

Association of tumor necrosis factor alpha-308 promoter polymorphism with spondyloarthritides patients in Colombia

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Abstract The pathogenesis of SpA is considered to be a complex and multi-factorial process and, similar to other autoimmune diseases, includes the activity of proinflammatory cytokines such as TNF alpha. Our study compared the -308 promoter polymorphism of TNF alpha with TNF alpha levels, HLA-B27 status, age at the onset of symptoms, SpA subtype and the clinical degree of activity in Colombian SpA patients and healthy subjects (HS). Comparisons of the TNF alpha-308A genotype among HS and SpA patients ($P = 0.004$), uSpA patients ($P = 0.040$), ReA patients ($P = 0.001$), were significantly different and AS patients ($P = 0.110$), as were alleles for SpAs ($P = 0.007$) between patients with SpAs and controls. Initial exploratory analyses demonstrated that the TNF alpha-308 SNP genotype frequencies were different among SpA patients and HS in the Colombian population studied. Furthermore, there was no significant correlation with activity and functional clinical index, serum TNF alpha level or HLA B27 status. Allele frequencies, on the other hand, were correlated with the activity clinical index.

Keywords TNF Alpha · Polymorphism · Spondyloarthritides

The spondyloarthritides (SpAs) are a heterogeneous group of diseases that share some genetic basis related to the HLA-B27 allele. The pathogenesis of SpA is considered to be a complex and multi-factorial process and, similar to other autoimmune diseases, includes the activity of proinflammatory cytokines such as TNF alpha. The TNF alpha gene contains several single nucleotide polymorphisms (SNPs), and the most studied, the -308 SNP, has been found to be involved in many diseases due to its ability to modify cytokine levels and clinical outcomes. The TNF alpha protein is a potent proinflammatory cytokine and immune modulator of joint destruction, and TNF alpha should possibly be considered as a risk factor for the development of SpA [1–5]. There are no previous reports in SpA Colombian population [6].

Our study compared the -308 promoter polymorphism of TNF alpha with TNF alpha levels, HLA-B27 status, age at the onset of symptoms, SpA subtype and the clinical degree of activity in Colombian SpA patients and healthy subjects (HS).

A total of 61 Colombian patients with SpA who fulfilled the European Spondyloarthropathy Study Group (ESSG) classification criteria were selected over a period of 1 year. These subjects included 17 ankylosing spondylitis (AS) patients, 33 undifferentiated spondyloarthropathy (uSpA) patients and 11 reactive arthritis (ReA) patients. There were 42 men and 19 women with an average age of 32.1 ± 9.1 years and an average age at the onset of symptoms of 27.3 ± 7.1 years. Patients with anti-TNF and steroid therapies were excluded. Disease activity was evaluated with BASDAI (Ankylosing Spondylitis Disease Activity Index), BASFI (Ankylosing Spondylitis Functional Index) validated score, erythrocyte sedimentation rate (ESR), C-reactive protein high sensitive (CRP). In addition, 83 unrelated and ethnically matched HS were selected who

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Table 1 Demographic data in SpA patients, subtypes and health subjects

	SpA (<i>n</i> = 61)	AS (<i>n</i> = 17)	USpA (<i>n</i> = 33)	ReA (<i>n</i> = 11)	HS (<i>n</i> = 83)
Age	32.1 (± 9.1)	32.7 (± 8.6)	32.2 (± 9.6)	30.7 (± 9.7)	30.4 (± 9.2)
Gender Male	42 (68%)	14 (82.3%)	19 (57.6%)	9 (69.2%)	58 (70%)
Age at the onset of symptoms	27.3 (± 7.1)	25 (± 5.6)	27.8 (± 7.3)	28.8 (± 8.4)	–
BASFI	5.42 (± 2.3)	5.0 (± 2.22)	5.7 (± 2.1)	4.9 (± 3.0)	–
BASDAI	6.0 (± 2.0)	6.3 (± 1.9)	6.0 (± 1.75)	5.7 (± 2.9)	–
HLA-B27	42.6%	76.5%	30.3%	27.3%	–
CRP*	8.1 (± 14.5)	8.12 (± 17.9)	4.5 (± 9.45)	18.83 (± 11.1)	1.13 (± 0.88)
ESR**	16.8 (± 13.3)	13 (± 12.6)	15.5 (± 11.7)	16.8 (± 15.3)	3.8 (± 0.7)
TNF alpha***	25.2 (± 38.4)	19.4 (± 8.5)	29.3 (± 50.0)	20.6 (± 7.1)	15.9 (± 12.5)

