Effect of interleukin-1β gene polymorphisms on clinicopathological features and disease activity of systemic lupus erythematosus

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Background
Systemic lupus erythematosus (SLE) is responsible for severe disability and represents a major cause of chronic illness. Interleukin (IL)1β is a proinflammatory cytokine. We aimed to explore the possible associations of IL1β-511C/T (rs16944) and IL1β +3954C/T (rs1143634) gene polymorphisms with SLE, and to detect whether these polymorphisms are associated with disease activity of SLE. Moreover, we aimed to clarify the effect of these polymorphisms on clinical and biochemical parameters of SLE.
Patients and methods
Polymorphisms of IL1β-511 and IL1β +3954 genes were assessed in a case-control study comprising 110 patients with SLE and 90 controls. Disease activities were assessed by systemic lupus erythematosus disease activity index (SLEDAI). Serum IL-1β was estimated using an enzyme-linked immune sorbent assay. Genetic variants were genotyped using PCR-restriction fragment length polymorphism.
Results
Our results revealed higher values of IL1β in patients with SLE. In addition, there was a significant positive correlation between IL-1β serum level and SLEDAI score. The CT genotype distribution was significantly higher in patients with SLE than controls. Regarding IL1β +3954 gene polymorphisms, our results showed nonsignificant difference between control and SLE groups. In an attempt to estimate the diagnostic power of serum IL1β serum in differentiating patients with SLE from the control group, we found that the sensitivity was 94.5%, and the specificity was 99%.
In conclusion, the CT genotype distribution of IL1β-511 was significantly higher in patients with SLE than controls. However, there was a nonsignificant difference regarding IL1β +3954 gene mutation.

Keywords:
interleukin1β single nucleotide polymorphisms, systemic lupus erythematosus, systemic lupus erythematosus disease activity index

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, inflammatory, immune-mediated disease with a broad spectrum of clinical presentations encompassing almost all organs and tissues, affecting 0.1% of the general population [1]. The prevalence of SLE is greater in non-white racial groups [2], and the disease affects women more frequently than men [3].

Interleukin-1β (IL1β), a proinflammatory cytokine with widespread biological activities expressed by activated macrophages and several other types of cells, is thought to play a crucial role in the pathogenesis of autoimmune diseases [4,5]. IL1β was initially known as one of the lymphocyte-activating factors, owing to its role in the induction of T-cell proliferation and maturation.

The IL1β gene has two single nucleotide polymorphisms (SNP), at position −511 in the promoter region (rs16944) and at position +3954 in the fifth exon (rs1143634) [6,7]. The polymorphisms of the IL1 family are involved in several autoimmune diseases such as SLE [8,9], rheumatoid arthritis [10], and autoimmune hemolytic anemia [11].

We aimed to explore the possible associations of IL1β-511C/T (rs16944) and IL1β +3954C/T (rs1143634) gene polymorphisms with SLE, and to detect whether these polymorphisms are associated with disease

activity of SLE. Moreover, we aimed to clarify the effect of these polymorphisms on clinical and biochemical parameters of SLE.

Patients and methods

This case-control study comprised 90 healthy women and 110 patients diagnosed with SLE according to 2012 Systemic Lupus International Collaborating Clinics classification criteria and recruited from the outpatient clinics of the Rheumatology and Rehabilitation as well as Internal Medicine departments at the Zagazig University hospitals. The ethics committee of Faculty of Medicine, Zagazig University, approved this work. All participants assigned informed written consent before their inclusion and had a disease duration of one year or greater.

All participants underwent complete history taking and thorough clinical examination including malar rash, discoid rash, photosensitivity, alopecia, oral ulcer, fever, arthritis, nervous system disorder, serositis, renal affection, and photosensitivity. The use of current and cumulative medications was determined both through chart review and the standardized interview.

We excluded patients with a history of myocardial infarction, angina, stroke, pregnancy, and diabetes. In addition, patients with hepatits C virus, hepatits B virus, other connective tissue diseases, as well as a history of propylthiouracil, isoniazid, or hydralazine use were excluded. A history of proteinuria was defined as 500 mg or more per 24 h. Disease activity was measured using the systemic lupus erythematosus disease activity index (SLEDAI) [12].

Blood sampling

Blood samples were drawn from all subjects after an overnight fast. Sera were separated after 1 h longstanding and stored at −80°C.

