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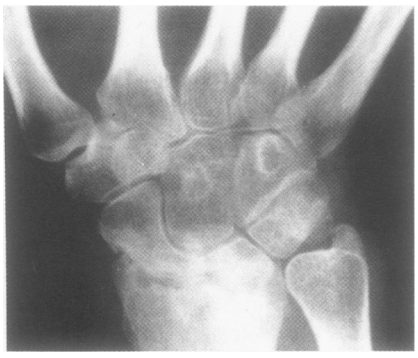
Autosomal dominant undifferentiated spondyloarthropathy not related to the HLA system

We were interested to read the article by Kidd and colleagues[1] on familial aggregation for undifferentiated spondyloarthropathy associated with HLA-B7. The authors described a single family in whom numerous members had a recurrent seronegative arthropathy or enthesopathy, or both, which fulfilled the European Spondylarthropathy Study Group criteria for spondyloarthropathy[2] in the absence of the HLA-B27 tissue type, coexistent psoriasis, or inflammatory bowel disease. They suggested that 'undifferentiated' spondyloarthropathy can be associated with genetic factors other than HLA-B27. We are in total agreement.

A few years ago, we studied a French family of 83 members distributed over five generations divided into four main branches, among whom 18 adult members had destructive arthropathy and enthesopathic changes.[3 4] In all patients, the disease began between the ages of 18 and 32 years. It affected predominantly the wrists, fingers, shoulders, and peripheral entheses and progressed as an oligoarthritis, with intermittent inflammatory episodes lasting for one to three months. Axial involvement of the cervical and lumbar spine and the sacroiliac joints was also seen, but was not prominent. The sites of involvement seemed to be influenced by mechanical factors. The right wrist was generally the first joint to be affected. Destructive abnormalities, followed by bony proliferation, and intra- or extra-articular bony ankylosis were the main radiological features of this familial arthropathy (figure).



Radiograph of the right wrist of a 29 year old female patient (disease duration six years), showing destruction of the radiocarpal joint.

The transmission of the disease was dominant and autosomal, with 100% penetrance. The clinical and radiological features were strikingly similar in all patients in successive generations and different branches of the genealogical tree, suggesting monogenic transmission. HLA typing of 12 patients and 13 healthy family members was performed. No HLA antigen was linked to the disease. None of the affected subjects had antigens B27, DR4 or DR7. The disease was not transmitted with any particular HLA haplotype.

Tests for rheumatoid factor yielded negative results. There was no history of psoriasis or chronic enteropathy in the members of this family. In none of the 18 patients did the arthropathy fulfil the American Rheumatism Association criteria.[5] A diagnosis of ankylosing spondylitis was also eliminated, because the New York criteria were not fulfilled.[6] This familial arthropathy could belong to the class of undifferentiated spondyloarthropathies proposed by Burns and Calin.[7] The spondyloarthropathies have in common a non-specific inflammation of the entheses, involving both the chondrified and the calcified parts. After a destructive phase, which causes bony erosion, repair takes the form of ossification.[8 9] An inherited abnormality in the collagen matrix of the enthese may predispose to destructive arthropathy and enthesopathic changes. Linkage analysis excluded COL2A1 as the disease causing locus in this family.[10] Further studies are needed to identify the genetic locus responsible for the disease.

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LETTERS TO THE EDITOR

HLA associations of systemic lupus erythematosus in Chinese from Singapore

A role for genetic factors in systemic lupus erythematosus (SLE) is strongly suggested by the substantial excess recurrence of the disease in monozygotic compared with dizygotic twins.[1] Genes within the major histocompatibility complex (MHC) contribute to SLE, but it has proved difficult to establish the precise locus(i) involved. Studying populations from diverse ethnic backgrounds can help to identify these loci for two reasons: first, there are substantial differences in gene frequencies (for example HLA) between different races; second, different MHC haplotypic combinations of alleles in different races can help to identify the primary relationships with disease, rather than those secondary to linkage disequilibrium. Previous studies in white populations have shown associations with HLA-DR3 and -DR2;[2 3] however, studies from south east Asia, while revealing a strong association with DR2 in Koreans[4] and Chinese from Hong Kong[5] and Malaysia,[6] did not reveal the association with DR3 observed in white subjects.

We studied HLA-DRB1 and -DQB1 alleles in 26 Chinese SLE patients (25 female) attending the National University Hospital in Singapore, and in 77 Chinese controls from the same area. All patients met four or more American Rheumatism Association criteria for SLE. The mean age was 36 years (range 20–64), and mean disease duration 7·1 years (range 1–20). Patients with any known non-Chinese ethnicity (Indians, Malayans, Europeans) were excluded. Renal involvement was present in 57% of the patients, arthritis in 46%, malar rash in 36%, central nervous system involvement in 21%, photosensitivity in 7·1%, and discoid lupus in 3·6%. Antinuclear antibodies were present in 96% of patients and 92% had dsDNA antibodies.

HLA-DRB1 alleles were assigned by polymerase chain reaction (PCR) amplification of genomic DNA probed with sequence specific oligonucleotides.[7] HLA-DQB1 alleles were typed by PCR using sequence specific primer pairs.[8] The statistical significance of differences between the groups was analysed using the χ^2 test.

The table shows the DR and DQ frequencies. There were non-significant increases in DR3, DR8, and DR9, but not in DR2. Furthermore, DQ2 and DQ*0601 were increased in the patients, but this was almost certainly due to linkage with DR3 and DR8, respectively. None of the DR or DQ antigens was associated with particular clinical manifestations of SLE.

Our data are interesting with respect to other published results from Asian populations. HLA-DR9, for instance, was found to be increased in Chinese SLE patients from Hong Kong[5] and Korea, in whom there was