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Increase of HLA-DRB1*0408 and -DQB1*0301 in HLA-B27 positive reactive arthritis

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Abstract

***Objective*—To study HLA class II association in reactive arthritis.**

***Methods*—63 patients with reactive arthritis and 46 with rheumatoid arthritis were included in the study. HLA-DR alleles were determined by using a sequence specific PCR method. Oligonucleotide hybridisation was used for definition of DRB1*04 subtypes and DQB1 alleles. HLA-B27 was determined by standard microcytotoxity test or by PCR. HLA-B27 subtyping was made by sequencing.**

***Results*—46 (73%) of 63 patients with reactive arthritis were HLA-B27 positive and 24 (38%) were HLA-DRB1*04 positive. When haplotypes were inferred according to the known associations between DRB1 and DQB1 alleles, the frequency of DRB1*04-DQB1*0301 haplotype was found to be 13% (12/92) in HLA-B27 positive reactive arthritis patients, in contrast to 0% in HLA-B27 negative reactive arthritis (P = 0.04) and 1% in random controls (P = 0.0009). However, this combination was also found in 5% of 84 HLA-B27 positive control haplotypes, showing a linkage disequilibrium between B27 and this particular class II haplotype. HLA-DRB1*0408 subtype was found in 8/24 (33%) of the HLA-DRB1*04 alleles in patients with reactive arthritis, accounting for most DQB1*0301 haplotypes, but only in 5/55 (9%) of the DRB1*04 alleles in random controls (P = 0.017). All reactive arthritis patients with this subtype were positive for HLA-B27. DRB1*04-DQB1*0302 haplotype was increased in patients with rheumatoid arthritis (28/92, 30%) compared with reactive arthritis (12/126, 10%) or with the controls (12/100, 12%; P = 0.003). HLA-B*2705 was by far the dominant B27 subtype both in reactive arthritis patients with the particular DRB1*0408-DQB1*0301 haplotype and in controls. It was found in 11 out of 12 DR analysed patients, as well as in 10 out of 11 randomly selected B27 positive controls.**

***Conclusions*—Although no single class II allele was found to be increased among patients with reactive arthritis, HLA-B27, DRB1*0408, and DQB1*0301 might exert a haplotypic effect in the pathogenesis of reactive arthritis, or they may be markers of a subset of B27 haplotypes conferring susceptibility.**

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Human leucocyte antigen (HLA)-B27 is associated with reactive arthritis but the mechanisms behind the association remain unclear.[1] A role for CD8 positive cytotoxic T cells recognising a cross reactive peptide with a specific affinity to HLA-B27 has been suggested.[2 3] Generation of cytotoxic effector cells is, however, a late event in the course of the immune response and dependent on the activation of CD4 positive helper cells recognising their nominal antigen in context of class II molecules. Therefore, class II molecules might be involved, in addition to HLA-B27, in the pathogenesis of reactive arthritis. However, the role of B27 as a class I restriction molecule in the pathogenesis of this type of arthritis has not been shown. The arthritis developing in B27 transgenic rat or mouse[4 5] does not demand the expression of functional class I molecule. It has recently been proposed that autologous peptides critical in triggering the disease might be derived from B27 molecule and be presented by class II molecules.[6] Elution studies have shown that peptides derived from HLA molecules themselves constitute a major proportion of autologous peptides occupying the peptide binding sites.[7] The effect of class II polymorphism in transgenic rat model has not been studied.

Reactive arthritis shares several clinical characteristics with rheumatoid arthritis, which has a well known class II association,[8] but reactive arthritis is unique among inflammatory arthritides because specific microbial triggers have been identified. Patients with rheumatoid arthritis were included as an additional study group because the association of rheumatoid arthritis to the particular DR-DQ haplotypes investigated is still incompletely characterised.

