Poly(ADP-ribose) polymerase (PARP) polymorphisms associated with nephritis and arthritis in systemic lupus erythematosus

J.-W. Hur, Y.-K. Sung, H. D. Shin¹, B. L. Park¹, H. S. Cheong¹ and S.-C. Bae

Objective. The objective of this study was to confirm whether polymorphisms of the poly(ADP-ribose) polymerase gene (PARP) are associated with genetic susceptibility to systemic lupus erythematosus (SLE) and to investigate the possible association of nephritis and arthritis in SLE with PARP polymorphisms.

Methods. Using direct DNA sequencing in 24 individuals, we identified 44 sequence variants within exons and their flanking regions, including the 1.5-kb promoter region of PARP. Six common polymorphic sites were selected for larger-scale genotyping (in 350 Korean SLE patients and 330 healthy controls), which identified six common haplotypes.

Results. Although no statistically significant association with the risk of SLE was observed, we found that two single-nucleotide polymorphisms (SNPs —1963A → G and +28077G → A) were significantly associated with an increased risk of nephritis, and one non-synonymous variant [+40329T → C(V762A)] was also significantly associated with an increased risk of arthritis, while the −1963A → G SNP showed a protective effect on arthritis in Korean SLE patients.

Conclusion. Our results demonstrate that PARP polymorphisms are not associated with SLE susceptibility, but that −1963A → G, +28077G → A and +40329T → C(V762A) are significantly associated with nephritis and arthritis in Korean SLE patients.

Key words: Poly(ADP-ribose) polymerases, Single-nucleotide polymorphism, Systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is characterized by the accelerated apoptosis of lymphocytes and a failure in the clearance of apoptotic cells [1]. It has been postulated that several antinuclear antibodies (Abs) are present [2] and that DNA repair is impaired in patients with SLE [3, 4]. It is widely recognized that several genetic factors, including a gene linkage to human chromosome 1q41-42, contribute to SLE susceptibility [5]. The gene for poly(ADP-ribose) polymerase (PARP) is one of the candidate genes located in this region. The human PARP gene is 43 kb long and split into 23 exons [6].

PARP has been demonstrated to be a nuclear enzyme that catalyses the synthesis of poly(ADP-ribose) using NAD⁺ as a substrate. This process is induced by DNA strand breaks that are generated directly or indirectly by genotoxic agents and enzymatic function, and it plays a pivotal role in DNA repair, proliferation, transcription regulation, apoptosis, genomic stability and malignancy [7, 8]. Several studies have suggested that levels of PARP activity and mRNA are subnormal in lupus patients (and intermediate in unaffected relatives of lupus patients), which consequently decreases poly(ADP-ribose) synthesis [9, 10]. These data implicate PARP in susceptibility to SLE.

It has been suggested that a microsatellite polymorphism—the CA dinucleotide repeat in the promoter region of PARP—affects transcription, because it is located close to the transcription factor Yin Yang 1 [11]. Family-based association studies have revealed that a polymorphic CA dinucleotide repeat in the promoter region of PARP is transmitted to affected offspring. An 85-bp PARP allele was found to be significantly associated with SLE, whereas a 97-bp PARP allele was protective in a multiethnic group comprising Caucasians, Hispanics, Asians and African Americans [5]. However, another study involving a similar cohort produced contradictory results [12], and case-control studies have shown no significant association in French and German Caucasians [13, 14].

Additionally, the human chromosome 1q31-42 region corresponds to the telomeric end of mouse chromosome 1, which is the region involving specific manifestations of murine lupus, including glomerulonephritis and IgG antichromatin Ab [15, 16]. Interestingly, it has been shown that PARP is overactivated in neighbouring cells by the massive synthesis of nitric oxide, which could lead to DNA breaks, and consequently necrosis triggered by depletion of NAD⁺ cellular stores results in inflammatory injury [17]. Thus, PARP has been suggested to regulate the transcription of genes related to inflammation. The lineage of marker D1S235 to chromosome 1q41-43 has been demonstrated in genome-wide screening in multiplex rheumatoid arthritis families [18]. Furthermore, it was recently reported that one PARP haplotype including the 97-bp CA repeat was associated with rheumatoid arthritis in a Spanish population [19]. However, there is no reported evidence of an association of PARP with nephritis and arthritis in SLE.

