IL18 GENE PROMOTER -607A/C AND -137G/C POLYMORPHISMS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Objective: To analyze the association of IL-18 promoter gene polymorphisms (-607A/C and -137C/G) with disease susceptibility and manifestations of SLE patients.

Methods: Forty seven SLE patients and 50 unrelated healthy subjects (a control group) were included. All SLE patients underwent thorough clinical examination and SLE disease activity assessment using SLEDAI. The IL-18 polymorphisms were genotyped by PCR amplification and RFLP analysis while, IL-18 plasma levels were determined by ELISA for both patients and controls.

Results: Our data indicated that the frequency of genotype -607/AC (P=0.04, OR: 2.58, 95% CI: 1.01-6.6) was significantly increased and the frequency of genotype -137/CC (P=0.049, OR: 0.27, 95% CI: 0.07-1.06) was significantly decreased in SLE patients. In addition, -607/CC genotype frequency was significantly increased in patients with serositis ($X^2$=6.75, $P=0.03$) while genotype -137/GG was significantly increased in patients with arthritis/arthralgia ($X^2$=7.06, $P=0.029$). Significantly elevated levels of plasma IL-18 were found in patients compared to controls ($P=0.002$) with significant correlation with disease activity ($p<0.001$). Patients with AC and CC (-607), and GG and GC (-137) genotypes have significantly higher IL-18 levels than those with AA and CC genotypes ($P<0.001$). Significantly higher IL-18 levels were found in control subjects with AC and CC (-607) genotypes ($P=0.014$).
Conclusion: Our results have provided evidence that IL18 promoter gene polymorphisms at position –607 and –137 contribute to genetic background of SLE susceptibility and presentation, as well as enhanced production of IL-18 protein in SLE patients.

Keywords: Gene polymorphisms, Single nucleotide polymorphisms, Interleukin 18, SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disorder characterized by loss of self-tolerance causing immune-mediated tissue destruction and various clinical presentations\(^{(1)}\).

A large body of evidence suggests that dysregulation of the production of various inflammatory cytokines plays an important role in the downstream pathological symptoms of the disease\(^{(2)}\).

Abnormal Th1 and Th2 cytokines profiles might be involved in the pathogenesis of the disease. Peripheral blood mononuclear cells of SLE patients show decreased production of the Th1 cytokines IL-2, IFN-\(\gamma\), TNF-\(\alpha\) and IL-12 and upregulation of the Th2 cytokines IL-4 and IL-10 \(^{(3)}\).

Interleukin-18 (IL-18), member of the IL-1 cytokine family, was previously characterized as a Th1 cytokine because of its property in inducing IFN-\(\gamma\) \(^{(4)}\). Later, it has been shown to be a pleiotropic cytokine that can mediate both Th1 and Th2 driven immune responses \(^{(5)}\). In combination with IL-12, IL-18 induces IFN-\(\gamma\) production in Th1 cells, B cells and natural killer cells, promoting Th1-type immune responses \(^{(6)}\), but it can also stimulate Th2 immune responses in the absence of IL-12 \(^{(7)}\). Abnormalities in the production of Th1 and Th2 cytokines have been shown in SLE patients \(^{(8)}\).

Because of its multiple functions in cytokine networks, IL-18 is likely to participate in the development of diseases. Elevated IL-18 levels have been reported in the urine of nephrotic patients, the serum of patients with multiple sclerosis,
SLE, adult-onset Still’s disease, type I diabetes mellitus, viral infection, sepsis, allergic conditions and asthma \(^9,10\).

IL-18 expression is regulated by the IL18 promoter gene \(^11\), which is located within a linkage region of SLE on chromosome 11 at 11q22.2–q22 \(^12\).

Polymorphisms in this gene could result in the imbalance of the immune response, which is a characteristic found in SLE \(^13\).

Two single nucleotide polymorphisms (SNPs) at position –607 and –137 in the promoter gene region have been considered to be significant because the change from cytosine to adenine (C to A) at position –607 disrupts a potential cAMP-responsive element binding (CREB) protein-binding site and a change at position –137 from guanine to cytosine (G to C) changes the H4TF-1 nuclear factor binding site to a binding site for an unknown factor found in the GM-CSF promoter \(^14\). Therefore, we analyzed the association of IL18 promoter gene polymorphisms (–607A/C and -137C/G) with disease susceptibility and manifestations of SLE patients.

