MICA Rather Than MICB, TNFA, or HLA-DRB1 Is Associated with Susceptibility to Psoriatic Arthritis

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ABSTRACT. ***Objective***. To analyze the genetic contribution of HLA in development of psoriatic arthritis (PsA) and to study whether MICA is primarily associated with PsA or whether its association is secondary to linkage disequilibrium with centromeric genes, such as MICB, TNFA, or HLA-DRB1.

Methods. DNA samples from 81 Spanish patients with PsA and 110 healthy controls were examined by polymerase chain reaction (PCR) sequence-specific primers to type HLA-Cw and HLA-DRB1, PCR sequence-specific oligonucleotides to determine HLA-B, and PCR restriction fragment length polymorphism for tumor necrosis factor-α promoter polymorphisms at positions –238 and –308. Analysis of microsatellite polymorphisms in the transmembrane region of MICA and in intron 1 of MICB was also carried out.

Results. HLA-Cw*0602 was significantly increased in PsA [60% vs 17%; $p_c < 0.00002$, OR 7.33, etiological fraction (EF) 0.52]. MICA-A9 (60% vs 30%; $p_c = 0.0002$, OR 3.57, EF 0.43) and the microsatellite MICB-CA-22 allele (23% vs 7%; $p_c = 0.028$, OR 3.9, EF 0.17) were also significantly increased in PsA. MICA-A9 was in linkage disequilibrium with MICB-CA-22 ($\Delta = 0.6$). The association of MICA-A9 was independent of MICB-CA-22 and Cw*0602, since it was also associated in MICB-CA-22 negative ($p_c = 0.0015$, OR 2.96, EF 0.34) and in Cw*0602 negative patients ($p_c = 0.034$, OR 2.83, EF 0.34). TNFA and DRB1 alleles were not significantly associated with PsA.

Conclusion. Cw*0602 and MICA-A9 appear to be the strongest genetic susceptibility factors for PsA. However, MICA-A9 was associated independently of Cw6. HLA-B alleles and MICB-CA22 are associated secondarily to linkage with MICA. TNFA and HLA-DRB1 were not associated with PsA susceptibility, and our data suggest that their reported association may only reflect the linkage disequilibrium with MICA-A9 among the different populations studied. (J Rheumatol 2002; 29:973–8)

Key Indexing Terms:
PSORIASIS ARTHRITIS MICA MICB HLA

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that occurs in 10–40% of psoriatic patients[1,2]. Convincing evidence of a genetic basis for both psoriasis and PsA exists. Part of this genetic predisposition is due to genes within the major histocompatibility complex (MHC)[3-10]. Psoriasis and PsA are mainly associated with HLA-Cw*0602 (Cw6). HLA-B13, B37, and B57 have been associated with psoriasis; however, their association is secondary to linkage disequilibrium with Cw6. We and other groups have recently reported that the susceptibility locus of psoriasis vulgaris (PSORS1) is located in a region telomeric to the HLA-C gene, and the association of Cw6 is also secondary to linkage disequilibrium with this locus[11-13]. Other HLA alleles have been classically associated with various forms of arthritis that appear to be independent of the presence of psoriatic skin lesions. Thus, HLA-B27 is associated with back involvement, while HLA-B38 and B39 are associated with PsA patients with peripheral polyarthritis[9,10].

We recently reported that a polymorphism of MICA (MHC class I chain related gene A), called MICA-A9, is associated with arthritis in patients with PsA[14,15]. MICA-A9 is not associated with psoriasis vulgaris without arthritis in our population, suggesting that MICA-A9 is associated with the arthritis itself. This gene is located centromeric to the HLA-B locus in the MHC class I region[16]. B38, B39, and B57 are in linkage disequilibrium with MICA-A9 polymorphism. B38 and B39 are not in linkage disequilibrium with Cw6 and their association to PsA is probably secondary to MICA-A9.