In an effort to confirm whether PARP polymorphisms are associated with genetic susceptibility to SLE and investigate the possible association of nephritis and arthritis in SLE with PARP...
polymorphisms, we explored sequence variations of PARP in a Korean population, examined the genetic associations of single-nucleotide polymorphisms (SNPs) with SLE, and analysed the association of PARP polymorphisms with nephritis and arthritis among SLE patients. The study cohort consisted of 350 patients with SLE and 330 ethnically matched controls. Written informed consent was obtained from each subject. The study was approved by the Institutional Review Board of Hanyang University Medical Center.

Materials and methods

Patients and controls

A total of 350 Korean SLE patients who fulfilled the 1997 American College of Rheumatology (ACR) criteria of SLE [20] were consecutively enrolled between September 1998 and February 2002 from the Hospital for Rheumatic Diseases, Hanyang University, Seoul, Republic of Korea. The ethnicity of all patients and controls was Korean, and the following clinical and laboratory data were obtained: sex, age, ages at first symptom onset and clinical diagnosis, ACR diagnosis, and SLICC/ACR (Systemic Lupus International Collaborating Clinics/ACR) damage index [21]. Renal disorder was defined as persistent proteinuria greater than 0.5 g per day or greater than 3+ if quantitation was not performed or cellular casts were present. Arthritis was defined as non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion according to ACR criteria [20]. As a control group, we included 330 healthy ethnically matched subjects in our examination of the genetic association of polymorphisms with susceptibility to SLE and related phenotypes. The mean age of the SLE patients was 35.6 yr (range 10.5–72.7 yr), and they comprised 15 males and 335 females. Antinuclear Abs were detected by indirect immunofluorescence using IT-1 cells and anti-double-stranded DNA (dsDNA) Abs in a Crithidia luciliae assay. Of these patients, 36.2% had renal disorders and 64.1% had non-erosive arthritis during any interval of observation.

PARP sequencing

We used the ABI Prism 3730 DNA analyser (Applied Biosystems, Foster City, CA, USA) to sequence exons and their flanking regions, including the promoter region (1.5 kb) of PARP in order to discover variants in 24 Korean unregulated individual DNA samples. Twenty-eight primer sets for the amplification and sequencing analysis were designed based on GenBank sequences (reference genome sequence for PARP: NT_004559.12, released in August 2004). The primer sets for amplification are listed in Supplementary Table 1. Sequence variants were verified in chromatograms.

PARP polymorphism genotyping

Genotyping was read blinded to clinical outcomes on the whole process. Polymorphic sites were genotyped using amplifying primers and probes designed for TaqMan [22]. Primer Express (Applied Biosystems) was used to design both the polymerase chain reaction (PCR) primers and the MGB TaqMan probes. One allelic probe was labelled with FAM	extsuperscript{TM} dye and the other with the fluorescent VIC	extsuperscript{®} dye. PCRs were run in the TaqMan Universal Master mix without UNG (Applied Biosystems), with PCR primer at a concentration of 900 nm and TaqMan MGB probe at a concentration of 200 nm. Reactions were performed in a 384-well format in a total reaction volume of 5 μl using 20 ng DNA.

