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Original Article

ADAM33 Polymorphisms Are Associated with Susceptibility to Systemic Lupus Erythematosus in a Korean Population

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Objective. The objective of this study is to assess whether genetic functional variants of disintegrin and metalloprotease 33 (*ADAM33*) are associated with susceptibility to systemic lupus erythematosus (SLE) in a Korean population. **Methods.** We previously identified 48 single nucleotide polymorphisms (SNPs) in *ADAM33*. Six SNPs were selected with regard to the linkage disequilibrium pattern. An association study of *ADAM33* was conducted in 190 patients with SLE and 469 control subjects. SNPs were genotyped using the TaqMan Real-time polymerase chain reaction method, and haplotype analyses of related variants were performed. **Results.** All SNPs were in Hardy-Weinberg equilibrium. Significant associations were found between the *ADAM33* polymorphisms and SLE at rs2787094 (adjusted odds ratio [OR] 1.88, 95% confidence interval [CI] 1.00 to 3.54; $p < 0.0001$). The rs554743 polymorphism was associated with the presence of the immunoglobulin M anti-cardiolipin antibody (adjusted OR 0.29, 95% CI 0.10 to 0.83; $p = 0.021$). **Conclusion.** *ADAM33* polymorphisms were associated with susceptibility to SLE and development of clinical disease manifestations in a Korean population. Further study is warranted to clarify the role of *ADAM33* in SLE pathogenesis. **(J Rheum Dis 2016;23:88-95)**

Key Words. Disintegrin and metalloproteinase domain 33 protein, Systemic lupus erythematosus, Single nucleotide polymorphism

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, heterogeneous autoimmune disease characterized by the production of autoantibodies to multiple nuclear antigens [1]. Epidemiological data on the sibling risk ratio, familial aggregation of SLE, and the disease concordance rate in twins all support a genetic component to the occurrence of SLE [2]. The pathological hallmarks of SLE are altered immune responses to autoantigens with autoantibody production and subsequent tissue injury mediated by deposition of immune complexes. $CD4^+$ T cells are critical drivers of the B-cell-dependent auto-antibody response by producing co-stimulatory signals and cytokines [3].

The disintegrin and metalloprotease 33 (*ADAM33*) gene has been identified and characterized in mice and humans [4,5]. *ADAM33* maps to human chromosome 20p13 and encodes an open reading frame of 2,442 bp consisting of 22 exons.

The membrane-anchored proteins of the *ADAM* gene family possess a unique domain structure containing not only disintegrin and a metalloprotease domains [6,7] but also a signal sequence prodomain, a catalytic domain, a cysteine-rich domain, an epidermal-growth-factor like domain, and a cytoplasmic domain [8,9]. These *ADAM* gene family domains have been suggested to be involved

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in adhesive interactions, cell fusion, and proteolysis in numerous biological processes, including myoblast fusion, neurogenesis, sperm maturation, and protein-ectodomain shedding of cell surface proteins such as cytokines [10-12]. The *ADAM33* gene is expressed in lung fibroblasts and heart and bronchial smooth muscles and is associated with asthma, chronic obstructive pulmonary disease, and bronchial hyper-responsiveness [13-15], where Th2 cytokines play a key role in the pathogenesis of the disease [16].

Th2 cells are also involved in SLE pathogenesis [17-19]. Th2 cytokines including interleukin (IL) 10 and IL13 are upregulated in patients with SLE due to aberrant DNA methylation of the $CD4^+$ T cell promoter regions, thereby contributing to activate the humoral immune machinery and trigger lupus disease activity [20]. Therefore, we hypothesized that *ADAM33* single nucleotide polymorphisms (SNPs) would be associated with susceptibility to SLE.

In our previous study, we reported the *ADAM33* polymorphic sites by scanning the entire gene sequence, including the promoter region, by direct sequencing. We found 48 genetic variants in *ADAM33*, among which six SNPs were genotyped in patients with SLE, healthy subjects, and patients with rheumatoid arthritis (RA) (n= 1,149). Herein, we investigated whether there were associations between *ADAM33* polymorphisms and susceptibility to SLE in a Korean population.

