Letters to the editor

Cytotoxic T lymphocyte antigen-4 (CTLA-4) polymorphism in patients with Behçet's disease

Sirs,

The immunopathogenesis of Behçet's disease (BD) remains unclear, but immune dysfunction to microorganisms have been postulated in genetically predisposed individuals. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is a costimulatory molecule expressed on T cells after cellular activation. It acts as a competitive inhibitor of the CD28 on T cells and down regulates the immune response and inhibits intracellular signalling, T-cell proliferation and IL-2 production. CTLA-4 gene polymorphism has been shown to affect the inhibitory function of CTLA-4 (1). A number of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and Graves' disease have been associated with genetic variation at CTLA-4 (2-4). *CTLA4* polymorphisms for four SNPs located at positions -1722, -1661, -318 and +49 of the *CTLA4 g*ene can be explored in several diseases. We analysed CTLA-4 49A/G polymorphism with BD in the Turkish population.

The CTLA-4 A/G (codon 17 Thr/Ala) transition at position 49 in exon 1 was genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RLFP) in 217 patients with BD (125M/92F, ages ranging 18–66, the mean ±SD 34±9.8 age), who fulfilled the International Study Group Criteria for the Diagnosis of Behçet's disease, and 154 healthy unrelated persons (82M/72F, ages ranging 20–59, the mean±SD 28±11.1 age). All study populations were collected mainly from the central part of Anatolia. Binary logistic regression models were statistically used to analyse the data. As shown in Table I, the distribution of the CTLA-4 +49A/G genotype and allele frequencies did not differ between all patients with BD and healthy controls. Sallakçi *et al*. reported similar results in a small group with 59 Turkish patients with BD and healthy controls. However, A allele and A/A genotype frequencies of CTLA-4 +49 were significantly higher in patients with ocular involvement than those without this symptom (90.6% *vs*. 65.1%, OR =9.67, p=0.011; and 81.25% *vs*. 39.5%, OR =9.56, p=0.015, respectively), and also BD patients with erythema nodosum-like lesions had a higher frequency of the A allele (5). In our study, no association could be shown in CTLA-4 +49A/G polymorphism and clinical manifestations including thrombosis and uveitis of BD.

Gunesacar *et al*. found that the CTLA-4 +49 GG genotype was significantly lower in 123 Turkish patients with BD than those of 179 healthy controls (4% *vs*. 10.6%, OR =0.357, 95% CI =0.130–0.983, p=0.05). They did not find significant associations between CTLA-4 +49 polymorphism and the main clinical features of BD (6). A highly significant difference between Tunisian 135 BD patients and 151 healthy controls was found regarding the distribution of CTLA-4 +49 A allele (odds ratio (OR) =4.63; 95% confidence interval (CI) =3.20–6.72) and genotype frequencies ($p<10^{-7}$; χ^2=71.02) and there was no association between CTLA-4 +49A/G polymorphism and all clinical features (7).

Our results were in discordance with those found in the Turkish population. However, there are some studies which reported results similar to ours. No association was observed between CTLA-4 SNP +49 polymorphism and BD subgroups in a Chinese population as well as other ethnic groups analysed by meta-analysis (8). Park *et al*. did not find any associations between the CTLA-4 +49 A/G polymorphism and BD susceptibility in Korean BD patients (9). Bye *et al*. reported that there was no association with CTLA-4 polymorphism in 236 patients with BD, 143 patients with intermediate uveitis and 180 controls from UK (10). These contradictory results for CTLA-4 +49 A/G in BD patients could be explained by the differences in case-control numbers, the clinical manifestations and populations.

Table I. Genotype distribution and allele frequency of CTLA-4 A49G gene codon 17 in all BD patients, healthy controls, patients with /without thrombosis and with /without uveitis.

CTLA-4 A49G	All BD patients (n=217)	%	Healthy control (n=154)	%	OR	*p*-value	95% CI	
Genotypes								
GG	23	11	9	6	1.91	0.113	0.86-4.25	
GA	83	38	69	45	0.76	0.206	0.50-1.186	
AA	111	51	76	49	1.07	0.732	0.71-1.62	
Alleles								
G	129	30	87	28	1.07	0.663	0.78-1.48	
A	305	70	221	72	0.93	0.663	0.67-1.28	
Genotypes	Trombosis (+) (n=62)	%	Trombosis (-) (n=155)	%				
GG	9	14	14	9	1.71	0.240	0.70	4.19
GA	24	39	59	38	1.03	0.930	0.56	1.88
AA	29	47	82	53	0.78	0.415	0.43	1.41
Alelles								
G	42	34	87	28	1.31	0.233	0.84	2.05
A	82	66	223	72	0.76	0.233	0.49	1.19
Genotypes	Ocular (+) (n=70)	%	Ocular (-) (n=147)	%				
GG	11	16	12	8	2.10	0.096	0.88	5.02
GA	23	33	62	42	0.67	0.190	0.37	1.22
AA	36	51	73	50	1.07	0.808	0.61	1.90
Alleles								
G	45	32	86	29	0.87	0.540	0.57	1.35
A	95	68	208	71	1.15	0.540	0.74	1.77

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