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The role of -318C/T and +49A/G polymorphisms in the CTLA-4 gene in systemic lupus erythematosus Iraqi patients

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Abstract

Background. In recent years, Systemic lupus Erythematosus (SLE) has become one of the common autoimmune diseases, where the body's immune system unintentionally targets and damages its own tissues, there are many factors that responsible for pathogenicity one of the most importance is genetic factor, the essential protein which encoded from cytotoxic T lymphocyte associated protein 4 gene is the important protein for the negatively regulation of immune responses

Purpose. To determine the impact of variants -318C/T and +49A/G in the *CTLA-4* gene in Systemic lupus Erythematosus Iraqi patients.

Materials and methods. 68 SLE Iraqi patients participated in the research study, 32 people in good healthy without any symptoms considers as a control group. The extract DNA was by used specific DNA Extraction Kit (gSYNCTM) made from Geneaid/Taiwan with technique "Polymerase chain reaction-restriction fragment length polymorphism" used for analysing the *CTLA-4* genes -318C/T and the +49A/G polymorphisms.

Results. The - 318T and +49 G alleles frequency in the *CTLA-4* gene carriers was significantly higher in patients compare with the control group ($P = 0.008$, OR 3.63, 95% CI 1.34 – 9.82; $P = 0.007$, OR 3.16, 95% CI 1.32 – 7.53, respectively), while the -318C and +49 A alleles frequency in the *CTLA-4* gene carriers was low significantly when compare with the control group. Our results presented a significant relationship between CT heterozygous genotypes and T allele in the variant -318C/T in the *CTLA-4* gene and AG heterozygous genotypes and G allele genotype in the +49G/A variant and SLE, addition that are more common in the SLE patients.

Keywords: systemic lupus erythematosus; CTLA-4 gene; -318C/T polymorphism; +49A/G polymorphism; genetic polymorphisms; autoimmune disease; allele frequency; Iraqi population; PCR-RFLP; susceptibility

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Introduction

In recent years, Systemic lupus Erythematosus (SLE) has become one of the common autoimmune diseases, where the body's immune system unintentionally targets and damages its own tissues [1]. It causes chronic inflammation and damage to several organs in the body, such as the CNS, skin, joints and kidneys [2; 3]. There are many factors responsible for the SLE pathology involves a wide range of genetic, environmental and hormonal factors [4; 5]. Between these factors, genetic inclination is an important determinant, and polymorphisms of significant immunoregulatory genes play a precarious role [6; 7]. One of the importance genes is the cytotoxic T lymphocyte associated protein 4 (*CTLA-4*) genes, which encodes a protein essential for the negative regulation of immune responses [8; 9]. The *CTLA-4* gene acts as an inhibitory checkpoint for T cell activation make certain that immune responses do not become too aggressive and inhibiting autoimmunity [10]. Changes in the *CTLA-4* gene can distressed this delicate balance, which can lead to the progress of autoimmune diseases such as SLE [11].

There are two identified and recognized variants -318C/T (rs5742909) and +49A/G (rs231775) in the *CTLA-4* gene has been many researched in connection with autoimmune diseases [12; 13]. The 318C/T region, positioned in the promoter region of the gene, can affect the level of gene expression, while the +49A/G polymorphism, positioned in the first exon, can affect the structure and function of the *CTLA-4* protein [14]. These genetic distinctions may vary the immunosuppressive functions of *CTLA-4*, contributing to the exposure and progression of autoimmune diseases, including SLE [15; 16]. Genetic background and environmental exposures vary among populations, which may affect the incidence and influence of specific genetic polymorphisms [17; 18]. Studying the association between the variants of the *CTLA-4* gene and SLE in Iraqi patients may make available valuable information about the genetic basis of the disease in this population, which may lead to the development of more effective diagnostic and therapeutic strategies. The current study aim is to investigated the

incidence and role of the variants -318C/T (rs5742909) and +49A/G (rs231775) in the *CTLA-4* gene in Iraqi patients with SLE. By associating the presence of these variants in SLE patients and healthy controls, designed to illuminate their contribution to disease susceptibility and clinical manifestations. Understanding the genetic factors associated with SLE among Iraqi patients may improve our knowledge of the disease and help develop more effective and personalized treatment approaches.

