Commentary

HLA-DRB1 genes and extraarticular rheumatoid arthritis

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Abstract

The factors that trigger the development of extraarticular features of rheumatoid arthritis (RA) are still unknown. HLA-DR alleles such as HLA-DR4 and HLA-DR1 are associated with the risk to develop RA. A large scale study from Sweden and the Mayo Clinic suggests that HLA-DR4, but not HLA-DR1, is associated with the risk to develop extraarticular RA.

Rheumatoid arthritis (RA), a systemic autoimmune condition, causes joint damage and sometimes extraarticular lesions (cutaneous vasculitis, neuropathy, Felty's syndrome, pericarditis, intersticial lung disease) that may be life threatening. The reason why extraarticular features will develop in rare RA patients is unknown.

In a previous issue of *Arthritis Research and Therapy*, Turesson and colleagues [1] analyse the influence of HLA-DR genes on the development of extraarticular RA in a series of 159 patients with extraarticular RA matched with 178 patients with purely articular RA.

HLA-DR genes are the principal genetic factor contributing to RA. HLA-DR alleles DRB1*0401, *0404, *0405 (serologically HLA-DR4), DRB1*0101,*0102 (HLA-DR1) and HLA-DRB1*1001 (HLA-DR10) are associated with RA [2]. HLA-DR genotypes (the two HLA-DRB1 genes expressed by any individual) determine the risk to develop RA. 'Double dose' genotypes such as DRB1*0401/DRB1*0404 carry very high risks to develop RA (it is very difficult to find healthy, RA free controls with the DRB1*0401/0404 genotype), whereas 'single dose' genotypes such as DRB1*0401/DR7 carry more limited risks [3].

The Turesson study includes patients with extraarticular RA defined by cutaneous vasculitis, neuropathy, Felty's syndrome, intersticial lung disease, pericarditis, pleuritis, scleritis, episcleritis and glomerulonephritis. It asks questions about HLA-DR alleles and HLA-DR genotypes and their association with extraarticular RA as a whole or with particular items included in extraarticular RA.

Its main findings are that shared epitope positive HLA-DR4 alleles (in this population, mostly HLA-DRB1*0401 and HLA-DRB1*0404) are associated with extraarticular RA globally, but that neither DRB1*0401 nor DRB1*0404 is associated with any particular clinical feature, except for HLA-DRB1*0401, which is associated with Felty's syndrome. When considering the influence of DRB1 genotypes, the findings are very similar. Genotypes containing two shared epitope positive DRB1*04 alleles (in most cases, DRB1*0404/0401, DRB1*0401/0401 and DRB1*0404/0404) are associated with extraarticular RA and the DRB1*0401/0401 genotype with Felty's syndrome.

The main strength of the Turesson study is its very large recruitment of patients with extraarticular RA and controls with articular RA, from Sweden and the Mayo Clinic.

In these two very homogeneous, very northern European populations, HLA-DRB1*0401 is overrepresented, with an allelic frequency that is almost three times that of DRB1*0404 and DRB1*01. Thus, the unique association of Felty's with DRB1*0401 might just reflect this. What is more striking is that DRB1*01, although it is more frequent in patients with purely articular RA (0.119) than DRB1*0404 (0.085), is not associated with extraarticular RA, and is not included in any of the genotypes associated with extraarticular RA. This finding is consistent with the rarity of extraarticular RA in southern Europe, where DRB1*01 is the most frequent RA associated allele [4]. However, it is very different from the only other study of similar size, a metaanalysis of 14 published studies of HLA-DRB1

RA = rheumatoid arthritis.

genotypes in RA vasculitis, including 129 patients from the US, Europe and Asia [5]. In this metaanalysis, three double dose genotypes were found associated with vasculitis, namely DRB1*0401/0401, DRB1*0401/0404 and DRB1*0401/0101 [5].

Conclusion

The Turesson study confirms that shared epitope positive DR4 alleles and double dose shared epitope positive DR4 genotypes are associated with extraarticular RA in populations of northern European descent.

What remains to be done is a similar study, comparing cohorts of patients with extraarticular RA and purely articular RA, in a population where DR4 and DR1 are more equally represented.

This could be the subject of a very exciting European project.

Competing interests

The author(s) declare that they have no competing interests.

References

1. Turesson C, Schaid DJ, Weyand CM, Jacobsson LTH, Goronzy JJ, Petersson IF, Sturfelt G, Nyhäll-Wåhlin BM, Truedsson L, Dechant SA, Matteson EL: **The impact of *HLA-DRB1* genes on extra-articular disease manifestations in rheumatoid arthritis.** *Arthritis Res Therapy* 2005, **7:**R1386-R1393.
2. Gregersen PK, Silver J, Winchester RJ: **The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis.** *Arthritis Rheum* 1987, **30:**1205-1213.
3. Reviron D, Perdriger A, Toussirot E, Wendling D, Balandraud N Guis S, Semama G, Tiberghien P, Mercier P, Roudier J: **Influence of shared epitope negative alleles on genetic susceptibility to rheumatoid arthritis.** *Arthritis Rheum* 2001, **44:**535-540.
4. Benazet JF, Reviron D, Mercier P, Roux H, Roudier J: **HLA-DRB1 alleles associated with rheumatoid arthritis in southern France. Absence of extraarticular disease despite expression of the shared epitope.** *J Rheumatol* 1995, **22:**607-610.
5. Gorman JD, David-Vaudey E, Pai M, Lum R, Criswell LA: **Particular HLA-DRB1 shared epitope genotypes are strongly associated with rheumatoid vasculitis.** *Arthritis Rheum* 2004, **50:** 3476-3484.