The possibility clearly exists that MICA itself is not the primary locus responsible for disease susceptibility and its association with PsA may be secondary to linkage disequilibrium with a nearby gene. In agreement, several studies have reported the association of several loci located

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centromeric to MICA, such as TNFA or HLA-DRB1, with PsA. Tumor necrosis factor-α is an inflammatory cytokine considered to be an important mediator in the development of psoriasis. Some studies have reported the association of TNFA promoter polymorphisms –238A and PsA[17]. Similarly, associations of DR7 with both psoriasis and PsA[8,9,18] or DR4 with patients who develop polyarticular symmetrical polyarthritis have also been reported[19]. Additionally, new MHC genes, such as MICB, have recently been described[16]. MICB belongs to the family of MHC class I chain related genes that are expressed in fibroblasts and epithelial cells[20]. MICB is the nearest gene located centromeric to MICA and linkage disequilibrium with it has recently been reported[21]. The linkage disequilibrium between MICB and MICA implies that the disease associations assumed to be associated with MICA should be analyzed for their association with MICB.

To elucidate whether MICA is associated with PsA or whether it is secondary to linkage disequilibrium with a nearby gene, we analyzed the polymorphism of MICB, TNF-α, and HLA-DRB1, all of which are located centromeric to MICA gene, and the polymorphism of HLA-B, which is the nearest gene located telomeric to MICA. Information on these polymorphic loci may be useful to clarify the genetic contribution of HLA in development of PsA.

MATERIALS AND METHODS

Patients and HLA typing. Eighty-one patients diagnosed in accord with the Moll and Wright criteria[22] were studied; 65 patients were previously reported[14] and 16 additional patients were obtained from a larger population with PsA[23]. These patients had been controlled since 1981 at the Rheumatology Unit, Hospital Central de Asturias, Oviedo, Spain. The mean age of the patients with arthritis was 48 ± 13 years; 49 were men and 32 women. The average age at onset of psoriasis was 31 ± 11 years and the mean age at presentation of arthritis was 36 ± 12 years. The duration of arthritis was 14 ± 7 years. According to clinical and radiological characteristics, these patients were divided into disease subsets[23]: 32 with oligoarthritis, 18 with polyarthritis, and 31 with spondyloarthritis. Typing was also performed on a control population of 110 random ethnically and geographically matched blood donors. HLA-B typing was carried out using the Dynal RELI™ SSO HLA-B test following the manufacturer's instructions. HLA-Cw and HLA-DRB1 were typed by polymerase chain reaction (PCR) sequence-specific primer[24,25].

Triplet repeat polymorphism in the transmembrane region of the MICA gene. For the analysis of microsatellite repeat polymorphism in the MICA gene, PCR was carried out using primers labelled at the 5' end with the fluorescent reagent Cy5. The primers flanking the TM region: sense MICA 5'-ACATTCCATGTTTCTGCTGTTG (MICA located 33 bp 3'- of exon 5) and the antisense primer 5'-TCACCTGGACCCTCTGCAG (MICA exon/intron 5 boundary region). Allele designation was based on the number of repeat units present in the PCR products. Fragment sizes were determined automatically using ALF express II (Amershan Pharmacia Biotech, Uppsala, Sweden). Four distinct alleles consisting of CGT repetitions were designated as A4 (104 bp), A5 (107 bp), A6 (110 bp), and A9 (119 bp). One additional A5 (A5.1) with one nucleotide insertion (G) was also detected (108 bp).

MICB microsatellite analysis. For MICB genotyping, a dinucleotide microsatellite polymorphism in its first intron was analyzed by PCR. The primers were: 5'-AAATGGGCAAGACTT CAATGGC-3' and 5'-CTAC-CTCCTTGCCAAACTTGCTGTTTGTG-3'. PCR was carried out using primers labelled at the 5' end with the fluorescent reagent Cy5, and the number of CA/TG repeats in the intron 1 of the MICB gene was determined using the ALF express II. For the MICB gene polymorphism, 13 alleles were designated as MICB-CA 14–28 according to the number of CA/GT repeats in the intron 1[26].

TNF-α promoter polymorphism. The polymorphisms at positions –308 and –238 in the promoter region of TNF-α were analyzed by PCR-double restriction fragment length polymorphism with amplification-created restriction sites (ACRS)[27]. This method was developed to detect the G to A transition at positions –308.1(G)/308.2(A) and –238.1(G)/238.2(A). The distribution of the –308 and –238 TNF-α genotypes was analyzed in patients with PsA and compared with 110 Spanish matched controls.

