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Lack of Association Between Promoter Polymorphism of the Tumor Necrosis Factor-α Gene and Psoriatic Arthritis in Japanese Patients

To the Editor:

The analysis of population-specific human leukocyte antigen (HLA) has provided evidence that susceptibility to psoriasis is linked to HLA with racial differences (Henseler, 1997). Tumor necrosis factor-α (TNF-α) gene is also mapped within the HLA region and its product has been reported as one of the most important cytokines in the pathogenesis of psoriasis (Uyemura *et al*, 1993). Recently, Höhler *et al* (1997) reported in this journal a significant increase of subjects carrying A at position -238 of TNF-α gene promoter region in the psoriatic arthritis (PsA) group, as well as in that of early-onset psoriasis vulgaris (PsV). These findings, however, are still controversial (Jacob *et al*, 1999; Höhler, 1999). Jacob *et al* (1999) have also shown in the journal that promoter polymorphism at -238 of the TNF-α gene was not associated with early onset PsV when tested by the transmission disequilibrium test. Very recently, it has been demonstrated that an increased frequency of the TNF-238.A (A at -238) allele detected only in male patients but not in female patients with early-onset PsV (Reich *et al*, 2000). On the other hand, there are only a few reports on whether polymorphism of the TNF-α promoter region and PsA are associated or not, because only a few cases are investigated. Moreover, three new polymorphisms at positions -1031 (T to C change), -863 (C to A), and -857 (C to T) have been identified in the Japanese population (Higuchi *et al*, 1998). In this study we evaluated the association between promoter polymorphism of the TNF-α gene and PsA in the Japanese population.

Twenty Japanese patients (eight females and 12 males) suffering from PsA were studied (the median age was 44 y, ranged from 25 to 70). The control population consisted of 87 locally recruited, unrelated volunteers (21 female and 67 males with a median age of 52 y ranged from 15 to 81). Peripheral blood mononuclear cells were separated by the Ficoll method for isolation of genomic DNA. A 1042 bp DNA fragment of the 5′ flanking region of the TNF-α gene at position -1107 to -66 was amplified by PCR with a sense primer 5′-GCTTGTGTGTGTGTCTGG-3′ and an anti-sense primer 5′-GGACACACAAGCATCAAGG-3′ (Higuchi *et al*, 1998). Polymerase chain reaction (PCR) products were run on ethidium bromide-stained agarose gel, and then excised DNA bands from the gel were purified using a GENECLEAN II kit (BIO 101, La Jolla, CA). These purified PCR products were directly sequenced by the dideoxy nucleotide dye terminator cycle sequencing method using two different primers, 5′-GCTTGTGTGTGTGTCTGG-3′ (Higuchi *et al*, 1998) for the polymorphism at -1031, -863, and -857, and 5′-TTCCTGCATCCTGTCTGGAA-3′ (D'Alfonso and Richiardi, 1994) for those at -308 and -238, respectively.

As shown in **Table I**, all patients with PsA studied have a genotype G/G at both -238 and -308, whereas 4.6% (four of 87) and 3.4% (three of 87) of controls have a genotype G/A at -238 and -308, respectively. Gene frequencies for the TNF-238A allele in the Japanese controls were similar to those reported by the authors for West European Caucasians (2.3% *vs* 3.5%) (Höhler *et al*, 1997) and the previous report for Japanese patients (2.3% *vs* 2.0%) (Higuchi *et al*, 1998). The frequencies for the TNF-308A (A at -308) allele in the Japanese controls, however, were less than those reported by the authors for West European Caucasians (2.9% *vs* 10%) (Höhlet *et al*, 1997), whereas no difference was seen between this study and the previous one (2.9% vs 1.7%) (Higuchi *et al*, 1998). Furthermore, we found no significant increase of subjects carrying C, A, and T at positions -1031, -863, and -857, respectively (**Table I**). In this region the frequency of alleles -1031C (C at -1031), -863A (A at -863), and -857T (T at -857) is similar to that previously reported by Higuchi *et al* (1998) (12.6% *vs* 16.0% for -1031C; 15.5% *vs* 14.0%, -863A; 15.5% *vs* 17.7%, -857T).