Materials and methods

68 SLE Iraqi patients participated in the research study, which occurred from March to July 2024 from many of hospitals and private clinic, of whom 37 were female and 31 were male. As a control group, 32 people in good health without any symptoms of SLE, consisting of 19 male and 13 female, were also included. The range of the ages of the two studies group (patients and the control) was from 25 to 73 years.

DNA extraction and PCR protocol

Under aseptic genomic DNA extraction was achieved from peripheral mononuclear cells nucleated cells. The extract DNA was by used specific “DNA Extraction Kit gSYNCTM made from Geneaid/Taiwan” was used to course whole blood samples from the study groups in order to extract DNA [19; 20]. The technique “Polymerase chain reaction-restriction fragment length polymorphism” was used for analyzing the *CTLA-4* gene -318C/T (rs5742909) polymorphism in the promoter region. PCR was using the exact primers sense (F: 5'-AA ATGAATTGGACTGGATG GT-3') and antisense (R: 5'-TTACGAGAAAGGAA GCCG TG-3'), Following initial denaturation at 94°C (2 min), amplification was performed subsequently 30 cycles at 94°C (30 s), 55 °C (30 s), 72°C (30 s) and a finally at 72°C (5 min). The amplified DNA was 247 bp. ethidium bromide staining was used to examine the PCR products on a 3% agarose gel after they had been digested with the restriction enzyme 5 µl MseI for three hours at 37°C. The amplified DNA consisted of TT genotype measuring three fragments (21, 96, 130 bp), CT genotype measuring four fragments (21, 96, 130, 226 bp), while CC genotype measuring two fragments (226, 21 bp). Also analyze the +49A/G (rs231775) polymorphism was detected by PCR–RFLP. PCR was using the exact primers forward 5'-GCTCTACTTCCTGAAGAC CT-3' and reverse 5'-AGTCTCACTCAC CTTTGC AG-3'. Following initial denaturation at 95°C (4 min), amplification was performed subsequently : denaturation for 60 s 95 °C, annealing for 60 s at 55 °C, extension for 60 s at 72 °C (30 cycles), and a final extension for 4 min at 72 °C. The product length was 162bp. Also by ethidium

bromide staining was used to examine the PCR products on a 3% agarose gel after they had been digested with the restriction enzyme 5 µl BbvI for three hours at 37°C, which cleaved the sequence if a AA genotype not digested and resulted in a 162 bp, GG genotype measuring two fragments (88, 74-bp), and AG genotype measuring three fragments (88, 74, 162 bp).

Analysis of Interactions between -318C/T and +49A/G polymorphisms in SLE

The study's -318C/T and +49A/G polymorphisms interaction was also examined using the MDR program (version 2.0 beta). Multi-locus genotypes are divided into high-risk and low-risk categories by MDR. Cross-validation and permutation testing, which reduce false positive results by repeatedly examining the data, can be used to assess this new multi-dimensional variable's capacity to categorize and predict disease state [21]. This MDR analysis employed 1,000 variations and ten-fold cross-validation as shown in Figure 4, and table 5.

Results and discussion

The *CTLA-4* gene variation with decreased encodes a protein which essential for the negatively regulation of immune responses. *CTLA-4* -318C/T (rs5742909). where a mutation from C to T occurs at positioned in the upstream region of the gene, can affect the level of gene expression, the PCR product of the *CTLA-4* – 318 gene on the gel electrophoresis was 247 bp as shown in fig. 1.