Serologic factors

We measured antinuclear antibodies (ANA), antidouble-stranded DNA antibody (anti-dsDNA), and anticardiolipin. The ANA was assessed by indirect immunofluorescence technique using the Indirect Immunofluorescent Kit NOVA Lite HEp-2 ANA kit (INOVA Diagnostics Inc., San Diego, California, USA). For anti-dsDNA, we used the anti-dsDNA indirect immunofluorescence Kit NOVA Lite dsDNA CrithidiaIuciliae kit (INOVA Diagnostics Inc.). Anticardiolipin was performed by enzyme-linked immune sorbent assay anticardiolipin IgG/IgM ORG515 (ORGENTEC DiagnostikaGmbh, Mainz, Germany). Erythrocyte sedimentation rate (ESR) was determined manually. C-reactive protein (CRP) and complement C3 and C4 were measured using immunoturbidimetric assay on Roche/Hitachi cobas system (c501) autoanalyzer (Roche Diagnostics, Mannheim, Germany).

DNA extraction

Genomic DNA was extracted from EDTA whole blood using a spin-column method according to the protocol (QIAamp Blood Kit; Qiagen, GmbH, Hilden, Germany). DNA was stored at −80°C till the time of use. Genomic DNA was extracted from EDTA-anticoagulated peripheral blood.

Genotyping of IL-1β-511 and IL-1β+3954 gene polymorphisms

Genotyping for IL-1β-511C/T and IL-1β+3954C/T polymorphisms in unrelated patients with SLE and healthy controls was done by PCR-restriction fragment length polymorphism method as described previously [13,14]. Amplification of the target region was carried out by polymerase chain reaction using the specific forward and reverse primers. Primers were designed and selected using Primer3, version 0.4.0 software. For IL-1β +3954C/T (rs1143634), the primers were as follows: forward 5′-GTTGTCATCAGACTTTGACC-3′ and reverse 5′-TTCAGTTCATATGGACCAGA-3′. For IL-1β–511C/T, the primers were as follows: forward 5′-TGGCATTGATCTGGTTCATC-3′and reverse 5′-GTTTAGGAATCTTCCCACTT-3′. PCR was performed in a final volume of 25 µl containing 5.5 µl of H_2O, 5 µl of genomic DNA, 1 µl of each primer (1 µmol/l) (Promega, Madison, Wisconsin, USA), and 1X PCR Master mix (12.5 µl) (Taq PCR Master Mix Kit; QIAGEN), containing 200 µmol/l of each dNTP, 5 µl of 10×reaction buffer, 1.25 U Taq Gold Polymerase, and 4 mmol/l $MgCl_2$. PCR protocol consists of an initial denaturing step of 4 min at 95°C, then 35 cycles of denaturing for 30 s at 95°C, annealing for 30 s at 56°C, extension for 30 s at 72°C, and a final extension step of 10 min at 72°C. Digestion of the amplified products of IL-1β +3954C/T and IL-1β-511C/T was done by using 10 units of restriction endonucleases *Taq 1* (New England Biolabs) and Ava1 (New England Biolabs), respectively, and incubated at 37°C for 16 h. The digested products were checked on 3% agaroses gel. The fragments for IL-1β +3954C/T were identified as C/C – 136 and 114 bp; T/T- 250 bp; and C/T-250, 136, and 114 bp; and for IL-1β–511C/T were identified as T/T-304 bp, C/C-190/114, and T/C-304/190/114 bp.

Urine sampling

Twenty-four hour urine samples were collected from each participant in sterilized urine containers and used to determine protein levels.

Statistical analysis

Statistical analyses were performed using the statistical package for the social sciences for Windows (version 21.0; SPSS Inc., Chicago, Illinois, USA). Data were expressed using descriptive statistic (mean±SD) and were analyzed using analysis of variance test. Genotype frequencies in cases and controls were tested for Hardy–Weinberg equilibrium, and any deviation between the observed and expected frequencies was tested for significance using the χ^2-test. The statistical significances of differences in the frequencies of variants between the groups were tested using the χ^2-test. In addition, the odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated as a measure of the association of IL-1β-511C/T and IL-1β +3954C/T genotypes with SLE. The appropriate sample size and power of the study were determined using PAWE-3D (32). Quantitative data analysis of variance test was done to assess the effect of IL1β-511 rs16944(C/T) and IL1β +3954 rs1143634 (C/T) mutations on clinical, anthropometric, and laboratory characteristics of patients with SLE. A difference was considered significant at *P* less than 0.05.