Table 1. Logistic analysis of PARP polymorphisms with SLE using age and sex as covariates in a Korean population

<table>
<thead>
<tr>
<th>Locus</th>
<th>Genotype</th>
<th>SLE n (%)</th>
<th>NC n (%)</th>
<th>OR (95% confidence interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1963A → G</td>
<td>A</td>
<td>164 (47.3)</td>
<td>157 (47.6)</td>
<td>1.08 (0.86–1.37)</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>142 (40.9)</td>
<td>146 (44.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>41 (11.8)</td>
<td>27 (8.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>−759C → T</td>
<td>C</td>
<td>207 (61.4)</td>
<td>194 (61.2)</td>
<td>1.04 (0.79–1.36)</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>114 (33.8)</td>
<td>112 (35.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>16 (4.8)</td>
<td>11 (3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+28077G → A</td>
<td>GA</td>
<td>243 (69.8)</td>
<td>224 (67.9)</td>
<td>1.02 (0.76–1.36)</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>93 (26.7)</td>
<td>100 (30.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>12 (3.5)</td>
<td>6 (1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+39794C → T</td>
<td>C</td>
<td>294 (84.5)</td>
<td>278 (84.2)</td>
<td>0.89 (0.60–1.32)</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>53 (15.2)</td>
<td>48 (14.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>1 (0.3)</td>
<td>4 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+40329T → C(V762A)</td>
<td>T</td>
<td>117 (33.5)</td>
<td>97 (29.4)</td>
<td>0.86 (0.69–1.07)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>171 (49.0)</td>
<td>162 (49.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>61 (17.5)</td>
<td>71 (21.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+46133C → T</td>
<td>C</td>
<td>301 (86.7)</td>
<td>288 (87.3)</td>
<td>0.85 (0.68–1.60)</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>44 (12.7)</td>
<td>40 (12.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ht1</td>
<td>−/−</td>
<td>148 (44.3)</td>
<td>132 (41.6)</td>
<td>0.89 (0.71–1.12)</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>−/ht1</td>
<td>149 (44.6)</td>
<td>137 (43.2)</td>
<td>0.89 (0.71–1.12)</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>ht1(ht1)</td>
<td>37 (11.1)</td>
<td>48 (15.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ht3</td>
<td>−/−</td>
<td>240 (71.9)</td>
<td>233 (73.5)</td>
<td>1.08 (0.79–1.49)</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>−/ht3</td>
<td>87 (26.1)</td>
<td>78 (24.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ht3(ht3)</td>
<td>7 (2.1)</td>
<td>6 (1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ht4</td>
<td>−/−</td>
<td>241 (72.2)</td>
<td>243 (76.7)</td>
<td>1.22 (0.89–1.67)</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>−/ht4</td>
<td>82 (24.6)</td>
<td>69 (21.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ht4(ht4)</td>
<td>11 (3.3)</td>
<td>5 (1.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Logistic regression models were used to calculate ORs (95% confidence intervals) and the corresponding P values for SNP sites and haplotypes, while controlling for age and sex as covariates. The common alleles were used as the reference genotype to the heterozygote and homozygote of the minor allele. Haplotypes with either equivalence with SNPs or with frequencies less than 5% were excluded from the statistical analyses.

aNormal control.
bAmino acid change.
of genomic DNA. The plates were then placed in a thermal cycler (PE 9700, Applied Biosystems) and heated at 50°C for 2 min and 95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 60°C for 1 min. The TaqMan assay plates were transferred to a real-time PCR system (Prism 7900HT, Applied Biosystems) that read the fluorescence intensity in each well of the plate. Fluorescence data files from each plate were analysed using automated software (SDS 2.1; Applied Biosystems). The primers sequences are provided in Supplementary Table 2.

