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Review

Age at disease onset: a key factor for understanding psoriatic disease

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Abstract

Psoriasis and PsA are immune-mediated diseases with a strong genetic component. More than 20 new loci have been recently linked to these diseases. However, interactions between these genes and the phenotypic traits of both diseases are poorly understood at present. Stratification of psoriatic disease according to the sex of the patients, genetic factors or age at onset has allowed in the last few years a better understanding of the principles governing the onset and progression of these processes. The age of onset of psoriasis has been used for decades as an appropriate descriptor to define two subpopulations of psoriatic patients (types I and II) whose clinical and immunogenetic characteristics have been very well differentiated. Moreover, in patients with PsA this distinction between type I and II psoriasis also seems equally operative. In patients with PsA expressing the *HLA-C*06* antigen, the latency between the onset of psoriasis and onset of joint symptoms is longer than in those without this marker. It is also known that PsA tends to appear earlier in patients with *HLA-B*27* positivity, and that these patients also show a shorter interval of time between the onset of cutaneous lesions and the onset of joint disease. This review highlights the growing importance of age at disease onset as a key stratification factor in worldwide clinical and genetic studies of psoriatic disease.

Key words: psoriasis, psoriatic arthritis, age at disease onset, *HLA-C*06*, *HLA-B*27*.

REVIEW

Psoriasis and PsA are immune-mediated diseases with a strong genetic component

Psoriasis is one of the most prevalent complex diseases worldwide and is characterized by a chronic autoimmune-mediated inflammation of the skin. In psoriasis, an unknown set of events induce T lymphocytes to chronically colonize the dermis and epidermis and promote inflammation. One of the consequences of the active immune infiltrate is an increase in the proliferation rate of keratinocytes, the cells that predominate in the epidermal skin layer, leading to red, raised and scaly plaque-like lesions. Psoriasis is considered a complex disease both etiologically and for its wide range of phenotypic manifestations. A combination of multiple genetic risk factors, triggering environmental agents and stochastic factors are thought to be responsible of its appearance [1, 2]. While little is known about the impact of environment on psoriasis, recent genome-wide association studies have markedly expanded the group of genomic loci that are associated with the susceptibility to develop this autoimmune disease [3–8]. Although psoriasis is likely a multigenic disease, the *PSORS1* locus on chromosome 6p21.3 is generally understood to confer the most risk for psoriasis [9]. A specific allele of this locus, *HLA-C*06*, is also the only genetic variant repeatedly observed to associate with phenotypic features of psoriasis, such as the age at disease onset [9, 10].

PsA is a highly pleomorphic entity with features resembling those of AS in some cases and RA in others. The disease is characterized by changing degrees of oligoarthritis, polyarthritis and spondylitis, with very typical features such as dactylitis, involvement of distal interphalangeal (DIP) joints or mutilating arthropathy [11]. PsA develops in 20–30% of psoriatic subjects, after an average interval of about one decade [11]. In psoriasis, *HLA-C*06* is present in about 60% of cases. An increased frequency of *HLA-C*06* has long been reported in patients with PsA [12, 13]. Thus in some reports the frequency of *HLA-C*06* is equivalent to the levels found in patients with psoriasis, ranging from 56% to 60%, a level of increase

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that would support the hypothesis that PsA and psoriasis are genetically homogeneous [13, 14]. In contrast, other investigators have reported much lower frequencies of *HLA-C*06* in PsA, which would be more consistent with the hypothesis of genetic heterogeneity [15, 16]. Therefore, in order to dissect the genetic susceptibility to PsA, it would be of interest to separate genetic factors contributing to cutaneous disease from those that delineate joint involvement (Fig. 1). There is evidence to suggest that carriage of the *HLA-C*06* allele is overexpressed in PsA patients with type I psoriasis, also known as early onset psoriasis [17, 18]. On the other hand, most of the alleles associated in the past with an earlier onset of disease in PsA, such as *HLA-B17*, *DR7* or *TNF-α* promoter polymorphisms, are in linkage disequilibrium (LD) with *HLA-C*06* or *MICA-A9* [12, 19, 20]. Thus it has been postulated that there are two different susceptibility loci associated with PsA in the *HLA* region: one located telomeric to *HLA-C*, which is associated with the psoriatic 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 *EH57.1* (*Cw6-B57-DRB1*07-DQA1*02-DQB1*03*) is associated with both psoriasis and inflammatory arthropathy, and this may explain why *HLA-Cw*06/DR7* appears related to an early onset disease in both conditions [19, 20].

