

Correspondence

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 3 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

Contact: The Managing Editor, The Journal of Rheumatology, 920 Yonge Street, Suite 115, Toronto, Ontario M4W 3C7, CANADA. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.

Influence of HLA-B27 on the Clinical Presentation of Psoriatic Arthritis

To the Editor:

We were interested to read the report in *The Journal* by Dr. Queiro and colleagues regarding the influence of HLA antigens on the clinical presentation of psoriasis and psoriatic arthritis (PsA)¹. We have also examined the relationship between HLA-B27 and age of onset and patterns of skin, nail, and joint disease in PsA. We would like to compare Dr. Queiro's data with our study of UK patients with PsA.

We studied 98 patients with PsA according to Moll and Wright² (50 men, 48 women, mean age 45 ± 12 yrs) recruited from rheumatology outpatient clinics. A careful history was taken about the onset and patterns of psoriasis and arthritis. All patients had a full skin, nail, and musculoskeletal examination. HLA-B27 was detected by polymerase chain reaction sequence-specific primers. Data were analyzed using contingency tables and Student *t* tests.

There were 20 (20.4%) patients with HLA-B27. We did not find a significant association between HLA-B27 and age of onset of skin or joint disease. The mean age of onset of psoriasis in the HLA-B27 positive group was 27 ± 15 years and in the HLA-B27 negative group 23 ± 11 years ($p = 0.2$). The mean age of onset of arthritis in the HLA-B27 positive group was 34 ± 13 years and in the negative group 32 ± 9 years ($p = 0.4$).

However, we found other associations with respect to psoriasis patterns and HLA-B27. Palmoplantar pustulosis occurred in 3/20 (15%) HLA-B27 patients versus 1/78 (1.3%) in HLA-B27 negative patients ($p = 0.006$). This finding has been reported in patients with psoriasis without arthritis³, but, to our knowledge, has not been reported in a cohort of patients with PsA. Interestingly, scalp psoriasis occurred less frequently in those with HLA-B27; 14/20 (70%) of those with HLA-B27 had evidence of scalp psoriasis compared with 73/78 (93.5%) of those without HLA-B27 ($p = 0.003$). There were no other associations found between HLA-B27 and psoriasis type. HLA-B27 was not associated with the presence of nail disease.

In summary, in contrast to the study of Spanish patients by Dr. Queiro and colleagues, our study of UK patients with PsA does not show an association between age of disease onset and HLA-B27. We accept that our

conclusions may be subject to type II error, but believe that the relationship between HLA-B27 and onset of disease is unlikely to be of clinical significance in our population. However, our data do suggest that the presence of HLA-B27 may modulate other clinical aspects of psoriasis.

NICOLA DALBETH, FRACP; JOANNE L. DOCKERTY, MB, ChB; LYN WILLIAMSON, MRCP, Department of Rheumatology, Nuffield Orthopaedic Centre, Oxford, UK.

Acknowledgment

Funded by an Oxford District Research Grant. Dr. Dalbeth is the Rose Hellaby Rheumatology Fellow 2002.

REFERENCES

1. Queiro R, Torre JC, Gonzalez S, Lopez-Larrea C, Tinture T, Lopez-Lagunas I. HLA antigens may influence the age of onset of psoriasis and psoriatic arthritis. *J Rheumatol* 2003;30:505-7.
2. Moll JHM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;3:55-78.
3. Zachariae H, Overgaard Peterson H, Kissmeyer Nielson F, Lamm L. HLA antigens in pustular psoriasis. *Dermatologica* 1977;154:73-7.

