C-Reactive Protein Gene Polymorphisms in Disease Susceptibility and Clinical Manifestations of Korean Systemic Lupus Erythematosus

HYOUN-AH KIM, HYE-YOUNG CHUN, SEUNG-HYUN KIM, HAE-SIM PARK, and CHANG-HEE SUH

ABSTRACT. Objective. C-reactive protein (CRP) is a sensitive marker of inflammation. It is hypothesized that polymorphism of CRP gene contributes to susceptibility to systemic lupus erythematosus (SLE). We tested this hypothesis by identifying CRP gene polymorphisms in Korean patients with SLE.

Methods. Approximately 1.5 kb of CRP promoter region was screened for single nucleotide polymorphism (SNP) using direct sequencing and 3 SNP in CRP exons by restriction fragment length polymorphism. The basal levels of CRP were measured by immunoturbidimetry. The effect of –390 C>A or T polymorphism on the promoter activity was analyzed by luciferase reporter assay in Hep3B cells.

Results. Allele frequency at polymorphisms within CRP promoter and exon in our Korean patients with SLE differed from that of Caucasians. The A allele was a major allele at position 2043 in Korean SLE patients, whereas G is a major allele in Caucasian SLE. Our SLE patients had minor allele in the –390 polymorphism more frequently versus controls (p = 0.033). CRP 1185 polymorphism was associated with thrombocytopenia (p = 0.043). The basal levels of CRP were significantly higher in individuals who had minor allele in –390 and 2043 polymorphisms (p = 0.03, p = 0.024, respectively). Promoter-reporter construct carrying the –390 A or T allele displayed significantly higher promoter activity than that with the –390 C allele (p < 0.001).

Conclusion. CRP gene –390 polymorphism plays a role in disease susceptibility of SLE through regulation of serum CRP level. Our results suggest that elevated basal CRP level may be important in the pathogenesis of SLE, even though CRP responsiveness to noninfectious inflammation of SLE is decreased. (First Release Sept 15 2009; J Rheumatol 2009;36:2238–43; doi:10.3899/jrheum.090243)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
SINGLE NUCLEOTIDE POLYMORPHISM
C-REACTIVE PROTEIN
PROMOTER ACTIVITY

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by highly variable clinical features. Although the exact pathogenesis of SLE remains elusive, extremely complicated and multifactorial interactions among various genetic and environmental factors are thought to contribute to the development of the disease1. Many genetic association studies have been performed among human populations with SLE, and various genes encoding proteins with regulatory or adaptive functions in the immune system have been considered as candidates2,3.

Several different approaches with variable validation have been used for genome wide scanning to identify novel susceptibility loci for SLE, and 13 major cytogenetic locations show significant evidence of linkage to SLE. Among the identified linkages are 8 SLE susceptibility regions that have also been replicated independently using lupus phenotypes only. They include 1q23, 1q41, 2q37, 4p16, 6p21, 11p13, 12q24, and 16q13. Within 1q23.2, C-reactive protein (CRP) gene has been considered as a lupus candidate gene2,4,5.

CRP is one of the major plasma proteins that increase in concentration during the acute phase. It recognizes pathogens and mediates their elimination by recruiting the complement system and phagocytic cells. Further, CRP appears to play a role in the clearance of apoptotic and necrotic cells, an effect that likely contributes to homeostasis and systemic autoimmune diseases6,7. The single CRP gene consists of 2 exons that have disproportionately long 3’ untranslated regions (3’-UTR)8, suggesting a possible regulatory role.

It is of interest to note that CRP may exert an ameliorative effect on murine models of SLE9,10. Also, in SLE patients, there is little or no increase of CRP level with flare-
up of the disease. When elevated CRP levels are detected, they are indicative of an intercurrent infection rather than of active lupus11-19. These findings raise the possibility that decreased amounts of CRP may contribute to the pathogenesis of SLE. Recently, some studies showed association between CRP gene polymorphism and SLE13-17. However, the SNP found to be associated with SLE has no known functional role in CRP production, and it remains unknown if any promoter SNP are associated with the disease.