Results

Our patients were matched for age, sex, and ethnicity with control group.

Clinical characteristics and laboratory parameters of patients with SLE are shown in

Distribution of genotype and allele frequencies of IL1β-511 and IL1β +3954 in healthy controls and patients with SLE (Table 1).

Genotype and allelic frequencies of IL1β-511C/T (rs16944) and IL1β +3954 rs1143634 (C/T) gene polymorphisms in patients with SLE and healthy

Table 1 Clinical characteristics and laboratory parameters of patients with systemic lupus erythematosus

Variables	*n*=110
Age (years)	31.94±6.57
Duration of disease (years)	4.25±2.04
Fever	15 (20)
SLEDAI	10.65±5.7
Hypertension	16 (21.3)
Malar rash	24 (32)
Photosensitivity	34 (45.3)
Oral ulcers	32 (42.7)
Alopecia	33 (44)
Pleurisy	26 (34.7)
Pericarditis	34 (68)
Arthritis	23 (30.7)
Vasculitis	9 (120)
Myositis	1 (1.3)
Retinal change	1 (1.3)
Cataract	3 (4)
Seizures	6 (8)
Psychosis	2 (2.7)
Headache	5 (6.7)
Proteinuria	12 (16)
Pus cell	11 (14.7)
Hematuria	10 (13.3)
Anemia	34 (45.3)
Thrombocytopenia (<100 000/mm)	9 (12)
Lymphopenia (<1500/mm)	6 (8)
Leucopenia (<4000/mm)	35 (46.7)
CRP (mg/dl)	8.67±1.977
ESR (mm/h)	47.83±24.82
Anti-dsDNA	29 (38.7)
C3 (mg/dl)	59.68±26.58
C4 (mg/dl)	20.8±16.71

ANA, antinuclear antibodies; C3, complement 3; C4, complement 4; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index. *P<0.05, statistically significant.

Table 2 Distribution of IL1β-511 and IL1β +3954 genotypes and allele frequencies in healthy controls and patients with SLE

	Healthy controls (*n*=90) [*n* (%)]	Patients with SLE (*n*=110) [*n* (%)]	OR (95% CI)	*P*
IL1β-511				
CC	26 (29)	14 (13)		
CT	34 (38)	58 (53)	3.16 (1.458–6.879)	<0.001*
TT	30 (33)	38 (34)	2.352 (1.049–5.272)	<0.051
C allele	86 (48)	86 (39)		
T allele	94 (52)	134 (61)	1.425 (0.956–2.123)	0.081
IL1β +3954				
CC	68 (76)	89 (81)		
CT	20 (22)	18 (16)	0.687 (0.337–1.391)	0.305
TT	2 (2)	3 (3)	0.509 (0.082–3.138)	0.466
C allele	156 (87)	196 (89)		
T allele	24 (13)	24 (11)	0.796 (0.435–1.455)	0.458

CI, confidence interval; IL1β, interleukin-1β; OR, odds ratio; SLE, systemic lupus erythematosus. *P<0.05, statistically significant.

volunteers are presented in Table 2. The genotype distributions were in Hardy–Weinberg equilibrium in each studied group.

Regarding IL1β-511C/T (rs16944) gene polymorphisms

The CT genotype distribution was significantly higher in patients with SLE than controls [OR (95% CI): 1.837 (1.042–3.239), $P<0.05$]. Regarding the TT genotype distribution, there were nonsignificant differences among both groups. In allele distribution, the frequency of the -511 T allele was 61% (134 out of 220) in the SLE group compared with 52% (94 of 180) in the controls; statistical analysis indicated no difference between those groups [OR (95% CI): 1.425 (0.811–2.505, $P=0.218$] (Table 2).

