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FcγRIIB Gene Polymorphisms Are Associated with Disease Risk and Clinical Manifestations of Systemic Lupus Erythematosus in Koreans

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Systemic lupus erythematosus (SLE) is chronic autoimmune disease with various autoantibodies, which are involved in tissue damage. Fc gamma receptors (FcγRs) bind the constant region of the immunoglobulin G and transmit stimulatory or inhibitory signal to immune cells. The FcγR genes map to 1q23, a susceptible locus for SLE. We have screened single nucleotide polymorphisms (SNPs) in one of *FcγR* gene, *FcγRIIB*, which is the only inhibitory receptor, after considering gene map and reported SNPs. There were 3 SNPs in *FcγRIIB*: 10849 T>C (rs1050501) in exon 5 and 10950 T>G (rs6666965) and 11045 G>T (rs12117530) in intron 5 in Koreans. The frequency of the minor allele (T) of rs12117530 was significantly higher in SLE patients (50 patients, 20.4%) than healthy controls (17 patients, 12%, $p = 0.041$). Leukopenia occurred more frequently in SLE patients carrying the minor allele (T) of rs12117530 ($p = 0.032$). Among 5 haplotypes, the frequency of decreased complement was significantly lower in SLE patients with haplotype 1 [TTG] ($p = 0.045$). Nephritis, lymphopenia and anti-dsDNA antibody were significantly less frequent in SLE patients with haplotype 2 [TGG] ($p = 0.046$, $p = 0.018$, $p = 0.002$, respectively). The frequency of thrombocytopenia and anti-dsDNA antibody was significantly higher in SLE patients with haplotype 3 [CTG] ($p < 0.001$, $p = 0.04$, respectively). These data reveal that genetic polymorphisms within *FcγRIIB* are associated with disease susceptibility and phenotypes of SLE in Koreans. Furthermore, *FcγRIIB* rs12117530 polymorphism (T allele) may be an important risk factor in SLE.

Keywords: immunoglobulin G receptor; phenotype; risk factor; single nucleotide polymorphism; systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease with a genetic predisposition and environmental or immunoregulatory triggering factors, which lead to chronic systemic inflammation (Tsao 2003; Rahman and Isenberg 2008). Different approaches with various validations have been tried for genome-wide association study to identify the novel susceptibility region for SLE, and 13 major cytogenetic locations show significant linkage to SLE (Nath et al. 2004). Among them, eight SLE susceptibility regions have been replicated independently using lupus phenotypes only (Nath et al. 2004; Rhodes and Vyse 2008; Harley et al. 2009). These include 1q23, 1q41, 2q37, 4p16, 6p21, 11p13, 12q24, and 16q13.

Fc gamma receptors (FcγRs) are hematopoietic cell surface glycoproteins, which bind the Fc portion (constant region) of the immunoglobulin G, and transmit stimulatory or inhibitory signals to immune effector cells. FcγRs play an important role in the pathogenesis of autoimmune diseases (Salmon and Pricop 2001). These receptors regulate various humoral and cellular immune responses including activation of B cells, transcriptional regulation of cytokine expression, antibody-dependent cellular cytotoxicity, and immune complex clearance with phagocytosis (Nimmerjahn and Ravetch 2006; Brown et al. 2007). *FcγR* genes map to 1q21-23, a linkage locus for SLE. Humans have 5 low-affinity FcγRs, termed FCGRs, encoded by *FCGRIIA*, *FCGRIIB*, *FCGRIIC*, *FCGRIIIA,* and *FCGRIIIB*. FCGRIIB is the only inhibitory FcγR, which contains an immunoreceptor tyrosine-based inhibitory motif (Smith and Clatworthy 2010) and is possible candidate gene for SLE

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(Kyogoku et al. 2002; Magnusson et al. 2004; Chen et al. 2006).

Serum concentrations of C-reactive protein (CRP) in humans are indicative of inflammation and pathological progression of an infection. However, we reported there is little or no increase in CRP levels in non-infectious inflammation of SLE (Suh et al. 2001, 2006). Additionally, we found that a -390 C>A or T polymorphism within the CRP promoter region might be involved in the regulation of CRP expression and the susceptibility of SLE in Koreans (Kim et al. 2009a). CRP is also known to bind to FcγRs (Stein et al. 2000).