MATERIALS AND METHODS

Study population and clinical evaluation

The study population consisted of 190 unrelated consecutive patients with SLE who fulfilled the American College of Rheumatology (ACR) 1987 classification criteria for SLE [21], 490 unrelated patients with RA who satisfied the ACR classification criteria for RA [22] as a disease control, and 469 healthy controls who had received comprehensive medical testing. All subjects were Koreans recruited from Eulji University Hospital, Chonnam University Hospital, and Wonkwang University Hospital. The mean age of the patients with SLE was 36.3 years, that of the patients with RA was 38.7 years, and that of the control subjects was 38.3 years. The patient characteristics are shown in Table 1. The study protocol was approved by the institutional review board at Eulji University Hospital, and venous blood samples and records were obtained after receiving written informed consent.

SNP selection

Six SNPs in the *ADAM33* gene, including three exonic SNPs (rs528557, rs2280090, and rs2280091) and two intronic SNPs (rs554743 and rs3918395) located in the 3' region near the SNPs (rs2787094) were selected based on a previous study [23]. All SNPs were studied correlation with asthma in European and Asian [13], especially rs2280091 was associated with bronchial hyper responsiveness in Korean asthmatics [24].

Autoantibodies

The presence of antinuclear antibody was determined by immunofluorescence using the Hep-2 cell line. Anti-ribonucleoprotein (RNP) antibody and anti-Sm antibody were detected by Alegria® test strip (Orgentec GmbH, Mainz, Germany). Anti-Sjögren's syndrome-related antigen A (SSA)/Ro and anti-Sjögren's syndrome-related antigen A (SSB)/La antibody were detected by autoimmune autoimmune EIA Anti-SS-A/Ro, SS-B/Ra test (Bio-Rad Laboratories, Hercules, CA, USA). Hematologic disorder was defined according to the ACR criteria; hemolytic anemia with reticulocytosis, leukopenia ($<4,000/mm^3$), lymphopenia ($<1,500/mm^3$), and thrombocytopenia ($<100,000/mm^3$). Nephritis, serositis, and malar rash

Table 1. Clinical characteristics of the study subjects

Clinical profile	SLE	RA	Control
No. of subject	190	490	469
Age (yr)	36.3±11.6	38.7±12.1	38.3±10.4
Sex (male/female)	1/20.1	1/3.2	1/1.1
Disease duration (yr)	6.7±4.04	7.1±4.21	-
ACR criteria			
Malar rash	107 (56.4)		
Discoid rash	6 (3.0)		
Photosensitivity	75 (39.3)		
Oral ulcers	62 (32.7)		
Arthritis	93 (48.8)		
Serositis	57 (30.3)		
Renal involvement	76 (40.0)		
CNS involvement	9 (5.0)		
Hematologic abnormities	171 (90.0)		
Immunologic abnormalities	114 (60.0)		
Antinuclear antibodies	190 (100.0)		

Values are presented as number only, mean±standard deviation, or number (%). ACR: American College of Rheumatology, CNS: central nervous system, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus.

were defined by the ACR criteria [25].

Anti-phospholipid antibodies

The presence of anti-cardiolipin antibody (aCL; immunoglobulin [Ig] G >15 IgG phospholipid units, IgM> 10 IgM phospholipid units; IncStar, Stillwater, MN, USA), lupus anticoagulant (LAC; partial thromboplastin time or Russell's viper venom time with mix), and anti-β 2 glycoprotein I antibody (anti-β2GPI; QUANTA Lite β 2GPI screen, INOVA Diagnostics Inc., San Diego, CA, USA) was tested in sera or plasma obtained from the study subjects. The three antiphospholipid antibodies (aCL, LAC, and anti-β2GPI) were classified into antibody-positive and antibody-negative groups based on the manufacturer's protocols.

ADAM33 gene genotyping

Genomic DNA was isolated from peripheral blood samples with the G-Spin Blood kit (iNtRON, Daejeon, Korea), and the DNA samples were stored at 4°C until use. The *ADAM33* SNP analysis was performed with the real-time polymerase chain reaction (PCR) allelic discrimination TaqMan assay (Applied Biosystems, Foster City, CA, USA). The real-time PCR analysis was carried out in a total volume of 10 μL with 10 ng genomic DNA, 1 pmol gene specific forward and reverse primers in 1× TaqMan and 2× Universal PCR Master Mix (Applied Biosystems). Real-time PCR was performed using an ABI 7900HT Real-time PCR System (Applied Biosystems) according to the manufacturer's instructions and analyzed with SDS 2.3 software (Applied Biosystems).

