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Interaction between SNP-SNP Gene Polymorphisms in Patients with Systemic Lupus Erythematosus in Najaf Governorate, Iraq

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ABSTRACT

Background: *Systemic lupus erythematosus (SLE) is a complex autoimmune disease involving multiple organs and systems. The IL1β-C>T and IL10-G>A genes are linked by the risk of developing several autoimmune diseases, including SLE in adults. The aim of this study was to test the hypothesis that the IL-1β, IL-10 SNP is interaction with susceptibility to SLE.* ***Methods.*** *In this case-control study, of both sexes, ranging in age from 20 to 61, of 113 patients with SLE and 122 healthy controls participated in this study, at the Al-Sader Medical City (specialized center for Rheumatology) in Al-Najaf Province, Iraq. Where IL-1β and IL-10 was analyzed, polymorphism performed using PCR-RFLP analysis. For the Detection of SNP-SNP interactions, a different statistical technique, multifactor dimensionality reduction analysis (MDR), was used.* ***Results:*** *The genotype frequency distribution among patients differed significantly from that of controls (p = 0.023). The frequency of IL1β +3954C>T was 6.2% in patients with SLE and 0.8% for control group, the OR value indicates the absence of a statistically significant association (OR (95% CI): 7.99 (0.98 - 65.43)), and the frequencies of the IL10-1082G>A genotype GA 38.1% and 27.0% (p =0.027); OR 95% CI:1.85 (1.07 - 3.20). The prevalence of the G allele of the investigated polymorphism was greater in patients with SLE than in controls (p = 0.001). When conducting MDR analysis of intergenic interactions IL1β +3954C>T - IL10-1082 G>A in a two-factor combination of these genes. Where TC/AA genes IL1β-C>T - IL10- G>A, respectively, are associated with the risk reduction of SLE between the groups, where found statistically significant (OR = 0.33; 95% CI = 0.16 - 0.69; p = 0.002, pbonf = 0.006).* ***Conclusion.*** *The obtained data indicate that the IL10-1082 G>A polymorphism is a significant risk factor for predisposition to SLE. Analysis of allele frequencies across alternative patient groups showed a reduced risk of SLE predisposition associated with carriage of the T allele at the IL1β +3954C/T (rs1143634) polymorphism.*

Keywords: Systemic lupus erythematosus, Gene polymorphism, IL-1β+3954C>T, IL10-1082G>A, SNP/SNP interactions, MDR.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune with a wide range of clinical manifestations spanning practically all tissues and organs, impacting 0.1% of individuals overall (1). Women are more likely than men to be affected by SLE (2), and the disease is more common among non-white racial groups (3).

The pathogenesis of SLE, a complex and persistent inflammatory systemic autoimmune disease, is unknown, which is characterized by systemic immunoinflammatory (autoimmune) damage to vital organs and a variety of clinical manifestations (4). In approximately 10–20% of patients with SLE, the first symptoms of the disease develop before reaching adulthood (5). According to modern concepts, SLE is a polygenic genetic model that can include up to 100 genes, and each gene makes only a

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moderate contribution to the overall genetic component (6).

Major Histocompatibility Complex (MHC) genes and genes outside of the MHC have been investigated, and a number of potential genes have been proposed (7). Where Ketlinskii et al. found that when a patient had active lupus, their interleukin-1β (IL-1β) levels increased (8). According to these reports, interleukin-1 (IL-1) has a role in the pathophysiology of SLE. Thus, it is believed that IL-1β, a proinflammatory cytokine with broad biological activity, plays a key role in the pathophysiology of autoimmune illnesses. Activated macrophages and a number of other cell types express it (9,10). Because it stimulates T-cell maturation and proliferation, IL-1β—initially identified as one of the lymphocyte-triggering factors—plays a vital role.

Several publications have appeared in recent years documenting that single-nucleotide polymorphisms (SNPs) in the IL1β gene are located at position +3954 in the fifth exon (rs1143634) (11,12). Therefore, SLE, rheumatoid arthritis (13), and autoimmune hemolytic anemia (14) are among the autoimmune disorders linked to polymorphisms in the IL1 family (15).

Because it may regulate macrophage activation and antigen presentation, interleukin-10 (IL-10) is a multipurpose cytokine with anti-inflammatory qualities (16). IL-10 plays an essential role in B cell activation and autoantibody synthesis. As a survival and differentiation factor, it also inhibits the generation of T helper 1 (Th1) cytokines (17).