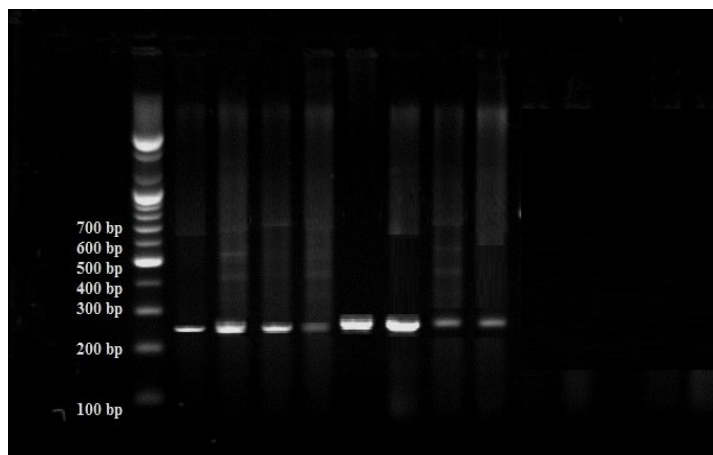


Fig. 1. *CTLA-4* gene -318C/T (rs5742909) PCR product (247 bp) compared to DNA molecular size marker (100bp Ladder) on agarose gel electrophoresis (3%) (100 volts for one hour).

Table 2.

Comparative investigation of the *CTLA-4* gene - 318C/T genotype frequency distribution between SLE patients and the control group

Genotypes	Patients n = 68	Controls n = 32	χ^2	P-value	OR	
					Value	95% CI
Genotype C/C	38(55.9%)	27(84.4%)	7.87	0.005	0.23	0.08 – 0.68
Genotype C/T	28(41.2%)	5(15.6%)			3.78	1.30 – 11.01
Genotype T/T	2(2.9%)	0(0)			2.44	0.11 – 52.39

* (P<0.05), ** (P<0.01), NS: Non-significant.

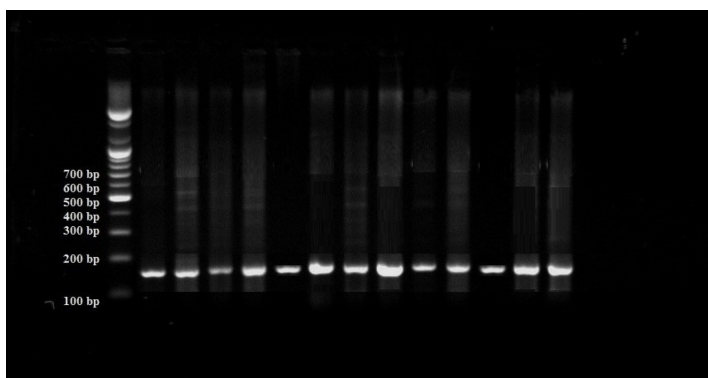


Fig. 3. *CTLA-4* gene +49A/G PCR product (162 bp) compared to DNA molecular size marker (100bp Ladder) on agarose gel electrophoresis (3%) (100 volts for one hour).

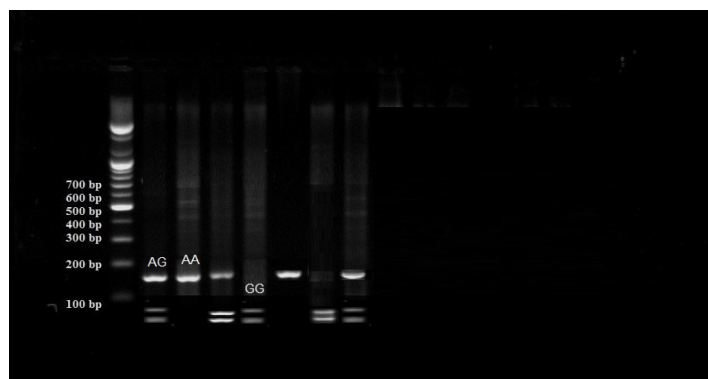


Fig. 4. The PCR-RFLP product of *CTLA-4* gene +49A/G, stained agarose gel by ethidium bromide. DNA molecular size marker (100bp Ladder), three genotypes showed: AA genotype (162 bp) , GG genotype (88, 74-bp) , and AG genotype (88, 74 ,162 bp).