Dr. Queiro replies

To the Editor:

On behalf of my colleagues, I deeply appreciate Dr. Dalbeth and colleagues' interest in our work¹. The authors studied the relative role of the HLA-B27 antigen on the clinical expression of a substantial number of UK patients with psoriatic arthritis (PsA), and present some interesting conclusions. The first is that in their population HLA-B27 seems to have a marginal role in disease susceptibility, as only 20% of their series showed this marker. It would be of interest to know whether the distribution of this allele differs among the different subgroups of their patients with PsA, as the figure of 20% is similar to that published by us in psoriatic polyarthritis, but clearly inferior to the frequencies noted in our spondylitis or oligoarthritis subgroups². On the other hand, the authors did not find a correlation between HLA-B27 and age at disease onset, in contrast to our results. It is well established that among psoriasis patients, HLA-Cw6 is associated with early onset of psoriasis and family aggregation (type I psoriasis). Thus, many HLA associations (B17 and DR7, for example) regarding the age at onset of psoriasis or arthritis published in previous years are better explained in the setting of the known phenomenon of linkage disequilibrium between these alleles and HLA-Cw6³. For this reason, it has been reported that the strongest disease associations are with combinations of alleles at multiple loci (haplotype) rather than with an individual gene³. In addition, most populations are made up of different subpopulations with different allele frequencies, and such population stratification is a major confounding factor in association studies like the present one. HLA-B27 has been variably associated with a later onset of arthritis, or with an early onset of psoriasis and arthritis as we noted, or on the other hand, not correlated with age at onset of disease. As HLA-B27 is not associated with linkage disequilibrium with HLA-Cw6, the relative contribution of the HLA-B27 to this point will remain elusive.

Other notable results of the Dalbeth group's work deserve consideration. They found a relationship between HLA-B27 and palmoplantar pustulosis, a finding also noted by others⁴. It is necessary to emphasize here in particular that this association is present in patients with anterior chest wall osteitis and sacroiliitis; moreover the strongest correlation of HLA-B27 is with bilateral sacroiliitis: therefore it would be necessary to carefully evaluate the pelvic radiographs of these subjects, since radiographic sacroiliitis may be present in the absence of symptoms⁵.

Finally, the authors found that scalp psoriasis occurred less frequently in HLA-B27 positive than in B27 negative individuals. For some investi-

gators, cervical spine involvement in PsA may occur more frequently in cases in which there is more severe scalp involvement with psoriasis⁶. In a previous work, we found that peripheral erosions and disease duration were predictive of cervical involvement in psoriatic spondyloarthritis over time, and additionally, our B27 negative patients showed more peripheral erosions than our B27 positive patients⁷. Thus, our own data, in conjunction with those of Dr. Dalbeth, *et al*, add support to the association between peripheral erosions, cervical involvement, HLA-B27 negativity, and scalp psoriasis.

We indeed concur with the authors that the presence of HLA-B27 may modulate other aspects of PsA and that this antigen may have a role in clinical expression, apart from its role in disease susceptibility. However, we should keep in mind that the association between a locus and a disease may reflect several situations, including a direct relationship between the marker allele and a phenotype or, alternatively, a linkage disequilibrium between the marker allele and a susceptibility locus.

RUBEN QUEIRO, MD, Consultant Rheumatologist, Hospital San Agustín, Avilés-Asturias, Spain. E-mail: ruquei@mixmail.com

REFERENCES

1. Queiro R, Torre JC, González S, López-Larrea C, Tinturé T, López-Lagunas I. HLA antigens may influence the age of onset of psoriasis and psoriatic arthritis. *J Rheumatol* 2003;30:505-7.
2. Queiro R, Sarasqueta C, Torre JC, Tinturé T, López-Lagunas I. Spectrum of psoriatic spondyloarthritis in a cohort of 100 Spanish patients. *Ann Rheum Dis* 2002;61:857-8.
3. Eastmond CJ. Psoriatic arthritis: genetics and HLA antigens. *Baillieres Clin Rheumatol* 1994;8:263-76.
4. Khan MF, Chaot AM. SAPHO syndrome. *Rheum Dis Clin North Am* 1992;18:225-46.
5. Braun J, Sieper J. The sacroiliac joint in the spondyloarthropathies. *Curr Opin Rheumatol* 1996;8:275-87.
6. Vasey FB, Espinoza LR. Psoriatic arthropathy. In: Calin A, editor. *Spondyloarthropathies*. New York: Grune and Stratton; 1984:151-85.
7. Queiro R, Sarasqueta C, Torre JC, Tinturé T, López-Lagunas I. Prevalence and predictors of cervical involvement in psoriatic spondyloarthritis. *J Clin Rheumatol* 2002;8:23-9.



Frequency of the HLA-B27 Alleles in Brazilian Patients with Ankylosing Spondylitis.