Statistical analysis

Chi-square tests were used to estimate the Hardy-Weinberg equilibrium (HWE). Linkage disequilibrium (LD) analyses were conducted by pairwise comparison of biallelic loci, and the haplotype frequencies of the *ADAM33* gene polymorphisms for multiple loci were estimated using gPLINK software ver. 1.06 (http://pngu.mgh.harvard.edu/purcell/plink). Logistic regression analyses were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs). The Bonferroni correction ($p<0.05$ divided by the number of SNPs analyzed) was used to account for multiple testing.

RESULTS

Six *ADAM33* polymorphisms were genotyped in the 190 SLE, 490 RA, and 469 control subjects. The basic clinical characteristics of the patients with SLE and controls are summarized in Table 1. Each group was selected for similar age, but the proportion of females in the SLE group was higher than that in the control group.

We compared the genotype frequencies between patients with SLE and controls. The minor allele frequencies of the six polymorphisms are summarized in Table 2. All genotype distributions of control subjects were consistent with those expected from the HWE (all $p>0.05$).

The results of the association between the *ADAM33* polymorphisms and SLE risk are shown in Table 3. Significant allelic differences were observed in the rs2787094 SNPs of the *ADAM33* gene between the case and control groups. G alleles at rs2787094 (OR 1.88, 95% CI 1.00 to 3.54; $p<0.0001$) resulted in an increased risk for SLE. The recessive rs2787094 model (CC/CG+GG) was significantly associated with SLE risk (OR 2.09, 95% CI 1.60 to 5.26; $p=0.000$) after Bonferroni correction for the 6 SNPs analyzed. We further investigated the same

Table 2. Basic information on the genotyped single nucleotide polymorphisms (SNPs) in the *ADAM33* gene

SNP No.	NCBI rs No.	Chromosome position*	Location	Base change	Amino acid	MAF				HWE‡	Success rate (%)
						JPT†	CHB†	SLE	control		
1	rs554743	3662142	Intron1	A>G		0.43	0.39	0.403	0.382	0.602	92.39
2	rs3918395	3653149	Intron13	G>T		0.13	0.09	0.082	0.073	1	95.52
3	rs528557	3651742	Exon19	G>C	Gly717Gly	0.27	0.20	0.236	0.234	0.135	92.99
4	rs2280091	3650234	Exon20	T>C	Met764Thr	0.14	0.09	0.063	0.068	1	97.01
5	rs2280090	3650205	Exon20	C>T	Pro774Ser	0.16	0.11	0.060	0.077	0.670	95.37
6	rs2787094	3649161	3'UTR	C>G		0.28	0.40	0.367	0.337	0.591	93.88

CHB: Han Chinese in Bejing, China, JPT: Japanese in Tokyo, Japan; MAF: minor allele frequency, NCBI: National Center for Biotechnology Information, SLE: systemic lupus erythematosus, UTR: untranslated region. *SNP position from the NCBI dbSNP (http://www.ncbi.nlm.nih.gov/snp). †MAF from http://browser.1000genomes.org/. ‡HWE indicates the p-value for the Hardy-Weinberg equilibrium in normal controls.

Table 3. Genotypic and allelic analysis of the *ADAM33* gene polymorphisms in the controls and patients with SLE or RA (disease control)