Table 3.
Comparative investigation of the allele frequencies of the polymorphic marker *CTLA-4* gene +49A/G, in the control group and patients with SLE

Alleles	Patients	Controls	χ^2	P-value	OR	
	n = 68	n = 32			value	95% CI
Allele A	98 (72%)	57 (89%)	7.22	0.007	0.32	0.13 – 0.76
Allele G	38 (28%)	7 (11%)			3.16	1.32 – 7.53

* (P<0.05), ** (P<0.01), NS: Non-significant.

Table 4.
Comparative investigation of the *CTLA-4* gene +49A/G genotype frequency distribution between SLE patients and the control group.

Genotypes	Patients	Controls	χ^2	P-value	OR	
	n = 68	n = 32			Value	95% CI
Genotype A/A	34 (50%)	25 (78.1%)	7.68	0.006	0.28	0.11 – 0.73
Genotype A/G	30 (44.1%)	7 (21.9%)			2.82	1.07 – 7.40
Genotype G/G	4 (5.9%)	0 (0)			4.53	0.24 – 86.82

* (P<0.05), ** (P<0.01), NS: Non-significant.

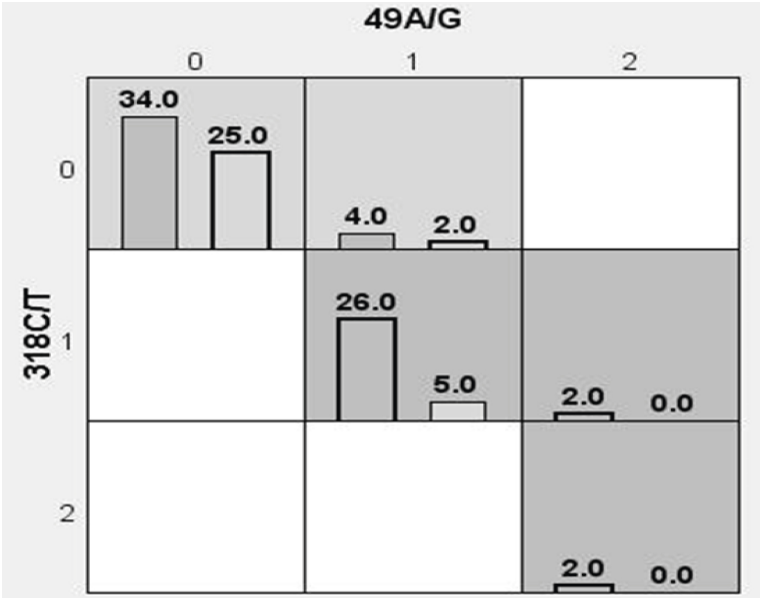


Fig. 5. The frequency distribution of the two locus combination of genotypes of *CTLA-4* gene polymorphism - 318C/T and +49A/G in patients with SLE.

Table 5.

MDR Model for -318C/T and +49A/G polymorphisms Interaction in SLE.

locus	Model	CVC	TBA	P-value	OR	95% C.I.	X ²
Two locus	- 318C/T and +49A/G	10 of 10	0.6705	0.002**	5.625	1.7461- 18.1212	9.5427

Data were expressed as CVC= Cross validation consistency, TBA= Testing accuracy. ** $p < 0.01$ significant.

The - 318T and +49 G alleles frequency in the *CTLA-4* gene carriers was significantly higher in patients compare with the control group ($P = 0.008$, OR 3.63, 95% CI 1.34 – 9.82; $P = 0.007$, OR 3.16, 95% CI 1.32 – 7.53, respectively). The -318C and +49 A alleles frequency in the *CTLA-4* gene carriers was low significantly when compare with the control group as shown in and Tables 1 and 3.