To the Editor:

Currently, 25 alleles of HLA-B27 (HLA-B*2701 to B*2725) have been identified¹. Some of them (B*2702, B*2704, B*2705, and B*2707) are clearly associated with ankylosing spondylitis (AS)². Our prospective study identified the prevalence of the HLA-B27 alleles in a Brazilian population of 108 patients (83 Caucasians, 24 African-Brazilians, and one Japanese-Brazilian) with the diagnosis of AS according to the modified New York

criteria³, and 111 HLA-B27 positive healthy individuals (94 Caucasians and 17 African-Brazilians) without a history of a seronegative spondyloarthritis (SpA), selected from healthy blood donors and solid organ or hematopoietic stem cell transplantation donors. These patients were from the State of São Paulo, in the southeast of Brazil, which has a population made up of Caucasians (Portuguese, Spanish, and Italian origin), African-Brazilians (including non-miscegenated Blacks and Mulattos of white and black heritage) and Japanese-Brazilians⁴. HLA-B27 alleles were typed using polymerase chain reaction amplified DNA hybridized with sequence specific high-resolution B27 primers (HLA-B*2701 to HLA-B*2721) (Dynal, Biotech Ltd., UK).

HLA-B*2705 was the predominant allele, observed in 90% of patients and 80% of controls, followed by the HLA-B*2702, present in 8% of patients and 10% of controls. HLA-B*2713 was found in one patient and one control, both Caucasians. HLA-B*2704 was found in one Japanese-Brazilian patient, and was absent in the control population. HLA-B*2703 (6%) and HLA-B*2707 (3%) alleles were observed only in controls. Statistical correlation was observed between the presence of B*2703 and B*2707 alleles and the control group ($p = 0.0086$), and between B*2703 allele and African-Brazilians ($p = 0.028$); there was a statistical trend between family history of AS and the B*2702 allele ($p = 0.084$).

Our findings show that this population did not differ from the majority of Caucasian populations in relation to the predominant allele, since our results revealed that B*2705 and B*2702 predominated in both the AS patients and controls. HLA-B*2705 may be an ancestral allele from which other alleles have evolved², which explains its extensive worldwide distribution, followed by the B*2702, which is an allele of the Caucasian race⁵, rarely observed in Asiatic populations⁶. The statistical trend between familial history of AS and B*2702 must be confirmed in other studies.

The B*2713 allele is considered extremely rare in the world, and there is only one report of a healthy individual with this allele in a control population from northern Spain⁷. The B*2704 allele is predominant in both healthy and AS Asiatic populations^{6,8}.

The B*2707 allele was found only in controls in our study, although it is predominantly associated with AS in Asiatic populations⁶, with some reports of its presence in Caucasians in Spain⁷ and in the Portuguese Azores Islands⁹. The presence of this allele in Brazil could be explained by the genetic admixture between Asiatic, Portuguese, and Spanish populations centuries ago.

The B*2703 allele is predominant in African sub-Saharan populations¹⁰, and has also been observed in Caucasian populations in Azores⁹ and African-Americans¹¹. Although HLA-B*2703 was statistically associated with the African-Brazilian controls, it was also observed in some Caucasian controls; this fact could be attributed to the strong genetic admixture in our country, and could be explained by studies conducted on White Brazilian populations demonstrating that 28% of the matrilineages and 2.5% of the patrilineages carry a genetic inheritance from Africans, even though they do not reflect these physical characteristics^{12,13}.

We conclude that the alleles B*2702, B*2704, B*2705, and B*2713 are related to AS in the Brazilian population, although more data are necessary regarding B*2704 and B*2713 to confirm their relationship with the disease. The presence of B*2703 and B*2707 alleles in the control population reflects the genetic admixture of our population.