**Subjects & Methods**

**Patients and controls**

Forty seven SLE patients were recruited from outpatient clinic and inpatient of Rheumatology and Rehabilitation Department Benha university hospitals. They fulfilled the American College of Rheumatology (ACR) criteria for classification of SLE \(^15\).

Fifty unrelated healthy volunteers were recruited from laboratory personnel and nursing staff, who had no history of autoimmune disease, served as controls. Informed consent was obtained from all subjects prior to the study and project approval was granted by the ethics committee of our institution.

All patients included in this study were subjected to full history taking, including ongoing medications. Clinical and serologic features of SLE, such as coetaneous manifestations, arthritis, serositis, kidney disease, neurological
manifestations, cardiovascular and
cerebrovascular diseases, lymph-
adenopathy, haematological manifest-
tations (leucopaenia, thrombocytopaenia, anaemia),
erythrocyte sedimentation rate
(ESR), ANA, anti-ds-DNA, complement C3/C4.

Disease activity was assessed using the SLE Disease Activity
Index (SLEDAI) \(^{16}\). It is a validated disease activity measure that
includes clinical and laboratory measures of SLE activity. The total
SLEDAI score ranges from 0 to 105.

. Genotyping

IL18 SNPs analysis was done to all patients and control subjects.
SNPs were analyzed by PCR amplification and restriction
fragment length polymorphism (RFLP) analysis according to
Bouzgarrou et al., \(^{17}\).

One mL of venous blood was collected from each patient and
control subject in EDTA tubes. All blood samples were processed on
the same day of collection.

Genomic DNA was extracted from
whole blood using Gene JETTM genomic DNA purification kit
(Fermentas) according to the manufacturer instructions. Purified
dNA samples were stored at -20°C till used in the amplification step.
The reaction mixture contains the following: 1 µg of genomic DNA, 25
µL of Dream Taq PCR Mastermix (2X) (Fermentas), 0.5 mM of each
primer (Fermentas), water (nuclease free) to a final volume of 50 µL. All
reagents were prior vortexed and 25 µL of mineral oil was added to the
reaction mixture and carried out in thermal cycler (Biometra, Germany).

IL18 -607C/A polymorphism analysis.

The polymorphism was analyzed by PCR amplification and RFLP analysis. A 171 bp PCR
amplification fragment was generated using the primers: 5’-
GCCCTCTTACCTGAATTTTGGTAGC
CCTC-3’ (forward) and 5’-
AGATTTACTTTTCAGTGGAGC
GTCC-3’ (reverse). The reaction
conditions were as follows: 95°C for
3 min followed by 30 cycles of (95°C
for 30 sec, 56°C for 30 sec and 72°C
for 1 min) and a final elongation
step carried out at 72°C for 15 min.
The product was digested with
Tru9I (90 min at 65°C). The -607A allele was cut into two fragments of 101 and 70 bp while the -607C allele remained uncut (171 bp).

**IL18 -137G/C polymorphism analysis.**

Similarly, the polymorphism at position -137 was analyzed by RFLP-PCR using the forward primer: 5'-ATGCTTCTAATGGACTAAGGA-3' and the reverse primer: 5'-GTAATATCATAATTTTCATGAATT-3'. The reaction conditions were as follows: 95°C for 3 min followed by 30 cycles (95°C for 30 sec, 43°C for 30 sec and 72°C for 1 min) and a final elongation step carried out at 72°C for 15 min. Restriction was performed using EcoRI. The -137G allele was cut into two fragments of 107 and 24 bp while the -137C allele remained uncut (131 bp). PCR-RFLP products were visualized using 1% agarose gel electrophoresis stained by ethidium bromide and visualized by UV light.

**ELISA**

The plasma IL-18 levels of 47 SLE patients and 50 control subjects who were randomly selected, were measured by enzyme-linked immunosorbent assay (ELISA) using the human bioactive IL-18 ELISA kit (BD Opt EIA) (USA) as described by the manufacturer instructions.