IL-10 may decrease the progression of lupus by controlling pathogenic Th1 cytokine responses and mediating certain regulatory B cells (18). IL-10 gene located on chromosome 1q31-32, the polymorphism, -1082 G>A (rs1800896), is located in the IL10 promoter at a possible Erythroblast Transformation Specific (Ets) transcription factor binds site (19), this is thought to be associated with changes in IL10 transcription in SLE. Several studies have studied the relationships between the *IL10* gene polymorphism −1082G/A (alternative nomenclature −1087G/A) and SLE development, but the published findings are contradictory (20). Furthermore, several autoimmune disorders, including SLE, have been linked to elevated IL-10 levels (21). There have been reports of associations between the promoter genotypes and in vitro IL-10 production (22); specifically, compared to the *A* allele, the *G* allele of the G/A polymorphism at nucleotide position 1082 has been linked to a "high producer" phenotype (23).

Our present study, we focused primarily on *IL-1B+3954C/T* (rs1143634) and *IL10-1082G/A* (rs1800896), because these 2 polymorphic sites appear to be functionally most relevant in SLE and carried out to determine the effects interaction between the *IL-1B+3954C/T* and *IL10-1082G>A* in SLE patients.

METHODS

A case-control study was conducted between November 2023 and January 2025 at the Al-Sader Medical City (specialized center for Rheumatology) in Al-Najaf Province, Iraq. SLE diagnosis was confirmed by a joint consultant physician using clinical examination and diagnostic criteria. 235 persons of both sexes, ranging in age from 20 to 61, participated in this study. Of these, 113 patients had been diagnosed with SLE by the physicians at a specialized rheumatology facility of Al-Sader Medical City. While control group: 122 adults who are not SLE or familial history of autoimmune disorders and other disease. Patients were selected at a specialized center for Rheumatology of the Al-Sader Medical City in Al-Najaf Province; investigations of genotypes were conducted out at the Clinical of Medical Laboratory of this Hospital.

In accordance with the Helsinki Declaration of the World Medical Association "Ethical Principles for Scientific Medical Research with Human Participation", All individuals in the research were informed and given consent (authorized by order of the Ministry of Health Iraq dated December 27, 2023 No. 53847, and the University of Baghdad, College of Science No. CSEC/1125/0168).

Genotyping of *IL-1β* polymorphism

The current investigation assessed the connection between the polymorphisms of *IL-1B+3954C>T (rs1143634)* and *IL10-1082G>A (rs1800896)* genes with study groups. The proinflammatory gene variation known as *IL-1β* and *IL10* SNP underwent genotyping. Table 1 is a list of the primer names, sequences, and associated PCR product sizes used in this study for the *IL-1β* and *IL10* gene.

Amplification by PCR

A genotyping effect was prepared using a total of 25 µL. This combination included 1 µL of 10 picomoles of both the forward and reverse primers, as well as 2 µL of genomic DNA template at a concentration of 40 ng. Furthermore, Qiagen's, Taq PCR Master Mix kit, which was obtained from Addbio in Korea, include 0.5 µL of each dNTPs mix, 2.5 µL of the 10X PCR buffer, Taq DNA polymerase 0.25 µL and $MgCl_2$ 1.5 µL. The final reaction volume was adjusted to 16.25 µL by adding distilled water. A Biobase standard PCR thermal cycler from Biobase in China was used Using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method described. The regions of interest were amplified by PCR using primers designed to flank the polymorphism.

The cycling environments were a 4-minute initial denaturation phase at 95 °C, then 35 cycles of denaturation for 30 seconds at 95°C, annealing for 30 s at 65 °C, and extension for 10 minute at 72 °C. Digestion of the amplified products of *IL-1β* +3954C/T was done by using 10 units of restriction endonucleases *Taq1* (New England Biolabs, USA) (24). Which genotype detection depended on agarose gel 2% of the digestion form: The homozygous mutant genotype (TT) shows one band of 324 bp. The presence of the restriction site causes the homozygous wild-type genotype (CC) to produce two pieces of 213 bp and 167 bp. The heterozygous genotype (CT) includes all three bands: 324 bp, 213 bp, and 167 bp.