Methods

PATIENTS

Sixty three patients of Finnish ethnicity with reactive arthritis were included in this study. In addition to clinical indices, the diagnosis of reactive arthritis was verified by stool culture, serological analysis of circulating antibodies, or by chlamydia antigen detection.[9] Yersinia infection was the trigger of reactive arthritis in 41 patients, salmonella in 16, and chlamydia in six. Forty six Finnish patients with rheumatoid arthritis diagnosed according to the criteria of the American College of Rheumatology (formerly, the American Rheumatism Association)[10] and 50 healthy blood donors from the same geographical area were included as reference groups. For the analysis of DR4 subtypes, 42 additional control haplotypes were

included, which were found in the families of patients with insulin dependent diabetes mellitus. All these haplotypes were found only in healthy family members (Reijonen H, *et al*, submitted) and were not transmitted to diabetic family members. They can thus be considered as representative haplotypes for background population. Similarly 84 B27 positive haplotypes found in the same families were analysed for DR4 subtypes and DQB1*03 alleles to confirm the allelic associations in the control population. Haplotypes were inferred according to known associations between DRB1 and DQB1 alleles.

HLA TYPING

DNA was extracted from anticoagulated blood samples using a salting out method.[11] HLA-DRB1 alleles were determined by sequence specific polymerase chain reaction (PCR) amplification.[12] For DRB1*04 subtyping, DRB1*04 sequences were specifically amplified using two different primer pairs.[12] The one primer pair amplified DRB1*0401, 0405, 0407, 0408, and 0409 alleles, whereas the other amplified 0402, 0403, 0404, 0406, 0410, and 0411 alleles. The allele specificity was further assessed by dot blot hybridisation of the amplification product using ^{32}P labelled sequence specific oligonucleotide probes.[13] Final results were obtained by combining information from the specific amplification and dot blot hybridisation. Thus both heterozygotes and homozygotes could be detected. Control samples for DRB1*04 subtyping were obtained from the FRC Blood Transfusion Service Tissue Typing Laboratory (Helsinki, Finland). HLA-DQB1 alleles were defined using conventional dot blot hybridisation assay.[14 15]

HLA-B27 typing was made by the standard microcytotoxicity test using flow cytometry and monoclonal antibodies (HLA-B27 kit, Becton Dickinson Immunocytometry Systems, San Jose, California, USA) or PCR amplification.[16 17] HLA-B27 subtyping was made by sequencing the PCR products amplified from polymorphic parts of exon 2 and exon 3 as described by Dominquez *et al*.[16] HLA-B27 specific PCR products were cut from agarose after electrophoresis and purified from agarose by β agarase (β-Agarase I, New England Biolabs, Beverly, MA, USA). Sequencing was made using ABI PRISM^{tm} Dye Terminator Ready Reaction kit and 373 DNA Sequencer (Applied Biosystems, The Perkin Elmer Corporation, Foster City, California, USA).

STATISTICS

The frequency of inferred HLA haplotypes and alleles in different groups was compared using the χ^2 test with continuity correction and Fischer's exact test when appropriate.

Results

No single DRB1 or DQB1 allele was increased among patients with reactive arthritis, but DR4 was found to be increased among rheumatoid arthritis patients (35/92, 38%) compared to controls (13/100, 13%; P = 0.0001, odds ratio 4.1, 95% confidence interval 1.9 to 9.01). Table 1 lists the frequencies of different HLA-DRB1-DQB1 haplotypes in 63 reactive arthritis patients, 46 rheumatoid arthritis patients, and 50 healthy controls. Haplotypes were deduced according to the known associations between DRB1 and DQB1 alleles. Nine unconventional combinations were observed, which are not previously known combinations of HLA-DRB1 and HLA-DQB1 alleles. These were not confirmed but are included as "others", as also are two untypable specimens, for which either DRB1 or DQB1 typing failed. Twelve (10%) of the DRB1-DQB1 haplotypes in reactive arthritis patients were DRB1*04-DQB1*0301 compared to only one found within 100 random control haplotypes (P = 0.0074, odds ratio 10.4, 95% confidence interval 1.4 to 56.2; table 1). Instead, the DRB1*04-DQB1*0302 haplotype was increased in patients with rheumatoid arthritis (P = 0.003, odds ratio 3.2, 95% confidence interval 1.4 to 7.3; table 1). However, neither of these differences is significant if multiplied by the number of comparisons made. The DRB1*04-DQB1*0301 haplotype was observed only in HLA-B27 positive reactive arthritis patients and not among the B27 negative ones (table 2). The difference between B27 positive patients and controls was significant even after correction (P = 0.0009, Pc = 0.013). HLA-DRB1*0408 subtype of DRB1*04 was found to be increased among DRB1*04 haplotypes of reactive arthritis patients compared to DRB1*04 haplotypes in rheumatoid arthritis and controls (P = 0.017, odds ratio 5.0, 95% confidence interval 1.2 to 21.0; table 3). It was as common as subtype DRB1*0401. No significant differences were found in the subtype distribution between rheumatoid arthritis patients and controls. All reactive arthritis patients with DRB1*0408 were also positive for HLA-B27, and all but one had the DQB1*0301 allele. When 84 B27 positive control haplotypes were analysed, four (5%) were DRB1*04-DQB1*0301. The DRB1*0408 subtype was further found in three of these. These figures remain clearly lower than the number of DRB1*04-DQB1*0301 haplotypes in B27 positive reactive arthritis patients, although exact haplotypic analysis was not possible in this patient group. When genotypes were analysed, no specific genotypic combinations of haplotypes were found to be associated with either reactive arthritis or rheumatoid arthritis. HLA-B27 subtype analysis was performed for reactive arthritis patients with DRB1*04-DQB1*0301 haplotype and for 11 random controls. Eleven out of 12 B27 subtypes were found to be B*2705 in reactive arthritis patients and 10 out of 11 in control haplotypes. One B*2702 subtype was found in both groups studied.

