

IL18 Polymorphism Is Associated with Behçet's Disease But Not Lupus in Patients from Turkey

To the Editor:

Sánchez, *et al* have recently reported an association between a putative functional genetic variant in the promoter region of *IL18* (rs360719) and systemic lupus erythematosus in Spanish patients¹. They found an increase in the relative expression of *IL18* mRNA in individuals with the rs360719 lupus-risk allele¹. Interleukin 18 (IL-18) is a pleiotropic cytokine that can induce Th1 and Th2 responses in the presence and absence, respectively, of IL-12². Studies have described overproduction of IL-18 in several autoimmune and inflammatory diseases including Behçet's disease (BD) and lupus^{3,4}. Indeed, serum IL-18 levels in patients with lupus and BD correlate with disease activity^{5,6}.

We attempted to replicate the results of Sánchez, *et al* in a set of Turkish patients with lupus. We examined if the same putative functional *IL18* polymorphism is associated with BD in Turkish patients. We genotyped 2 additional potentially functional single-nucleotide polymorphisms (SNP) in the *IL18* promoter region (rs1946518, -607 C/A, and rs187238, -137 G/C). Our sample set consisted of 189 patients with lupus, 156 with BD, and 253 ethnically matched healthy controls.

All lupus patients and all BD patients fulfilled the 1997 American College of Rheumatology classification criteria for lupus⁷ and the 1990 International Study Group classification criteria for BD⁸, respectively. Genotyping was performed using TaqMan allelic discrimination assays (Applied Biosystems, Foster City, CA, USA). The genotyping success rate was $\geq 97.5\%$. Only individuals successfully genotyped in at least 2 out of the 3 SNP were included in the analysis. There was no departure from Hardy-Weinberg equilibrium in controls. Data analysis was performed using PLINK and Haploview 4.2.

We found no genetic association between *IL18* and lupus in Turkish patients (Table 1). The frequency of the minor allele in rs360719 was 19.3% in cases and 19.5% in controls (OR 0.99, 95% CI 0.70–1.40, $p = 0.95$). This is in contrast to the findings of Sánchez, *et al*, suggesting that the genetic association with *IL18* might be limited to specific ethnicities. Our study had 91% power to detect a genetic association in rs360719 with the previously reported odds ratio of 1.53 (assuming a dominant model, disease prevalence = 0.001, $\alpha = 0.05$). More recent work using a large set of lupus patients and controls also failed to demonstrate a genetic association between *IL18* and lupus⁹.

We found a genetic association between allele “A” in rs1946518 (–607 C/A) and BD (OR 1.48, 95% CI 1.10–1.97, $p = 0.0088$). Our data indicate that allele “A” is the minor allele in rs1946518 in Turkish individuals, consistent with the European-derived CEU samples in HapMap. This is contrary to the findings of Keskin, *et al*, who reported that allele “C” is the minor allele and BD-associated allele in rs1946518 from studies in an independent Turkish sample¹⁰. A genetic association of rs1946518 albeit with allele “C” was also reported in Korean patients with BD¹¹. This association was not found in another independent Korean sample set¹². Of note, our study had 85% power to detect a genetic association in rs1946518 (assuming a dominant model, disease prevalence = 0.001, $\alpha = 0.05$). We detected no genetic association with rs360719 or rs187238 in BD (Table 2).

However, our study was underpowered to detect an association in these 2 SNP given the minor allele frequencies and odds ratios detected.

We found a genetic association between *IL18* and BD but not lupus in Turkish patients. Palomino-Morales, *et al* have reported a similar association between allele “A” in rs1946518 and giant cell arteritis¹³. In addition, the association between rs187238 and Henoch-Schönlein purpura has been reported¹⁴. This suggests that *IL18* might be a common susceptibility locus for at least 3 vasculitic diseases. Whether *IL18* is a susceptibility gene in other vasculitides remains to be investigated.

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Table 1. Genetic association analysis of single-nucleotide polymorphisms located in the promoter region of *IL18* in lupus cases and controls.

Marker	Position	Frequency			OR	(95% CI)	p
		Minor Allele	Cases, n (%)	Controls, n (%)			
rs187238	–137	C	70 (19.4)	98 (20.2)	0.96	(0.68–1.35)	0.80
rs1946518	–607	A	141 (39.2)	172 (35.8)	1.15	(0.87–1.53)	0.32
rs360719	–1297	C	69 (19.3)	93 (19.5)	0.99	(0.70–1.40)	0.95

Table 2. Genetic association analysis of single-nucleotide polymorphisms located in the promoter region of *IL18* in Behçet's disease cases and controls.

Marker	Position	Minor Allele	Frequency		OR	(95% CI)	p
			Cases, n (%)	Controls, n (%)			
rs187238	-137	C	68 (22.2)	98 (20.2)	1.13	(0.80–1.60)	0.49
rs1946518	-607	A	140 (45.2)	172 (35.8)	1.48	(1.10–1.97)	0.0088
rs360719	-1297	C	66 (22.0)	93 (19.5)	1.17	(0.82–1.67)	0.39

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