Acknowledgment

The authors would like to thank Andreia Semolini and Cleide Moreira Silva for statistical support. Supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

ROSENEIDE A. CONDE, Biologist, Laboratory of Rheumatology; PERCIVAL D. SAMPAIO-BARROS, MD, PhD, Assistant Rheumatologist; EDUARDO A. DONADI, MD, PhD, Associate Professor, Immunology Unit; MARIA HELENA S. KRAEMER, PhD, Assistant Professor, Department of Clinical Pathology; LIGIA PERSOLI, PhD, Assistant Professor, Hematology Unit; IBSEN B. COIMBRA, MD, PhD, Assistant

Professor, Rheumatology Unit; LILIAN TEREZA L. COSTALLAT, MD, PhD, Professor of Rheumatology; ADIL M. SAMARA, MD, PhD, Professor of Rheumatology, University of São Paulo at Ribeirão Preto; MANOEL B. BÉRTOLO, MD, PhD, Assistant Professor, Rheumatology Unit, State University of Campinas, São Paulo, Brazil.
E-mail: conde@fcm.unicamp.br

REFERENCES

1. Khan MA. Update on spondyloarthropathies. *Ann Intern Med* 2002;136:896-903.
2. Reveille JD, Ball EJ, Khan MA. HLA-B27 and genetic predisposing factors in spondyloarthropathies. *Curr Opin Rheumatol* 2001;13:265-72.
3. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
4. Sampaio-Barros PD, Bértolo MB, Kraemer MHS, Marques-Neto JF, Samara AM. Primary ankylosing spondylitis: Patterns of disease in a Brazilian population of 147 patients. *J Rheumatol* 2001;28:560-5.
5. Gonzalez-Rocoz S, Brautbar C, Peña M, et al. Molecular analysis of HLA-B27 haplotypes in Caucasoids. *Hum Immunol* 1994;41:127-34.
6. Lopez-Larrea C, Sujirachato K, Mehra NK, et al. HLA-B27 subtypes in Asian patients with ankylosing spondylitis. *Tissue Antigens* 1995;45:169-76.
7. Gonzalez S, Garcia-Fernandez S, Martinez-Borra J, et al. High variability of HLA-B27 alleles in ankylosing spondylitis and related spondyloarthropathies in the population of northern Spain. *Hum Immunol* 2002;63:673-6.
8. Yamaguchi A, Ogawa A, Tsuchiya N, et al. HLA-B27 subtypes in Japanese with seronegative spondyloarthropathies and healthy controls. *J Rheumatol* 1996;23:1189-93.
9. Armas JB. Espondilartrites e doenças associadas. Heterogeneidade genética e sua expressão [thesis]. University of Porto; Portugal: 2001.
10. Mijiyawa M, Oniankitan O, Khan MA. Spondyloarthropathies in sub-Saharan Africa. *Curr Opin Rheumatol* 2000;12:281-6.
11. Khan MA. A worldwide overview: the epidemiology of HLA-B27 and associated spondyloarthritides. In: Calin A, Taurog JD, editors. *The spondylarthritides*. Oxford: Oxford University Press; 1998:17-27.
12. Alves-Silva J, Santos MS, Guimarães PEM, et al. The ancestry of Brazilian mtDNA lineages. *Am J Hum Genet* 2000;67:444-61.
13. Carvalho-Silva J, Santos FR, Rocha J, Pena SDJ. The phylogeography of Brazilian Y chromosome lineages. *Am J Hum Genet* 2001;68:281-6.

Correction

Cohen M, Wolfe R, Mai T, Lewis D. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. *J Rheumatol* 2003;31:523-8.

On page 524, under the heading, "Interventions," the first sentence should correctly read as follows: "The glucosamine/chondroitin preparation was a water-soluble cream containing glucosamine sulfate (3.0 mg/g), chondroitin sulfate (7.2 mg/g), and shark cartilage (14 mg/g), of which 10% to 30% is chondroitin sulfate, camphor (32 mg/g), and scented with peppermint oil (9 mg/g)."

Furthermore, in paragraph 2 of the Discussion, page 526, sentences 2 and 3 should correctly read as follows: "Based on a total usage of 5.5 tubes and an average usage of around 2.5 applications per day, it is estimated that the topical dosages applied in this study were roughly 30 mg of glucosamine sulfate and 78 mg chondroitin sulfate per day. If transdermal absorption is between 20 and 40%, it is estimated that between 6 and 12 mg of glucosamine sulfate and 16 to 30 mg of chondroitin sulfate is delivered through topical application." We regret the error.