Therefore, we tried to identify single nucleotide polymorphisms (SNPs) within *FCGRIIB*, determine their frequency in Koreans, and evaluate their significance in the susceptibility and clinical phenotypes of SLE.

Materials and Methods

Subjects

Two hundred forty-five SLE patients and 142 normal controls (NCs) were enrolled from Ajou University Hospital. All SLE patients satisfied at least four criteria in the 1982 revised American College of Rheumatology classification criteria for SLE (Tan et al. 1982) and the patients were excluded if they were younger than 18 years-old. Information on the medical history, clinical symptoms, physical examinations, and laboratory results was registered in a database from the onset of the disease by reviewing the medical records and interviews. The NCs, older than 18 years-old, were chosen from the general population using a screening questionnaire to indicate that there is no history of autoimmune disorders. All subjects participating in this study were ethnically Korean and gave their informed consents. The study was approved by the Institutional Review of Board.

DNA isolation

Genomic DNA was extracted from whole blood using the QuickGene DNA whole blood kit S (Fujifilm Life science, Tokyo, Japan) according to the manufacturer's instructions.

Identification and genotyping of SNPs in FCGRIIB

Forty patients with SLE and 40 NCs were enrolled for screening an SNP. After considering gene sequence of *FCGRIIB* published in the National Center for Biotechnology Information and single nucleotide polymorphisms (SNPs) reported in the database of SNP, we chose the gene region to be screened for possible SNP in Koreans. A region of *FCGRIIB* located between intron 4 and intron 6 was amplified by PCR with Amfisure PCR Master Mix (GenDEPOT, Barker, TX, USA). The following primers were used for amplification and sequencing: intron 4 ~ intron 6 forward primer: 5′ TGGAGA AACCTCGGTAAGCA 3′, reverse primer: 5′ TTGGGTGGCCCC TGGTTCTCA 3′. Potential polymorphisms of *FCGRIIB* were screened by direct sequencing (Bionics Co., Seoul, Korea). We considered a mutation as an SNP if a minor allele frequency was greater than 5%. Follow up genotyping was performed for SNPs detected in *FCGRIIB* using direct sequencing (Bionics Co., Seoul, Korea) in an additional 205 patients with SLE and 102 NCs.

Statistical analysis

The genotype frequency was tested for significant departures from Hardy-Weinberg equilibrium at each SNP by chi-square analysis. Differences in genotype frequency between cases and controls were tested by the chi-square test and calculation of the odds ratio and the 95% confidence interval. Three logistic regression models (codominant, dominant, and recessive) were used to analyze each SNP after controlling for age and sex as covariates. Differences in the mean value of the phenotypic characteristics between groups were compared by an analysis of variance test and a t-test. A p value of < 0.05 was considered statistically significant. Haplotypes were analyzed using Haploview version 4.2 based on the EM algorithm (Barrett et al. 2005). Linkage disequilibrium between loci was measured using the absolute value of Lewontin's /D′/ and r^2 (Hedrick 1987). Statistical analyses were conducted using SPSS version 12.0 software (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics of the study subjects

The mean age of SLE patients was 30.4 ± 8.6 years, and 89.4% of them were women (Table 1). The mean age of NCs was 29.7 ± 5.7 years, and 89.4% of them were women. Clinical features of SLE patients were as follows in order of decreasing frequency: arthritis (72.2%), oral ulcer (53.1%), rash (37.6%), lupus nephritis (LN, 25.7%), and serositis (14.3%).

Genotype frequencies of FCGRIIB

The genotype distributions of all polymorphisms within *FCGRIIB* were consistent with Hardy-Weinberg equilibrium for patients with SLE and the NCs ($p > 0.05$). Based on a minor allele frequency of greater than 5%, three SNPs within *FCGRIIB* were identified: 10849 T>C (rs1050501) in exon 5 and 10950 T>G (rs6666965) and 11045 G>T (rs12117530) in intron 5. The allele and genotype frequencies of the *FCGRIIB* polymorphisms are provided in Table 2. In the rs12117530 polymorphism, the genotype frequency of the minor allele (T) of patients with SLE was significantly higher than that of the NCs (codominant model; $p = 0.047$ and recessive model; $p = 0.041$).