**Statistical analysis**

The collected data were analyzed using SPSS version 16 software, categorical were presented as number and percentages using chi square (X²) and "Z" tests for their analysis, Odds Ratio (OR) and the corresponding 95% CI were calculated when applicable. Quantitative data were expressed as mean and standard deviation using student "t" test and ANOVA (F) test for their analysis, 2 tailed P value <0.05 was considered significant.

**Results**

Forty seven SLE patients (age range, 9 to 52 years) and 50 healthy unrelated controls (age range, 26 to 54 years) were studied. The female-to-male ratios in SLE patients and controls were 10.75:1 and 3.2:1, respectively.

The study groups characteristics are shown in Table 1.
Association of IL18 gene polymorphism with SLE susceptibility (Table 1):

The differences reflect statistically significant increase of genotype -607/AC (P=0.04, OR: 2.58, 95% CI: 1.01-6.6) and decrease of genotype -137/CC (P=0.049, OR: 0.27, 95% CI: 0.07-1.06) in SLE patients. The genotypes -607/AA and -607/CC were higher in SLE patients, but were found not to be statistically significant (p=0.36 and p=0.34, respectively). For position -137, the genotypes GG and GC showed non significant increase in SLE patients (p=0.49 and p=0.5, respectively) when compared to controls.

Non significant differences of the A and C alleles at position -607 (p=0.149 and p=0.149, respectively) as well as G and C alleles at position -137 (p=0.52 and p=0.52, respectively) between SLE and controls.

Association of IL18 gene polymorphism with clinical manifestations of SLE:

The association between the clinical features profile of SLE patients with various genotypes and alleles at -607 and -137 positions was analyzed and the result was shown in Tables 3 and 4. There were significant associations between genotype -607/AC with serositis ($X^2$=6.75, P=0.03) and genotype -137/GG with arthritis/arthralgia ($X^2$=7.06, P=0.029).

Plasma IL-18 levels and genotypes at SNP -607 and -137 (Table 5).

In the patients group, the plasma level of IL-18 in patients who had AA genotype at position -607 was 124.2 ± 32.2 (mean ± SD) pg/mL, while its level for patients who had AC genotype was 295.2± 69.3 pg/mL. The patients with CC genotype had a level of 284.9± 66.8 pg/mL. Significant differences were observed among the 3 subgroups (F= 33.02, P <0.001).

Also, patients with GG and GC genotypes at SNP -137 had significantly higher IL-18 plasma levels (296.8 ± 67.2 and 306.1 ± 77.5, respectively ) than those with CC genotype (79.3 ± 24.4), F=107.7 and P <0.001.
In the control group, subjects with AA genotype at SNP -607 had significantly lower IL-18 plasma level when compared to subjects with AC and CC genotypes (F=4.66, P =0.014). The means for the 3 subgroups were 59.6 pg/mL, 115.7 pg/mL and 121.2 pg/mL respectively.

Non significant differences were observed among patients with GG, GC or CC genotypes at SNP -137 (F=0.66, P=0.52).

- On the other hand, patients had significantly higher plasma IL-18 levels (283.5 ± 61.2 pg/mL) than controls (83 ± 24.3 pg/mL), p=0.002 (Fif. 1). Furthermore, a significant positive correlation between IL-18 plasma level and SLE disease activity (SLEDAI score) were found, where r=0.64 and p <0.001.