Given that psoriasis and PsA appear to share some common genetic features but also exhibit marked differences, it is necessary to approach the study of both conditions through various methods of stratification. Some of these methods include family history of disease, age of onset or phenotypic expression differences of disease attributable to sex. For example, psoriasis and PsA are both diseases with a clear familial aggregation; however, the arthritic form has a substantially higher level of familial aggregation compared with the global psoriasis disease (sibling recurrence risk in PsA ~42, sibling recurrence risk in psoriasis ~7) [21, 22]. Furthermore, a paternal transmission bias in PsA has been reported that has not been seen in psoriasis [23]. With respect to differences attributable to sex as a stratification factor, it has been found that the male:female ratio differs markedly depending on the articular subphenotype of PsA [24]. Thus we know that axial forms (linked to *HLA-B27*) tend to predominate in males while polyarticular forms are predominantly seen in women, who also seem to have more functional disability due to the illness [25]. Nevertheless, for decades the main stratification factor for the study of psoriatic disease has been age at symptoms onset. Therefore this review will cover the importance of this factor, which in turn may be the key to understanding these processes.

Age at disease onset and psoriasis

Psoriasis has been subclassified according to age of onset. Early onset psoriasis (also referred to as type I) has onset before the age of 40 years, with peak onset at 16–22 years of age, and comprises 70% of all psoriatics. Late-onset psoriasis, also termed type II psoriasis, shows onset at or after age 40 years, with a peak age of onset between 57 and 60 years [10, 11]. Although these forms of psoriasis cannot be distinguished on clinical or histopathological grounds, a distinct pattern of HLA association has been reported [26]. Hence, with early onset psoriasis, which also displays a strong family history, a strong association with class I HLA alleles, and specifically *HLA-C*06*, is observed. In contrast, type II psoriasis is more sporadic and rarely familial and its genetic background is unclear [26, 27]. Several genes telomeric to *HLA-C*, such as α-helical coiled coil rod (HCR) and corneodesmosin (CDSN), have also been related to an earlier onset form of psoriasis; however, as shown in Fig. 1, this is a highly polymorphic area where the high degree of LD between these and other genes with *HLA-C* should be taken as a confounding factor [27, 28].

The age ranges for late- and early onset psoriasis represent two overlapping normal distributions. Thus it is possible that the weaker associations observed for *PSORS1* alleles in cohorts of type II psoriasis may result from a number of type I psoriasis patients within the area of overlap of the two normal distributions. Indeed, when the stratification age is ⩾50 years, no evidence is found for allelic association with the alleles at the *PSORS1* locus [27]. Thus what we see from these findings is a slow decline in the association with *PSORS1* alleles in parallel with an increasing age at the onset of psoriasis [27].

As mentioned previously, age at disease onset is a putative discriminator, and separating psoriasis into early and late-onset disease based on a cut-off of 40 years has been useful [10, 11]. However, onset before the age of 40 years has been reported in ~75% of patients with psoriasis and thus this definition of early onset comprises the majority of patients with psoriasis. Unfortunately, most genetic studies use this classification and lack a more detailed stratification. In that sense, some recently presented data reveal a more complex scenario

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Fig. 1 Map of the MHC region