Also, The final volume of IL-10 was used in RFLP digestion was 25 µL in the reaction mixture containing 5 U of *MnII* (New England Biolabs, USA) (25). For -1082G>A, where 0.5 µL of dNTPs mix, 100 ng of template DNA, 10X PCR buffer (GeNet Bio, Korea), 2 mM $MgCl_2$, 0.5 µL forward and 0.5 µL reverse primers and 1.5 µL U Taq polymerase as follows: initial denaturation at 94ºC for 5 min, 35 cycles of 94ºC for 30 s, annealing for 30 s at 60 °C, 72ºC for 90 s, and final extension at 72ºC for 5 min. The product fragments of restriction were separated on a 3% agarose gel stained with ethidium bromide and viewed under a UV transilluminator with a gel information system. Processing patterns revealed three distinct genotypes: The AA genotype (homozygous mutant) formed two pieces (347 and 139 bp), while the GA genotype (heterozygous) yielded three bands (486, 347, and 139 bp). The GG genotype (homozygous wild-type) stayed undigested at 486 bp. These findings promote the hypothesized genotype-specific trends.

Table 1: The sequence of primers that were used in the present study.

Locus	Polymorphism (rs number)	Specific primers
IL-1β	+3954C>T (rs1143634)	FP-5′-GTTGTCATCAGACTTTGACC-3′ RP-5′-TTCAGTTCATATGGACCAGA-3′.
IL10	-1082G>A (rs1800896)	FP-5′-CTCGCCGCAACCCAACTGGC-3′ RP-5′-TCTTACCTATCCCTACTTCC -3′

Statistical analysis

The effect size, α and β error probability were calculated via G* power software version 3.1.9.4. In addition, the data of age was checked for normality, homogeneity. The direct gene counting approach was used to estimate the allele frequency of SNPs, and the Pearson χ^2 goodness-of-fit test was used. The odds ratio (OR) and 95% confidence interval (CI) were calculated for males *vs.* females. A two-tailed Fisher's exact probability and the p-value of ≤ 0.05 were used to determine the significance of the difference using the IBM SPSS software version 27.0. The online Hardy-Weinberg equilibrium (HWE) calculator for alleles (26), WinPepi software version 11.65, were used to perform these analyses (27).

Detection of SNP- SNP interaction

The SNP-SNP interaction was tested successively using a different statistical technique. A pair-wise non-parametric epistasis test was applied using multifactor dimensionality reduction analysis (MDR) (28,29).

RESULTS

The effect size of the studied groups was 0.8 at two tailed, the value of each α and β error probability was 0.0017, and the power of sample was 0.998. The characteristics of systemic lupus erythematosus compared to the healthy controls in the study groups in terms of age and sex are shown in numbers and percentages in Table 2.

Table 2. Characteristics of systemic lupus erythematosus in study groups.

Variables		Patients No. 100(%)	Control No. 80(%)	Probability
Age mean ± SD (Years)				
Age groups	20-29 y	16 (16)	21 (26.3)	
	30-39 y	19 (19)	18 (22.5)	
	40-49 y	37 (37)	29 (36.3)	
	>49 y	28 (28)	12 (15.0)	
Sex	Males	4 (4)	9 (11.3)	
	Females	96 (96)	71 (88.7)	

When studying the distribution of genotype frequencies for the IL1β +3954C>T, different significances were appeared between the SLE and control groups. The frequency of the TT genotype was significantly increased in the SLE group compared to the controls (6.2% vs. 0.8%, OR: 7.99, Pc: 0.016), also, the high OR value referred that this genotype might had a risk role in the susceptibility of disease. While other genotypes CC, CT, and C allele, in addition to T allele showed non-significant differences between the SLE and control groups (67.3%, 26.5%, 81.0%, and 19.0% respectively for the SLE group compared to 64.8%, 34.4%, 82.0%, and 18.0% respectively for the control group) (Table 3). Also, all the SLE and control frequencies were compatible to Hardy-Weinberg equilibrium (P > 0.05) (Table 3).

Table 3. Distribution of genotypes frequencies and alleles the *IL1β +3954C/T* gene (rs1143634) in the SLE and control groups.