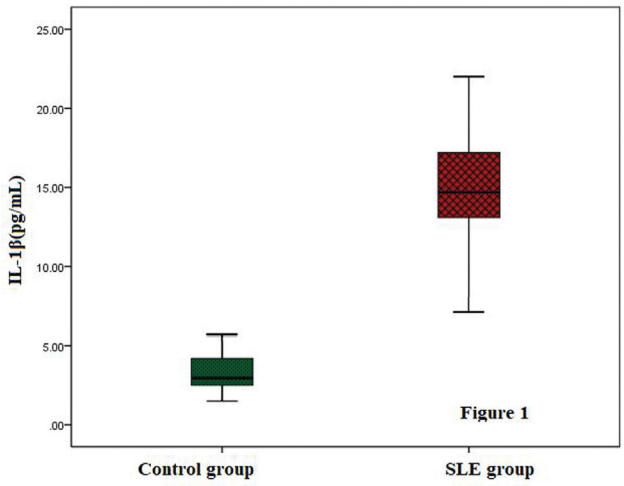
Regarding IL1β +3954 rs1143634 (C/T) gene polymorphisms

Our results showed that there was a nonsignificant difference between control and SLE groups. The OR (95% CI) of CT genotype distribution was 0.687 (0.337–1.391), with $P=0.295$, and the OR (95% CI) of TT genotype distribution was 0.509 (0.082–3.138), with $P=0.820$. Regarding allele distribution, the frequency of the +3954 T allele was 11% (24 of 220) in the SLE group compared with 13% (24 of 180) in the controls; statistical analysis indicated no difference between those groups [OR (95% CI): 0.796 (0.435–1.455), $P=0.60$] (Table 2).

Comparison of IL1β serum levels in studied groups

SLE group had a significantly higher values of IL1β serum levels (14.62±3.64) compared with control group (3.68±1.96), with P less than 0.001* (Fig. 1).

Figure 1



Comparison of IL1β serum levels in studied groups. IL, interleukin.

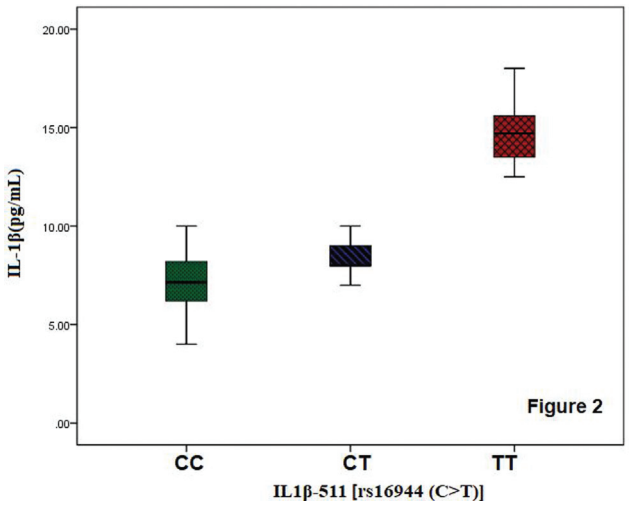
Effect of IL1β-511 rs16944 (C/T) mutations on clinical and laboratory characteristics of patients with SLE

Patients carrying TT genotype of IL1β-511 had significantly higher values of IL-1β (Fig. 2). However, patients carrying CT genotype had higher values regarding SLEDAI (Fig. 3) and ESR ($P<$ 0.05*) (Table 3).

Effect of IL1β +3954 rs1143634(C/T) mutations on clinical and laboratory characteristics of patients with SLE is shown in Table 4

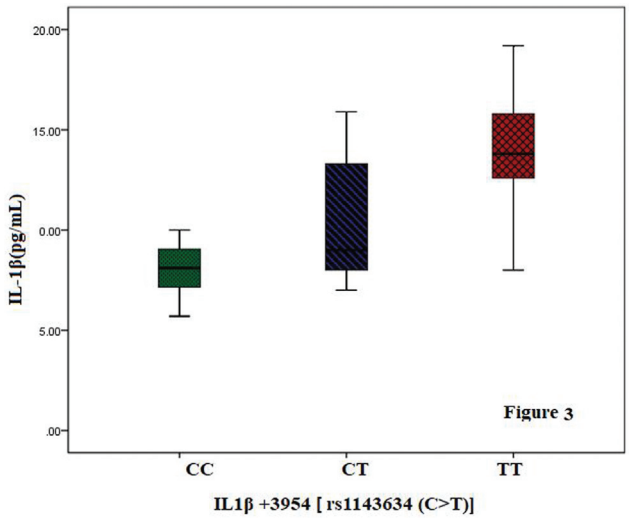
Regarding IL1β +3954, patients carrying TT genotype of +3954 had significantly higher values of IL1β

Figure 2



Effect of IL1β-511 [rs16944 (C>T)] mutations on IL1β serum levels. IL, interleukin.