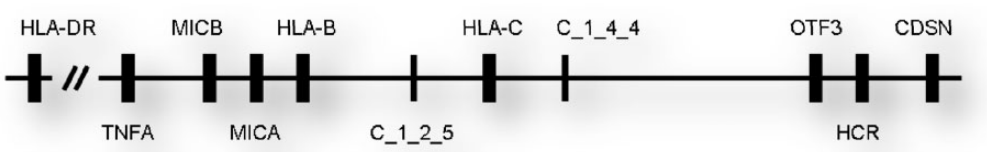
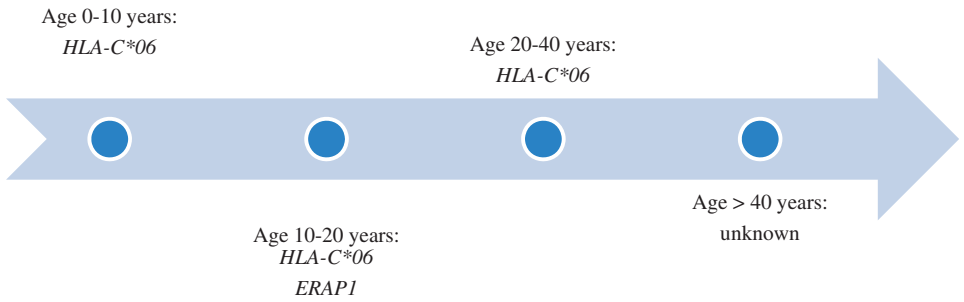


Fig. 2 The complex scenario between age of onset of disease and susceptibility genes in psoriasis



where patients with onset of psoriasis during adolescence (10–20 years) emerge as a distinct group compared with those with onset before puberty [29]. According to this, children with disease onset at <10 years of age had a prevalence of *HLA-C*06:02* similar to that of patients with adult onset (21–40 years) and lacked association with endoplasmic reticulum aminopeptidase 1 (*ERAP1*) single-nucleotide polymorphisms (SNPs), whereas cases with onset of disease between 10 and 20 years of age had a significantly higher prevalence of *HLA-C*06:02* irrespective of phenotype and also showed a significant association with *ERAP1* [29]. Another recent study in a small group of childhood psoriasis patients, separating early and late onset at 18 years of age, showed results in accordance with the data presented in the previous study, with a stronger association with *ERAP1* rs27524 in the group with onset of disease before 18 years of age [30]. Taken together, these data indicate an age-dependent difference in the genetic background among patients with early and very early onset of psoriasis that is not entirely dependent on *HLA-C*06* (Fig. 2).

Most of the information that is currently available regarding the age of onset of psoriasis and genetic contributing factors comes from case–control studies with a relatively small number of cases compared with controls. Thus many of the putative associations between genes and age at onset of illness must be corroborated with genome-wide association studies (GWASs) that have the statistical power required to validate these associations. In only 2 years, >20 new loci have been convincingly associated with psoriasis aetiology, confirming the success of the GWAS approach in the study of the genetic basis of this complex disease [31]. In a recent psoriasis GWAS, the strongest association with the age at onset of skin disease in both the PsA and psoriasis cohort analysis was observed for the *HLA-C* locus [32]. The presence of a single risk allele in *HLA-C* was strongly associated with an earlier development of disease [mean age at onset 34.3 (S.D. 17), 27.3 (S.D. 16.4), 27.5 (S.D. 16.1) years for 0, 1 and 2 copies, respectively, of the *HLA-C* T risk allele, $P = 4.88 \times 10^{-14}$]. To a lesser degree, variation at locus *LCE3D* was also significantly associated with an earlier start of cutaneous disease. Three additional genes were found correlated with age at disease onset, *COG6* and *FBXL19* (earlier onset) and *MMP27* (later onset), the latter being associated with a later onset of psoriasis in the PsA cohort [32].

In a less consistent manner than the relationship between *HLA-C*06* and type I psoriasis, several polymorphisms have been associated with late-onset psoriasis; however, the majority of these studies have included a relatively small number of psoriatic patients and have not yet been replicated [33–40].

