

Association of Interleukin 1 α Promoter Polymorphism (–889C/T) with Susceptibility to Systemic Sclerosis

To the Editor:

We read with great interest 2 articles^{1,2} about the association of interleukin 1 α (IL-1 α) –889C/T promoter polymorphism with systemic sclerosis (SSc). Hutyrová, *et al*¹ suggested that overexpression of IL-1 α -889 T allele carriers among patients with SSc in a Slovak population was significantly associated with risk of SSc. Mattuzzi, *et al*² showed that IL-1 α -889C/T was not significantly associated with SSc susceptibility in whites. In fact, IL-1 plays a critical role in connective tissue remodeling, which modulates both degradation and synthesis of extracellular matrix, and has been implicated in the fibrogenic phenotypes of SSc fibroblasts^{3,4}. Kawaguchi⁵ demonstrated that constitutive IL-1 α production might lead to a major share of the abnormalities of SSc fibroblasts.

Several investigations into the association of IL-1 α gene polymorphism and SSc have been carried out. Kawaguchi, *et al*⁶ found that the frequencies and carriage rates of allele T at –889 were negatively associated with SSc in a Japanese population. By contrast, this association was not replicated in the study by Beretta and colleagues in an Italian population⁷.

This discrepancy may arise from many aspects. First, we found a significant difference in the distribution of genotypes in patients, for example, in a Slovak population — i.e., CC:CT:TT of IL-1 α -889 C/T was 37.0%:50%:13.0%, while the ratio was 90%:10%:0.0% in a Japanese population. However, we found a similar distribution in controls between the 2 populations (58.0%:32.7%:9.3% in the Slovak group, 54.3%:34.4%:11.4% in the Japanese group). Second, the same polymorphism seems to play different roles in different ethnic populations. Evidence suggests that ethnicity influences the genetics in SSc. Genetic factors that have been implicated in predisposition, such as HLA and non-HLA genes, differ from ethnic group to ethnic group, suggesting that ethnic factors might be an independent determinant of prognosis⁸. Third, Hutyrová, *et al*¹ explained that the contradictory results might be caused by a different degree of linkage disequilibrium within the IL-1 cluster in different populations. However, it remains unknown whether IL-1 α -889C/T polymorphism is in linkage disequilibrium with other single-nucleotide polymorphisms (SNP). Fourth, SSc is a multifactorial disease that results from complex interactions of various genetic factors. Most current studies were based on a single polymorphism strategy. Limited data could not provide enough evidence for gene-gene interactions among cytokine SNP in the context of SSc. Further, the contribution of environmental factors to the etiology of SSc should also be considered.

Considering these findings, much study is needed to determine the relationship between IL-1 α -889C/T promoter polymorphism and SSc, including studies of gene-gene and gene-environment interactions in different ethnic populations to confirm this association.

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REFERENCES

1. Hutyrová B, Lukác J, Bosák V, Buc M, du Bois R, Petrek M. Interleukin 1 α single-nucleotide polymorphism associated with systemic sclerosis. *J Rheumatol* 2004;31:81-4.
2. Mattuzzi S, Barbi S, Carletto A, Ravagnani V, Moore PS, Bambara LM, et al. Association of polymorphisms in the IL1B and IL2 genes with susceptibility and severity of systemic sclerosis. *J Rheumatol* 2007;34:997-1004.
3. Dinarello CA. Biologic basis for interleukin-1 in disease. *Blood* 1996;87:2095-147.
4. Postlethwaite AE, Raghov R, Stricklin GP, Poppleton H, Seyer JM, Kang AH. Modulation of fibroblast functions by interleukin 1: Increased steady-state accumulation of type I procollagen messenger RNAs and stimulation of other functions but not chemotaxis by human recombinant interleukin 1 alpha and beta. *J Cell Biol* 1988;106:311-8.
5. Kawaguchi Y. IL-1 alpha gene expression and protein production by fibroblasts from patients with systemic sclerosis. *Clin Exp Immunol* 1994;97:445-50.
6. Kawaguchi Y, Tochimoto A, Ichikawa N, Harigai M, Hara M, Kotake S, et al. Association of IL1A gene polymorphisms with susceptibility to and severity of systemic sclerosis in the Japanese population. *Arthritis Rheum* 2003;48:186-92.
7. Beretta L, Bertolotti F, Cappiello F, Barili M, Masciocchi M, Toussoun K, et al. Interleukin-1 gene complex polymorphisms in systemic sclerosis patients with severe restrictive lung physiology. *Hum Immunol* 2007;68:603-9.
8. Reveille JD. Ethnicity and race and systemic sclerosis: How it affects susceptibility, severity, antibody genetics, and clinical manifestations. *Curr Rheumatol Rep* 2003;5:160-7.

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