**Statistical analysis**

The χ² test was used to quantify the distribution of PARP alleles in SLE patients. We examined the linkage disequilibrium (LD), expressed as Lewontin's D' (D'), where D' = D/Dmax, and the LD coefficient r² and the LD of absolute LDs (|D| = 1 and r² = 1) (Fig. 1A). Several complete LDs (|D'| = 1 and r² = 1) were also found (Fig. 1B). Six SNPs (−1963A → G, −759C → T, −28077G → A, +39794C → T, +40329T → C and +46133C → T) were selected for larger-scale (n = 680) genotyping based on LDs and frequencies (frequency > 0.05). The genotype distributions and frequencies of these six SNPs are listed in Supplementary Table 3. Three variants (+28077G → A, +39794C → T and +46133C → T) were newly identified in this study, and the others (−1963A → G, −759C → T and +40329T → C) have been reported previously [26, 27]. Six haplotypes (ht1 to ht6) inferred using the algorithm developed by Stephens et al. [25] were observed at frequencies higher than 5% (Fig. 1C). Because the three haplotypes ht2, ht5 and ht6 were almost equivalent to +28077G → A, +39794C → T and +46133C → T, respectively, they were excluded from further statistical analyses.

** PARP polymorphisms and SLE susceptibility**

These six SNPs and three haplotypes (ht1, ht3 and ht4) were used in the subsequent association study. A multiple logistic regression analysis controlling for age and sex as covariates revealed that none of the PARP polymorphisms was associated with SLE susceptibility (Table 1).

### Table 2. Logistic analysis of PARP polymorphisms with nephritis in SLE

<table>
<thead>
<tr>
<th>Locus</th>
<th>Genotype</th>
<th>Renal disorder</th>
<th>Co-dominant</th>
<th>Dominant</th>
<th>Recessive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% confidence interval)</td>
<td>P</td>
<td>OR (95% confidence interval)</td>
</tr>
<tr>
<td>−1963A → G</td>
<td>A</td>
<td>Positive</td>
<td>1.47 (1.03–2.11)</td>
<td>0.03</td>
<td>1.76 (1.07–2.89)</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−759C → T</td>
<td>C</td>
<td>Positive</td>
<td>0.81 (0.53–1.25)</td>
<td>0.34</td>
<td>0.34 (0.08–1.34)</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+28077G → A</td>
<td>G</td>
<td>Positive</td>
<td>2.07 (1.33–3.21)</td>
<td>0.001</td>
<td>2.49 (1.46–4.24)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+39794C → T</td>
<td>T</td>
<td>Positive</td>
<td>0.70 (0.36–1.38)</td>
<td>0.31</td>
<td>0.71 (0.36–1.43)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+40329T → C(V762A)</td>
<td>T</td>
<td>Positive</td>
<td>0.72 (0.50–1.04)</td>
<td>0.08</td>
<td>0.70 (0.41–1.19)</td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Positive</td>
<td>1.01 (0.53–1.95)</td>
<td>0.97</td>
<td>0.96 (0.48–1.94)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+46133C → T</td>
<td>T</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1963A → G</td>
<td>−/−ht1</td>
<td>Positive</td>
<td>0.72 (0.49–1.06)</td>
<td>0.10</td>
<td>0.75 (0.45–1.24)</td>
</tr>
<tr>
<td>−1963A → G</td>
<td>−/ht1/ht1</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1963A → G</td>
<td>−/ht1</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1963A → G</td>
<td>−/ht2</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1963A → G</td>
<td>−/ht3</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−1963A → G</td>
<td>−/ht4</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Logistic regression models were used to calculate ORs (95% confidence intervals) and the corresponding P values for SNP sites and haplotypes, while controlling for age, disease duration and sex as covariables. Genotype distributions and P values for logistic analyses of three alternative models (co-dominant, dominant, and recessive) are listed. Haplotypes with either equivalence with SNPs or with frequencies less than 5% were excluded from the statistical analyses. Significant associations are in bold type.
A. Map of PARP (poly (ADP-ribose) polymerase family, member 1) on chromosome 1q41-q42

