Lack of influence of non-inherited maternal HLA-DR alleles on susceptibility to rheumatoid arthritis

Alan J Silman, Elaine M Hay, Jane Worthington, Wendy Thomson, Lynne Pepper, Jude Davidson, Phil A Dyer, William E R Ollier

Abstract

Objective—To reproduce findings from previous reports that non-inherited maternal HLA class II antigens might contribute to rheumatoid arthritis (RA) susceptibility in the offspring.

Methods—Families were recruited from the Arthritis and Rheumatism Council's National Repository of RA families and HLA-DRB1 alleles were examined in these individuals and their first degree relatives using DNA typing methods.

Results—There was no evidence of an increase in either non-inherited maternal HLA-DR4 or the HLA-DRB1 shared epitope as a whole compared with the frequency expected using the non-inherited paternal antigens as controls.

Conclusions—The numbers of probands who were shared epitope negative were small, but we are unable to confirm in these families the findings that non-inherited maternal HLA contributes an additional susceptibility factor to rheumatoid arthritis.

Subjects and methods

The subjects for this analysis came from the Arthritis and Rheumatism Council's National Repository of RA families. All affected individuals were interviewed and examined using a standardised protocol, blood was taken for determination of rheumatoid factor (RF), and past data on RF seropositivity and radiological erosions were sought. Only those individuals who satisfied the 1987 American College of Rheumatology criteria modified for genetic studies were included; in all, they comprised 74 individuals from 39 families.

DNA was extracted from samples of all these individuals and their first degree relatives and polymerase chain reaction based oligonucleotide typing was undertaken for HLA-DRB1. HLA-DRB1*04 subtyping was undertaken using an amplification refractory mutation system restriction length fragment polymorphism. For the purposes of this analysis, all samples were categorised as being (i) DR4 positive/negative (to permit comparison with the earlier study) and (ii) shared epitope positive/negative depending on the presence of one of the following alleles: HLA-DRB1*0101, *0401, *0404, *0405, *0408. No other DRB1*01 subtypes were seen in this population. Families were eligible for inclusion in this analysis if they had at least one affected offspring and parental HLA haplotypes could be unambiguously assigned based on the available relatives. The segregation of the parental haplotypes in the affected offspring permitted identification of both the inherited and non-inherited haplotypes.

The analysis was undertaken in the following manner. First, the frequencies of NIMA bearing (i) DR4 and (ii) any shared epitope allele were compared with those frequencies in
of type NIMA NIPA. All (n = 65) (n = 71) with NIPA.

NIPA of the NIMA of the risk of (with NIMAs of the was no positive, = CI the NIMA father was restricting consideration if unweighted from NIMA. There involvement had the remainder of the study. ‘0

differential involvement of the NIMA probands. There were two affected siblings, the NIMA and NIPA score was multiplied by 0.5, so that the total contribution to the overall NIMA and NIPA frequencies from any one mother or father was 1. Third, the analysis was repeated restricting consideration to those probands who were shared epitope heterozygote on the basis that the homozygotes did not need any involvement from NIMA. There were too few probands who were shared epitope negative for useful separate analysis.

Results

Data were available from 65 NIMA and 71 NIPA of the 74 probands (table). Of the 39 families, nine had a single affected proband, three had three affected siblings and the remainder had an affected sibling pair. In all, 64 (86%) of the probands were HLA-DR4 positive, of whom 27 were DR4 homozygous. There was no evidence of an increase in NIMA carrying either DR4 or the shared epitope compared with NIPA, in either the weighted or the unweighted analysis. Further, there was no such increase when the analysis was restricted to only those probands who were shared epitope heterozygous. There were too few who were DR4 negative/shared epitope negative for definitive comment, but only one of the NIMAs of the DR4 negative probands carried a DRB1*04 allele.

Discussion

Unlike the authors of an earlier report,10 we were unable to confirm an increase in DR4-bearing alleles in the NIMA of RA probands, whatever the DR4 status of the proband. Given the small numbers of RA probands who were HLA-DR4 negative, it remains possible that, in such patients, DR4-bearing NIMA could contribute to disease susceptibility. There is, however, one major methodological difference between the two studies. The current study utilised the families collected for a multicase family study and the majority of the families had at least two affected siblings. Given the association between RA and HLA-DR, it is hardly surprising that in such families there was a high frequency of DR4. Indeed, it was expected that both the mothers and fathers of such multiple affected sibships would have an increased frequency of these susceptibility alleles. Nevertheless, more than 67% of the NIMA did not carry HLA-DR4 and more than half were shared epitope negative. These proportions were smaller than those observed in the NIPA collected from the same probands. The hypothesis being addressed was that both inherited and non-inherited maternal alleles are important in leading to disease susceptibility, whereas it is only the inherited paternal ones that are of relevance. There was no evidence from our analysis to support this.

There may, indeed, be genetic heterogeneity, with different genetic contributions to sporadic and ‘familial’ RA as has been previously proposed.13 The only difference reported though, is the increase in DR416 which would be expected from the known association between HLA and RA. Others have found no such excess in familial disease.17 Thus it seems unlikely that the failure to find an effect of NIMA in these families is a result of the relative lack of importance of HLA in explaining disease susceptibility. The converse is more likely, given the high level of homozygosity in these cases.

We acknowledge the financial support of the Arthritis and Rheumatism Council who established the Repository with a special grant. We are also grateful to support from the European Union’s Concerted Action on Immunotherapy. We are most grateful to our rheumatology colleagues for notifying us of families and providing clinical data.

Lack of influence of non-inherited maternal antigens on RA susceptibility


Lack of influence of non-inherited maternal HLA-DR alleles on susceptibility to rheumatoid arthritis.

A J Silman, E M Hay, J Worthington, W Thomson, L Pepper, J Davidson, P A Dyer and W E Ollier

Ann Rheum Dis 1995 54: 311-313
doi: 10.1136/ard.54.4.311

Updated information and services can be found at:
http://ard.bmj.com/content/54/4/311

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/