Figure 3



Effect of IL1β-511 [rs16944 (C>T)] mutations on SLEDAI. IL, interleukin; SLEDAI, systemic lupus erythematosus disease activity index.

Table 3 Effect of IL1β-511 [rs16944 (C>T) mutations on clinical and laboratory characteristics of patients with SLE

	IL1β-511 rs16944 (C>T)			
	CC (*N*=14)	CT (*N*=58)	TT (*N*=38)	*P*
Fever	4 (28.6)	10 (17.2)	8 (21.1)	0.458
SLEDAI	7.57±3.41	13.98 ±8.47	13.56 ±8.18	<0.05*
Discoid rash	4 (28.6)	25 (43.1)	18 (47.4)	0.166
Photosensitivity	3 (21.4)	19 (32.8)	14 (36.8)	0.583
Oral ulcers	4 (28.6)	27 (46.6)	16 (42.1)	0.351
Alopecia	4 (28.6)	23 (39.7)	18 (47.4)	0.134
Pleurisy	3 (21.4)	20 (34.5)	15 (39.5)	0.164
Pericarditis	2 (14.3)	31 (53.4)	17 (44.7)	0.138
Arthritis	4 (28.6)	17 (29.3)	12 (31.6)	0.449
Vasculitis	0 (0)	15 (25.9)	3 (7.9)	0.436
Myositis	1 (7.1)	2 (3.4)	0 (0)	0.458
Cataract	2 (14.3)	4 (6.9)	1 (2.6)	0.107
Retinal change	1 (7.1)	2 (3.4)	0 (0)	0.147
Seizures	4 (28.6)	5 (8.6)	3 (7.9)	0.073
Psychosis	1 (7.1)	2 (3.4)	1 (2.6)	0.382
Headache	2 (14.3)	5 (8.6)	4 (10.5)	0.504
proteinuria	2 (14.3)	17 (29.3)	12 (31.6)	0.183
Pus cell	2 (14.3)	16 (27.6)	11 (28.9)	0.228
Hematuria	2 (14.3)	16 (27.6)	10 (26.3)	0.312
Anemia	8 (57.1)	25 (43.1)	18 (47.4)	0.423
Thrombocytopenia	2 (14.3)	11 (19)	8 (21.1)	0.361
Lymphopenia	4 (28.6)	5 (8.6)	3 (7.9)	0.068
Leucopenia	6 (42.9)	25 (43.1)	20 (52.6)	0.245
C3 (mg/dl)	67.2±29.8	46.5±29.4	52.6±26.8	0.054
C4 (mg/dl)	16.9±4.4	17.9±14.3	19.9±17.1	0.739
CRP (mg/dl)	7.8±1.6	10.8±5.6	10.5±3.8	0.111
ESR (mm/h)	40.2±10.2	67.1±35.1	66.8±41.2	0.044
IL-1β (pg/ml)	7.6±1.54	9.2±2.54	14.2±1.46	<0.001*

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; SLE, systemic lupus erythematosus. *P<0.05, significant.

Table 4 Effect of IL1β +3954 [rs1143634 (C>T)] mutations on clinical and laboratory characteristics of patients with SLE

