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LETTER TO THE EDITOR

The single nucleotide polymorphisms of matrix metalloproteinase-1 in patients with systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by endothelial cell damage and activation, excessive accumulation of extracellular matrix (ECM), and fibrosis of the skin and internal organs. The regulation of production and breakdown of ECM is a central event in some physiologic (such as wound healing) and pathological conditions (SSc) [1].

Matrix metalloproteinase 1 (MMP-1) is the only enzyme capable of degrading types I, II, and III interstitial collagen [2], and its genetic variation resulting from a guanine insertion at −1607 bp (genotype GA vs. GGA) is known to cause an increase in the transcriptional activity of MMP-1 [3]. Although this single nucleotide polymorphism did not show any association with the development and clinical manifestations of SSc in Caucasians, African–Americans, or Hispanics [4], there has been no report on this issue in the Asian population. The objective of our study is to examine the association between SNP of the MMP-1 promoter and the development and clinical manifestations in Korean patients with SSc.

Materials and methods

This study comprises 63 Korean patients with SSc (female:male = 58:5; age at diagnosis, mean ± SD: 43.4 ± 13.4 years) fulfilling the preliminary criteria for the classification of SSc [5]. The controls included 62 healthy, disease-free Koreans (female:male = 60:2, age at enrollment: 44.3 ± 12.9 years). Some of the patients and controls (whose DNA samples were available at the time of this study) were previously recruited for a past study at our institute [6]. We retrospectively reviewed medical records to collect clinical and laboratory data at the time of diagnosis and at follow-up. Genomic DNA was prepared from peripheral blood and polymerase chain reaction was performed using a standard method with the following primers:

- sense: 5′-CCCTCTTGAACTCACATGTTATGC-3′
- anti-sense: 5′-biotin-TGGCCTGTTTTATCACTTCAGCA-3′

SNP genotyping was processed by a pyrosequencing reaction. The nucleotide sequences were determined from the signal peak in a pyrogram. The sequencing primer was as follows: 5′-ATTGTAGTTAAATAATTAGA-3′.

The frequency difference of SNP of MMP-1 promoter between SSc and controls, and its association with clinical manifestations of SSc, were assessed using Chi-square and Fisher's exact tests.

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Table 1 Clinical characteristics of patients with SSc

Clinical characteristics	SSc, $n = 63$ (%)	Subset	
		Diffuse, $n = 32$ (%)	Limited, $n = 31$ (%)
Raynaud's phenomenon	62 (98.4)	31 (96.9)	31 (100.0)
Sclerodactyly	54 (85.7)	30 (93.8)	24 (77.4)
Digital pitting scar	25 (39.7)	15 (46.9)	10 (32.3)
Distal phalangeal resortion	14 (22.2)	12 (37.5)*	2 (6.5)
Telangiectasia	11 (17.5)	6 (18.8)	5 (16.1)
Subcutaneous calcinosis	1 (1.6)	0 (0.0)	1 (3.2)
Interstitial lung disease	28 (44.4)	18 (56.3)	10 (32.3)
Anti-topoisomerase I	11 (17.5)	4 (12.5)	7 (22.6)
Anticentromere	3 (4.8)	1 (3.1)	2 (6.5)
Anti-nRNP	7 (11.1)	5 (15.6)	2 (6.5)

SSc systemic sclerosis
*$P = 0.003$ versus limited type

Table 2 Distribution of MMP-1 allele and genotypes in SSc patients and controls

		No.	Allele frequency			Genotype frequency			
			GGA	GA	*P*-value	GA/GA	GA/GGA	GGA/GGA	*P*-value
Korean	SSc	63	81 (64.3)	45 (35.7)	0.613	11 (17.5)	23 (36.5)	29 (46.0)	0.91 (D)
	Control	62	83 (67.0)	41 (33.0)		6 (9.7)	29 (46.8)	27 (43.6)	0.25 (R) 0.62 (Co-D)
SSc patients	Diffuse	32	34 (53.1)	30 (46.9)	0.0075*	8 (25.0)	14 (43.8)	10 (31.3)	0.016 (D)*
	Limited	31	47 (75.8)	15 (24.2)		3 (9.7)	9 (29.0)	19 (61.3)	0.109 (R) 0.017 (Co-D)*

