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Serum IL-17A Levels and Association with *IL-17A (rs2275913-G/A) gene* polymorphism in patients with Systemic Lupus Erythematosus

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Abstract: Background: *SLE Autoimmune illness is a multiorgan disease that starts with B and T cell dysregulation and produces autoantibodies, particularly against double-stranded DNA.*
Aim: *Current investigation aims to evaluate gene variations and blood levels of IL-17A in the susceptibility to SLE.*
Methods: *The paper involved 40 patients with Systemic Lupus Erythematosus who were hospitalized between March and August of 2023; the remaining 40 groups were made up of people who appeared to be in good condition. Five milliliters of blood were drawn, with two milliliters of each sample being used for the polymerase chain reaction amplification and CD14 method detection. The remaining (3ml) for IL-17A ELISA Kit (Mabtech USA) test.*
Results: *The IL17A genotype did not substantially enhance the incidence of SLE (P= 0.079). Subjects with the AA genotype, on the other hand, had greater serum levels of IL-17A than those with the GA or GG genotype (P= 0.013). In contrast to the healthy group, the concentration of IL-17A were considerably higher in SLE patients.*
Conclusion: *a substantial relationship between SLE patients' serum IL-17A levels and IL-17A genotype.*
Keyword: *SLE, IL-17, polymorphism*

INTRODUCTION

SLE is a chronic, multi-system autoimmune illness characterized by the overproduction of autoantibodies and the deposition of immune complexes (IC) in multi organs. These autoantibodies lead to inflammation in different organs including skin, kidneys, and joints[(1)]. The prevalence of SLE is 30-50 cases per 100,000 people, which corresponds approximately 250,000 patients in the United States and 500,000 patients in Europe[(2)]. Despite the pathogenesis of SLE is yet uncertain, it is clear from the etiology and progression of the disease onset that an imbalance in the immune regulation mechanism-particularly between pro- and anti-inflammatory cytokines—plays a major role [(3)].

Pro-inflammatory cytokines such as interleukin-17 (IL-17) are primarily released by activated T helper-17 (Th-17) cells, double-negative (DN) T cells, neutrophils, and macrophages [(4)].The cytokine family IL-17 is comprised of six members: IL17A to IL-17F. Of these, IL-17A, sometimes referred to as IL17, was the first cytokine to be identified and has undergone extensive research[(5)]. Thus, this research will emphasis on IL-17. Numerous diseases, such as asthma, inflammatory-bowel disease (IBD), juvenile-onset rheumatoid arthritis, and SLE, have been linked to Th-17 cells and IL-17[(6)]. Meta-analysis containing twenty papers published up till November 2018, which revealed that circulating IL-17 concentration in SLE patients were greater than healthy controls[(7)], indicating a potential role for IL-17 in the pathophysiology and disease activity of SLE. Nevertheless is still debate regarding the relation between circulating IL-17 levels and SLE activity.The earlier researches has established a significant association between IL-17 levels and SLE activity[(8,9)]. However, another study have not detected this positive correlation[(10)].

The defining feature of systemic lupus erythematosus disease are autoantibodies production and immune-complexes deposition with followed by infiltration of cytokine and inflammatory cell in different tissue.Recent research has been focusing on genetic variations of cytokines as possible factors for risk of SLE, because it is thought that the cytokine milieu is essential to lupus pathogenesis[(11)]. Cytokine genetic variation are known to alter he structure of proteins and play a role in the immunopathogenesis a variety of illnesses[(12)]. The human genome's chromosome 6p12.23 contains the IL-17A gene, which encodes for IL-17A. In recent studies, several SNP in the IL-17A gene have been discovered, including, *rs1974226 and rs3748067* in the 3' UTR, and *rs2275913* SNP in the upstream regions of the *IL-17A gene*. It is situated within a binding domain of the nuclear factor-activated T cell (NFAT), which are important regulators of IL-17 expression, and have been shown a functional role in determining an individual's sensitivity to a wide

range of human illness[13]. The polymorphism IL-17A 197 is associated with elevated production of IL-17, probably because the resultant sequence has a greater affinity for NFAT [14]. Therefore, the current study's goal is to evaluate the relation between IL-17A genetic variation and IL-17A concentration in SLE patients.