	IL1β +3954 rs1143634 (C>T)			
	CC (*N*=27)	CT (*N*=52)	TT (*N*=31)	*P*
Fever	8 (29.6)	8 (15.4)	6 (19.4)	0.228
SLEDAI	8.55±3.97	12.72 ±7.28	17.34 ±9.41	<0.001*
Discoid rash	7 (25.9)	16 (30.8)	16 (48.4)	0.124
Photosensitivity	10 (37)	22 (42.3)	15 (48.3)	0.232
Oral ulcers	10 (37)	24 (46.2)	13 (41.9)	0.427
Alopecia	10 (37)	19 (36.5)	16 (48.4)	0.154
Pleurisy	7 (25.9)	18 (34.6)	13 (41.9)	0.372
Pericarditis	9 (33.3)	32 (61.5)	9 (29)	0.163
Arthritis	9 (33.3)	16 (30.8)	8 (25.8)	0.312
Vasculitis	0 (0)	8 (15.4)	10 (32.3)	0.001
Myositis	1 (3.7)	1 (1.9)	1 (3.2)	0.614
Cataract	2 (7.4)	3 (5.8)	2 (6.5)	0.547
Retinal change	1 (3.7)	1 (1.9)	1 (3.2)	0.614
Seizures	4 (14.8)	4 (7.7)	4 (12.9)	0.507
Psychosis	1 (3.7)	2 (3.8)	1 (3.2)	0.598
Headache	2 (7.4)	4 (7.7)	5 (16.1)	0.177
Proteinuria	2 (7.4)	17 (32.7)	12 (38.7)	0.017
Pus cell	2 (7.4)	2 (3.8)	5 (16.1)	0.377
Hematuria	2 (7.4)	16 (30.8)	10 (32.3)	0.024
Anemia	17 (63)	22 (42.3)	12 (38.7)	0.047
Thrombocytopenia	2 (7.4)	10 (19.2)	9 (29)	0.028
Lymphopenia	4 (14.8)	4 (7.7)	4 (12.9)	0.507
Leucopenia	12 (44.4)	21 (40.3)	13 (41.9)	0.173
C3 (mg/dl)	58.8±30.3	54.9±26.3	38.6±29.3	<0.05*
C4 (mg/dl)	15.8±5.2	23.5±19.2	12.5±5.1	<0.05*
CRP (mg/dl)	7.87±1.8	9.7±4.4	13.5±5.6	<0.05*
ESR (mm/h)	38.9±11.7	60.1±37.7	90.6±34.8	<0.05*
IL-1β (pg/ml)	8.56±1.98	10.4±2.64	13.6±3.35	0.131

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index. *P<0.05, significant.

(Table 4 and Fig. 4), SLEDAI (Fig. 5), ESR, and CRP compared with patients carrying CT and CC genotypes. On the contrary, patients carrying TT genotype of IL1β +3954 had significantly lower values of C3 and C4 (P<0.05*) (Table 4).

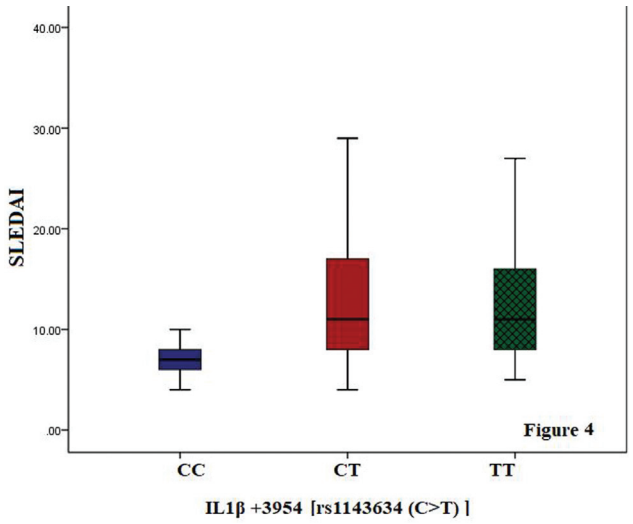
Correlation between IL-1β (pg/ml) serum level and SLEDAI

Our results revealed a significant positive correlation between IL-1β (pg/ml) serum level and SLEDAI score (Fig. 6).

ROC curve for estimating the diagnostic power of IL1β serum level in differentiating patients with SLE from the control group

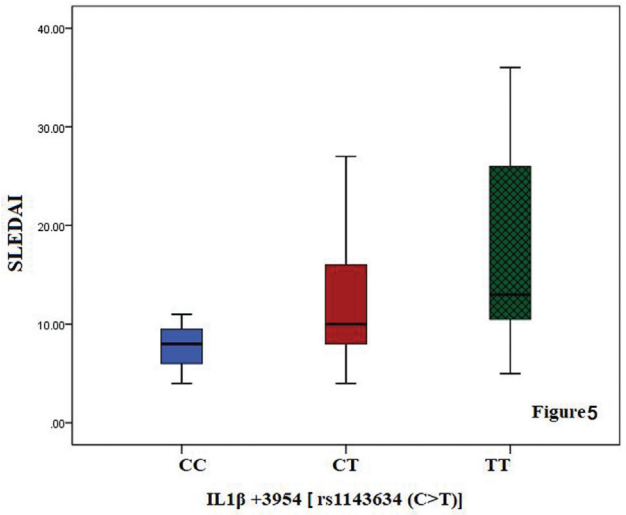
We further investigated our results by ROC test. We found that among patients with SLE, the AUC of IL1β was 0.989 (95% CI=0.979–0.998), with sensitivity of 94.5%, specificity of 99%, and the cut-off value of 7.15 (Fig. 7).