Haplotype frequencies of FCGRIIB

Linkage disequilibrium between SNPs was examined locus by locus. The three polymorphisms identified in *FCGRIIB* were not in linkage disequilibrium, and five common haplotypes for these polymorphisms were constructed using Haploview software: haplotype 1 (HT1) [TTG], HT2 [TGG], HT3 [CTG], HT4 [TGT], HT5 [other] (Fig. 1). There was a trend of differences observed in the frequency of HT1 [TTG] between SLE and NC groups (recessive model; $p = 0.050$) (Table 3).

Associations between SLE phenotype and SNPs

The clinical characteristics according to genotype are summarized in Table 4. The frequency of leukopenia was significantly higher in SLE patients carrying the minor allele (T) rs12117530 than those not ($p = 0.032$).

The clinical characteristics according to the haplotype

Table 1. Clinical characteristics of the study subjects.

Characteristics	SLE (n = 245)	NC (n = 142)	*p* value
Age (year)	30.4 ± 8.6	29.7 ± 5.7	0.360
Sex			0.988
Male	26 (10.6%)	15 (10.6%)	
Female	219 (89.4%)	127 (89.4%)	
Oral ulcer	130 (53.1%)		
Arthritis	177 (72.2%)		
Serositis	35 (14.3%)		
Rash	92 (37.6%)		
Nephritis	63 (25.7%)		
Leukopenia	149 (60.8%)		
Lymphopenia	225 (91.8%)		
Thrombocytopenia	35 (14.3%)		
Decreased complement	113 (46.1%)		
Antinuclear Ab	235 (95.9%)		
Anti-dsDNA Ab	169 (69.0%)		
Anticardiolipin Ab	115 (46.9%)		

Values are mean ± S.D. or n (%).
SLE, systemic lupus erythematosus; NC, normal control; Ab, antibody.

Table 2. The genotype and allele frequencies of polymorphism in the exon5 and intron5 region of *Fcγ Receptor IIB* gene.

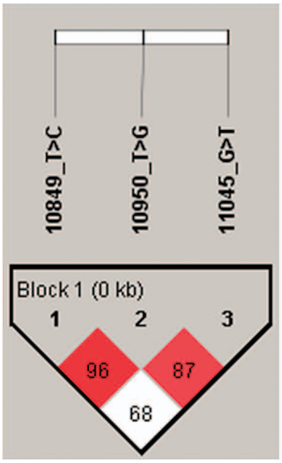
		SLE (n = 245)	NC (n = 142)	SLE vs. NC	
				p value	OR (95% CI)
10849 T>C	TT	149 (60.8%)	80 (56.3%)	co: 0.424	1.157 (0.809 ~ 1.656)
(rs1050501)	TC	86 (35.1%)	56 (39.4%)	do: 0.943	1.019 (0.607 ~ 1.710)
(Exon5)	CC	10 (4.1%)	6 (4.2%)	re: 0.388	1.102 (0.893 ~ 1.360)
	q.	0.216	0.239		
10950 T>G	TT	100 (40.8%)	52 (36.6%)	co: 0.266	1.202 (0.869 ~ 1.662)
(rs6666965)	TG	123 (50.2%)	73 (51.4%)	do: 0.336	1.179 (0.843 ~ 1.649)
(Intron5)	GG	22 (9.0%)	17 (12.0%)	re: 0.389	1.194 (0.887 ~ 1.360)
	q.	0.341	0.377		
11045 G>T	GG	195 (79.6%)	125 (88.0%)	co: 0.047	0.569 (0.327 ~ 0.992)
(rs12117530)	GT	47 (19.2%)	16 (11.3%)	do: 0.623	0.751 (0.239 ~ 2.357)
(Intron5)	TT	3 (1.2%)	1 (0.7%)	re: 0.041	0.733 (0.544 ~ 0.987)
	q.	0.110	0.063		

