Letters to the Editors

Could the clinical differences between men and women with psoriatic arthritis be explained in part by genetic factors?

Sirs,

Psoriasis and psoriatic arthritis (PsA) are relatively common T-cell mediated diseases in which both environmental and genetic factors contribute to its pathogenesis and clinical expression (1). In PsA, it has been shown that males tend to suffer from more severe spinal disease while females are more likely to have peripheral joint involvement (2). However, gender-related differences have not been thoroughly explored in this entity.

For the purposes of this study, 110 consecutive patients who fulfilled the ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria (3) were randomly selected from the rheumatology outpatient clinic of a tertiary care hospital. A standard clinical protocol was applied to both men and women with PsA. The study was carried out with the approval of the ethics committee of our hospital. All patients gave written informed consent before enrolling in the study. Several genes and polymorphisms within the major histocompatibility complex (MHC) region were analysed as described previously (4). A total of 110 random blood donors matched ethnically and geographically served as controls. The differences between the frequencies of these allelic markers in patients and controls, as well as the differences found in accordance to sex were assessed by univariate analyses. The *p*-values were corrected (*pc*) by multiplying them by the number of alleles at each locus. The extent of linkage disequilibrium between two loci is expressed as the observed disequilibrium value (λs). The λs were calculated using the formula: λs = λ/λmax = Pab-(Pa. Pb)/Pa.(1-Pb).

Clinical features of PsA according to gender are shown in Table I.

The global study population showed a relationship between the presence of HLA-C*06 (56.4% *vs*. 17%, OR 6.18, 95% CI: 3.32-11.5, *pc*<0.0001), MICA*002 (60% *vs*. 30%, OR 3.5, 95% CI: 2.0-6.12, *pc*<0.001), HLA-B*27 (31.8% *vs*. 7.3%. OR 5.9, 95% CI: 2.6-13.4, *pc*=0.001), and the risk of suffering PsA. The following markers were over-expressed in women with PsA: HLA-B*27 (27.3% *vs*. 7.3%. OR 4.8, 95% CI: 1.5-15.5, *pc*=0.01), HLA-C*06 (56.4% *vs*. 16.4%. OR 6.6, 95% CI: 2.7-16.1, *pc*=0.0001), C*07 (49% *vs*. 25.5%. OR 2.8, 95% CI: 1.3-6.3, *pc*=0.01), TNF-308A (45.5% *vs*. 22%. OR 3.0, 95% CI: 1.3-6.9, *pc*=0.009) and MICA*002 (60% *vs*. 32.7%. OR 3.1, 95% CI: 1.4-6.7, *pc*=0.004). In turn, in men only the following markers were significantly elevated with respect to the male control population: HLA-C*06 (56.4% *vs*. 18.2%. OR 5.8, 95% CI: 2.4-13.8, *pc*=0.0001), HLA-B*27 (36.4% *vs*. 7.3%. OR 7.3, 95% CI: 2.3-23.2, *pc*=0.0004) and MICA*002 (60% *vs*. 27.3%. OR 4.0, 95% CI: 1.8-8.9, *pc*=0.001).

Table I. Clinical characteristics of the study population.

Variables	Men n=55	Women n=55	*p*-values
Age (yr)	46.5 ± 11.6	46.4 ± 15.9	NS
Psoriasis onset age (yr)	27.5 ± 10.4	27.0 ± 14.9	NS
Arthritis onset age (yr)	34.2 ± 9.4	35.1 ± 13.1	NS
Psoriasis duration (yr)	19 ± 11	18.2 ± 8.8	NS
Arthritis duration (yr)	13 ± 7.4	12.5 ± 6.7	NS
Psoriasis-arthritis latency (yr)	7 ± 6.4	7.5 ± 5.6	NS
Family history	40%	45.5%	NS
Oligoarthritis	42%	34.5%	NS
Polyarthritis	20%	40%	<0.05
Axial disease	38.2%	23.6%	NS
Nail disease	36.4%	47.3%	NS
DIP disease	29%	34.5%	NS
IBP (ever)	62%	67.3%	NS
Enthesitis	34.5%	25.5%	NS
Dactylitis	31%	31%	NS
HAQ	0.62 ± 0.42	1.10 ± 0.53	<0.01
Swelling joint count	3.4 ± 4.2	5.2 ± 4.6	<0.05
Tender joint count	10.2 ± 3.4	11.0 ± 4.1	NS
Erosive disease	34.5%	41.8%	NS
PASI	5.4 ± 4.5	5.7 ± 3.8	NS
VSG	15 ± 5.3	16 ± 4.7	NS
HLA-C*06	56.4%	56.4%	NS
HLA-B27	36.4%	27.3%	NS

DIP: Distal interphalangeal joint; IBP: inflammatory back pain; HAQ: Health Assessment Questionnaire; PASI: Psoriasis Area and Severity Index.