Statistical analysis. The differences between the frequencies in the populations were assessed using the chi-square test with Yates' correction. Allelic and haplotypic frequencies were calculated by direct counting. The p values (p_c) were corrected by multiplying by the number of comparisons at every locus. The odds ratio (OR) was calculated by the cross-product ratio[28]. The potential influence of each marker was estimated by the etiological fraction (EF), which indicates the proportion of disease cases among the total population that is attributable to one allele when OR > 1[29]. The extent of linkage disequilibrium between 2 loci is expressed as the observed disequilibrium value (Δ), that is, a proportion of the theoretical maximum disequilibrium value (Δ_{max}) achievable for this combination of alleles[30]. The Δ was calculated using the formula:

$$\Delta = \Delta/\Delta_{max} = Pab - (Pa \cdot Pb)/Pa \cdot (1 - Pb)$$

Since familial studies were not carried out, haplotype assignments were as stated above. Percentages of inclusion (% relative frequency) were used for the most probable haplotype assignments.

RESULTS

HLA typing. HLA analysis was performed using PCR in 81 Spanish patients with PsA and 110 controls (Table 1). HLA typing revealed that Cw*0602 was significantly increased in patients with PsA (60% vs 17%; $p_c < 0.00002$, OR 7.33, EF 0.52). HLA-B38 (11% vs 2%), HLA-B39 (7% vs 1%), and HLA-B57 (14% vs 6%) were also increased in these patients, but not significantly.

Table 1. Distribution of HLA alleles reported to be associated with psoriatic arthritis (PsA). Values in parentheses are percentages.

	Controls, n = 110	PsA, n = 81	p_c	OR	EF
Cw* 0602	19 (17)	49 (60)	< 0.000001	7.33	0.52
B*13	0	5 (6)	NS		
B*27	9 (8)	13 (16)	NS		
B*38	3 (2)	9 (11)	NS		
B*39	1 (1)	6 (7)	NS		
B*57	7 (6)	12 (14)	NS		
MICA-A9†	33 (30)	49 (60)	0.0002	3.57	0.43
TNF-238A	14 (12)	15 (18)	NS		
TNF-308A	24 (21)	25 (31)	NS		
DR4	24 (21)	8 (9)	NS		
DR7	33 (30)	30 (37)	NS		

† MICA-A9 was also significantly increased in Cw6 negative patients (53% vs 29%; $p_c = 0.034$, OR 2.83, EF 0.34). p_c: corrected p value; OR: odds ratio; EF: etiological fraction.

Analysis of HLA-DRB1 and TNF-α revealed no significant differences between patients and controls (data not shown). HLA-DR4 and DR7, which have been reported to be associated with PsA, were not significantly increased in our population (Table 1). Additionally, there were no significant differences in the distribution of the polymorphisms of any locus (HLA-B, HLA-C, HLA-DRB1, and TNFA) among any of the clinical forms of the disease (data not shown).

Analysis of the polymorphism of MICA and MICB genes. Analysis of microsatellite polymorphism in the TM region of MICA gene showed an association between MICA-A9 and PsA (Table 1). This allele was carried by 60% of patients with PsA and 30% of the control group (p_c = 0.0002, OR 3.57, EF 0.43). The association between MICA-A9 and PsA was independent of Cw*0602, since MICA-A9 was also significantly increased in Cw6 negative patients (53% vs 28%, p_c = 0.034, OR 2.83, EF 0.34). MICB is the nearest gene located centromeric to MICA. A microsatellite has been described in intron 1 of the MICB gene and 13 alleles have been reported according to the number of CA/GT repetitions (MICB-CA14 to MICB-CA28)[26]. The allele MICB-CA16 was absent in our population, and consequently only 12 alleles were detected (Table 2). The gene frequency of MICB-CA-22 (22 repetitions of CA/TG dinucleotide) was found to be significantly increased in PsA patients (23% vs 7%; p_c = 0.028, OR 3.9, EF 0.17). There were no significant differences in MICA and MICB distribution among any of the clinical forms of the disease (data not shown).