SNP No.	NCBI rs No.	Genotype	Control	SLE	Adjusted OR (95% CI)	p-value* (control vs. SLE)	p-value* (control vs. RA)
1	rs554743	Total (AA, AG, GG)	429 (100.0)	190 (100.0)			487
		AA	165 (38.5)	62 (32.6)	1.00 (reference)	0.796	0.616
		AG	200 (46.6)	97 (51.1)	1.13 (0.69∼1.87)		
		GG	64 (14.9)	31 (16.3)	0.93 (0.48∼1.80)		
		AG/GG vs. AA	264 (61.5)	128 (67.4)	1.07 (0.67∼1.72)	0.768	0.650
		AA/AG vs. GG	365 (85.1)	159 (83.7)	0.87 (0.48∼1.57)	0.637	0.502
		G allele freq.	0.382	0.403	1.09 (0.12∼0.87)	0.459	0.271
2	rs3918395	Total (GG, GT, TT)	462 (100.0)	178 (100.0)			485
		GG	389 (84.2)	156 (87.6)	1.00 (reference)	0.801	1.000
		GT	71 (15.4)	19 (10.7)	0.83 (0.43∼1.59)		
		TT	2 (0.4)	3 (1.7)	1.41 (0.16∼12.20)		
		GT/TT vs. GG	73 (15.8)	22 (12.4)	0.86 (0.46∼1.61)	0.641	0.990
		GG/GT vs. TT	460 (99.6)	175 (98.3)	1.44 (0.17∼12.46)	0.740	0.997
		T allele freq.	0.074	0.082	1.12 (0.74∼1.69)	0.588	0.482
3	rs528557	Total (GG, GC, CC)	463 (100.0)	160 (100.0)			477
		GG	274 (59.2)	98 (61.3)	1.00 (reference)	0.864	0.281
		GC	156 (33.7)	52 (32.5)	0.87 (0.53∼1.43)		
		CC	33 (7.1)	10 (6.3)	0.97 (0.38∼2.45)		
		GC/CC vs. GG	189 (40.8)	62 (38.8)	0.89 (0.56∼1.42)	0.618	0.914
		GG/GC vs. CC	430 (92.9)	150 (93.8)	1.02 (0.41∼2.54)	0.969	0.122
		C allele freq.	0.234	0.237	1.02 (0.78∼1.32)	0.913	0.810
4	rs2280091	Total (AA, AG, GG)	457 (100.0)	192 (100.0)			487
		TT	389 (85.1)	178 (92.7)	1.00 (reference)	0.172	0.864
		TC	66 (14.4)	13 (6.8)	0.50 (0.24∼1.05)		
		CC	2 (0.4)	1 (0.5)	0.52 (0.04∼7.72)		
		TC/CC vs. TT	68 (14.9)	14 (7.3)	0.50 (0.25∼1.03)	0.061	0.603
		TT/TC vs. CC	389 (85.1)	191 (99.5)	2.04 (0.14∼30.29)	0.604	0.985
		C allele freq.	0.069	0.063	0.92 (0.59∼1.43)	0.702	0.282
5	rs2280090	Total (AA, AG, GG)	449 (100.0)	190 (100.0)			489
		CC	379 (84.4)	177 (93.2)	1.00 (reference)	0.141	0.245
		CT	68 (15.1)	12 (6.3)	0.47 (0.22∼1.01)		
		TT	2 (0.4)	1 (0.5)	1.89 (0.06∼56.43)		
		CT/TT vs. CC	70 (15.6)	13 (6.8)	0.50 (0.24∼1.05)	0.066	0.147
		CC/CT vs. TT	447 (99.6)	189 (99.5)	2.02 (0.07∼60.49)	0.684	0.250
		T allele freq.	0.077	0.060	0.77 (0.50∼1.19)	0.235	0.348
6	rs2787094	Total (CC, CG, GG)	445 (100.0)	184 (100.0)			489
		CC	186 (41.8)	91 (49.5)	1.00 (reference)	0.000	0.913
		CG	211 (47.4)	48 (26.1)	0.36 (0.21∼0.61)		
		GG	48 (10.8)	45 (24.5)	1.88 (1.00∼3.54)		
		CG/GG vs. CC	259 (58.2)	93 (50.5)	0.63 (0.40∼1.00)	0.048	0.970
		CC/CG vs. GG	397 (89.2)	139 (75.5)	2.09 (1.60∼5.26)	0.000	0.970
		G allele freq.	0.338	0.368	1.14 (0.90∼1.44)	0.266	0.768

Values are presented as number only or number (%). CI: confidence interval, freq.: frequency, NCBI: National Center for Biotechnology Information, OR: odds ratio, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, SNP: single nucleotide polymorphism. *Sex and age adjusted.

polymorphic sites in patients with RA. However, we found no association between the *ADAM33* SNPs and susceptibility to RA (Table 3).

Next, we conducted a subgroup analysis in patients with SLE to determine whether the *ADAM33* polymorphisms were associated with the development of any specific SLE

Table 4. Genotype frequencies of the *ADAM33* polymorphisms in dominant phenotypic model for patients with SLE