SpA spondyloarthritis, AS ankylosing spondylitis, USpA undifferentiated spondyloarthritis, ReA reactive arthritis, HS healthy subject

* mg/L; ** mm/h; *** pg/ml

Table 2 Genotypic/allelic frequencies of TNF alpha-308 promoter polymorphism in Colombian SpA patients and health subjects

Subjects (<i>n</i>)	Genotypes				Alleles		
	G/G <i>n</i> (%)	A/G <i>n</i> (%)	A/A <i>n</i> (%)	<i>P</i> value	G <i>n</i> (%)	A <i>n</i> (%)	<i>P</i> value
SpA(61)	43 (70.5)	18 (29.5)	0 (0)	0.004	104 (85.2)	18 (14.8)	0.021
AS(17)	12 (70.6)	5 (29.6)	0 (0)	0.110	29 (85.3)	5 (14.7)	0.052
USpA(33)	25 (54.5)	8 (24.5)	0 (0)	0.040	58 (88.1)	8 (11.9)	0.158
ReA(11)	6 (54.5)	5 (45.5)	0 (0)	0.001	17 (77.3)	5 (22.7)	0.036
HS(83)	74 (89.2)	9 (10.8)	0 (0)		157 (94.6)	9 (5.4)	

had neither symptoms nor a previous diagnosis of systemic disease and an average age of 30.4 ± 9.2 years, including 70.0% men and 30.0% women (Table 1). TNF alpha levels were tested using a cytometric bead array (BD Biosciences, San Jose, CA); the -308 SNP in the TNF alpha promoter was analyzed by PCR-RFLP [7] and HLA was detected by PCR-SSP. The continuous variables were reported as frequencies, medians and ranks. Hardy–Weinberg equilibrium was tested, and comparisons were made using the Mann–Whitney test and the proportions test.

Comparisons of the TNF alpha -308A genotype among HS and SpA patients ($P = 0.004$), uSpA patients ($P = 0.040$) and ReA patients ($P = 0.001$), were significantly different and AS patients ($P = 0.110$), as were alleles for SpAs ($P = 0.007$) between patients with SpAs and controls (Table 2). The frequency of the TNF alpha-secreting allele -308A was increased in patients with SpA, AS and ReA, suggesting that TNF alpha -308A could be a non-protective allele for SpA.

Among the 61 subjects, 43 had the GG genotype (0.705), and 18 had the GA genotype (0.295); we did not identify the AA genotype in any of our subjects. The mean serum TNF alpha level in patients with SpA was 25.2 ± 38.4 pg/ml. When analyzed by SpA subtype, the

mean serum TNF alpha level was 19.4 ± 8.5 pg/ml among AS patients, 29.3 ± 50.7 pg/ml among USpA patients, 20.6 ± 7.1 pg/ml among ReA patients and 15.9 ± 12.5 pg/ml among HS patients (Table 1). Significant differences were observed when comparing the serum TNF alpha levels between patients with SpA and its subtypes and HS ($P < 0.05$). TNF alpha levels were higher in those positive for B27; however, they were not significantly different. Genotype and allele comparisons in patients with SpA and its subtypes based on serum TNF alpha levels, HLA-B27 status, age at the onset of symptoms, BASFI and BASDAI scores, CRP and ESR were not statistically significant. A comparison of the alleles only showed significant differences for the G allele with the BASDAI score. Initial exploratory analyses demonstrated that the TNF alpha-308 SNP genotype frequencies were different among SpA patients and HS in the Colombian population studied. Furthermore, there was no significant correlation with activity and functional clinical index, serum TNF alpha level or HLA-B27 status. Allele frequencies, on the other hand, were correlated with the activity clinical index. These findings are similar to those previously reported for Mexican and Argentine patients and different from those reported for Taiwanese patients [8–10].

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