SSc systemic sclerosis, *No*. number, *statistically significant, *D* dominant, *R* recessive, *Co-D* co-dominant

Results and discussion

Table 1 shows the clinical characteristics of the SSc patients. The diffuse type showed more distal phalangeal resorption (37.5 vs. 6.5%; $P = 0.003$) than the limited type did.

All observed allele and genotype frequencies met Hardy–Weinberg equilibrium. The frequency of the genotypes and SNP of the MMP-1 promoter did not show significant differences between the SSc patients and the controls (Table 2). The allele and genotype distribution of MMP-1 among controls in this study were quite similar to those of the study, which examined the relationship between MMP-1 promoter SNP and the risk of cervical cancer in Korean women [7]. These distributions were also similar to those of a previous, similar study evaluating three different ethnicities [4]. Contrary to the previous study, however, the limited type of SSc was significantly associated with the GGA allele (75.8 vs. 53.1%; $P = 0.007$) and genotype ($P = 0.016$, OR = 3.631, 95% CI = 1.266–10.416 in the dominant model; $P = 0.017$, OR = 2.49, 95% CI = 1.18–5.257 in the co-dominant model). As with the previous study, there was no association with the presence of major clinical manifestations or autoantibodies.

There have been few studies regarding the different biologic activities of skin fibroblasts in patients afflicted with different subsets of SSc. Skin fibroblasts from patients with diffuse and limited forms of SSc have been reported to show distinct adhesion molecule expression profiles [8]. Genetic variation might explain the differences seen in skin fibroblast biology of the two SSc subsets.

Although there was no significant association with the development of SSc in the Korean study group, in contrast to the previous study evaluating three different ethnicities, the high activity promoter genotype of MMP-1 seemed to significantly correlate with the limited subset of Korean SSc patients.

References

1. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, Rowell N, Wollheim F (1988) Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 15:202–205
2. Birkedal-Hansen H, Moore WG, Bodden MK, Windsor LJ, Birkedal-Hansen B, DeCarlo A, Engler JA (1993) Matrix metalloproteinases: a review. Crit Rev Oral Biol Med 4:197–250
3. Rutter JL, Mitchell TI, Buttice G, Meyers J, Gusella JF, Ozelius LJ, Brinckerhoff CE (1998) A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter creates an Ets binding site and augments transcription. Cancer Res 58:5321–5325
4. Johnson RW, Reveille JD, McNearney T, Fischbach M, Friedman AW, Ahn C, Arnett FC, Tan FK (2001) Lack of association of a functionally relevant single nucleotide polymorphism of matrix metalloproteinase-1 promoter with systemic sclerosis (scleroderma). Genes Immun 2:273–275

5. Masi AT, Rodman GP, Medsger TA (1980) Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 23:581–590
6. Joung CI, Jun JB, Chung WT, Song GG, Choe JY, Chang HK, Yoo DH (2006) Association between the HLA-DRB1 gene and clinical features of systemic sclerosis in Korea. Scand J Rheumatol 35:39–43
7. Ju W, Kang S, Kim JW, Park NH, Song YS, Kang SB, Lee HP (2005) Promoter polymorphism in the matrix metalloproteinase-1 and risk of cervical cancer in Korean women. Cancer Lett 217:191–196
8. Iannone F, Matucci-Cerinic M, Falappone PC, Guiducci S, Cinelli M, Distler O, Lapadula G (2005) Distinct expression of adhesion molecules on skin fibroblasts from patients with diffuse and limited systemic sclerosis. A pilot study. J Rheumatol 32:1893–1898