Psoriatic arthritis (PsA) appears to be more frequent in men than in women, particularly in its axial presentations (5,6). Nevertheless, little is known of the differential clinical expression of PsA between males and females. The explanation for these differences is not clear, and the participation of multifactorial parameters cannot be discarded (7, 8). Our study offers a preliminary evaluation of these gender differences referred to both clinical and genetic aspects. The results obtained confirm the existence of such clinical and genetic differences in a cohort of patients that fully covers the joint spectrum of PsA (oligoarthritis, polyarthritis and spondylitis). In PsA female, we confirmed a greater peripheral involvement as well as a greater physical functional impairment as measured with the HAQ (7, 8).

This study confirmed HLA-C*06, B*27 and MICA*002 as three of the most relevant PsA risk genes within the MHC (9). All three were significantly over-expressed in men and women with PsA. However, we found certain markers to be over-expressed in women, such as C*07 and TNF-308A. In women there was certain LD between TNF-308A and DR17 (λs: 0.3). It is interesting to note that C*07, TNF-308A and DRB1*03 form part of the extended haplotype 8.1, which also contains an allele recently linked to PsA risk (HLA-B*08); as a result, it is nowadays difficult to establish which of these alleles are the true disease risk markers (10).

To sum up, men and women with PsA show differences in the expression of the disease, and this is probably due in part to a differential over-expression of certain MHC genes between the two genders.

R. QUEIRO, *MD*, *PhD*[1,2]
P. TEJÓN, *MD*[1]
P. COTO, *MD*, *PhD*[2,3]
M. ALPERI, *MD*[1]
S. ALONSO, *MD*[1]
C. SARASQUETA, *PhD*[4]
S. GONZÁLEZ, *PhD*[5]
J. MARTÍNEZ-BORRA, *PhD*[6]
C. LÓPEZ-LARREA, *PhD*[6]
J. BALLINA MD, *PhD*[1]

[1]Rheumatology Department; [2]Psoriasis Unit; [3]Dermatology Department, Hospital Universitario Central de Asturias (HUCA), Oviedo, Asturias, Spain; [4]Clinical Epidemiology Unit, BIODONOSTIA, San Sebastian, Basque Country, Spain; [5]Department of Functional Biology, Oviedo University School of Medicine, Oviedo, Asturias, Spain; [6]Immunology Service, HUCA, Oviedo, Asturias, Spain.

Please address correspondence to:
Dr Rubén Queiro, Rheumatology Department, HUCA, C/Celestino Villamil s/n, 33006 Oviedo, Spain.
E-mail: rubenque7@yahoo.es

Competing interests: none declared.

References

1. CASTELINO M, BARTON A: Genetic susceptibility factors for psoriatic arthritis. *Curr Opin Rheumatol* 2010; 22: 152-6.
2. GLADMAN DD, ANTONI C, MEASE P, CLEGG DO, NASH P: Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005; 64 (Suppl. 2): ii14-7.
3. TAYLOR W, GLADMAN D, HELLIWELL P, MARCHESONI A, MEASE P, MIELANTS H; CASPAR STUDY GROUP: Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; 54: 2665-73.

4. QUEIRO R, ALPERI M, ALONSO-CASTRO S *et al*.: Patients with psoriatic arthritis may show differences in their clinical and genetic profiles depending on their age at psoriasis onset. *Clin Exp Rheumatol* 2012; 30: 476-80.
5. QUEIRO R, SARASQUETA C, TORRE JC, TINTURÉ T, LÓPEZ-LAGUNAS I: Spectrum of psoriatic spondyloarthropathy in a cohort of 100 Spanish patients. *Ann Rheum Dis* 2002; 61: 857-8.
6. QUEIRO R, SARASQUETA C, TORRE JC, TINTURÉ T, LÓPEZ-LAGUNAS I: Comparative analysis of psoriatic spondyloarthropathy between men and women. *Rheumatol Int* 2001; 21: 66-8.
7. GLADMAN DD, BRUBACHER B, BUSKILA D, LANGEVITZ P, FAREWELL VT: Psoriatic spondyloarthropathy in men and women: a clinical, radiographic, and HLA study. *Clin Invest Med* 1992; 15: 371-5.
8. EDER L, THAVANESWARAN A, CHANDRAN V, GLADMAN, DD: Gender related differences in severity of psoriatic arthritis. [abstract]. *Arthritis Rheum* 2011; 63 (Suppl. 10): 2486C.
9. WINCHESTER R, MINEVICH G, STESHENKO V *et al*.: HLA associations reveal genetic heterogeneity in psoriatic arthritis and in the psoriasis phenotype. *Arthritis Rheum* 2012; 64: 1134-44 [Epub 2011 Oct 17].
10. EDER L, CHANDRAN V, PELLET F *et al*.: Human leucocyte antigen risk alleles for psoriatic arthritis among patients with psoriasis. *Ann Rheum Dis* 2012; 71: 50-5.