Discussion

In this study we showed an increased frequency of DRB1*04-DQB1*0301 haplotype in reactive arthritis, although the majority

Table 1 Frequency of different HLA-DRB1-DQB1 haplotypes in ReA, RA and controls

DRB1-DQB1* haplotype	ReA		RA		Controls	
	n	(%)	n	(%)	n	(%)
01-0501	24	19	11	12	24	24
015/016-0602	13	10	6	7	9	9
03-0201	12	10	11	12	10	10
04-0301	12*	10	5	5	1	1
04-0302	12	10	28†	30	12	12
011/012-0301	8	6	7	8	11	11
013/014-0301	0	0	2	2	2	2
013/014-0503	0	0	1	1	1	1
013/014-0603	7	6	1	1	6	6
013/014-0604	4	3	5	5	2	2
07-0201	6	5	1	1	6	6
07-0303	1	1	0	0	1	1
08-04	18	14	5	5	9	9
09-0301	1	1	0	0	0	0
09-0303	3	2	3	3	4	4
010-0501	0	0	1	1	1	1
Others	5	4	5	5	1	1
Total number of chromosomes sampled	126		92		100	

* P = 0.0074 *v* controls; † P = 0.003 *v* controls.
ReA, reactive arthritis; RA, rheumatoid arthritis.

Table 2 Frequency of HLA-DRB1-DQB1 haplotypes in HLA-B27+ and HLA-B27− ReA patients and controls*

DRB1-DQB1 haplotype	ReA				Controls	
	HLA-B27+ patients		HLA-B27− patients			
	n	(%)	n	(%)	n	(%)
01-0501	18	20	6	18	24	24
015/016-0602	12	13	1	3	9	9
03-0201	8	9	4	12	10	10
04-0301	12*	13	0	0	1	1
04-0302	10	11	2	6	12	12
011/012-0301	3	3	5	15	11	11
013/014-0301	0	0	0	0	2	2
013/014-0503	0	0	0	0	1	1
013/014-0603	5	5	2	6	6	6
013/014-0604	1	1	3	9	2	2
07-0201	3	3	3	9	6	6
07-0303	1	1	0	0	1	1
08-04	13	14	5	15	9	9
09-0301	1	1	0	0	0	0
09-0303	2	2	1	3	4	4
010-0501	0	0	0	0	1	1
Others	3	3	2	6	1	1
Total number of chromosomes sampled	92		34		100	

* P = 0.0009 *v* controls, P = 0.04 *v* B27 negative ReA patients.
ReA, reactive arthritis.

of B27 positive cases did not carry this specific haplotype. No single triggering agent was found in cases with DRB1*04-DQB1*0301: the arthritis was triggered by yersinia in six and by salmonella in five cases, but the haplotype was also found in a subject with chlamydia triggered reactive arthritis.