Distinguishing patients carrying *HLA-C*06 vs* non-carriers is not only a matter of genetic stratification, but there are clear phenotypic differences in both populations. Several studies have confirmed that *HLA-C*06*-positive patients have a younger age of onset, more familial aggregation, a higher incidence of guttate and eruptive types of psoriasis, more frequent exacerbations with throat infections, a higher incidence of the Koebner's phenomenon and more extensive disease [41, 42]. *HLA-C*06*-positive women also had more frequent remissions during pregnancy [41]. All types of nail changes are more common in the *HLA-C*06*-negative patients and they more often had multiple types of nail lesions [41].

Although stratification by age of onset in psoriatic populations is a good descriptor in clinical and genetic terms, there are some differences when considering the geographical and ethnic diversity of the studies analysed. For example, an Iceland study reported a negative association between *HLA-C*06* and the presence of psoriatic nail disease, but the same finding was not observed in a Spanish study [41, 42].

Another aspect of interest in the study of psoriatic disease when stratified by age of onset is that cardiovascular comorbidities are clearly greater in subjects with psoriasis onset age >40 years, even when the age factor is included in logistic regression models [43, 44]. This is especially true for type II diabetes, which seems to correlate well with the presence of arthritis and onset age >40 years [44].

Age at disease onset and PsA

Currently there is no consensus on what we mean by early onset PsA compared with what might be considered late-onset disease. To address this issue, most researchers have determined two potential cut-offs, one at 40 years (as in psoriasis) and the other at 60 years (as in

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RA) [45–47]. Both RA and PsA may have a late onset. Elderly onset RA is usually defined as a disease presenting at $\geqslant$60 years of age. It appears to be a heterogeneous disease, with a seropositive subset resembling adult onset RA and a less severe seronegative subset that sometimes exhibits features overlapping with those of polymyalgia rheumatica. The SpA complex includes definite entities as well as undifferentiated forms. Each of these may have a late onset. Late-onset undifferentiated SpA appears to be relatively more common than late-onset AS. Its clinical spectrum seems to be as broad as that observed in young and middle-aged adults, with the exception of distal inflammatory swelling with pitting oedema (more frequently seen in late-onset cases) [47]. PsA may begin in the elderly and shows some differences from the younger-onset disease [48, 49]. In a Finnish epidemiological study, 17 of 65 (26.1%) incident cases of PsA started after the age of 55 years [50]. However, if we admit that most cases of PsA debut about a decade after the onset of psoriasis, and that the skin disease tends to appear before 30 years of age in most subjects, it may be agreed that the cut-off at 40 years seems more in line with reality. So it seems that setting a cut-off value at 40 years to distinguish early onset disease from late-onset disease is an appropriate descriptor in the study of PsA. Nevertheless, there are very few studies that have addressed this issue so far.

Unlike adult disease, juvenile PsA seems to comprise two distinct populations. Among patients with juvenile PsA, the age at onset is biphasic, with peaks occurring at ~2 years of age and again in late childhood. Compared with children $\geqslant$5 years of age, younger patients are more likely to be female, exhibit dactylitis and small joint involvement and express antinuclear antibodies. Progression to polyarticular disease (five or more joints) is more common in younger children, although joint involvement remains oligoarticular in the majority of children. In contrast, older patients tend to manifest enthesitis, axial joint disease and persistent oligoarthritis. Uveitis is equally represented in both age groups. Younger patients with juvenile PsA usually require more intensive therapy with MTX to achieve remission. In this age group, the presence of dactylitis, rather than age, has the greatest capacity to predict essential features of the clinical phenotype [51]. Unfortunately, in adults with PsA these distinguishing factors are not clearly appreciated.