Figure 4



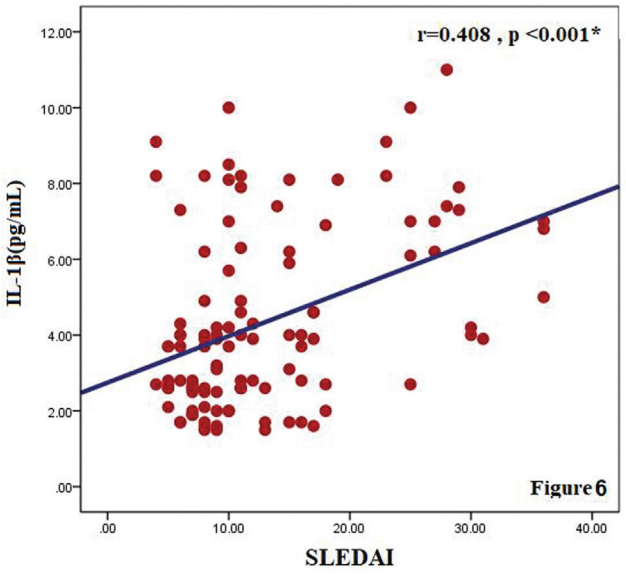
Effect of IL1β +3954 [rs1143634 (C>T)] mutations on IL1β serum levels. IL, interleukin.

Figure 5



Effect of IL1β +3954 [rs1143634 (C>T)] mutations on SLEDAI. IL, interleukin; SLEDAI, systemic lupus erythematosus disease activity index.

Figure 6

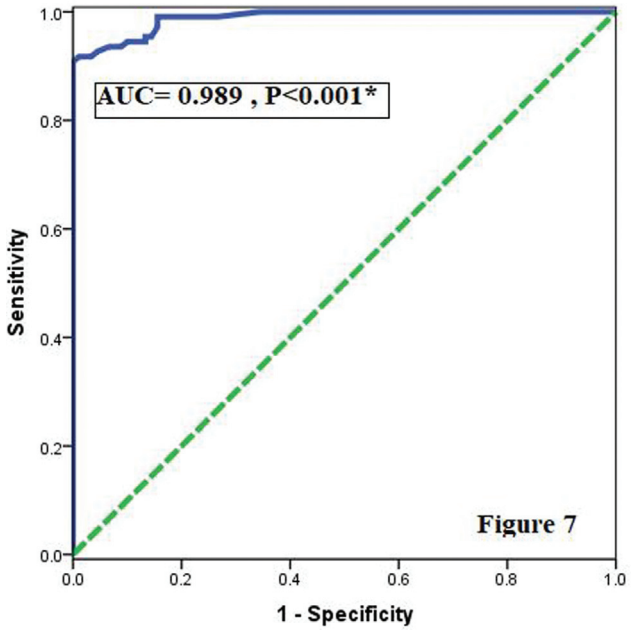


Correlation between IL-1β (pg/ml) serum level and SLEDAI. IL, interleukin; SLEDAI, systemic lupus erythematosus disease activity index.

Discussion

As a matter of fact, individuals or family members with autoimmune disease are at higher risk of developing another immune-mediated disorder. Over the past decade, a close association between thyroid autoimmunity and SLE has become increasingly clear. Polymorphisms in the IL1 gene have been associated with other autoimmune diseases such as rheumatoid arthritis [15] and SLE [8]. IL1β has pleiotropic effects and can alter cytokine production, cell signaling, and migration [16].

Figure 7



ROC curve of interleukin-1β serum level for prediction of SLE. SLE, systemic lupus erythematosus; ROC, receiver operating characteristic.

Intriguing reports suggesting that there are several common polymorphisms of IL1β gene have been most frequently investigated. In that context, IL1β gene has two SNP, at position −511 in the promoter region (rs16944) and at position +3954 in the fifth exon (rs1143634) [6,7].