The present results show that in the *CTLA-4* – 318 gene CT heterozygous genotype relative frequency was found to be 15.6% and 41.2% that was statistically significant in the control group and the SLE patients, respectively. The TT homozygous genes revealed significant differences in the SLE patients' 2.9 %, while in the healthy subjects this genotype was present in 0. In 84.4 % of the controls, the CC homozygous genotype was present, whereas it was 55.9% in the SLE patients as shown in table 2. In contrast to the control group, SLE patients had significantly higher levels of the *CTLA-4* – 318 gene CT heterozygous genotypes and T allele ($P < 0.05$), as shown in table 1. While the results show that in the *CTLA-4* +49 gene AG heterozygous genotype relative frequencies was found to be 21.9% and 44.1% that was statistically significant in the control group and the SLE patients, respectively. The GG homozygous genes revealed significant differences in the SLE patients' 5.9 %, while in the healthy subjects this genotype was present in 0. In 78.1% of the controls, the AA homozygous genotype was present, whereas it was 50% in the SLE patients as shown in table 4. In contrast to the control group, SLE patients had significantly higher levels of the *CTLA-4* +49 gene AG heterozygous genotypes and G allele ($P < 0.05$), as shown in table 3.

There was a strong correlation found between *CTLA-4* gene and SLE. For patients with SLE showed an increased risk of SLE for genotypes- 318C/T and +49A/G ($\chi^2 = 9.5427$, $p\text{-value} = 0.002$) as shown in table 5. Thus, it was found that the combination of one genotype allelic variants of two polymorphisms of *CTLA-4* gene which increases the risk of SLE. Even greater differences in intergenic associations between the control group and patients with SLE for persons identified in a genotype which has allelic variants of the *CTLA-4* gene genotypes -318C/T and +49A/G.

In current study we experimental a significant difference in the dispersal of *CTLA4* +49G/A and *CTLA4*-318C/T mutant alleles frequency between two groups controls and SLE in Iraqi patients. Our results presented a significant relationship between CT heterozygous genotypes and T allele in the *CTLA*-4 gene polymorphism -318C/T and AG heterozygous genotypes and G allele genotype in the *CTLA*-4 gene polymorphism +49G/A and SLE, addition that are more common in the SLE patients, there are many researchers have presented results agreement with our result those described that the *CTLA4* gene polymorphism +49A/G may be a linked as one of the genetic risk factor for SLE [22; 23]. Also some researchers suggestion that The *CTLA*-4 gene polymorphisms -318C/T and +49G/A were observed impact SLE susceptibility with MHC class II molecules [24]. Devaraju P., [25] reported the presence of heterozygous (AG) and homozygous mutant (GG) genotype was linked with a significant risk to progress SLE. Mahdieh S. et al., [26] presented study, that a clear correlation between the *CTLA*-4 gene polymorphisms and susceptibility to SLE in the Iranian population. In contrast many of results disagreement with our result which finding, to show a positive association between -318C/T polymorphism and SLE. With deference to the *CTLA*-4 gene, there are many researches obtained that no linked were found between the *CTLA*-4 gene polymorphism -318C/T and SLE patients from many countries such as the Spain [27], USA [28], Korea [29], England [30], Malaysia [31], Japan [32].

Jie Liu and Hong-Xin Zhang reported by meta-analysis on the obtainable studies presented that the G allele was not significantly linked with increased SLE risk [33]. And also, when grouped into Asia and Europe, the + 49A/G site (rs231775) was still not significantly linked with SLE. Others did not find any association and did not consider it to be a risk factor for SLE [34; 35]. Other studies have described that no correlation between 318C/T polymorphism and SLE [36; 37].

Conclusions

According to our research, Iraqi patients' the susceptibility to SLE may be attributed to the *CTLA*-4 gene polymorphism -318C/T and +49A/G. SLE development has been linked to the polymorphism marker -318C>T and +49A>G in the *CTLA*-4 gene. In -318C/T polymorphism compared to allele carriers C and genotype C/C carriers, allele carriers T and genotype T/T and in +49A/G polymorphism allele carriers A and genotype A/A carriers, allele carriers G and genotype G/G have a greater risk of getting SLE.

Conflict of interest information. The authors declare no conflict of interest.

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