Phenotype	NCBI rs No.											
	rs554743		rs3918395		rs528557		rs2280091		rs2280090		rs2787094	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Sm	0.90 (0.10～1.79)	0.790	0.83 (0.20～3.38)	0.791	1.60 (0.65～3.91)	0.302	0.59 (0.06～5.55)	0.646	-	0.999	0.83 (0.39～1.77)	0.638
RNP	2.10 (0.97～4.59)	0.061	0.56 (0.17～1.84)	0.343	0.98 (0.42～2.26)	0.973	1.05 (0.21～5.23)	0.952	0.88 (0.15～4.93)	0.890	1.18 (0.56～2.48)	0.651
Ro	1.58 (0.75～3.35)	0.232	0.89 (0.26～3.00)	0.859	1.24 (0.54～2.83)	0.601	1.28 (0.22～7.18)	0.777	0.95 (0.15～5.72)	0.955	1.37 (0.67～2.18)	0.382
La	1.29 (0.54～3.09)	0.562	0.19 (0.02～1.65)	0.135	0.44 (0.16～1.18)	0.104	-	0.999	-	0.999	1.49 (0.66～3.37)	0.336
Anticoagulant	1.21 (0.39～3.71)	0.728	1.98 (0.46～8.49)	0.353	0.60 (0.19～1.91)	0.394	3.10 (0.48～9.95)	0.233	2.66 (0.41～6.95)	0.299	1.45 (0.52～4.03)	0.475
IgG aCL	0.70 (0.26～1.93)	0.501	2.31 (0.62～8.58)	0.211	0.96 (0.35～2.65)	0.947	0.87 (0.09～8.01)	0.903	1.00 (0.10～9.63)	0.995	1.47 (0.57～3.81)	0.424
IgM aCL	0.29 (0.10～0.83)	0.021	0.92 (0.18～4.67)	0.927	0.26 (0.19～1.98)	0.425	1.17 (0.12～0.96)	0.887	1.39 (0.14～3.54)	0.777	1.07 (0.39～2.88)	0.892
Malar rash	1.11 (0.54～2.24)	0.771	1.45 (0.49～4.21)	0.494	1.07 (0.51～2.23)	0.857	0.61 (0.13～2.77)	0.526	0.44 (0.08～2.47)	0.354	0.892 (0.46～1.73)	0.738
Serositis	1.56 (0.71～3.41)	0.265	0.68 (0.20～2.30)	0.539	0.58 (0.25～1.34)	0.206	0.29 (0.03～2.51)	0.263	0.33 (0.03～2.98)	0.329	0.85 (0.42～1.72)	0.653
Nephritis	0.36 (0.31～1.30)	0.215	0.51 (0.15～1.72)	0.284	0.91 (0.43～1.94)	0.823	0.23 (0.02～1.96)	0.179	-	0.999	1.10 (0.57～2.12)	0.776
Hemolytic anemia	1.43 (0.55～3.70)	0.465	0.73 (0.15～3.54)	0.699	1.11 (0.43～2.84)	0.827	-	0.999	-	0.999	1.09 (0.46～2.57)	0.840
Leukopenia	0.96 (0.48～1.97)	0.945	0.90 (0.31～2.61)	0.854	1.09 (0.52～2.25)	0.817	0.41 (0.09～1.83)	0.244	0.27 (0.05～1.52)	0.140	1.18 (0.61～2.28)	0.614
Lymphopenia	0.36 (1.10～1.48)	0.165	3.8 (0.41～34.63)	0.236	1.31 (0.39～4.32)	0.656	1.47 (0.14～5.06)	0.744	1.37 (0.13～4.57)	0.790	0.79 (0.26～2.42)	0.685
Thrombocyto-penia	1.19 (0.58～2.41)	0.630	1.59 (0.56～4.53)	0.380	1.71 (0.81～3.58)	0.153	1.74 (0.40～7.44)	0.455	0.24 (0.26～5.97)	0.783	0.72 (0.37～1.40)	0.337

aCL: anti-cardiolipin antibodies, CI: confidence interval, Ig: immunoglobulin, NCBI: National Center for Biotechnology Information, OR: odds ratio, RNP: ribonucleoprotein, SLE: systemic lupus erythematosus.

Table 5. The distribution of rs554743 genotype in SLE patient with IgM aCL feature

Genotype	IgM aCL		p-value	OR (95% CI)
	Negative	Positive		
AA	30 (27.5)	10 (52.6)	0.021	0.293 (0.103～0.831)
AG/GG	79 (72.5)	9 (47.4)		

Values are presented as number (%). aCL: anti-cardiolipin antibodies, CI: confidence interval, IgM: immunoglobulin M, OR: odds ratio, SLE: systemic lupus erythematosus.

phenotype. We investigated the association between the SLE phenotypes sm, RNP, Ro, La, anticoagulatni IgG aCL, IgM aCL, Malar rash, serositis, nephritis, hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia with the *ADAM33* polymorphisms. Interestingly, the dominant rs554743 model (AA/AG, +GG) showed a decreased risk for the development of IgM aCL in patients with SLE (OR 0.29, 95% CI 0.10 to 0.83; p=0.021) (Tables 4 and 5).