HLA-B38, B39, B57, and MICB-CA22 are in linkage disequilibrium with MICA-A9. To analyze which of these genes is more strongly associated with PsA, we studied the linkage disequilibrium among them. HLA-B38 (Δ = 0.9), HLA-B39 (Δ = 1), and HLA-B57 (Δ = 1) were in linkage disequilibrium with MICA-A9. However, B38, B39, and B57 were not significantly associated with PsA when p values were corrected. All patients carrying HLA-B38, B39, and B57 were MICA-A9. Our data suggest that the increase of HLA-B alleles may be secondary to MICA-A9 linkage.

MICB-CA-22 was in linkage disequilibrium with MICA-A9 (Δ = 0.6) and was also found to be increased in PsA. We investigated which of the 2 genes was primarily associated with PsA (Table 3): we analyzed the association of MICA-A9 in a group of 62 MICB-CA-22 negative patients and 102 MICB-CA-22 negative controls. MICA-A9 was also significantly increased in MICB-CA-22 negative PsA patients (51% vs 26%; p_c = 0.0015, OR 2.96, EF 0.34). In contrast, MICB-CA-22 was not found to be significantly increased independent of MICA-A9.

Further, HLA-B/MICA haplotypes associated with PsA such as B38-MICA-A9, B39-MICA-A9, and B5701-MICA-A9 were found to carry different MICB and HLA-DRB1 polymorphisms. MICB-CA-22 was part of the extended haplotype Cw6-B5701-MICA-A9 (RF = 100%), MICB-CA-25 was in linkage disequilibrium with HLA-B38-MICA-A9 (RF 87%), and MICB-CA-20 with B39-MICA-A9 (RF 50%). HLA-DR4 and HLA-DR7, which have been reported to be associated with PsA in some populations[18,19], were also part of the extended haplotypes EH38.1 (HLA-B38-MICA-A9-DR4) and EH57.1 (HLA-B57-MICA-A9-DR7). However, we found a weaker linkage disequilibrium of MICA-A9 with DR4 and DR7 in our population (Δ = 0.06 and Δ = 0.08, respectively).

Table 2. Phenotype frequencies of microsatellite located in intron 1 of the MICB gene. The 12 alleles have been assigned according to the number of CA/GT repetitions (MICB-CA14 to MICB-CA28). Values in parentheses are percentages.

	Controls, n = 110	PsA, n = 81	p_c	OR	EF
MICB-CA14	47 (42)	27 (33)	NS		
MICB-CA15	33 (30)	18 (22)	NS		
MICB-CA17	21 (19)	20 (24)	NS		
MICB-CA18	20 (18)	13 (16)	NS		
MICB-CA20	9 (8)	10 (12)	NS		
MICB-CA21	18 (16)	11 (13)	NS		
MICB-CA22	8 (7)	19 (23)	0.028	3.9	0.43
MICB-CA23	6 (5)	7 (8)	NS		
MICB-CA24	16 (14)	13 (16)	NS		
MICB-CA25	11 (10)	14 (17)	NS		
MICB-CA27	1 (1)	1 (1)	NS		
MICB-CA28	1 (1)	0 (0)	NS		

PSA: Psoriatic arthritis; P_C: corrected p value; OR: odds ratio; EF: etiological fraction.

DISCUSSION

The association of MHC with PsA has been established[3-10]. However, several MHC loci, such as HLA-C, HLA-B, TNFA, and HLA-DRB1, have been associated with PsA in different populations[17-19]. We also recently reported the association of a polymorphism in the transmembrane region of the MICA gene, called MICA-A9, with PsA[14,15]. All these genes are in strong linkage disequilibrium and it is difficult

Table 3. The table shows the association of MICA-A9 and psoriatic arthritis is independent of MICB-CA-22. Values in parentheses are percentages.

	MICB-CA-22 Negative*	
	Control, n = 102	PsA, n = 62
With MICA-A9	27 (26.4)	32 (51.6)
Without MICA-A9	75 (73.5)	30 (48.3)
	MICA-A9 Negative†	
	Control, n = 78	PsA, n = 32
With MICB-CA-22	3 (3.8)	2 (6.2)
Without MICB-CA-22	75 (96.1)	30 (93.7)

* p_c = 0.0015, OR 2.96, EF 0.34; † NS.

to elucidate which of these are primarily or secondarily associated with linkage disequilibrium.