MATERIALS AND METHODS

From March to August of 2023, 40 individuals, 14 of whom were male and 26 of whom were female, in the age range of 20 to 40 years, participated in the current study. A control group of 40 people, 16 men and 24 women, who did not have a history of systemic disease and were deemed clinically healthy, were also included in this study. Patients with infectious disorders, DM, malignant tumors, and other rheumatologic disorders were excluded. Five milliliters of blood were drawn via vein puncture with aseptic technique and disposable syringes. In order to prevent repetitive thawing and freezing for the polymerase chain reaction amplification and detection of the *IL-17A (rs2275913-G/A)* gene (ARMS-PCR) approach, 2 ml of each sample were put into an EDTA tube and immediately frozen at -20 C until further use.The remaining (3 ml) were transferred to sterile Gel tubes, allowed to clot at room temperature, and centrifuged at 2500 rpm for 10 min, for the IL-17A ELISA Kit (Mabtech USA) test. After separation, the serum was stored in Eppendorf tubes and kept frozen at -20 C^{o} until needed. This research was in agreement with ethics of Al-Diwaniyah Teaching Hospital and oral informed consent was received from all patients.

RESULTS

Table (1) summarizes the features of patients and control participants, who were statistically similar in terms of age and sex.The mean age of patient was 29.37 ± 3.9 and that of control subjects was 28.18 ± 4.7 years, however, this variation not statistically significant among patients with SLEand control (P = 0.794). In the patients' group, there were 14 (35.0%) males and 26 (65.0%) females; in the control group, there were 15 (37.5%) males and 25 (62.5%) females. The frequency distribution of patients and control subjects did not differ significantly based on gender (P= 0.816). The current finding show the absence of a significant difference in the ages and genders of participants in both groups—is a requirement to prevent age and gender bias in case control studies. The Tetra-ARMS-PCR method was used to identify the distribution of the *IL-17A (rs2275913-G/A)* genetic variation (polymorphism).There are 3 genotypes at this locus: GG, GA, and AA.Lane (AA) mutant homozygote was detected only A allele at 266bp T-ARMS-PCR product, whereas the (GA) heterozygote were showed as both G and A allele at 298bp and 266bp T-ARMS-PCR product . The outer internal control was observed at 508bp T-ARMS-PCR product, figure (1). In every one of the study groups, the genotype distribution did not deviate from Hardy-Weinberg equilibrium and was consistent with the findings of Pasha et al.,[15]. Compared to their controls, SLE patients had greater rates of IL-17A G/A and AA genotypes, however these differences were not statistically significant (P=0.079). Additionally, SLE patients had a higher frequency of the A allele of the IL-17A polymorphism than did healthy respondents (P=0.013) Table (2).P-value was (P < 0.001) and the median serum concentration of IL-17A level in SLE patients was substantially greater than that of the healthy control group, 1.9 (0.7) versus 1.05 (0.48). Specifically, the current data indicate that patients with the rs2275913 GA or AA genotype present with greater serum IL17A levels compared to those with the rs2275913 GG genotypes (P< 0.05) following a thorough comparison of rs2275913 genotypes and serum IL17A levels. Nevertheless, rs2275913 GA and rs2275913 AA genotype carriers did not substantially differ in serum IL-17A levels (P > 0.05) table (4).

Table (1): Demographic characteristics of patients with SLE and healthy control subjects

Characteristic	Patients *n* = 40	Healthy control *n* = 40	*P*
Age (years)			
Mean ±SD	29.37 ± 3.9	28.18 ± 4.7	0.794 † NS
Range	19– 40	22 – 38	
< 30, *n* (%)	18 (45.0%)	16 (40.0%)	0.651

30-40, *n* (%)	22 (55.0%)	24 (60.0%)	¥ NS
Gender			
Male, *n* (%)	14 (35.0 %)	15 (37.5 %)	0.816 ¥ NS
Female, *n* (%)	26 (65.0%)	25 (62.5%)	

n: number of cases; **SD**: standard deviation; †: independent samples t-test; ¥: Chi-square test; NS: not significant at P > 0.05

Table (2): Distribution of *IL-17A (rs2275913-G/A)* Genotype and Alleles Frequency