Each *p* value was calculated with co-dominant (co), dominant (do), and recessive (re) models. Logistic regression analysis was applied to control for age and sex as covariable. q.: minor allele frequency.
SLE, systemic lupus erythematosus; NC, normal control; OR, odds ratio; CI, confidence interval.

are summarized in Table 5. Among 5 haplotypes for these polymorphisms, the frequency of decreased complement was significantly lower in SLE patients with HT1 [TTG] ($p = 0.045$). The frequency of LN ($p = 0.046$), lymphopenia ($p = 0.018$), and anti-dsDNA antibody ($p = 0.002$) were significantly lower in patients with HT2 [TGG]. The frequency of thrombocytopenia ($p < 0.001$) and anti-dsDNA ($p = 0.04$) were significantly higher in patients with HT3 [CTG].

Discussion

Many genetic association studies have been performed amongst human populations with SLE, and various genes encoding proteins with regulatory or adaptive functions in the immune system have been considered as candidates for such studies (Tsao 2003; Nath et al. 2004; Croker and Kimberly 2005; Rhodes and Vyse 2007). To date, results of several genome-wide association studies suggest that the major histocompatibility complex, FcγR, CRP, programmed



L1	L2	D'	r^2
10849_T>C	10950_T>G	0.969	0.149
10849_T>C	11045_G>T	0.684	0.014
10950_T>G	11045_G>T	0.879	0.145

No	Hyplotype	%
HT1	TTG	0.42
HT2	TGG	0.266
HT3	CTG	0.219
HT4	TGT	0.086
HT5	other	0.009

Fig. 1. Haplotype and linkage disequilibrium (LD) coefficients among three SNPs in *FCGRIIB* gene. Allele and genotype frequency for each SNP was calculated from unrelated probands and tested for departure from Hardy-Weinberg equilibrium using a χ^2 test. Estimates of LD between SNPs were determined by calculating pair-wise Lewontin's /D′/ and r^2 statistics in unrelated individuals.

Table 3. The haplotype frequencies of *Fcγ Receptor IIB* gene.

Haplotype		SLE (n = 245)	NC (n = 142)	SLE vs. NC	
				p value	OR (95% CI)
HT1	+/+[a]	46 (18.8%)	16 (11.3%)	co: 0.074	1.415 (0.967 ~ 2.070)
[TTG]	+/−	166 (67.8%)	103 (72.5%)	do: 0.453	1.117 (0.837 ~ 1.492)
	−/−	33 (13.5%)	23 (16.2%)	re: 0.050	1.358 (1.000 ~ 1.845)
HT2	+/+	11 (4.5%)	10 (7.0%)	co: 0.220	0.799 (0.558 ~ 1.143)
[TGG]	+/−	131 (53.5%)	79 (55.6%)	do: 0.337	0.901 (0.728 ~ 1.115)
	−/−	103 (42.0%)	53 (37.3%)	re: 0.293	0.789 (0.507 ~ 1.227)
HT3	+/+	9 (3.7%)	5 (3.5%)	co: 0.663	0.916 (0.616 ~ 1.361)
[CTG]	+/−	45 (18.4%)	30 (21.1%)	do: 0.568	0.931 (0.730 ~ 1.188)
	−/−	191 (78.0%)	107 (75.4%)	re: 0.935	1.024 (0.586 ~ 1.787)
HT4	+/+	2 (0.8%)	1 (0.7%)	co: 0.882	0.941 (0.425 ~ 2.086)
[TGT]	+/−	9 (3.7%)	6 (4.2%)	do: 0.942	1.032 (0.435 ~ 2.453)
	−/−	234 (95.5%)	135 (95.1%)	re: 0.911	1.072 (0.316 ~ 3.631)
HT5	+/+	0 (0%)	0 (0%)	co: 0.980	1.009 (0.514 ~ 1.978)
[other]	+/−	3 (1.2%)	2 (1.4%)	do: 0.359	0.987 (0.961 ~ 1.014)
	−/−	242 (98.8%)	140 (98.6%)	re: NA	NA

Haplotypes (HT) were analyzed using Haploview version 4.2 based on the EM algorithm. Each *p* value was calculated with co-dominant (co), dominant (do), and recessive (re) models. Logistic regression analysis was applied to control for age and sex as covariable.