Our results suggest that the susceptibility to PsA is associated with the coexistence of HLA alleles related to both the psoriatic skin lesions and arthritis. On one hand, there is an increase of Cw6 and those HLA-B alleles that are in linkage disequilibrium with Cw6 (HLA-B13 and B57) in patients with PsA. This association has also been found in Spanish patients with psoriatic skin lesions (without arthritis)[11,14], and this suggests that the association of Cw6 with PsA is linked to the psoriatic skin lesion rather than the arthritis itself. We recently described that the gene responsible for the susceptibility to psoriasis in the Spanish population is not Cw6 itself. The putative gene responsible for psoriasis is an interval located 147 kb telomeric to HLA-C. Thus, the association of Cw6 with psoriasis is secondary to linkage disequilibrium with this susceptible locus. Recently, the interval containing this susceptible locus (PSORS1) was narrowed to a segment of 60 kb telomeric to HLA-C[12]. On the other hand, there was also an increase of MICA-A9 in patients with PsA, and alleles that are in linkage disequilibrium with it (HLA-B38 and B39). The possibility exists that the association of MICA-A9 is secondary to linkage disequilibrium with the susceptible locus associated with psoriasis (PSORS1). Therefore, our data strongly suggest that the association of MICA-A9 is independent of PSORS1. First, MICA-A9 is associated with PsA in Cw6 negative patients. Second, MICA-A9, B38, and B39 are not associated with psoriasis (without arthritis) in our population[11]. Third, B38 and B39 are neither in linkage disequilibrium with Cw6 nor do they share polymorphic markers telomeric to HLA-C with those haplotypes associated with psoriasis vulgaris (EH13.1 and EH57.1)[11]. Thus, we suggest that there are 2 different susceptible loci associated with this disease: one located centromeric to HLA-C, which is associated with the psoriatic skin lesions (present in the EH13.1, EH37.1, and EH57.1), and another, MICA-A9, associated with the susceptibility to PsA (present in EH38.1, EH39, and EH57.1). In agreement with this, EH13.1, EH37.1 are exclusively associated with psoriatic skin lesion. EH38.1 and EH39.1 are exclusively associated with PsA. EH57.1 is associated with both psoriasis vulgaris and PsA.

To analyze the putative contribution of other MHC genes located centromeric to MICA we analyzed the association of the MICB gene, the nearest known gene located centromeric to MICA. We investigated a dinucleotide polymorphism in intron 1 of MICB gene, even though it remains unknown how this polymorphism affects MICB. MICB-CA-22 is statistically significantly increased in PsA patients. However, MICB-CA-22 is part of the extended haplotype Cw6-B5701-MICA-A9 and our data suggest that the association of MICB with PsA is secondary to this haplotype context. In agreement with this, MICB-CA-22 was not associated independently of MICA-A9. Additionally, other extended haplotypes classically described to be associated with PsA, such as B38-MICA-A9-MICB-CA-25 and B39-MICA-A9-MICB-CA-20, carry a different MICB polymorphism. Thus, our results strongly suggest that the association of MICB with PsA is also secondary to MICA-A9. MICA appears to be the gene most associated with susceptibility to arthritis development in psoriatic patients. We analyzed the nearest genes located centromeric and telomeric to MICA, and their associations are secondary to linkage disequilibrium with MICA, suggesting that MICA is the strongest susceptibility factor associated with the development of arthritis in psoriatic patients.