### Table 1: Characteristics of SLE patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>SLE patients (n = 47)</th>
<th>Controls (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ,female / male</td>
<td>43 / 4</td>
<td>38 / 12</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>9 – 52</td>
<td>26 - 54</td>
</tr>
<tr>
<td>mean±SD</td>
<td>28 ± 7</td>
<td>31 ± 5</td>
</tr>
<tr>
<td>Disease duration(years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-16</td>
<td>NA</td>
</tr>
<tr>
<td>mean±SD</td>
<td>7± 3.5</td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous features, no(%)</td>
<td>34 (72.34)</td>
<td>NA</td>
</tr>
<tr>
<td>Serositis, no (%)</td>
<td>23 (48.93)</td>
<td>NA</td>
</tr>
<tr>
<td>Arthritis/arthralgia, no (%)</td>
<td>36 (76.59)</td>
<td>NA</td>
</tr>
<tr>
<td>Renal features, no (%)</td>
<td>27 (57.44)</td>
<td>NA</td>
</tr>
<tr>
<td>CNS features, no (%)</td>
<td>12 (25.53)</td>
<td>NA</td>
</tr>
<tr>
<td>Hematologic features, no (%)</td>
<td>27 (57.44)</td>
<td>NA</td>
</tr>
<tr>
<td>SLEDAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>5-26</td>
<td>NA</td>
</tr>
<tr>
<td>mean±SD</td>
<td>15.7 ± 4.9</td>
<td></td>
</tr>
<tr>
<td>ANA, +ve no (%)</td>
<td>43 (91.48)</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-dsDNA, +ve no (%)</td>
<td>42 (89.36)</td>
<td>NA</td>
</tr>
<tr>
<td>↓C3, no (%)</td>
<td>17 (36.17)</td>
<td>NA</td>
</tr>
<tr>
<td>↓C4, n (%)</td>
<td>13 (27.65)</td>
<td>NA</td>
</tr>
</tbody>
</table>

CNS; Central nervous system
ANA; Antinuclear antibodies.
Anti-dsDNA; Anti double stranded DNA.
N; Number of patients.
C (3 & 4); Complement (3 & 4)
NA; Non applicable
Table 2: Distribution of IL18 genotypes and alleles frequencies in SLE patients and controls.

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Controls (n=50)</th>
<th>SLE patients (n=47)</th>
<th>OR</th>
<th>95% Confidence interval (CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL18-607A/C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>17 (34)</td>
<td>12 (25.5)</td>
<td>0.66</td>
<td>0.28-1.6</td>
<td>0.36</td>
</tr>
<tr>
<td>AC</td>
<td>9 (18)</td>
<td>17 (36.17)</td>
<td>2.58</td>
<td>1.01-6.6</td>
<td>0.04*</td>
</tr>
<tr>
<td>CC</td>
<td>24 (48)</td>
<td>18 (38.29)</td>
<td>0.67</td>
<td>0.3-1.5</td>
<td>0.34</td>
</tr>
<tr>
<td>A allele</td>
<td>54 (54)</td>
<td>41 (43.6)</td>
<td>0.66</td>
<td>0.37-1.2</td>
<td>0.149</td>
</tr>
<tr>
<td>C allele</td>
<td>46 (46)</td>
<td>53 (56.4)</td>
<td>1.5</td>
<td>0.86-2.7</td>
<td>0.149</td>
</tr>
<tr>
<td>IL18-137G/C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>21 (42)</td>
<td>23 (48.9)</td>
<td>1.3</td>
<td>0.59-2.9</td>
<td>0.49</td>
</tr>
<tr>
<td>GC</td>
<td>19 (38)</td>
<td>21 (44.7)</td>
<td>1.3</td>
<td>0.59-2.96</td>
<td>0.5</td>
</tr>
<tr>
<td>CC</td>
<td>10 (20)</td>
<td>3 (6.4)</td>
<td>0.27</td>
<td>0.07-1.06</td>
<td>0.049*</td>
</tr>
<tr>
<td>G allele</td>
<td>66 (66)</td>
<td>66 (72.8)</td>
<td>1.2</td>
<td>0.66-2.2</td>
<td>0.52</td>
</tr>
<tr>
<td>C allele</td>
<td>34 (34)</td>
<td>28 (27.2)</td>
<td>0.82</td>
<td>0.45-1.5</td>
<td>0.52</td>
</tr>
</tbody>
</table>

OR: odds ratio. CI: Confidence interval.

N: Number of patients.

* = Significant (P<0.05).