[a] + means having a HT, − means not having a HT.

SLE, systemic lupus erythematosus; NC, normal control; OR, odds ratio; CI, confidence interval; NA, not applicable.

cell death 1, signal transducer and activator of transcription 4, and integrin alpha M genes show significant evidence of linkage to SLE (Rhodes and Vyse 2008; Harley et al. 2009; Hellquist et al. 2009).

In the present study, we evaluated the association of genetic polymorphisms in *FCGRIIB* with SLE in Koreans. We have identified three SNPs (rs1050501, rs6666965, and rs12117530) in *FCGRIIB*. In the rs12117530 polymorphism, the genotype frequency of the minor allele was significantly higher in SLE patients than in the NCs. There was a significant difference in the observed frequency of HT1 [TTG] between patients with SLE and the NCs. In addition, several clinical manifestations were associated with the haplotypes of *FCGRIIB*: decreased complement (HT1), LN, lymphopenia and anti-dsDNA antibody (HT2), and thrombocytopenia and anti-dsDNA antibody (HT3).

Association of Fc*γ*R genes with various diseases in Korean populations have been previously reported, such as

Table 4. Clinical characteristics according to the *Fcγ Receptor IIB* gene in SLE patients.

Characteristics	10849 T>C			10950 T>G			11045 G>T		
	TT	TC,CC	*p* value	TT	TG,GG	*p* value	GG	GT,TT	*p* value
	n = 149 (60.8%)	n = 96 (39.2%)		n = 100 (40.8%)	n = 145 (59.2%)		n = 195 (79.6%)	n = 50 (20.4%)	
Oral ulcer	81 (54.4%)	49 (51.0%)	0.611	53 (53.0%)	77 (53.1%)	0.987	101 (51.8%)	29 (58.0%)	0.433
Arthritis	111 (74.5%)	66 (68.8%)	0.327	69 (69.0%)	108 (74.5%)	0.346	141 (72.3%)	36 (72.0%)	0.965
Serositis	18 (12.1%)	17 (17.7%)	0.219	14 (14.0%)	21 (14.5%)	0.915	29 (14.9%)	6 (12.0%)	0.605
Rash	55 (36.9%)	37 (38.5%)	0.797	39 (39.0%)	53 (36.6%)	0.697	79 (40.5%)	13 (26.0%)	0.059
Nephritis	33 (22.1%)	30 (31.2%)	0.112	29 (29.0%)	34 (23.4%)	0.328	52 (26.7%)	11 (22.0%)	0.501
Leukopenia	84 (56.4%)	65 (67.7%)	0.076	60 (60.0%)	89 (61.4%)	0.828	112 (57.4%)	37 (74.0%)	0.032
Lymphopenia	135 (90.6%)	90 (93.8%)	0.380	91 (91.0%)	134 (92.4%)	0.691	177 (90.8%)	48 (96.0%)	0.228
Thrombocytopenia	20 (13.4%)	15 (15.6%)	0.631	17 (17.0%)	18 (12.4%)	0.313	32 (16.4%)	3 (6.0%)	0.061
Decreased complement	65 (43.6%)	48 (50.0%)	0.483	46 (46.0%)	67 (46.2%)	0.666	91 (46.7%)	22 (44.0%)	0.090
Anti-dsDNA Ab	97 (65.1%)	72 (75.0%)	0.102	70 (70.0%)	99 (68.3%)	0.774	135 (69.2%)	34 (68.0%)	0.867
Anticardiolipin Ab	69 (46.3%)	46 (47.9%)	0.888	46 (46.0%)	69 (47.6%)	0.969	92 (47.2%)	23 (46.0%)	0.317

Logistic regression analysis was applied to control for age and sex as covariable.
Ab, antibody.