Moreover, that the haplotypes carrying MICA-A9 associated with PsA carry different MICB alleles makes unlikely any direct role of other MHC genes located more centromeric to this gene, such as TNFA or HLA-DRB1, in this disease. In agreement with this, no significant association of HLA-DRB1 and TNFA with PsA was detected in our population. The reported association of TNFA –238A or HLA-DR4 and -DR7 with PsA is an apparent contradiction to our results[17-19]. However, TNF-238A and HLA-DR7 are part of the EH57.1 (HLA-B57-MICA-A9-HLA-DR7), and DR4 is part of the EH38.1 (HLA-B38-MICA-A9-HLA-DR4). HLA-DR4 and -DR7 were not in strong linkage disequilibrium with MICA-A9 in our population, and this may explain the lack of association of these alleles in our patients. Therefore, haplotype analysis suggests that the association of HLA-DR4 and DR7 or TNF-238A could be explained as being secondary to the association of these conserved haplotypes in other populations. Genetic studies are now necessary in these populations in order to draw definite conclusions. Figure 1 represents extended haplotypes possibly containing susceptibility factors of PsA in Caucasians.

MICA is a membrane protein that is mainly expressed in epithelial cells of the intestine and is recognized by NKG2D receptor expressed on most NK cells, CD8αß T cells, and γδ T lymphocytes[21] and thus plays a role in the innate defence against a biological stress. Our data strongly suggest that a trinucleotide repeat polymorphism in the transmembrane region of MICA gene (A9) is associated with PsA. Recent studies have shown that MICA-A9 is also overrepresented in other autoimmune diseases such as Type I diabetes in Orientals[31] and familial Mediterranean fever[32]. However, its functional role is not exactly clear. Most of the case-control disease-association studies of MICA have been focused on polymorphisms at the transmembrane region, and few of these analyzed the polymorphism of exon 2–4 encoding the external domains of the molecule. At least 6 different alleles of MICA carrying the A9 polymorphism in the transmembrane region have been described: MICA*002, 015, 017, 021, 041, and 046[21]. Neither the linkage disequilibrium of these alleles with those of HLA-B nor their pattern of expression have been fully established in population studies.

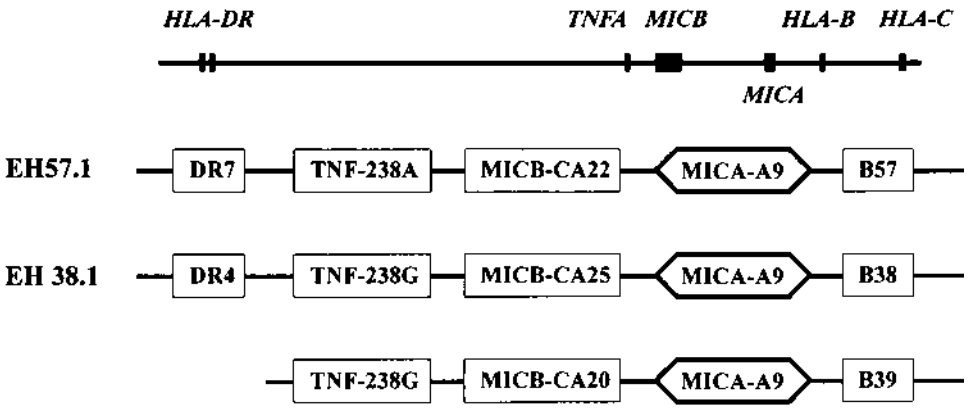

Figure 1. The extended haplotypes associated with PsA. The different splits and relationships between HLA-B, MICA, MICB, TNFA, and HLA-DRB1 of the most prevalent haplotypes described in Caucasians associated with PsA are represented. HLA-B38 ($\Delta = 0.9$), -B39 ($\Delta = 1$), and -B57 ($\Delta = 1$) were in strong linkage disequilibrium with MICA-A9. HLA-DR4 ($\Delta = 0.06$) and DR7 ($\Delta = 0.08$) were weakly associated with MICA-A9 in our population.

Interestingly, MICA-017 has been shown to contain a transmembrane region followed by a truncation[33]. Recent research describes a single biallelic amino acid at position 129 in the α2 domain associated with weak (Val) and strong (Met) binding to NKG2D receptors[34]. All the MICA alleles described as carrying the transmembrane variant A9 represent strong binding alleles. Interaction of high affinity MICA-A9 alleles with NKG2D could play a role in the development of the autoimmune response. However, it is not possible at present to elucidate whether the polymorphism transmembrane region of MICA is associated with the disease or whether the association is limited to a particular allele. Further analyses and population studies are needed to clarify the role of MICA in the development of PsA.

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