Table (3): The association of polymorphism IL18 607A/C with clinical manifestations in SLE patients.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Genotype distribution</th>
<th>X²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA (n=12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murcuteaneous (34)</td>
<td>9 (75)</td>
<td>0.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Serosal (23)</td>
<td>5 (41.7)</td>
<td>6.75</td>
<td>0.03*</td>
</tr>
<tr>
<td>Arthritis/arthralgia (36)</td>
<td>9 (75)</td>
<td>2.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Renal (27)</td>
<td>7 (58.3)</td>
<td>0.04</td>
<td>0.98</td>
</tr>
<tr>
<td>CNS (12)</td>
<td>3 (25)</td>
<td>0.24</td>
<td>0.887</td>
</tr>
<tr>
<td>Hematologic (27)</td>
<td>8 (66.66)</td>
<td>0.58</td>
<td>0.75</td>
</tr>
<tr>
<td>Immunologic (43)</td>
<td>11 (91.66)</td>
<td>0.31</td>
<td>0.86</td>
</tr>
</tbody>
</table>

CNS: Central nervous system. N: number of patients

* = Significant (P < 0.05).

Table (4): The association of polymorphism IL18 137G/C with clinical manifestations in patients with SLE.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Genotype distribution</th>
<th>X²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG (n=23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murcuteaneous (34)</td>
<td>17 (73.9)</td>
<td>1.5</td>
<td>0.47</td>
</tr>
<tr>
<td>Serosal (23)</td>
<td>11 (47.8)</td>
<td>0.4</td>
<td>0.82</td>
</tr>
<tr>
<td>Arthritis/arthralgia (36)</td>
<td>21 (91.3)</td>
<td>7.06</td>
<td>0.029*</td>
</tr>
<tr>
<td>Renal (27)</td>
<td>12 (52.2)</td>
<td>0.53</td>
<td>0.76</td>
</tr>
<tr>
<td>CNS (12)</td>
<td>5 (21.7)</td>
<td>0.37</td>
<td>0.83</td>
</tr>
<tr>
<td>Hematologic (27)</td>
<td>13 (56.5)</td>
<td>0.11</td>
<td>0.94</td>
</tr>
<tr>
<td>Immunologic</td>
<td>21 (91.3)</td>
<td>0.31</td>
<td>0.85</td>
</tr>
</tbody>
</table>

CNS: Central nervous system. N: number of patients

* = Significant (P < 0.05).
**Table (5):** Comparison between plasma IL-18 levels among its promoter gene polymorphisms at position –607 and –137 in SLE patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Position –607</th>
<th></th>
<th></th>
<th>Position –137</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genotype (N)</td>
<td>Mean ± SD (pg/mL)</td>
<td>p</td>
<td>Genotype (N)</td>
<td>Mean ± SD (pg/mL)</td>
<td>p</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA(12)</td>
<td>124.2 ± 32.2</td>
<td>&lt;0.001*</td>
<td></td>
<td>GG(23)</td>
<td>296.8 ± 67.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>AC(17)</td>
<td>295.2 ± 69.3</td>
<td></td>
<td></td>
<td>GC(21)</td>
<td>306.1 ± 77.5</td>
<td></td>
</tr>
<tr>
<td>CC(18)</td>
<td>284.9 ± 66.8</td>
<td></td>
<td></td>
<td>CC(3)</td>
<td>79.3 ± 24.4</td>
<td></td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA(17)</td>
<td>59.6 ± 26.8</td>
<td></td>
<td>0.014*</td>
<td>GG(21)</td>
<td>78.3 ± 27.6</td>
<td>0.52</td>
</tr>
<tr>
<td>AC(9)</td>
<td>115.7 ± 78.4</td>
<td></td>
<td></td>
<td>GC(19)</td>
<td>83.2 ± 38.9</td>
<td></td>
</tr>
<tr>
<td>CC(24)</td>
<td>121.2 ± 79.3</td>
<td></td>
<td></td>
<td>CC(10)</td>
<td>92.6 ± 27.5</td>
<td></td>
</tr>
</tbody>
</table>

N; Number of patients. *= Significant (P<0.05).

**Fig. (1):** Plasma IL-18 levels in SLE patients and controls.
Discussion

Many studies have examined the relationship between cytokine gene polymorphisms and the incidence of SLE, including IL-4, IL-6, IL-10, TNF-a and IFN-γ receptor \(^{(18, 19, 20, 21)}\).