Early assessment of SLE severity deserves particular attention because it may help us to plan preventive and therapeutic approaches. Cytokines are crucial in the regulation of immune and inflammatory responses. Hence, cytokine genes might be good candidates for SLE activity prediction and treatment. To our knowledge, this is the first study conducted in Egypt to explore the possible associations of IL1β-511C/T (rs16944) and IL1β +3954C/T (rs1143634) gene polymorphisms with SLE, and to detect whether these polymorphisms are associated with disease activity of SLE, in addition to clarifying the effect of these polymorphisms on clinical and biochemical parameters of SLE.

The main finding of the present study is that, in the SLE group, there were significantly higher values of IL1β serum levels compared with the control group. Interestingly, we observed significant positive correlation between IL-1β serum level and SLEDAI score in SLE. Similarly, reports of Rus *et al.* [17] confirmed higher levels of IL-1β in SLE.

Current evidence indicates that IL-1 is one of the most potent proinflammatory cytokines with widespread biological activities, and it has a central role in joint inflammation and destruction. Increased spontaneous release of IL-1 from SLE monocytes has been reported by several researchers [17]. Furthermore, increased release of IL-1α and IL-1β correlated with serum autoantibodies and ribonucleoprotein. Therefore, IL-1 is thought to play an important role in the immunopathology of SLE [9,17,18].

The results presented here are innovative, as this study was the first Egyptian study that investigated the possible association of genotype and allele frequencies of IL1β-511 and IL1β +3954 with patients with SLE.

Our results revealed that the CT genotype distribution of IL1β-511was significantly higher in SLE than controls.

A study conducted by Parks *et al.* [9] on African Americans found that carriage of the IL1β-511 T allele was associated with a higher risk of SLE than the control group.

On the contrary, a study by Huang *et al.* [19] observed no association between IL-1 β polymorphisms and SLE in Chinese patients.

In contrast, a study by Camargo *et al.* [20] conducted on Colombian patients with SLE, as well as in clinically healthy individuals, observed protective role of IL-1β polymorphisms.

The aforementioned diverse results summarized may be owing to the differences in the ethnicity of the studied populations and sample size.Regarding IL1β +3954 rs1143634)C/T) gene polymorphisms, our results showed that there was a nonsignificant difference between control and SLE groups.

In agreement with our results, Afshari *et al.* investigated the association of IL-1β +3954 gene polymorphism with susceptibility to SLE in north-eastern of Iran. They found no significant differences in the frequency of IL-1β exon 5 alleles between patients with SLE and controls [21].

In this study, we attempted to pierce out the association between IL1β gene mutations at −511 and +3954 with SLE disease activity (SLEDAI). The current study revealed that there were significant higher scores of SLEDAI in patients carrying CT genotype of IL1β-511. However, patients carrying TT genotype of IL1β +3954 had significant higher scores of SLEDAI.

To better elucidate the effect of IL1β gene mutations at −511 and +3954 on clinical and laboratory characteristics of SLE, the current study revealed that patients carrying CT genotype of IL1β-511 had significantly higher values of ESR compared with patients carrying CC and TT genotypes.

The results of Camargo *et al.* [20] regarding the influence of IL-1β polymorphisms on clinical and immunologic characteristics of patients with SLE revealed no significant differences between genotypes of IL1β-511. These differences could be due to the high lupus activity in our study population compared with the participants in the study by Camargo *et al.* [20].

Regarding IL1β +3954, patients carrying TT had significantly higher values of ESR and CRP compared with patients carrying CC and CT genotypes. Moreover, patients carrying TT genotype of IL1β +3954 had significantly lower values of C3 and C4.

Afshari *et al* did not detect any association of IL-1β exon 5 (+3954) genotype with clinical and laboratory profiles in patients with SLE [21].

Our results investigated the diagnostic power of IL-1β by ROC test. We found that among patients with SLE, the AUC was 0.989 (95% CI=0.979–0.998), with sensitivity of 94.5%, specificity of 99%, and the cut-off value of 7.15.

In conclusion, this study revealed higher values of IL1β in patients with SLE. In addition, there was a significant positive correlation between IL-1β serum level and SLEDAI score. Even more importantly, the CT genotype distribution of IL1β-511was significantly higher in patients with SLE compared with controls. However, there were nonsignificant differences regarding IL1β +3954 between patients with SLE and control group. Early prediction of SLE disease activity decreases the health hazards associated with SLE. Further future multicenter studies with bigger sample size are needed to validate our findings.

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Conflicts of interest
There are no conflicts of interest.

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