expression of MICA has been involved in the pathogenesis of rheumatoid arthritis and other T-cell-mediated autoimmune diseases (18-20). However, the role of MICA-A9 polymorphism in the pathogenesis of PsA remains to be elucidated.

Late-onset psoriasis was initially described as sporadic due to the lack of association of HLA-Cw6 (10). However, recent studies have described the lack of association of HLA-Cw*0602 with PsA susceptibility in some populations, such

as Jewish (2), and the association of other polymorphic markers in the MHC region independently of HLA-Cw*0602 (2, 3, 22). In accordance, our study suggests the existence of other loci in the MHC region that may be also involved in the susceptibility of late-onset of psoriasis. First, MICA-A9 was associated with PsA susceptibility independently of the age of psoriasis onset. These data are in accordance with a recent study which has reported that MICA-A9 occurred more frequently in PsA with late-onset psoriasis (23). Balding *et al*. found that -308 TNFA/G heterozygotes had the highest mean age at psoriasis onset in their PsA population (24). This polymorphism was also increased in late-onset PsA patients in our study and it was in linkage disequilibrium with MICA-A9, which may suggest that this association could be secondary to MICA-A9. Second, we found the association of the microsatellite C1_4_4 (384 allele), located 34 kb telomeric to HLA-C locus, with susceptibility to PsA in patients with late-onset psoriasis. This allele has been described to be in linkage disequilibrium with HLA-Cw*0602 (3), however, this allele was not in linkage disequilibrium with HLA-Cw*0602 or MICA-A9 in our study. Together with previous results, the association of C1_4_4 with PsA in our study supports the existence of an additional susceptibility locus located telomeric to HLA-C (2, 3) and suggests that it may have a significant impact on some clinical characteristics of psoriatic patients such as the age of disease onset.

In conclusion, our study supports the hypothesis that there are different susceptibility loci in the MHC region associated with PsA susceptibility which may have an important impact on the development of psoriatic lesions. Although the CASPAR proposal has allowed a better definition of PsA as a unique clinical entity, our results together with those in recently published papers clearly suggest that the age of onset of psoriasis should be taken into account in future epidemiological and genetic studies of PsA (25, 26).

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