Therefore, we attempted to identify single nucleotide polymorphisms (SNP) in the CRP promoter region, determine their frequency in Korean populations, and elucidate their significance in susceptibility and clinical phenotype of SLE. Also, we evaluated whether CRP gene polymorphisms are associated with serum levels of CRP.

MATERIALS AND METHODS

Subjects. One hundred forty-eight patients, diagnosed with SLE, were enrolled. All met the revised criteria of the American College of Rheumatology (ACR) for classification of SLE18. As well, 137 normal control subjects (NC) were recruited. Whole blood samples were collected for the genetic study, and serum samples were collected for the measurement of CRP.

Medical history, clinical symptoms, physical examination, and laboratory results were registered in a database from the onset of disease until admission to the study through review of medical records. All subjects gave their informed consent and the study was approved by the Institutional Review Board.

Preparation of genomic DNA and identification of single nucleotide polymorphism. Genomic DNA was prepared from whole blood samples using the QIAamp DNA Blood Kit (Qiagen, Germany) according to the manufacturer’s instructions.

Polymorphisms identified by PCR-RFLP were confirmed by direct sequencing for SLE patients (n = 98) and NC (n = 87). Also 3 SNP in CRP exon region that have been reported in European populations were genotyped by restriction fragment length polymorphism (RFLP)16. Polymorphisms identified by PCR-RFLP were confirmed by sequencing.

Serum CRP level. The serum CRP levels were immunoturbidimetrically measured using AU640e Chemistry Immunoanalyser (Olympus, Southhall, UK). Serum samples were collected at clinic visits in SLE patients without infection and flareup.

Effect of –390 C>A or T polymorphism on promoter activity. We prepared 577-bp fragment of the promoter of human CRP by PCR amplification using either –390 C homozygote, –390 A homozygote, or –390 T homozygote human genomic DNA as a template. Each of the PCR products were gel purified with an agarose-gel purification kit (iNtRON Biotechnology), and ligated into TA vector (Invitrogen, Carlsbad, CA, USA). All constructs were verified by direct sequencing. Plasmid DNA were prepared from these constructs.

Hep3B cells (human liver hepatoma cell line) were cultured with RPMI 1640 (Invitrogen, Grand Island, NY, USA) at 37°C in a 5% CO2 incubator. Hep3B cells were transfected by using FuGENE6 (Roche, Mannheim, Germany) according to the manufacturer’s instructions.

Luciferase reporter assays were performed following the protocol supplied by the manufacturer (Promega). Thus cells were lysated with 100 µl of reporter lysis buffer per well. Twenty microliters from 100 µl of the cell lysate were assayed for luciferase activity using a luciferase assay kit and a luminometer TD20/20 (Turner BioSystems, Sunnyvale, CA, USA). Assays were conducted in triplicate, and experiments were repeated at least 3 times.

Statistical analysis. The genotype frequency at each SNP was examined for significant departure from Hardy-Weinberg equilibrium by using a chi-square test. Three logistic regression models (codominant, dominant, recessive) were used to analyze SNP after controlling for age and gender as covariables. Haplotypes of CRP gene were analyzed using Haploview version 4.0 based on the EM algorithm. CRP basal levels according to the SNP genotype in SLE were assessed using logistic regression analysis to control for disease duration and Bonferroni adjustment for multiple comparisons, and CRP value is shown as median (25th percentile, 75th percentile). Differences of promoter activity assay among each group were examined by using chi-square test. Differences in the frequency of the phenotypic characteristics within SLE patients were assessed using logistic regression analysis to control for age and gender as covariables. A p value ≤ 0.05 was regarded as significant. All statistical analyses were performed using SPSS software (version 12.0; SPSS Inc, Chicago, IL, USA).

