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 patients[1]. They found an increase in the relative expression of *IL18* mRNA in individuals with the rs360719 lupus-risk allele[1]. Interleukin 18 (IL-18) is a pleiotropic cytokine that can induce Th1 and Th2 responses in the presence and absence, respectively, of IL-12[2]. 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 lupus[7] and the 1990 International Study Group classification criteria for BD[8], respectively. Genotyping was performed using TaqMan allelic discrimination assays (Applied Biosystems, Foster City, CA, USA). The genotyping success rate was ≥ 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 lupus[9].

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 sample[10]. A genetic association of rs1946518 albeit with allele "C" was also reported in Korean patients with BD[11]. This association was not found in another independent Korean sample set[12]. 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 arteritis[13]. In addition, the association between rs187238 and Henoch-Schönlein purpura has been reported[14]. 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.

JASMINE HTOON; AJAY NADIG, BSc; TRAVIS HUGHES, BSc, Oklahoma Medical Research Foundation; SULE YAVUZ, MD; HANER DIRESKENELI, MD, Department of Rheumatology, Marmara University, School of Medicine, Istanbul, Turkey; GÜHER SARUHAN-DIRESKENELI, MD, Department of Physiology, Istanbul University, Istanbul School of Medicine, Istanbul, Turkey; AMR H. SAWALHA, MD, Oklahoma Medical Research Foundation; Department of Medicine, University of Oklahoma Health Sciences Center; US Department of Veterans Affairs Medical Center, Oklahoma City, Oklahoma, USA. Address correspondence to Dr. A.H. Sawalha, 825 NE 13th Street, MS 24, Oklahoma City, OK 73104. E-mail: amr-sawalha@omrf.ouhsc.edu

Supported by the Fleming Scholarship Program at the Oklahoma Medical Research Foundation (J. Htoon); and National Institutes of Health (NIH) grant R03AI076729 from the National Institute of Allergy and Infectious Diseases, NIH grants P20RR020143 and P30AR053483; and funding from the American College of Rheumatology Research and Education Foundation Rheumatology Investigator Award (Dr. Sawalha). The authors thank Dr. Elena Sanchez for her insightful suggestions.

REFERENCES

1. Sánchez E, Palomino-Morales RJ, Ortego-Centeno N, Jimenez-Alonso J, Gonzalez-Gay MA, Lopez-Nevot MA, et al. Identification of a new putative functional IL18 gene variant through an association study in systemic lupus erythematosus. Hum Mol Genet 2009;18:3739-48.
2. Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 regulates both Th1 and Th2 responses. Annu Rev Immunol 2001;19:423-74.
3. Esfandiari E, McInnes IB, Lindop G, Huang FP, Field M, Komai-Koma M, et al. A proinflammatory role of IL-18 in the development of spontaneous autoimmune disease. J Immunol 2001;167:5338-47.
4. Oztas MO, Onder M, Gurer MA, Bukan N, Sancak B. Serum interleukin 18 and tumour necrosis factor-alpha levels are increased in Behcet's disease. Clin Exp Dermatol 2005;30:61-3.
5. Park MC, Park YB, Lee SK. Elevated interleukin-18 levels correlated with disease activity in systemic lupus erythematosus. Clin Rheumatol 2004;23:225-9.
6. Musabak U, Pay S, Erdem H, Simsek I, Pekel A, Dinc A, et al. Serum interleukin-18 levels in patients with Behcet's disease. Is its expression associated with disease activity or clinical

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

Marker	Position	Minor Allele	Frequency Cases, n (%)	Frequency Controls, n (%)	OR	(95% CI)	p
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 Cases, n (%)	Frequency Controls, n (%)	OR	(95% CI)	p
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

presentations? Rheumatol Int 2006;26:545-50.

7. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
8. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990;335:1078.
9. Guerra SG, Morris DL, Gateva V, Graham RR, Vyse TJ, Cunninghame Graham DS. Dense mapping of IL18 shows no association in SLE. Hum Mol Genet 2010 Dec 23. [Epub ahead of print]
10. Keskin F, Pay S, Musabak U, Sagkan RI, Erdem H, Simsek I, et al. IL-18 promoter polymorphisms confer susceptibility to Behcet's disease, particularly to the mucocutaneous form, in a Turkish population. Clin Exp Rheumatol 2009;27 Suppl 53:S108-9.
11. Lee YJ, Kang SW, Park JJ, Bae YD, Lee EY, Lee EB, et al. Interleukin-18 promoter polymorphisms in patients with Behcet's disease. Hum Immunol 2006;67:812-8.
12. Jang WC, Park SB, Nam YH, Lee SS, Kim JW, Chang IS, et al. Interleukin-18 gene polymorphisms in Korean patients with Behcet's disease. Clin Exp Rheumatol 2005;23 Suppl 38:S59-63.
13. Palomino-Morales RJ, Vazquez-Rodriguez TR, Torres O, Morado IC, Castaneda S, Miranda-Filloy JA, et al. Association between IL-18 gene polymorphisms and biopsy-proven giant cell arteritis. Arthritis Res Ther 2010;12:R51.
14. Torres O, Palomino-Morales R, Miranda-Filloy JA, Vazquez-Rodriguez TR, Martin J, Gonzalez-Gay MA. IL-18 gene polymorphisms in Henoch-Schonlein purpura. Clin Exp Rheumatol 2010;28 Suppl 57:114.

J Rheumatol 2011;38:5; doi:10.3899/jrheum.101202