Table 5. Clinical characteristics according to the haplotype of *Fcγ Receptor IIB* gene in systemic lupus erythematosus (SLE).

Characteristics	HT1 [TTG]			HT2 [TGG]			HT3 [CTG]		
	+/+[a]	+/−, −/−	*p* value	+/+	+/−, −/−	*p* value	+/+	+/−, −/−	*p* value
	n = 46 (18.8%)	n = 199 (80.2%)		n = 11 (4.5%)	n = 234 (95.5%)		n = 9 (3.7%)	n = 236 (96.3%)	
Oral ulcer	26 (56.5%)	104 (52.3%)	0.602	7 (63.6%)	123 (52.6%)	0.472	4 (44.4%)	126 (53.4%)	0.598
Arthritis	33 (71.7%)	144 (72.2%)	0.932	10 (90.9%)	167 (71.4%)	0.157	6 (66.7%)	171 (72.5%)	0.703
Serositis	5 (10.9%)	30 (15.1%)	0.463	1 (9.1%)	34 (14.5%)	0.614	1 (11.1%)	34 (14.4%)	0.782
Rash	19 (41.3%)	73 (36.7%)	0.560	5 (45.5%)	87 (37.2%)	0.580	4 (44.4%)	88 (37.3%)	0.663
Nephritis	13 (28.3%)	50 (25.1%)	0.661	0 (0.0%)	63 (26.9%)	0.046	2 (22.2%)	61 (25.8%)	0.807
Leukopenia	24 (52.2%)	125 (62.8%)	0.183	4 (36.4%)	145 (62.0%)	0.089	6 (66.7%)	143 (60.6%)	0.714
Lymphopenia	41 (89.1%)	184 (92.5%)	0.457	8 (72.7%)	217 (92.7%)	0.018	8 (88.9%)	217 (91.9%)	0.742
Thrombocytopenia	5 (10.9%)	30 (15.1%)	0.463	0 (0.0%)	35 (15.0%)	0.166	5 (55.6%)	30 (12.7%)	< 0.001
Decreased complement	17 (37.0%)	96 (48.2%)	0.045	6 (54.5%)	107 (45.7%)	0.510	5 (55.6%)	108 (45.8%)	0.845
Anti-dsDNA Ab	28 (60.9%)	141 (70.9%)	0.187	3 (27.3%)	166 (70.9%)	0.002	9 (100.0%)	160 (67.8%)	0.040
Anticardiolipin Ab	20 (43.5%)	95 (47.7%)	0.873	5 (45.5%)	110 (47.0%)	0.923	6 (66.7%)	109 (46.2%)	0.235

Logistic regression analysis was applied to control for age and sex as covariable.
[a] + means having a HT, − means not having a HT.
HT, haplotype; Ab, antibody.

SLE (*FCGRIIA* 131 R/H and *FCGRIIIA* 176 F/V) (Song et al. 1998; Yun et al. 2001; Lee et al. 2002; Lee et al. 2003), adult onset Still's disease (*FCGRIIA* H/R131, *FCGRIIIA* F/V176, and *FCGRIIIB* NA1/NA2) (Oh et al. 2002; Woo et al. 2009), and ischemic stroke (*FCGRIIA* rs7511868, rs6427595, rs7512140, and rs6696854) (Kim et al. 2009b). In a study of *FCGRIIA* polymorphisms, there were no significant differences in the observed genotype frequencies between SLE patients and NCs (Song et al. 1998). However, there was a significant decrease in the *FCGRIIA* H131 genotype and H131 allelic frequency in patients with LN. Yun et al. (2001) identified that *FCGRIIA* R131 homozygote was a major predisposing factor for SLE and LN, and H131/V176 was a protective allele combination in LN. However, *FCGRIIA* was not associated with Chinese (Yap et al. 1999) and Japanese SLE (Hatta et al. 1999; Sato et al. 2001).