Ex1 2 3 4 5 6 7 8 9 10 13 14 15 16 18 20 23

$+1$

2 kb

$−409G>A (0.458)$

$−759C>T (0.214)^*$

$−389T>A (0.458)$

$−1963A>G (0.313)^*$

$+242G>C (0.473)$

$+5673C>T D81D (0.395)$

$+5798A>G (0.456)$

$−449G>A (0.458)$

$+254G>C (0.473)$

$+549T>C (0.473)$

$+5922A>G (0.152)$

$+15610C>A (0.458)$

$+15538G>A (0.458)$

$+15925G>A (0.021)$

$+17532G>A (0.108)$

$+17584C>A (0.386)$

$+19335C>T (0.458)$

$+19361T>C (0.391)$

$+21643G>T (0.02)$

$+22229A>G (0.458)$

$+22267C>T A284A (0.145)$

$+24791G>A L352L (0.369)$

$+26769C>T R403W (0.02)$

$+26966A>G (0.02)$

$+28044G>C (0.021)$

$+28068G>C (0.456)$

$+28077G>A (0.169)^*$

$+28459T>G (0.022)$

$+28623C>G (0.5)$

$+28905G>T (0.413)$

$+29230A>C (0.413)$

$+30754G>A A625T (0.02)$

$+30940A>G (0.13)$

$+33870G>C (0.395)$

$+37754A>G (0.045)$

$+39794C>T (0.082)^*$

$+40329T>C V762A (0.461)^*$

$+46133C>T (0.068)^*$

B. LD coefficients among PARP SNPs

| D' | 0.041 | . . . . . . Others | 0.067 | T T C G T A ht6 | 0.087 | C C T G C A ht5 | 0.141 | C T C G C G ht4 | 0.145 | C T C G T A ht3 | 0.170 | C T C A C G ht2 | 0.349 | C C C G C A ht1 |

Frequency

FIG. 1. Gene map and haplotypes of PARP. Coding exons are marked by black blocks, and 5' and 3' UTRs by white blocks. The first base of the translational start site is denoted as nucleotide +1. *Indicate polymorphisms genotyped in a larger population ($N = 680$). The frequencies of polymorphisms not subjected to larger-scale genotyping were based on sequence data ($n = 24$).

(A) Polymorphisms identified in PARP on chromosome 1q41-42 (reference genome sequence: NT_004559.12). (B) Linkage disequilibrium coefficients ($|D'|$ and $r^2$) among PARP polymorphisms. (C) Haplotypes of PARP. Only those with frequencies of at least 0.05 are shown. Others contain rare haplotypes: AGCCTC, GGGCCC and ATGCCC. Only two individuals (0.03%) showed haplotype probabilities lower than 95% in our study by PHASE.
PARP polymorphisms and SLE nephritis and arthritis

We next tested the effect of PARP polymorphisms on renal manifestations using age, disease duration and sex as covariables in lupus patients. Two SNPs (−1963A → G and +28077G → A) were significantly associated with an increased risk of lupus glomerulonephritis among SLE patients (Table 2). The minor allele of −1963A → G and +28077G → A showed a strong susceptibility to lupus glomerulonephritis among SLE patients, in that the frequencies of the G-allele-containing genotypes of −1963A → G and the A allele of +28077G → A were significantly higher among SLE patients who were positive for renal disorder than among those who were negative [P = 0.03, odds ratio (OR) = 1.76 and P = 0.0008, OR = 2.49, respectively] (Table 2).

PARP polymorphisms and arthritis in SLE

We also investigated the genetic association with arthritis. Two SNPs (−1963A → G and +40329T → C(V762A)) and two common haplotypes (ht1 and ht3) were significantly associated with arthritis in SLE patients (Table 3). Variants −1963A → G and ht4 showed a strong protective effect in a gene-dose-dependent manner on arthritis in SLE patients (P = 0.002–0.03, OR = 0.56–0.31 and P = 0.004–0.01, OR = 0.51–0.22, respectively) (Table 3). On the other hand, +40329T → C(V762A) and ht1 had opposite effects on arthritis in SLE patients (P = 0.02–0.12, OR = 1.77–1.55 and P = 0.006–0.05, OR = 2.72–1.79, respectively) (Table 3). It was likely that the significant associations of ht1 (ACGCC(C)) depended on +40329T → C(V762A), because ht1 was almost tagged (frequency > 0.90) by +40329T → C(V762A), which showed a positive association (Fig. 1B).