Genetic factors have been considered to be important in studies of both susceptibility to and the expression of PsA. There are at least nine psoriasis loci, designated *PSORS1*–*PSORS9*, and several potential loci, but the strongest association is with a locus on chromosome 6p, probably the *HLA-C*06* gene itself [52]. However, the pathogenic nature of these associations remains elusive. Thus it is unclear whether *HLA-C*06* itself or a closely related gene is related to the presence of arthritis in psoriasis patients, and few studies have addressed this question so far. In a study from Canada, the *HLA-C*06* allele was increased among PsA patients, and these patients also showed an earlier age of onset of their psoriasis [17]. Another study from Poland had similar results, but also showed that patients expressing this allele had an earlier age of onset of their arthritis [14]. Nonetheless, both studies did not show whether these associations were due to the presence of psoriasis in PsA patients or, in contrast, whether it represented true associations with arthritis. In general, the information extracted from these studies shows that, as in skin psoriasis, *HLA-C*06* remains the primary marker of type I psoriasis in subjects with PsA; however, it does not seem to be a marker for early arthritis [9, 16]. In fact, in studies of PsA patients, the age of onset of psoriasis in subjects positive for *HLA-C*06* compared with those without this marker were not strikingly different [53, 54]. In these studies, however, *HLA-C*06*-positive patients with psoriasis without arthritis showed age of onset of disease significantly earlier when compared with the age of onset of psoriasis in the PsA population carrying the same allele, a fact that opens the possibility of epistatic interactions between *HLA-C*06* and other genes in the aetiology of PsA [53, 54]. It is interesting to note that, as in psoriasis, the risk effect attributable to *HLA-C*06* declines with increasing age in patients with PsA (Fig. 3) and the strongest association is observed in subjects with age of onset <30 years (OR = 6.4, 95% CI 2.3, 18.2, $P = 0.0003$), so it has been postulated that this age limit is suitable for distinguishing between type I and type II psoriasis in PsA [55]. By using this age limit, a recent report found that PsA patients with early onset psoriasis more frequently showed a longer psoriasis–arthritis latency [9.9 (S.D. 6) *vs* 3.8 (S.D. 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 [Psoriasis Area and Severity Index (PASI) 8.2 (S.D. 4) *vs* 3.6 (S.D. 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, $P = 0.04$) [56]. Therefore, dividing the PsA according to an age limit of 30 years seems to

Fig. 3 The declining susceptibility effect of *HLA-C*06* is parallel to increasing age at psoriasis onset in patients with PsA

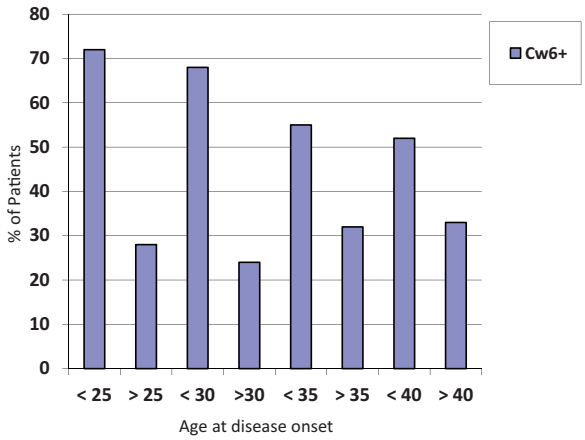

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Table 1 Positive and negative associations between HLA-B27 positivity and several loci in a recent GWAS

Locus	Chr	SNP	OR (95% CI)	*P*-value
REL	2	rs702873	1.38 (1.02, 1.88)	0.042
ERAP1	5	rs27524	1.4 (1.04, 1.89)	0.029
HLA-C	6	rs10484554	0.48 (0.32, 0.71)	0.00033
CSMD1	8	rs10088247	0.66 (0.45, 0.96)	0.035
SMARCA4	19	rs12983316	1.76 (1.17, 2.64)	0.0084
SDC4	20	rs1008953	1.55 (1.04, 2.3)	0.037

Results refer to PsA patients. The inverse association between *HLA-B27* and *HLA-C* is highly significant.

Table 2 Phenotypic traits linked to *HLA-C*06* and *HLA-B*27* in patients with PsA

*HLA-C*06*	*HLA-B*27*
Earlier age of onset of psoriasis	Earlier age of onset of arthritis
Longer psoriasis–arthritis latency	Shorter psoriasis–arthritis latency
No sex predominance	Male predominance
No association with joint pattern	Association with axial pattern and bilateral SI
Linked to family history of psoriasis	Probably linked to family history of arthritis
No linked to uveitis	Linked to uveitis
Defined risk factor for cutaneous disease	Defined risk factor for joint disease

be an appropriate descriptor from a clinical and genetic standpoint.

