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## Extended HLA haplotypes and RA susceptibility

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## Keywords

Haplotypes, HLA, MIB, microsatellites, rheumatoid arthritis

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## Context

Many studies have shown that susceptibility to rheumatoid arthritis (RA) is associated with HLA-DRB1 alleles which encode similar amino acid sequences (QKRAA, QRRAA or RRRAA) in the third hypervariable region of the HLA-DR ? molecule. This provides the basis for the shared epitope (SE) hypothesis. An alternative RA protection (RAP) hypothesis has been proposed in which susceptibility to RA is conferred by HLA-DQ alleles (DQB1\*03-DQA1\*03 and DQB1\*0501-DQA1\*01) while protection is provided by DRB1 alleles encoding a DERAA motif instead of the SE. Other loci within the MHC may contribute to the linkage of this region with RA susceptibility, and some studies suggest that an extended MHC haplotype predisposes to RA. The aim of this study was to examine the possible contribution of genes other than DQ and DR to the association between HLA and RA.

## Significant findings

The allele distribution of six microsatellites (D6S1014, D6S2673, D6STNFa, MIB, C1-2-5, and C1-3-2) located in the telomeric part of the HLA region was examined in RA patients and controls. Nineteen conserved microsatellite clusters (c1-c19) were identified within the controls. Twelve of these clusters were in linkage disequilibrium with DQB1-DRB1 haplotypes and corresponded to previously described ancestral haplotypes. The c1 haplotype contained an allele (MIB\*350) which was associated with RA when analysed as part of a three point cluster at adjacent loci, i.e. within cluster D6S273\*139-D6STNFa\*99-MIB\*350, D6STNFa\*99-MIB\*350-C1-2-5\*196, or MIB\*350-C1-2-5\*196-C1-3-2\*354. This association with RA at the MIB locus was independent of RA-predisposing DQB1-DRB1 haplotypes. The authors conclude that the telomeric part of the HLA region contains a genetic factor which predisposes to RA independently of the HLA class II genes; any locus between that encoding TNF-a and the end of the chromosome could be regarded as a candidate.

# Comments

This study provides further evidence that genes outside the MHC class II region may contribute to RA susceptibility. The association of the microsatellite cluster c1 with predisposition to RA is consistent with previous work by Singal and colleagues (see Additional information) who demonstrated an association between the microsatellite D6S273\*139 and RA independent of HLA class II. These studies add a further level of complexity to our understanding of the association between RA and the HLA region, and underline the difficulties in identifying the genetic factors responsible. Further large population studies which include more microsatellite loci may help to narrow down the HLA region to the likely gene(s) of interest.

## Methods

Case-control study, PCR, DNA sequencing

## Additional information

Singal DP, Li J, Lei K: **D6S273 microsatellite polymorphism and susceptibility to rheumatoid arthritis.** *Tissue Antigens* 1998, **52**:353-358 ([http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=9820598&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9820598&dopt=Abstract)>PubMed abstract</a>).

Singal DP, Li J, Lei K: **Genetics of rheumatoid arthritis (RA): Two separate regions in the major histocompatibility complex contributes to susceptibility to RA.** *Immunol Lett* 1999, **69**:301-306 ([http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=10528792&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10528792&dopt=Abstract) target="---PubMed abstract---/a---").

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