RESULTS

Clinical characteristics of the study subjects. The mean age of SLE patients was 35.7 ± 12.4 years and 89.9% were women. In NC, mean age was 25.7 ± 4.1 years and 70.1% were women. There were differences in age and gender between both groups, so the data were analyzed with logistic regression analysis to control for age and sex. Clinical features of SLE patients are as follows with decreasing frequency: ANA positivity (98.6%), arthritis (73%), hypocomplementemia (72.3%), anti-dsDNA positivity (68.2%), oral ulcer (53.4%), leukopenia (50%), anticardiolipin antibody positivity (44.6%), malar rash (37.2%), nephritis (32.4%), photosensitivity (25%), thrombocytopenia (22.3%), serositis (18.2%), lupus anticoagulant positivity (14.2%), and anti-Sm antibody positivity (7.4%).

SNP discovery of promoter region of CRP gene. We sequenced a 1.5 kb of CRP promoter region from 50 SLE patients and 50 NC to identify polymorphism sites. Three SNP of CRP promoter region were identified: –861 T>C, –821 A>G, and –390 C>T or A (Figure 1).

Genotyping frequencies of CRP gene. The distribution of genotype frequencies for all polymorphisms was consistent with Hardy-Weinberg equilibrium in SLE and NC (p > 0.05). The genotype frequency of each SNP of CRP promoter region in Korean SLE is presented in Table 1. The frequency of the genotype that contained the –390 A or T allele was significantly higher in SLE compared with NC (p = 0.033 for the recessive model). There were no significant differences in allele and genotype frequencies in SNP of CRP exon region between SLE and NC (data not shown).

Linkage disequilibrium between SNP, and locus by locus was examined. Two genetic polymorphisms of the CRP gene, 839 G>C and 1185 C>T, were in linkage disequilibrium (1D’1 = 1 and r2 = 0.12), and 7 common haplotypes,
ht1[TACGCA], ht2[TGCCGC], ht3[CAAGCG], ht4[TATTGTG], ht5[TACCCA], ht6[TACGCG], and ht7[TACGTG], were constructed utilizing the EM algorithm. There was no difference in the frequency of each haplotype between SLE and NC (data not shown).

CRP basal levels according to SNP genotype and haplotype in SLE. We evaluated associations between SNP genotype and CRP basal levels. Table 2 shows that SLE patients who carried the –390 A or T allele had higher basal levels of CRP than those who had the homozygous CC genotype (p = 0.03). The basal CRP levels were higher in SLE patients who carried the 2043 G allele versus those who had the homozygous AA genotype (p = 0.024). Effect of 2043 A>G polymorphism on CRP expression has been reported by Russell, et al16. Also, the basal level of CRP was lower in SLE patients who had haplotype ht1[TACGCA] and higher

Figure 1. Schematic representation of the C-reactive protein (CRP) gene. CRP consists of 2 exons separated by a single intron. Filled boxes denote translated regions and open boxes untranslated regions. Arrows mark the locations of single nucleotide polymorphisms (SNP) within CRP locus.

Table 1. The genotype and allele frequencies of polymorphisms in the promoter region of CRP gene.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>SLE, n = 148 (%)</th>
<th>NC, n = 137 (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>–861 T&gt;C</td>
<td>TT</td>
<td>105 (70.9)</td>
<td>108 (78.8)</td>
<td>cod: NS</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>41 (27.7)</td>
<td>29 (21.2)</td>
<td>dom: NS</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>rec: NS</td>
</tr>
<tr>
<td></td>
<td>q.</td>
<td>0.152</td>
<td>0.106</td>
<td>al: NS</td>
</tr>
<tr>
<td>–821 A&gt;G</td>
<td>AA</td>
<td>122 (82.4)</td>
<td>101 (73.7)</td>
<td>cod: NS</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>23 (15.5)</td>
<td>32 (23.4)</td>
<td>dom: NS</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>3 (2.0)</td>
<td>4 (2.9)</td>
<td>rec: 0.079</td>
</tr>
<tr>
<td></td>
<td>q.</td>
<td>0.098</td>
<td>0.146</td>
<td>al: NS</td>
</tr>
<tr>
<td>–390 C&gt;A or T</td>
<td>CC</td>
<td>78 (52.7)</td>
<td>96 (70.1)</td>
<td>cod: 0.051</td>
</tr>
<tr>
<td></td>
<td>AC</td>
<td>41 (27.7)</td>
<td>26 (19.0)</td>
<td>dom: NS</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>27 (18.2)</td>
<td>12 (8.8)</td>
<td>rec: 0.033</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AT</td>
<td>0 (0.0)</td>
<td>3 (2.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>q.</td>
<td>0.243</td>
<td>0.161</td>
<td>al: 0.071</td>
</tr>
</tbody>
</table>