***IL1β +3954C>T* polymorphism (rs1143634) genotypes/allele**	**SLE patients' group n=113 (%)**	**Control group n=122 (%)**	***χ2***	***P***	***Pc***	**OR (95% CI)**
C	182 (81.0)	200 (82.0)	0.159	0.723	0.639	0.91 (0.57- 1.45)
T	44 (19.0)	44 (18.0)				1.10 (0.69 - 1.75)
C/C	76 (67.3)	79 (64.8)	0.164	0.783	0.681	1.12 (0.63- 1.99)
C/T	30 (26.5)	42 (34.4)	1.71	0.205	0.161	0.69 (0.39- 1.20)
T/T	7 (6.2)	1 (0.8)	5.154	**0.030**	0.016	7.99 (0.98 - 65.43)

IL1β +3954C>T polymorphism (rs1143634) genotypes/allele	SLE patients' group n=113 (%)	Control group n=122 (%)	*χ2*	*P*	*Pc*	OR (95% CI)
HWE (χ2)	2.6572	3.3032				
***P*-HWE**	0.1031	0.0691				

X^2 - Pearson chi-square, p - significance level of Fisher's exact probability (two tailed), OR - odds ratio, 95% confidence interval – CI, Pc – Bonferroni corrected probability P-HWE – Probability of Hardy-Weinberg equilibrium.

Differences were found in the distribution of the genotypes and alleles frequencies of the IL10-1082G/A gene in the SLE and control groups of the population in Al-Najaf province. In particular, the frequency of the GG, GA genotype and G allele were significantly increase in the SLE patient's group compared to the controls (8.0%, 38.1% and 28.0% respectively for the SLE group vs. 2.5%, 27.0% and 16.0% respectively for the control group) (Table4), and the high value of OR referred that these genotypes and allele may have risk roles in the susceptibility of SLE. In addition, the frequencies of AA genotype and A allele were significantly decreased in the SLE patients' group compared to the controls (40.7% and 72.0% for the SLE group vs. 70.5% and 84.0% for the controls) (Table 4), also the OR values of this genotype and A allele referred that may have a protective role from SLE development.

Table 4. Distribution of genotypes and alleles frequencies of the *IL10-1082G>A* gene (rs1800896) in the SLE and control groups.

IL10-1082G>A polymorphism (rs1800896) genotypes/allele	SLE patients' group n=113 (%)	Control group n=122 (%)	*χ2*	*P*	*Pc*	OR (95% CI)
G	64 (28.0)	39 (16.0)	10.432	**0.002**	**0.001**	**2.08 (1.33– 3.25)**
A	162 (72.0)	205 (84.0)				**0.48 (0.31– 0.75)**
GG	9 (8.0)	3 (2.5)	3.670	0.075	**0.044**	**3.43 (0.91 - 12.94)**
GA	46 (38.1)	33 (27.0)	4.904	**0.028**	**0.020**	**1.85 (1.07 - 3.20)**
AA	58 (40.7)	86 (70.5)	9.080	**0.003**	**0.002**	**0.44 (0.26 - 0.75)**
HWE (χ2)	0.001	0.0062				
***P*-HWE**	0.9771	0.9372				

X^2 - Pearson chi-square, p - significance level of Fisher's exact probability (two tailed), OR - odds ratio, 95% confidence interval – CI, Pc – Bonferroni corrected probability P-HWE – Probability of Hardy-Weinberg equilibrium.

The risk of SLE has been observed to be reduced with one combination of genotype distribution in developing recessive models, TT vs. CT + CC in IL1β +3954C>T and AA vs. GA + GG in IL10-1082G>A polymorphisms were statistically (P = 0.023; OR = 7.99; 95% CI = 0.98 – 65.43 and P = 0.003; OR = 0.44; 95% CI = 0.26 – 0.75). The high OR value for the recessive model (TT vs. CT + CC) of IL1β +3954C>T refereed to an increase risk, while in the model AA vs. GA + GG of IL10-1082G>A observed a reduced risk (Table 5).

At the same time, there was no statistically significant difference in the construction of the dominant model of the two genes (TT + CT vs. CC in IL1β +3954C>T and AA + GA vs. GG in IL10-1082G>A) in the analyzed groups, as shown in Table 5.

Table 5. The dominant and recessive models of *IL1β +3954C>T* and *IL10-1082G>A* genotypes in the study groups.