PsA seems to develop in a larger fraction of patients without any copy of the *HLA-C* risk allele. A recent psoriasis GWAS suggested that within the group of *HLA-C*-negative PsA patients there was, however, a higher proportion of *HLA-B27*-positive patients compared with the frequency in *HLA-C*-positive patients (OR = 2.23, 95% CI 1.41, 3.53, $P = 0.0007$) (Table 1), indicating an independent risk mechanism in this neighbouring loci for PsA [32]. Conversely, when patients were stratified according to *HLA-B27* status, the risk variation at *HLA-C* was significantly associated with the *HLA-B27*-negative group [32]. The role of *HLA-B27* as a risk antigen for PsA has been recognized for decades, although its exact role in the pathogenesis of the disease has been refined recently [57, 58]. For example, in one study the onset age of psoriasis in *HLA-B27*-positive patients was 24 (S.D. 8) *vs* 32 (S.D. 14) years in *HLA-B27*-negative patients ($P = 0.026$), whereas the onset age of arthritis was 30 (S.D. 10) years in *HLA-B27*-positive patients compared with an age of onset of 40 (S.D. 12) years in *HLA-B27*-negative patients ($P = 0.0056$) [54]. Therefore the time elapsed between the onset of psoriasis and the onset of articular symptoms was significantly shorter in the *HLA-B27*-positive individuals compared with the *HLA-B27*-negative individuals, a finding corroborated by an independent group of researchers [57]. In contrast, the opposite behaviour is seen in *HLA-C*06*-positive subjects, where latency between psoriasis and arthritis is significantly longer compared to subjects without this allele [16, 53, 54].

It is possible that, as occurs in psoriasis, where the age of onset below or above 40 years marks phenotypic characteristics that depend on the presence of *HLA-C*06*, likewise in PsA the presence of *HLA-B27* may act not only as an aetiological factor, but also as a modulator of phenotypic expression [57, 58] (Table 2). Thus patients with PsA and disease onset before 40 years of age tend to have higher familial aggregation, bilateral SI, B27 positivity, uveitis, isolated axial pattern and enthesitis compared with those with disease onset after this age limit [59]. However, this information is not as solid compared with that derived from the field of psoriasis, where the relationship between age of onset, phenotypic traits and *HLA-C*06* is much clearer.

Age of onset, gender, genes and clinical expression in PsA

Female sex has been associated with earlier development of psoriasis [10]. In a recent psoriasis GWAS, it was found that women tended to develop the disease ~3.5 years earlier [mean female age 28.68 (S.D. 17.6) years, mean male age 32.2 (S.D. 16.5) years] and this difference was significant ($P = 3.9 \times 10^{-5}$) [32]. Furthermore, it appears that the clinical behaviour of SpA varies between men and women. It has been shown that males with SpA tend to suffer from more severe spinal disease, while females are more likely to have peripheral joint involvement [60–62]. Nevertheless, gender-related differences have not been thoroughly explored in PsA. In a recent investigation among patients with PsA, men tended to