Discussion

Several studies have suggested that interactions of multiple genes and environmental factors result in susceptibility to SLE. Linkage analyses have shown that chromosome 1q41-42, which contains PARP, is one of the loci with a significant linkage to SLE [28, 29]. A case–control study involving Japanese subjects identified five PARP polymorphisms, including a CA-repeat polymorphism [30], and detected complete LD between C1362T and the (CA)11 allele corresponding to the 85-bp allele [26]. Two SNPs identified in our study (−759C → T and −449G → A, which was linked with −1963A → G by absolute LD) correspond to C1362T and G1672A. Even though the −759C → T SNP is not considered to be linked to the (CA)11 allele by absolute LD, our results show that −759C → T is not associated with an increased risk of SLE in Koreans and that its allele frequency (21.4%) is low, as in Japanese subjects (19.3–20.4%), compared with Caucasians (54%) [26].

PARP has been demonstrated to be a nuclear protein binding to DNA via two zinc-finger motifs, and to play a key role in DNA repair, which has led to the suggestion that PARP is crucial in the processing of DNA lesions by triggering the base-excision repair pathway; it has also been shown that PARP-deficient mice are hypersensitive to genotoxic agents [31, 32]. Furthermore, the significant delay in cell death in an experimental model with a non-cleavable variant of the enzyme during apoptosis led to the suggestion that loss of PARP function is required for the efficient completion of apoptosis [33]. Thus, it is likely that dysregulation of apoptosis by decreased PARP activity contributes to the development of SLE. However, a recent study implicated translocation of apoptosis-inducing factor (AIF) from the mitochondria to the nucleus in the initiation of apoptosis, and showed that PARP activation is necessary for...
the translocation of AIF [34]. Therefore, further investigations are needed to clarify the role of PARP during apoptosis in SLE.

Tissue injury results from immune complex deposition, with a high level of autoantibodies directed to nuclear antigens in SLE. In particular, renal disorder with severe proteinuria and renal failure is a major complication of lupus. Although anti-dsDNA Abs have been shown to be strongly associated with renal involvement through deposition of these Abs directly on the glomerular basement membrane [35, 36], lupus glomerulonephritis can occur in the absence of anti-dsDNA Abs and breaking tolerance to nuclear antigens [37, 38]. Recently it was shown that breaking tolerance to dsDNA, nucleosomes and other nuclear antigens was not required for the development of lupus nephritis [39]. An immune response involving both T cells and B cells to kidney antigens is implicated in the pathogenesis of lupus nephritis [39]. On the other hand, increased IgG Abs reacting to PARP were observed in patients with SLE and autoimmune bowel diseases [40, 41]. These autoantibodies prevent caspase-3-mediated PARP cleavage during early apoptosis, which, if not regulated, can lead to prolonged autoimmune stimulation by increasing autoimmune cell survival [42]. These findings support the hypothesis that the PARP −1963A → G and +28077G → A SNPs identified in the present study can influence enzyme activity and subsequently result in an increased risk of lupus nephritis. Moreover, the common (frequency 0.313) promoter SNP, −1963A → G, was analysed for a putative transcription-factor-binding site using TFSEARCH software (Searching Transcription Factor Binding Sites, V1.3: putative score >0.90), which revealed that it is located in the consensus sequence of ADR1 and NIT2 (zinc-finger transcription factor) binding sites. Thus, a nucleotide change from A to G was partially supported by a grant of the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (no. 01-PJ3-PG6-01GN11-0002).

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Supplementary data

Supplementary data are available at Rheumatology Online.

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References