Polymorphisms		Genotypes	Cases n=113(%)	Controls n =122(%)	χ^2	*P*	OR (95% CI)
IL1β +3954C>T	Dominant	TT + CT *vs.* CC	37 (32.7) 76 (67.3)	43 (35.2) 79 (64.8)	0.164	0.686	0.89 (0.52 – 1.53)
	Recessive	TT *vs.* CT + CC	7 (6.2) 106 (93.8)	1 (0.8) 121 (99.2)	**5.154**	**0.023**	**7.99 (0.98 – 65.43)**
IL10-1082G>A	Dominant	AA + GA *vs.* GG	104 (92.0) 9 (8.0)	119 (97.5) 3 (2.5)	3.670	0.055	0.29 (0.08 – 1.10)
	Recessive	AA *vs.* GA + GG	58 (51.3) 55 (48.7)	86 (70.5) 36 (29.5)	**9.08**	**0.003**	**0.44 (0.26 – 0.75)**

P: probability, X^2: Chi-square, OR: odds ratio, CI: confidence intervals.

When conducting MDR analysis of intergenic interactions *IL1β +3954C>T* - *IL10-1082G>A* in a two-factor combination of these genes, characterized by 100% reproducibility and prediction accuracy of 59% (p = 0.0002) (Table 6). A correction for multiple comparisons (Bonferroni correction, *Pc*) was introduced to reduce the statistical error of the first type in the study of intergenic effects. This correction was calculated by dividing the initial significance level of *Pc* (α = 0.05) by the number of genotype pairings involving the two loci under consideration, which equals 8. If the associated p-values were less than or equal to 0.006, the differences were determined to be significant. Thus, CT/AA of *IL1β* C/T - *IL10*-G/A genes are associated with a high-risk genotype for developing the disease of SLE between the groups, where found statistically significant (OR = 0.33; 95% CI = 0.16 - 0.69; *P* = 0.002, *Pc* = 0.006) and CC/GG of *IL1β* C/T - *IL10*-G/A genes, respectively. While found statistically significant associated with a reduced risk, a protective genotype risk (OR = 9.22; 95% CI = 1.14 - 74.28; *P* = 0.012, *Pc* = 0.006). In addition, CT/AG of *IL1β* C/T - *IL10*-G/A genes, respectively, where found statistically significant (OR = 2.52; 95% CI = 1.05 - 6.08; *P* = 0.035, *Pc* = 0.006) (Fig. 1).

As can be seen from the entropy interaction plot shown in Fig. 2, the *IL1β* - *IL10* genes pair demonstrated some not association and contributed -1.09% to the predisposition to SLE, while independently of each other, the *IL1β* and *IL10* genes contributed only 2.08% and 3.20% to the risk of SLE, respectively. At the same time, the nature of the interaction of genes *IL1β C/T* - *IL10-G/A* was also pronounced antagonism (blue color).

Table 6. Analysis of gene-gene interactions (*IL1β +3954C>T -IL10-1082G>A*) using the dimensionality reduction (MDR) method.

polymorphisms in the model	(TBA)	(CVC)	X^2	*P*	OR (95% CI)
IL1β +3954C>T / IL10-1082G>A	0.59	10/10	13.52	0.0002	2.71 (1.58 - 4.65)

