Table 1 Disease activity (BASDAI), functional impairment (BASFI), pain (VAS) and morning stiffness in patients with ankylosing spondylitis treated either in the community or in tertiary centres, or in controls with back pain but without inflammatory rheumatic diseases

	Community (n = 555)	Tertiary centre (n = 129)	Controls (n = 153)
BASDAI	4.8 (0–9.6)	4.4 (0.4–10)	2.7* (0.9–8.4)
BASDAI ⩾4, n (%)	524 (78.8)	84 (65.1)	64* (41.8)
BASDAI >7, n (%)	107 (16.1)	18 (14.0)	5* (3.3)
BASFI	4.4 (1–10)	3.7† (0–10)	1.8* (0.7–9)
BASFI >7, n (%)	122 (18.3)	21 (16.3)	11* (7.5)
Pain (VAS)	5 (1–10)	5 (0–10)	2* (0–10)
VAS >7, n (%)	177 (26.7)	37 (30.1)	14* (9.3)

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; VAS, Visual Analogue Scale. Values are median (range) unless otherwise indicated.
*p<0.001 versus community and tertiary centre patients.
†p<0.05 versus community patients.

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Association of tumour necrosis factor α promoter polymorphisms with ankylosing spondylitis in Taiwan

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Ankylosing spondylitis is a genetic-susceptible inflammatory spondyloarthropathy that mainly affects the sacroiliac joints. Tumour necrosis factor (TNF)α, a potent proinflammatory cytokine and immune modulator of joint destruction, is suggested to be a risk factor for the development of ankylosing spondylitis.[1] Evidence of an association between TNFα gene polymorphisms and ankylosing spondylitis showed conflicting results. Most of such studies focused on Caucasian subjects; few in the Taiwanese population were documented except for a recent study that reported the association between the interleukin 1 gene cluster and ankylosing spondylitis.[2]

Our study examined the distribution of TNFα promoter polymorphisms among Taiwanese patients with ankylosing spondylitis. A total of 143 patients with ankylosing spondylitis (97 men and 46 women, mean (standard deviation (SD)) age 41.7 (11.5) years), defined by the modified New York diagnostic criteria,[3] were enrolled. The control population consisted of 166 unrelated and ethnic-matched healthy people (107 men and 59 women, mean (SD) age 37.7 (13.2) years). Distribution of TNFα G−238A genotypes (p = 0.007) and alleles (p = 0.007), as well as that of G−308A genotypes (p = 0.045) and alleles (p = 0.018), between patients with ankylosing spondylitis and controls were significantly different (table 1). Frequencies of high TNFα-secreting alleles −238*A and −308*A were markedly decreased in patients with ankylosing spondylitis, which suggests that TNFα −238*A and −308*A are protective alleles for the development of ankylosing spondylitis. These observations supported previous reports which stated that frequencies of the rarer TNF-α −238*A and −308*A alleles are lower in patients with ankylosing spondylitis,[1 4] and the observation that T cell production of TNFα in patients with ankylosing spondylitis was decreased.[1]

The significant difference of B27 positivity in our patients with ankylosing spondylitis (97.9%) and controls (4.2%) further indicated the important contribution of B27 to the incidence of ankylosing spondylitis. Both TNFα G−308A genotypes (p = 0.01) and alleles (p = 0.012) were significantly correlated with B60 positivity in B27+ patients (table 1). Notably, the high TNFα secreting −308*A allele was significantly decreased in B60+ patients, compared with B60− patients. It further supported the previous hypothesis that the TNFα −308*A is a protective allele for ankylosing spondylitis because B60 is an independent predisposing factor for ankylosing spondylitis.[5]

Variations in linkage disequilibrium between TNFα genotypes with *HLA* genes is suggested to explain the conflicting results regarding genotypic data among ethnically different populations with ankylosing spondylitis.[6] Some studies reported that the association between TNFα and ankylosing spondylitis is secondary to B27, therefore, TNFα polymorphism is not likely to be involved in susceptibility to ankylosing spondylitis.[7 8] This scenario does not seem suitable for the Taiwanese population because both TNFα −238*G and −308*G are the predominant

Table 1 Genotypic/allelic frequencies of tumour necrosis factor α promoter polymorphisms in patients with ankylosing spondylitis and controls

	G−238A						G−308A					
	Genotypes				Alleles			Genotypes			Alleles	
Subjects	G/G	A/G	A/A	p Value	G	A	p Value	G/G	A/G	A/A	G	A	p value
Control (n = 112)	104 (92.9)	8 (7.1)	0 (0)	0.007	216 (96.4)	8 (3.6)	0.007	84 (75.0)	25 (22.3)	3 (2.7)	193 (86.2)	31 (13.8)	0.018
AS (n = 143)	142 (99.3)	1 (0.7)	0 (0)		285 (99.6)	1 (0.4)		121 (84.6)	22 (15.4)	0 (0)	264 (92.3)	22 (7.7)	
B27+ AS													
B60+ (n = 29)	29 (100)	0 (0)	0 (0)	NA	58 (100)	0 (0)	NA	29 (100)	0 (0)	0 (0)	58 (100.0)	0 (0.0)	0.012
B60− (n = 48)	48 (100)	0 (0)	0 (0)		96 (100)	0 (0)		39 (81.2)	9 (18.8)	0 (0)	87 (90.6)	9 (9.4)	

AS, ankylosing spondylitis; NA, not available; +, positive.

alleles in our controls, in which 95.8% are B27−. Moreover, the prevalence of TNFα −238*A and −308*A alleles were markedly decreased even though the linkage disequilibrium of TNFα and B27 existed in the Taiwanese population.

Infections with *Klebsiella pneumoniae* and other Gram-negative enterobacteria have been implicated in the pathogenesis of ankylosing spondylitis.[9] Individuals carrying TNFα −238*A or −308*A and the resultant higher TNFα levels might be more competent in combating infections and less likely in developing ankylosing spondylitis. Accordingly, differences in TNFα levels which result from the genotypic/allelic difference may affect the defence against certain ankylosing spondylitis-related microbial infections, and ultimately the development of ankylosing spondylitis, irrespective of the initial triggering event for an inflammatory response.

Our study showed a significant association of TNFα genotypes with susceptibility to ankylosing spondylitis in the Taiwanese population, and supported previous conclusions that TNFα −238*A and −308*A alleles are protective alleles for the development of ankylosing spondylitis. Hopefully, the study can provide new clues for uncovering the pathogenesis of ankylosing spondylitis of Taiwanese patients.

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