Owing to IL-18’s well-established role in inflammatory and autoimmune processes \(^{(22)}\), and that IL-18 gene variation may influence IL-18 production, we conducted this study with the aim of discovering variants that may have impact on SLE disease susceptibility as well as clinical presentation.

We found the genotype SNP-607/AC to be significantly higher in SLE patients when compared to control subjects. A significant decrease of genotype CC at position -137 was also observed in SLE patients compared to controls.

In the same context, a study was done on IL-18 polymorphisms at position -656, -607 and -137 in a cohort of taiwan Chinese SLE patients, providing evidence for genetic association conferred by these polymorphisms with the clinical features of the disease \(^{(23)}\).

Sánchez and coworkers (2009) \(^{(24)}\), reported an association between a putative functional genetic variant in the promoter region of IL-18 (rs360719) and systemic lupus erythematosus in Spanish patients. Also, in the same study, they found an increase in the relative expression of IL-18 mRNA in individuals with the rs360719 lupus-risk allele.

These results do not agree with those of Xu et al. (2007) \(^{(9)}\), who reported that -607 CC and -137 CC genotypes of IL-18 gene were associated with SLE susceptibility in Singapore Chinese.

Htoon et al. (2011) \(^{(25)}\), found a genetic association between IL-18 and Behçet’s Disease but not lupus in Turkish patients.

For position -137, a change from G to C changes the H4TF-1 nuclear factor-binding site to a binding site for an unknown factor found in the GM-CSF promoter. It was
postulated that because H4TF-1 nuclear factor would not bind to C allele of position –137, the SNP–137/C allele would have lower IL-18 mRNA expression (9, 14).

Our result suggests that CC genotype of IL-18 (−607) is a risk for serositis and GG genotype (−137) is a risk for arthritis/arthralgia.

However, our results are contradictory to another study where no positive association was found between polymorphism in IL-12 and IL-18 genes and susceptibility to SLE in Thais (26). However, when they analyzed polymorphism of the IL-12 and IL-18 genes with clinical manifestations, they found significant association of the C allele of IL-18 (−137) with arthritis.

Warchoł and his colleagues (2009) (27), did not observe differences in the distribution of the IL-18 105 A/C polymorphism between patients with SLE and controls. However, they found a significant association of renal symptoms with the IL-18 105 AA genotype.

Takada et al. (2002) (28), reported that in patients with sarcoidosis, the C allele of IL-18 at position -607 was a risk factor for sarcoidosis in the Japanese population.

In RA patients, Sivalingam et al (2003) (29), found that the A allele at position -607, in the homozygous state, has a protective effect against the development of RA.

These large contradictions could be explained by the small samples used, the different diseases analyzed and the ethnic groups investigated.

In the same context, Love (30), postulated that the variability of the influence of the IL-18 polymorphism on SLE manifestation and incidence in different populations can be due to genetic heterogeneity, which usually confounds the study of multigenic disorders.

Furthermore, various environmental factors together with genetic heterogeneity may also modulate the effect of the IL-18
polymorphism on clinical manifestations. Several functional studies have shown that the level of IL-18 production is related to the IL-18 promoter gene (14, 31).

In the present study, SLE patients had significantly higher plasma IL-18 levels that correlated well with disease activity. Our results are in line with two independent studies that have shown higher IL-18 levels in SLE patients than in control subjects, and a significant positive correlation with SLEDAI score (32, 33).

We demonstrated significantly higher IL-18 levels in patients with AC and CC (-607), and GC and GC (-137) genotypes.

Our results coincide with others (9), who demonstrated significantly higher IL-18 levels associated with AC and CC genotypes at position -607 of IL-18 promoter gene in both SLE patients and controls.

The deficiency in enhanced gene transcription will be beneficial for the individual, as elevated levels of the proinflammatory IL-18 protein mediate many of the acute and chronic inflammatory processes. Indeed, studies in anticytokine therapy including TNF, IL-6, IL-18 and IFN-γ in SLE have become an important issue in preventing from tissue damage (34).

**Conclusion**

Our results have provided evidence that IL-18 promoter gene polymorphisms at position -607 and -137 contribute to genetic background of SLE susceptibility and presentation as well as enhanced production of IL-18 protein in SLE patients.

**REFERENCES**