Each p value was calculated with co-dominant (cod), dominant (dom), and recessive models (rec). al: p value of each allele frequency. Logistic regression analysis was applied to control for age and gender as covariables. SLE: systemic lupus erythematosus; NC: normal control; NS: not significant.

Table 2. C-reactive protein (CRP) basal levels according to the SNP genotype in SLE. CRP values are median (25th percentile, 75th percentile).

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>CRP levels (mg/l)</th>
<th>p</th>
<th>p\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>–861 T&gt;C</td>
<td>TT</td>
<td>0.2 (0.0, 0.4)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>CT, CC</td>
<td>0.4 (0.2, 0.5)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>–821 A&gt;G</td>
<td>AA</td>
<td>0.2 (0.0, 0.4)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>AG, GG</td>
<td>0.4 (0.3, 0.6)</td>
<td>0.042</td>
<td>NS</td>
</tr>
<tr>
<td>–390 C&gt;A or T</td>
<td>CC (n = 78)</td>
<td>0.2 (0.0, 0.4)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>CT, AC, AA, AT, or TT (n = 70)</td>
<td>0.3 (0.2, 0.5)</td>
<td>0.023</td>
<td>0.03</td>
</tr>
<tr>
<td>839 G&gt;C</td>
<td>GG</td>
<td>0.3 (0.1, 0.5)</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>CG, CC</td>
<td>0.1 (0.0, 0.3)</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>1185 C&gt;T</td>
<td>CC</td>
<td>0.2 (0.0, 0.5)</td>
<td>0.2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>CT, TT</td>
<td>0.3 (0.2, 0.5)</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>2043 A&gt;G</td>
<td>AA (n = 60)</td>
<td>0.2 (0.0, 0.4)</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>AG, GG</td>
<td>0.3 (0.2, 0.5)</td>
<td>0.05</td>
<td>0.024</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Logistic regression analysis to control for disease duration as a covariable. \textsuperscript{b} Bonferroni adjustment for multiple comparisons. NS: not significant.
in SLE patients who had haplotype ht4[TATGTG]; however, significance was lost after Bonferroni adjustment (Table 3). The data are consistent with the basal CRP level according to genotype.

Therefore, we assayed the promoter activity of −390 C > A or T polymorphism of CRP gene, which showed a significant difference of allelic frequency in SLE versus NC, and we evaluated the association of promoter activity and basal CRP levels in SLE patients.

**Table 3.** C-reactive protein (CRP) basal levels according to the haplotype of CRP gene. CRP values are median (25th percentile, 75th percentile).