These results are quite different from those reported by Höhler *et al* (1997). In their report, 32% (20 in 62) of PsA patients have genotype G/A at -238, whereas 7% of controls (seven of 99) have the genotype (Höhler *et al*, 1997). We calculated on gene frequencies for the TNF-238A allele in PsA patients 16.1% from the data demonstrated. The discrepancy does not seem to depend on the racial difference, because gene frequencies for the TNF-238A allele in their controls were not different from the data by our or other studies (3.5% *vs* 2.3% or 2.0%) (Höhlet *et al*, 1997; Higuchi *et al*, 1998). Although a small number of PsA cases was investigated, this study clearly shows that promoter polymorphism at -238 of the TNF-α gene is not associated with PsA in the Japanese population as well as at other positions, including -1031, -863, -857, and -308.

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Table I. TNF-α gene promoter polymorphism in 20 Japanese PsA patients and 87 controls

		PsA		Control	
Position	Genotype	Number (%)	Allele (frequency, %)	Number (%)	Allele (frequency, %)
	T/T	16 (80.0)		65 (74.7)	
			–1,301T (90.0)		–1,301T (87.4)
–1301	T/C	4 (20.0)		22 (25.3)	
			–1,301C (10.0)		–1,301C (12.6)
	C/C	0 (0.0)		0 (0.0)	
	C/C	15 (75.0)		63 (72.4)	
			–863C (85.0)		–863C (84.5)
–863	C/A	4 (20.0)		21 (24.1)	
			–863A (15.0)		–863A (15.5)
	A/A	1 (5.0)		3 (3.5)	
	C/C	14 (70.0)		62 (71.3)	
			–857C (82.5)		–857C (84.5)
–857	C/T	5 (25.0)		23 (26.4)	
			–857T (17.5)		–857T (15.5)
	T/T	1 (5.0)		2 (2.3)	
	G/G	20 (100)		83 (95.4)	
			–308G (100.0)		–308G (97.1)
–308	G/A	0 (0)		3 (3.4)	
			–308A (0.0)		–308A (2.9)
	A/A	0 (0)		1 (5.0)	
	G/G	20 (100)		83 (95.4)	
			–238G (100.0)		–238G (97.7)
–238	G/A	0 (0)		4 (4.6)	
			–238A (0.0)		–238A (2.3)
	A/A	0 (0)		0 (0.0)	

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Reply

To the Editor:

In a small study with 20 patients suffering from psoriatic arthritis, Hammamoto *et al* have investigated TNF-α promoter polymorphisms and failed to confirm the previously published (Höhler *et al*, 1997; Arias *et al*, 1997) association of psoriatic arthritis and psoriasis with a G to A transition polymorphism (TNF238.A) in the TNF-α promoter region. This polymorphism has attracted particular interest as it seems to influence the transcription of the TNF-α gene and decreases the production of TNF-α in particular by T lymphocytes (Kaluza *et al*, 2000). We have forwarded the hypothesis that this polymorphism could be an additional major histocompatibility complex (MHC) encoded susceptibility factor for the development of psoriasis favoring persistence of cutaneous skin infections, e.g. by streptococci. The TNF238A polymorphism is part of the ancestral haplotype B57.1 (TNF238.A-B57-Cw6) that has been linked to psoriasis. This is the most common haplotype in Western European Caucasians with the disease (Jenisch *et al*, 1999). In addition, a number of other haplotypes have been associated with the occurrence of psoriasis, e.g. B13-Cw6, B8-Cw7, and B37-Cw6 (Jenisch *et al*, 1999), the latter being the most common disease associated haplotype in Japan (Imanishi *et al*, 1992). The strong haplotype conservation within the MHC makes the investigation of TNF-α polymorphisms in conjunction with HLA-B and Cw-alleles mandatory. Unfortunately, Hamamoto *et al* do not provide any data concerning HLA-B- and -Cw-allele haplotypes and frequencies in their psoriatic arthritis group. Considering the high frequency of the B37-Cw6 haplotype in Japanese psoriasis patients (Imanishi *et al*, 1992) it is not surprising that the authors do not find an association with the TNF238.A promoter variant, which is almost exclusively found on the B57-Cw6 haplotype. Nevertheless, the findings of this small study are interesting as they underline ethnic heterogeneity in the genetics of psoriasis. These results should be confirmed in a larger set of Japanese patients with psoriasis vulgaris and psoriatic arthritis including HLA-B and Cw alleles in the analysis.

Very recent data by Nair *et al* (2000) indicate that the MHC encoded PSORS1 susceptibility locus, which has been confirmed in a number of different studies, is located 100 kB telomeric to HLA-C. This group has identified a 60 kB fragment of the ancestral haplotype 57.1 that is shared by all identifiable risk haplotypes.

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