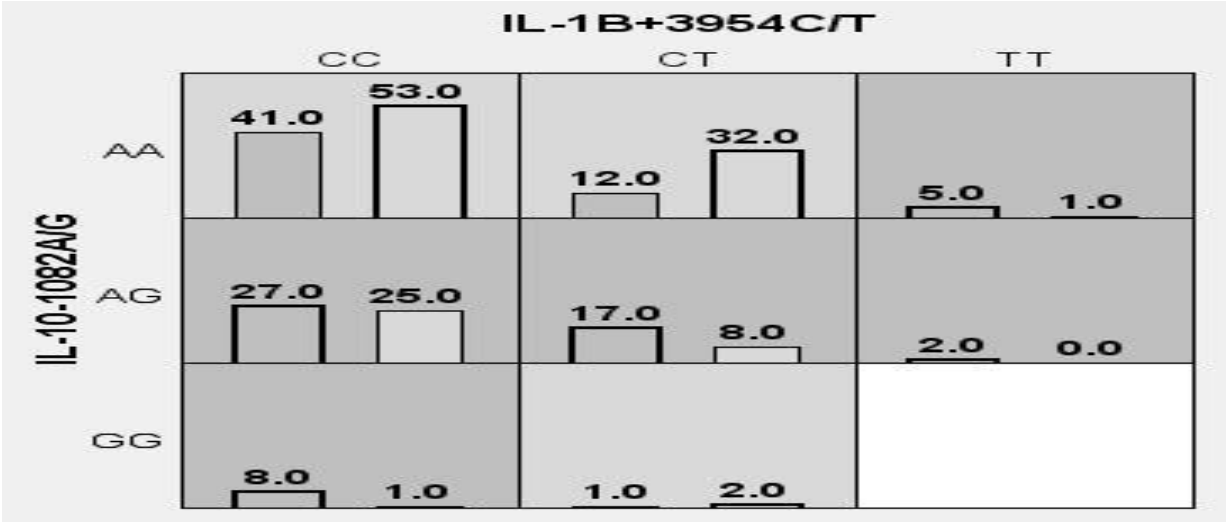

Fig. 1. Distribution of frequencies of two-locus genotypes of the *IL1β +3954C/T / IL10-1082G/A* genes in SLE of both groups *(dark gray cells are combinations of high-risk genotypes, light gray are low-risk, white are no combinations of genotypes, left columns in the cells are the number of SLE subjects, right columns are the number of subjects in the control group; AA, CC are homozygotes for the first allele, AG, CT are heterozygotes, GG, TT are homozygotes for the second allele).*

Fig. 2. Dendrogram of interactions between *IL1β +3954C/T* / *IL10-1082G/A* genes in both groups. *Blue: Strong antagonism. Figure keys: Red: high degree of synergistic interaction (synergy), orange: less interaction, green: weak interaction, blue: no interaction (redundancy), gold: interaction intermediate between synergy and redundancy.*

DISCUSSION

Cytokine-mediated immunity plays a crucial role in the pathogenesis of SLE. The role of pro-inflammatory cytokines in the pathogenesis of SLE, as well as the effect of cytokine blockade, is still controversial. SLE is a potentially severe autoimmune disease that demonstrates variations in incidence, prevalence, disease activity, and prognosis based on race and ethnicity (30). SLE is a chronic systemic disease with a variable clinical presentation. The exact pathological mechanisms of SLE remain elusive, and the etiology of SLE is known to be multifactorial, involving genes, sex hormones, and environmental factors including sunlight, drugs, and infections (31). This study included 235 participants, 113 of them were suffering from SLE. In this study, we investigated the influence of *IL-1β* and *IL-10* genes polymorphisms within and their interaction on SLE susceptibility. IL1β has pleiotropic effects and can alter cytokine production, cell signaling, and migration (32). Even the present study was established for the first time in the Al-Najaf population, no association of the *IL-1β* gene rs1143634 polymorphism with a predisposition to SLE was appeared. Therefore, SLE is considered a multifactorial autoimmune disease with a complex genetic inheritance (33).

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 (Dinarello, 1996; Dinarello, 2004; Kany et al., 2019). Increased spontaneous release of IL-1 from SLE monocytes has been reported by Rus et al. study (34). These increased release of IL-

1α and IL-1β were correlated with serum autoantibodies and ribonucleoprotein. Therefore, IL-1 is thought to play an essential role in the immunopathology of SLE (35). In contrast, several studies did not detect any association of *IL-1β* exon 5 (+3954) genotype with clinical and laboratory profiles in patients with SLE (36) (37). The same results appeared in a study done by Huang et al., which they observed no association between *IL-1β* polymorphisms and SLE in Chinese patients (38). In addition, In contrast, a survey by Camargo et al. (39) conducted on Colombian patients with SLE, as well as in clinically healthy individuals, observed the protective role of *IL-1β* polymorphisms.

IL-10 is an important immunoregulatory cytokine that inhibits T cell function by suppressing the expression of proinflammatory cytokines (40). On the other hand, IL-10 promotes B cell-mediated functions, enhancing survival, proliferation, differentiation, and antibody production. Consequently, the high IL-10 level in SLE patients is known to be pathogenic and to correlate with disease activity, and its blockade ameliorates the disease (41,42). Several studies suggest that IL-10 could be a strong candidate gene influencing SLE susceptibility (42). Our study revealed that there was a significant increase in the distribution of *IL-10* (-1082G/A) GG and GA against AA genotypes in SLE patients compared to controls, also the distribution of allele *A* was increased significantly more than *G* allele in both groups. Although the *A* allele increased more than the *G* allele in both groups, this increase was statistically significant in the *G* allele.

