Rheumatoid arthritis (RA) is a common autoimmune disease of unknown cause. The symptoms and signs of the disease are caused by a chronic inflammatory process in the synovial membrane. Extra-articular or systemic manifestations such as fever, anaemia, rheumatoid nodules, pleurisy may occur with considerable frequency. The clinical heterogeneity of RA is well known. More than 50% of patients have seriously progressive disease leading to joint destruction. In some cases extra-articular manifestations can be life-threatening. This illustrates the double aspect of the disease, articular and systemic. Although the pathogenesis is unknown, several reports provide evidence suggesting that both genetics and environmental factors determine host susceptibility to RA.

In Northern Europe and in the USA, most patients with RA express particular HLA-DRB1 alleles. These alleles share a very conserved 3rd hypervariable region, the 'shared epitope', which determines host susceptibility to RA. How the 'shared epitope' influences the development of RA is still unknown. Studies have shown that patients who express the 'shared epitope' have more severe disease than patients who do not. However, genetic differences exist among countries and between Europe and the USA. These differences may reflect different clinical expression and different outcome in these patients.

In 1984 studies from Ioannina, a small city in Northwest Greece, have shown that RA patients had a high frequency of Ro(SSA) antibodies in their sera and these patients experienced a high frequency of D-penicillamine (DP) side-effects. One year later the same investigators reported that Ro(SSA) positive RA patients were predominantly female, had high incidence of positive minor salivary gland biopsy compatible with Sjögren’s Syndrome (SS) and experienced a high frequency of DP side-effects. In 1987 another study by the same university centre in Greece showed that extra-articular manifestations in RA were observed in lower frequency compared to those reported by others.

To answer the question as to whether these Ro(SSA) positive patients represent an overlap between RA, SS or lupus these authors conducted a longitudinal study comparing 25 Ro(SSA) positive versus 50 Ro(SSA) negative RA patients. The major conclusions from this study were that 80% of all patients had features of erosive arthritis. The Ro(SSA) positive patients had more often features of secondary SS and once more these patients presented DP side-effects. Regarding the prevalence of secondary SS in Greek patients the same group of investigators showed that SS was common (31%), benign and subclinical, requiring specific testing for its diagnosis.

These clinical and serological differences observed in Greek RA patients prompted the investigators to conduct a comparative clinical study between Greek and British RA patients. For this reason 108 Greek and 107 British consecutive unselected RA patients, being followed-up at the Ioannina University Hospital and Guy’s Hospital London, respectively, were evaluated by the same investigator. The major conclusions from this study were that (a) British patients had more severe articular and extra-articular manifestations, (b) British patients had more severe joint damage on radiological examination, and, (c) Greek RA patients more frequently had features of SS manifestations and Ro(SSA) antibodies in their sera. Two years later, in 1994, another study coming from Spain compared 63 RA patients followed-up at the Alicante General Hospital.
Hospital, with 63 British RA patients followed-up at Guy's Hospital London, confirmed the Greek results that RA in Spain was milder with less extra-articular manifestations.

To clarify these clinical and serological differences observed between Greek and British patients we conducted an immunogenetic study. We examined HLA class II DNA polymorphism in 92 Greek RA patients and compared these findings with those of 84 healthy ethnically matched individuals. HLA-DRB polymorphism was characterized by restriction fragment length polymorphism (RFLP) and DRB subtypes were examined by polymerase chain reaction (PCR), amplification and oligonucleotide hybridization. Our results showed that RA in Greece is associated with the same HLA-DRβ alleles which confer susceptibility in Northern European Caucasians. However, whereas 83% of Northern European patients carry the HLA DRβ motif, this was found in only 43.5% of Greek RA patients. Thus, most patients with RA lack this putative HLA epitope and probably this reflects differences in disease expression in Greeks.[10, 11] Recently, another study from Southern France (Marseille) reported that despite the fact that 76% of RA patients express the 'shared epitope', most of them do not develop extraarticular manifestations. This may be caused by the low frequency of HLA-DRβ1 0401 allele found in this population.[11]

Finally, to examine whether HLA-DR4 is a severity marker for RA patients we evaluated 84 Greek RA patients. HLA-DR typing was performed by RFLPs and HLA-DR4 subtypes by PCR. Twenty-five percent of our patients were DR4+. There were no differences between the DR4+ and DR4- patients with respect to disease duration, severity of arthritis, functional and anatomical joint score. There were no statistical differences in the clinical manifestations among patients with different DR4 subtypes. Our results showed that HLA-DR4 is not a severity marker in Greek RA patients and indicate further differences in the clinical expression of RA observed in Greece.[12]

From these data we can conclude that in Southern Europe RA seems to be milder than in Northern Europe.[9, 11, 13] This may be because in Southern Europe many patients with RA do not express the HLA-DRβ1 allele that contains the 'shared epitope'. Further European studies between countries or between Europe and the USA may provide information regarding the role of genetics and/or the environment in the differences observed between RA in Southern and Northern European countries.

References

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22 Bold KA, Drosos AA, Tzioufas AG, Lancbury JS, Panayi GS, Moutsopoulos HM. Examination of HLA-DR4 as a severity marker for rheumatoid arthritis in Greek patients. Rheum Dis 1993; 52: 517-19.