Fc*γ*R IIB is the only inhibitory receptor with immunoreceptor tyrosine-based inhibitory motif, which inhibits activating signals in immune cells (Smith and Clatworthy 2010). Because Fc*γ*R IIB is an important regulator of B lymphocytes, it is expected to be involved in the pathogenesis of SLE. Direct evidence for the role of Fc*γ*R IIB in SLE is that Fc*γ*R IIB-deficient mice develop SLE-like dis-

ease (Bolland and Ravetch 2000). In addition, the FcγR IIB-expressing retrovirus transfection in bone marrow cells of F1 mice (NZB x NZW) prevent autoimmunity (McGaha et al. 2005). Furthermore, decreased expression of FcγR IIB is reported in memory B cells of SLE patients (Mackay et al. 2006).

The possible association between *FCGRIIB* polymorphisms and Korean SLE has not been studied. Therefore, we evaluated the potential association of genetic polymorphisms of *FCGRIIB* with SLE in Koreans.

We have identified three SNPs within *FCGRIIB*, rs1050501, rs6666965, and rs12117530 in Koreans. The rs12117530 polymorphism was significantly associated with SLE. We found that the minor allele (T) of the rs12117530 polymorphism was associated with significantly higher disease susceptibility. Moreover, SLE patients carrying the minor allele (T) of rs12117530 suffered from leukopenia more often. The frequency of decreased complement was significantly lower in patients with HT1. The frequency of LN, lymphopenia and anti-dsDNA antibody were significantly lower in patients with HT2. Thrombocytopenia and anti-dsDNA were more common in patients with HT3. These results suggest that the disease phenotype is more common in SLE patients carrying the minor allele (GT or TT) of rs12117530 polymorphism than those carrying the major homozygous genotype (GG). The *FCGRIIB* rs12117530 polymorphism might play an important role in lupus development. This is the first study to indicate that an intronic genetic polymorphism located within *FCGRIIB* rs12117530 is significantly associated with SLE.

Of the three SNPs identified, the most frequently investigated polymorphism is rs1050501, which codes for a non-synonymous substitution, Ile232Thr polymorphism in the transmembrane domain of the *FCGRIIB* gene. Several genetic association studies of *FCGRIIB* have been reported in different ethnic populations with SLE, including Japanese (Kyogoku et al. 2002), Thais (Siriboonrit et al. 2003), Chinese (Chu et al. 2004; Chen et al. 2006; Pan et al. 2008), and Swedish (Magnusson et al. 2004).

In the present study, however, the rs1050501 genotype was not associated with Korean SLE. Our *FCGRIIB* rs1050501 genotype result was consistent with that of Chinese (Chu et al. 2004) and Swedish (Magnusson et al. 2004) results. However, in a study on Chinese patients, although genotype frequencies of rs1050501 were not significantly different between SLE and NCs, allele carrier frequency of *FCGRIIB* 232T was also significantly increased in patients with LN (Chu et al. 2004). Another Chinese family-based association study showed that the *FCGRIIB* 232T was significantly associated with genetic susceptibility to SLE (Pan et al. 2008). In studies of Japanese and Thai populations, the frequency of the *FCGRIIB* 232T/T genotype was significantly increased in SLE patients than in the healthy individuals (Kyogoku et al. 2002; Siriboonrit et al. 2003). Most studies of Asian SLE populations showed association with rs1050501 of the *FCGRIIB* gene, which is not associated with SLE in Koreans. These data demonstrate that genetic variations in SLE are related to the ethnic background.

Our study has few limitations. First, this study was performed in a single population of patients without replication. In addition, the studied population was relatively small, which likely prevented identification of small differences in the genetic susceptibility to SLE. Therefore, further studies with larger populations are required to confirm these results. Second we did not evaluate the functional effects of the rs12117530 polymorphisms. Further studies should be designed to address the functional effects of rs12117530 polymorphisms.

In conclusion, we have identified three SNPs within *FCGRIIB* in Koreans. Our data suggest that genetic polymorphisms within *FCGRIIB* may be associated with disease susceptibility and phenotypes of SLE in Koreans. In particular, rs12117530 polymorphism of *FCGRIIB* is possibly an important risk factor in the development of lupus.

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Conflict of Interest

The authors declare no conflict of interest.

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