*Table 3 Distribution of DRB1*04 subtypes in total DR4 bearing haplotypes in patients and controls*

DRB1 allele	DR4+ ReA		DR4+ RA		DR4+ controls[a]	
	n	(%)	n	(%)	n	(%)
0401	8	33	15	43	24	44
0402	0	0	0	0	0	0
0403	1	4	0	0	3	5
0404	7	29	14	40	23	42
0405	0	0	0	0	0	0
0408	8*	33	6	17	5	9
Total	24		35		55	

* P = 0.017 *v* controls.
[a] Random controls + DIME controls; ReA, reactive arthritis; RA, rheumatoid arthritis.

Class II association has not been demonstrated in reactive arthritis, although in juvenile and adult ankylosing spondylitis a contribution by class II genes has been proposed.[18 19] In reactive arthritis a few such studies have been carried out,[20–22] but none using methods of molecular biology to define DRB1-DQB1 haplotypes. The genetic characteristics of our population may also have made detection of the association more easy. The actual DRB1*04-DQB1*0301 haplotype is rare in Finland and Scandinavian countries compared to DRB1*04-DQB1*0302 which in these countries is the most common DRB1*04 haplotype.[23] The latter haplotype was also increased among rheumatoid arthritis patients, confirming our earlier results from Finland,[24] although some patients were positive for the DRB1*04-DQB1*0301 haplotype. HLA-B27 positive rheumatoid arthritis patients often have this haplotype together with the Dw14.[25] HLA-Dw14 has been shown to represent both DRB1*0404 and DRB1*0408 alleles[14]; thus the specific B27 positive haplotype in both reactive arthritis and rheumatoid arthritis may be the same. This haplotype seems to represent an extended haplotype characteristic to the Finnish population. When combining B27 and DR4 alleles it is not unexpected that it is found increased both in reactive arthritis and in rheumatoid arthritis. In both diseases the particular haplotype may also confer other disease risk or severity associated factors. HLA-DR4 associated DQ7 or by allelic terminology DQB1*0301 allele has also been reported to be associated with the most severe cases of rheumatoid arthritis[26] and Felty syndrome.[27 28]

No significant differences between DRB1*04 subtypes in rheumatoid arthritis patients and the controls positive for DRB1*04 were seen, but alleles with rheumatoid arthritis associated "shared epitope"[8] were also present in the vast majority of control haplotypes. In fact, only three haplotypes with DRB1*0403 were detected in the control group and none in rheumatoid arthritis patients.

The association of DRB1-DQB1 haplotypes with susceptibility to reactive arthritis might reflect an interplay of class I and class II molecules in the pathogenesis of this disease, as has also been suggested in rheumatoid arthritis.[29] Such an interaction is supported by the finding that the specific class II haplotype was associated only with B27 positive disease and no class II association was observed in our study of HLA-B27 negative patients with reactive arthritis either.[30] However, the lack of any genotypic effect is against this hypothesis. The observed haplotypic association may be caused by genes other than class II alleles themselves. HLA-DRB1*04 occurs in 28% of normal B27 positive Finnish haplotypes,[25] and DRB1*0408 together with DRB1*0404 are the DRB1*04 subtypes commonly associated with B27 in the Finnish population.[31 32] In the two latter studies, HLA-DQB1 specificity carried by these haplotypes was not described. Although the increased haplotype may thus be only one of many associated with B27 in the normal population, it probably is not just secondarily

increased due to increase of B27; DRB1 alleles other than DRB1*04, such as DRB1*01, DRB1*11-12, and DRB1*08—commonly associated with B27 in the normal population[25]—were not found to be increased. Furthermore, this haplotype was still found to be increased in reactive arthritis patients compared to 84 B27 positive control haplotypes. The DRB1*04-DQB1-0301 haplotype in reactive arthritis patients was associated with the common B*2705 allele in all but one case; 10 of 11 random cases were also of this subtype, which represents the most common B27 subtype in Caucasian populations.[33] Thus it seems that the increase of the particular class II alleles in reactive arthritis is not secondary to variations in B27 subtypes.

Gene alleles of TAP1 or TAP2 gene loci have also been reported to be associated with a subtype of ankylosing spondylitis[34] or Reiter syndrome,[35] even though a recent study suggests that TAP polymorphisms with functional consequences only occur in the rat.[36] Nevertheless, the gene region between HLA-DP and HLA-DQ contains several loci important for peptide processing and intracellular transport, and an interactive effect with class I alleles is feasible. Therefore the final nature and role of genes associated with reactive arthritis within the HLA region still remains unresolved, and further multi-loci analyses are needed.

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