The LD values between each pair of *ADAM33* SNPs are presented in Figure 1. A one haplotype block was defined in our analysis. A haplotype analysis was performed with the six SNPs, and the 10 haplotypes were analyzed. However, no significant differences were observed between the case and control groups.

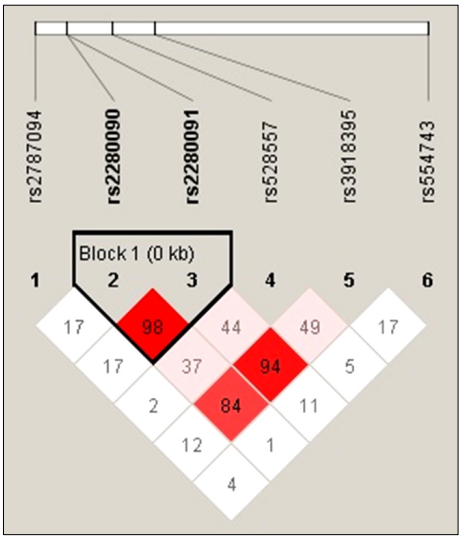

Figure 1. Linkage disequilibrium pattern in the *ADAM33* gene.

DISCUSSION

ADAM33 has been identified as an asthma susceptibility factor using a positional cloning strategy [13,14]. SLE is a disease of unclear etiology and is characterized by a pathogenic autoantibody-related reaction to various organs and tissues. Individual differences in the risk for SLE are mainly genetic and are further modified by environmental exposure and/or chance events experienced by the patient [26]. We found an association between susceptibility to SLE and the *ADAM33* SNPs in this study. The female sex ratio of SLE patients is higher than male, about 20:1, so we conducted sex and age adjusted logistic regression analysis. One SNP showed a significant difference between patients with SLE and the control group. This association was expected, as SLE is a Th2 dominant disease.

In contrast, RA is considered a Th1 dominant disease, suggesting that the immunological process is dominated by interferon- γ -secreting $CD4^+$ T cells [27]. Therefore, we found no association between the *ADAM33* SNPs and RA.

Stimulation of Th2 cytokines, such as IL-4 and IL-13, increases *ADAM33* mRNA expression in lung fibroblasts [16]. IL-4 increases the number of splenic B cells by increasing net migration of circulating B cells to the spleen and by increasing splenic B cell survival [28]. An altered B cell subset in peripheral blood has also been found in patients with SLE who have an increase in the number of immature transitional B-cells, memory B-cells, plasmablasts, and circulating plasma cells that spontaneously produce autoantibodies [29-32].

We observed a significant association between *ADAM33* rs554743 and the presence of IgM aCL in the subtype analysis of patients with SLE stratified by disease-related phenotype. IgM aCL was first identified in association with SLE [33]. IgM aCL is associated with various infections or could be an epiphenomenon during thrombotic events.

Our present study had several limitations. First, we analyzed a relatively small number of patients with SLE compared to those of RA and control in a Korean population. The pathogenesis of SLE is highly complex and involves

both the genetic background and environmental conditions of patients. Conducting this study with a specific ethnicity of subjects made it difficult to interpret the data. This problem can be overcome in future studies by using replicate groups from other regions of Korea and other ethnic groups.

Second, we did not examine the functional aspects of *ADAM33* SNPs. Further study regarding to the functional role of *ADAM33* SNPs on the pathogenesis of lupus should be conducted.

Our data reveal the association between *ADAM33* and susceptibility to SLE. Further investigations assessing the functional role of *ADAM33* in patients with SLE will be helpful to clarify the etiology of SLE.

CONCLUSION

We identified 6 SNPs of *ADAM33* gene in Korean SLE patients and healthy controls. We demonstrated that *ADAM33* polymorphisms are significantly associated with susceptibility to SLE and development of clinical disease manifestation in a Korean population. Investigation on *ADAM33* in other ethnic groups and larger population of SLE patients are necessary in the future to further elucidate the pathogenesis of SLE with regard to the current results.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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