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>CRP Levels mg/l</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ht1[TACGCA]</td>
<td>TACGCA (n = 172)</td>
<td>0.2 (0.0, 0.4)</td>
<td>3 (0.1, 0.5)</td>
</tr>
<tr>
<td></td>
<td>− (n = 124)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ht2[TGCGGC]</td>
<td>TGCGGC (n = 29)</td>
<td>0.4 (0.3, 0.5)</td>
<td>0.3 (0.2, 1.0)</td>
</tr>
<tr>
<td></td>
<td>− (n = 267)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ht3[CAAGCG]</td>
<td>CAAGCG (n = 43)</td>
<td>0.4 (0.2, 0.5)</td>
<td>0.2 (0.0, 0.4)</td>
</tr>
<tr>
<td></td>
<td>− (n = 253)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ht4[TATGTG]</td>
<td>TATGTG (n = 23)</td>
<td>0.3 (0.2, 0.5)</td>
<td>0.2 (0.0, 0.4)</td>
</tr>
<tr>
<td></td>
<td>− (n = 273)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ht5[TACCCA]</td>
<td>TACCCA (n = 12)</td>
<td>0.1 (0.0, 0.3)</td>
<td>0.3 (0.1, 0.5)</td>
</tr>
<tr>
<td></td>
<td>− (n = 284)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ht6[TACGCG]</td>
<td>TACGCG (n = 6)</td>
<td>0.8 (0.2, 1.2)</td>
<td>0.3 (0.1, 0.5)</td>
</tr>
<tr>
<td></td>
<td>− (n = 290)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ht7[TACGTG]</td>
<td>TACGTG (n = 4)</td>
<td>0.2 (0.0, 0.4)</td>
<td>0.3 (0.1, 0.5)</td>
</tr>
<tr>
<td></td>
<td>− (n = 292)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Logistic regression analysis to control for disease duration as a covariate. <sup>b</sup> Bonferroni adjustment for multiple comparisons. NS: not significant. * SLE patients who did not have haplotype.

The −390 C>A or T polymorphism was associated with altered promoter activity, we employed a luciferase reporter assay to compare the reporter activity of plasmids that contained −390 C, −390A or −390T in the CRP promoter. Figure 2 shows that constructs containing −390 A and −390 T exhibited significantly greater luciferase activity than the constructs containing −390 C (p < 0.001).

**Associations between SLE phenotype and SNP.** We evaluated a possible association between the CRP polymorphisms and clinical characteristics of SLE. As seen in Table 4, the thrombocytopenia rate was more common in patients who carried the 1185 T allele than in those who had the homozygous 1185 CC genotype (p = 0.043).

As for associations between SLE phenotypes and 7 common haplotypes, the frequency of hypocomplementemia was significantly higher in patients who had haplotype ht1[TACGCA], whereas it was significantly lower in haplotype ht2[TGCGGC] (Table 4).

**DISCUSSION**

We investigated whether a polymorphism at the CRP promoter region might contribute to genetic susceptibility to human SLE. In fact, several studies have found that a polymorphism in the CRP gene is associated with an increased risk of developing SLE, and clinical and experimental evidence suggests a possible participatory role of CRP in pathogenesis. Two studies have found evidence of association between CRP variants and SLE or lupus nephritis in Caucasians. One study showed that a CRP promoter variant, −707, was associated with the SLE phenotype in African Americans and Caucasians. A recent study in a British family-based cohort found that 5 SNP (−861, −390, −390 C>A or T polymorphism was associated with altered promoter activity, we employed a luciferase reporter assay to compare the reporter activity of plasmids that contained −390 C, −390A or −390T in the CRP promoter. Figure 2 shows that constructs containing −390 A and −390 T exhibited significantly greater luciferase activity than the constructs containing −390 C (p < 0.001).

**Figure 2.** Effect of −390 C>A or T polymorphism on the transcription activity of human CRP promoter. A reporter assay was performed in Hep3B cells transfected with luciferase reporter constructs. The relative luciferase activity is represented as the ratio to the activity of pGL3-Basic. Each experiment was conducted in triplicate, and the results are expressed as mean ± SEM for 3 independent experiments. p value was determined by paired t test.
ical manifestations of SLE was examined. Thrombo-

luciferase activity than constructs that contained –390C.

Controlling for age and gender as covariables. NS = not significant; ACA = anticardiolipin antibody. * Did not have haplotype. 90, 838, 2043) were not associated with SLE risk individu-

ally, but there was an association with the 5 SNP haplo-

types17. In our present study, we investigated SNP in the

cRP promoter region and found 3 SNP (–861 T>C, –821

A>G, –390 C>A or T) in Koreans. Further, we found that

the rare allele frequency of –390 C>A or T polymorphism

was significantly higher in SLE than NC. Also, the allele

frequencies for 6 CRP polymorphisms in Koreans were

remarkably different versus Caucasians: The A allele was

a major allele in Korean patients at position 2043, whereas G

allele was reported as a major allele in Caucasian and

African Americans13,15,16. These results clearly indicate

genetic variation among different ethnic groups.