At the same time, Zhou et al. (43) suggested that the *IL-10* promoter -1082G/A polymorphism is associated with SLE susceptibility, and showed no significant association in allele distribution in either European or Asian populations. Another meta-analysis has found significant associations between the *IL-10* -1082G/A polymorphism and SLE in Europeans (44) and Brazilians (45). However, several studies found no such association between *IL-10* -1082G/A gene polymorphism and SLE in Colombian, Caucasian, mixed, and Anglo-Saxon populations (46,47). In accordance with previous studies (43,48), we showed that the increase GG genotype and *G* allele of the *IL-10* –1082G/A polymorphism in patients were associated with SLE susceptibility. A significant increase in IL-10 serum concentration was detected in SLE patients versus healthy subjects, elevated IL-10 levels correlated well with the SLE activity index as well as disease severity. This result is consistent with previous reports (49,50). Moreover, the *IL-10* (-1082G/A) GG and GA genotypes were significantly higher in our SLE patients compared to controls.

Regarding to the *IL1β* +3954C>T and *IL10*-1082G>A polymorphisms, there were no statistically significant differences in developing recessive models of genotypes. As a result, such research gives support and explanation for the association with a reduced risk between *IL1β* +3954C>T, *IL10*-1082G>A and SLE revealed in the current study. However, there were non-significant 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 multicenter studies with larger sample sizes are needed to validate our findings.

Therefore, the present study's findings suggest that carriers of recessive variants in *IL1β* +3954C>T and *IL10*-1082G>A have a protective effect against SLE. In several studies, it was observed that Egyptian studies showed no statistically significant results for *IL10* polymorphisms, and this is consistent with the current study (37,51). Whereas, a previous meta-analysis suggested that *IL-10*

polymorphisms confer susceptibility to SLE in Europeans and Asians (44). There is also another study in Poland that revealed no statistically significant results (52); therefore, it does not agree with the current study results. Other research, contradicting the present study findings, in Iranian populations carriers with either genotype had the inverse effect, particularly being related to an increased obesity risk (25).

In order to stumble on if any interactions among SNPs of the cytokine genes, the genotypes were analyzed using MDR tool, and two combinatorial models have been assessed. The MDR was applied to two SNPs, furthermore, by virtue of different properties of cytokines and nature of their functions. Based on MDR analysis, a high-risk combination between *IL-1b* and *IL-10* genes suggests that these SNPs interact synergistically, affecting signaling impairment and, hence, effector mechanisms, which significantly contribute to SLE. Therefore, the present study demonstrates that *IL-1β* CT and *IL-10* AA genotypes may be helpful for early detection of the disease in high-risk individuals, specifically household contacts. However, there is a need to evaluate the data in a large sample size.

The current study had limitations related to the small number of patients, which reduces the power of the statistical analysis. Therefore, further replication studies with a larger sample size are needed from populations other than Najaf province to include the Iraqi population, as well as studying other potential polymorphisms that would be useful to interpret the study results and formulate a reasonable conclusion about the role of *IL-1β* and *IL-10* in the pathogenesis of SLE.

CONCLUSION

This pilot study confirmed a reduced risk of SLE predisposition associated with carriage of the *T* allele at the polymorphism position of *IL1β* +3954C/T (rs1143634). Whereas the analysis of *IL-10* (-1082G/A) polymorphism revealed a significant increase in the SLE patient group compared with controls ($P < 0.05$) in a population from Najaf province. Therefore, this elevation was highly significant in GG and GA genotypes. This is the first study to establish that patients with SLE are at an increased risk of developing arthritis. In addition, our observations suggest that the combined genotypes were interaction with the *IL1β/IL10* genotype in the Al-Najaf population of Iraq. The present study had limitations, including a small number of patients, which reduced the power of the statistical analysis. Therefore, further replication studies with larger sample sizes from other populations are needed, as well as the investigation of other potential polymorphisms, which will aid in interpreting the study results.

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Conflicts of interest

There are no conflicts of interest.

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