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accumulate more peripheral and axial joint damage compared with women. However, it was unclear whether these findings were secondary to differences in occupational physical activity, hormonal changes or other factors [63]. It is also plausible that some of these gender-observed differences in PsA could be attributed to genetic factors [64]. Indeed, some studies have shown a close correlation between male sex, HLA-B27 positivity and risk of psoriatic SpA [58, 59]. However, very few studies have analysed these differences in depth [63]. In a recent paper, when compared with PsA males, females tended to be affected more frequently by polyarthritis as the main joint pattern during follow-up, higher HAQ values and higher swollen joint counts. There were no gender differences in age at onset of psoriasis or arthritis, family history of disease, DIP involvement, dactylitis, nail disease, the presence of erosive disease in the radiological study or severity of psoriasis [65]. The only discordant data between genders in the patients with psoriasis developing before 40 years of age were a shorter psoriasis–arthritis latency period in men [5.5 (S.D. 7.1) years] than in women [9.3 (S.D. 6.6) years] and a greater frequency of polyarthritis during follow-up in women (37.5% *vs* 17.7%). Women with early psoriasis showed greater nail involvement than men, though the difference was not statistically significant. In women with type II psoriasis, polyarthritis likewise was the dominant PsA pattern (53.3% *vs* 30%). In the same way, in men with type II psoriasis the dominant joint pattern was axial involvement (70% *vs* 33.3%). There were no significant differences in age at onset of psoriasis between men and women with early psoriasis and *HLA-C*06* positivity, although women tended to have an earlier age at psoriasis onset [18 (S.D. 8.9) *vs* 21 (S.D. 8.3) years]. However, among the individuals with late psoriasis (>40 years of age) and *HLA-C*06* positivity, the age at onset of psoriasis was significantly younger in men [44.3 (S.D. 3.2) years] than in women [57 (S.D. 4.2) years]. Similarly, men with *C1_4_4 (384)* microsatellite positivity and the development of psoriasis after 40 years of age were significantly younger at disease onset [45.7 (S.D. 3.8) years] than the women with the same marker [53.3 (S.D. 7) years]. The women developing psoriasis before 40 years of age showed significant elevation of the following markers *vs* the female control population: *HLA-C*06* (65% *vs* 16.4%), *HLA-C*07* (50% *vs* 25.5%), *HLA-*B27* (30% *vs* 7.3%) and *MICA-A9* (62.5% *vs* 32.7%). The women developing psoriasis after 40 years of age in turn showed overexpression of the following markers: *TNF-308A* (66.7% *vs* 22%) and *HLA-DR17-DRB1*03* (53% *vs* 18%). The men developing psoriasis before 40 years of age showed overexpression of the following markers: *HLA-C*06* (58% *vs* 18.2%), *HLA-B*27* (42.2% *vs* 7.3%) and *MICA-A9* (60% *vs* 27.3%). The men developing psoriasis after 40 years of age in turn showed a significant increase in the following markers: *HLA-C*06* (50% *vs* 18.2%), *MICB-CA23* (50% *vs* 5.5%), *C1_4_4* (80% *vs* 22%) and *MICA-A9* (60% *vs* 27.3%). Of note was the observation that the impact of the *HLA-C*06* allele upon disease risk was found to decrease more clearly with age among females (only 33% of the women with psoriasis onset after 40 years of age proved positive for this allele) than in males (50% positivity for this allele in individuals with late psoriasis onset) [65]. Therefore, in addition to the age of onset of disease, the sex of patients should be another stratification element in studies of genetic aetiology of psoriasis and PsA. In fact, in recent GWASs it has been found that including sex information in the regression model seems to improve the association of several risk loci. Although the improvement is relatively small, investigators advocate the use of a sex covariate in the analysis of age at onset [32].

Conclusions

Psoriasis and PsA are complex immunological entities with a strong heritability component. The division of psoriasis into two subgroups of disease, depending on the age of onset and the presence of the *HLA-C*06* allele, has been a descriptor of broad use in the study of this process. A similar stratification has been useful to distinguish type I and type II psoriasis in PsA populations. The presence of *HLA-C*06* is associated with early onset disease both in patients with psoriasis and PsA. This marker influences the age of onset of psoriasis but has no influence on the age at the onset of arthritis. In contrast, the *HLA-*B27* allele acts not only as a susceptibility factor for PsA, but also has been associated with certain phenotypic traits, such as an earlier age of onset of PsA. Therefore, at present, these two genetic biomarkers establish marked traits (such as early onset disease) that in turn allow phenotypic differentiations in both populations.

Rheumatology key messages

- Psoriasis and PsA are highly polygenic diseases.
- *HLA-C*06* determines early onset skin disease in both psoriasis and PsA.
- Patients expressing the HLA-B*27 antigen show an earlier PsA onset age.

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