We also examined whether these polymorphisms had any

effect on serum CRP levels, and found that basal levels of

CRP were significantly higher in individuals who had minor

allele in –390 C>A or T and 2043 A>G polymorphisms than

in those who had the major homozygous genotype, even

after conservative Bonferroni adjustment for multiple com-

parisons (p = 0.03, 0.024, respectively). These results are

comparable with the previous reports in Caucasians16,17,20-22.

Further, we extended this finding to basal CRP level accord-

ing to haplotype, and found that basal level of CRP was

lower in haplotype h1[TACGCA] containing major alleles

of CRP –390 and 2043, while it was higher in haplotype

h4[TATGTTG] containing minor alleles of CRP –390 and

2043, although the significance disappeared with Bonferroni

adjustment.

We thought that the –390 C>A or T polymorphism would

be associated with altered promoter activity. Using a

luciferase reporter assay, we observed that constructs con-

taining –390 A and –390 T exhibited significantly greater

luciferase activity than constructs that contained –390C.

The influence of genetic polymorphisms in CRP on clinical

manifestations of SLE was examined. Thrombo-

cytopenia developed significantly more in SLE patients who

had minor allele in 1185 T>C polymorphisms than those

who had major homozygous genotype. Although the patho-
genesis of lupus thrombocytopenia has not yet been clar-

ified, one possible explanation of the association between

1185 C allele and thrombocytopenia in our study could be a

reduced capacity for antiinflammatory effects of CRP in

patients with the variant allele C. A recent report suggested

that CRP generates suppressive macrophages through FcγRI

to decrease platelet clearance in a model of immune throm-

bocytopenic purpura23. The frequency of hypocomple-

mentemia was significantly higher in haplotype h1[TACG-

CA] and lower in haplotype h2[TGCGCG]. These results

suggest that the combination of –821 A>G and 2043 A>G

polymorphism may be important for hypocomplementemia.

However, we could not replicate the association between

CRP 2043 polymorphism and lupus nephritis14.

It is of an interest to note that our results were in contrast

with previous data that showed an ameliorative effect of

CRP on SLE. In a previous genetic study, a polymorphism

in the human CRP gene, 2043 A>G, which results in a lower

basal level of CRP, has been associated with an increased

risk of developing SLE16. Using a sensitive method, how-

ever, some studies observed that most SLE patients have ele-

vated CRP levels during the evolution of the disease process,

irrespective of concomitant active infection24,25. One recent

study assessed the relationship among high-sensitivity CRP

(hsCRP), clinical features, autoantibody and organ damage,

and found that hsCRP was associated with a broad range of

clinical features and organ damage in SLE26.

Our present data showed that –390 C>A or T polymor-

phism, which was associated with elevated basal CRP, was

associated with susceptibility to SLE. This SNP is associat-

ed with higher promoter activity based on functional studies

in transfected cells. Further studies on how elevated basal

CRP levels contribute to resting status without flareup of
disease are needed.

Our study also has some limitations. The study was per-

formed in a single population of patients without replication,
and the studied population was relatively small. Also, there are possible biases of using young people as controls, who may develop lupus later; however, this is rather unlikely due to the low incidence rate.

It is not clear how elevation of basal CRP level in complex disorders such as SLE is a risk factor of chronic inflammation or a contributing factor to the pathogenesis of the disease. If elevation of baseline CRP level has a role in the pathogenesis of SLE, the alleles related to elevation of baseline CRP could also be a contributing factor to disease pathogenesis. These data appear to be useful in understanding basal CRP expression and its relation to SLE.

In conclusion, our results suggest that –390 C>A or T polymorphism within CRP promoter region may be involved in regulation of CRP expression and susceptibility to SLE in Koreans. In addition, multiple polymorphisms with CRP gene may be involved in clinical manifestation.

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