Mode	***IL-17A (rs2275913)***	**Patients *n* = 40**	**Control *n* = 40**	***P***	**OR**	**95% CI**	**PF**	**EF**
Co-dominant	AA	10 (25.0%)	4 (10.0 %)	0.079 ¥ NS	4.1	1.07-15.6	…..	0.315
	G/A	16 (40.0%)	13 (32.5 %)		2.02	0.75 -5.43	……	0.269
	GG	14 (35.0 %)	23 (57.5 %)		Reference			
Dominant	AA+G/A	26 (65.0 %)	17 (42.5%)	0.067 ¥ NS	Reference			
	GG	14 (35.0%)	23 (57.5 %)		0.43	0.173-1.07	0.327	…..
Recessive	AA	10 (25.0%)	4 (10.0 %)	0.077 ¥ NS	3.0	0.85-10.5	…..	0.166
	G/A+GG	30 (75.0%)	36 (90.0 %)		Reference		……	
Alleles	A	36 (45.0%)	21 (26.2 %)	0.013 ¥ S	2.29	1.18-4.46		0.254
	G	44 (55.0%)	59 (73.8 %)		Reference		0.254	

¥: Chi-square test; NS: not significant at *P*> 0.05; **S**: significant at *P* ≤ 0.05

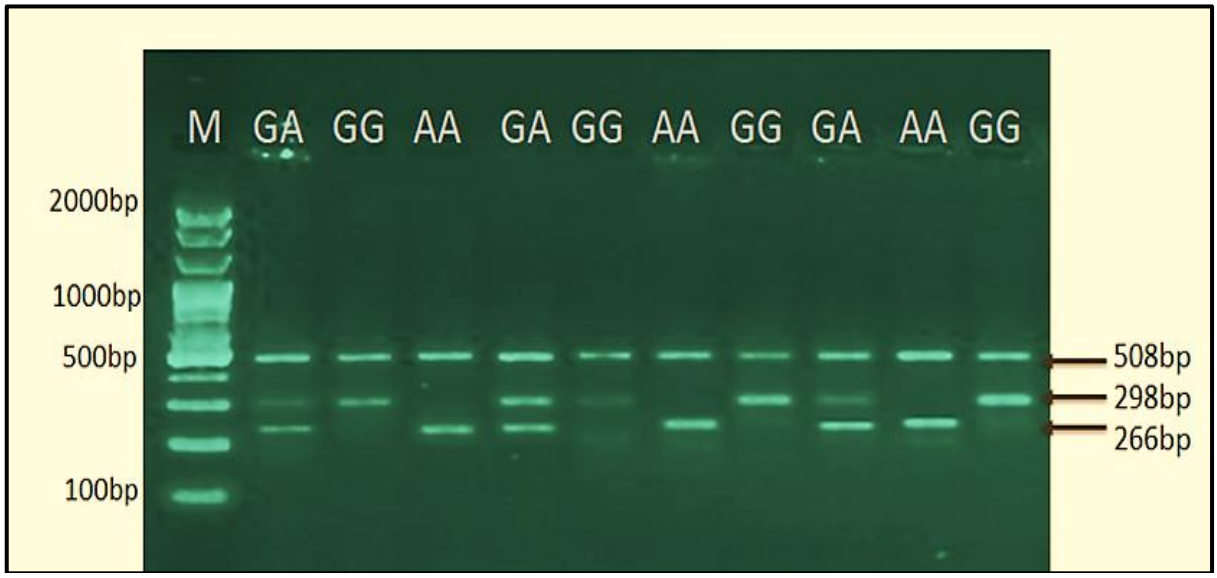

Figure (1): Agarose gel electrophoresis image that show the Tetra-ARMS-PCR product analysis of *IL-17A (rs2275913 G/A)* gene polymorphism. Where M: marker (2000-100bp). The lane (GG) wild type homozygote was showed only G allele at 298bp PCR product. The lane (AA) mutant type homozygote was showed only A allele at 266bp PCR product, whereas the (GA) heterozygote were showed as both G and A allele at 298bp and 266bp PCR product. The outer internal control was observed at 508bp PCR product.

Table (3): The compared between the study groups regarding IL-17A levels.

IL-17A levels	Patients	Healthy control	P value
Range	(1.3- 2.7)	(0.60- 1.6)	<0.001 ¥ (S)
Median (inter-quartile)	1.9 (0.7)	1.05 (0.48)	
SD	0.43	0.31	
N	40	40	

†: Mann-Whitney U test; **S**: significant at $P \leq 0.05$

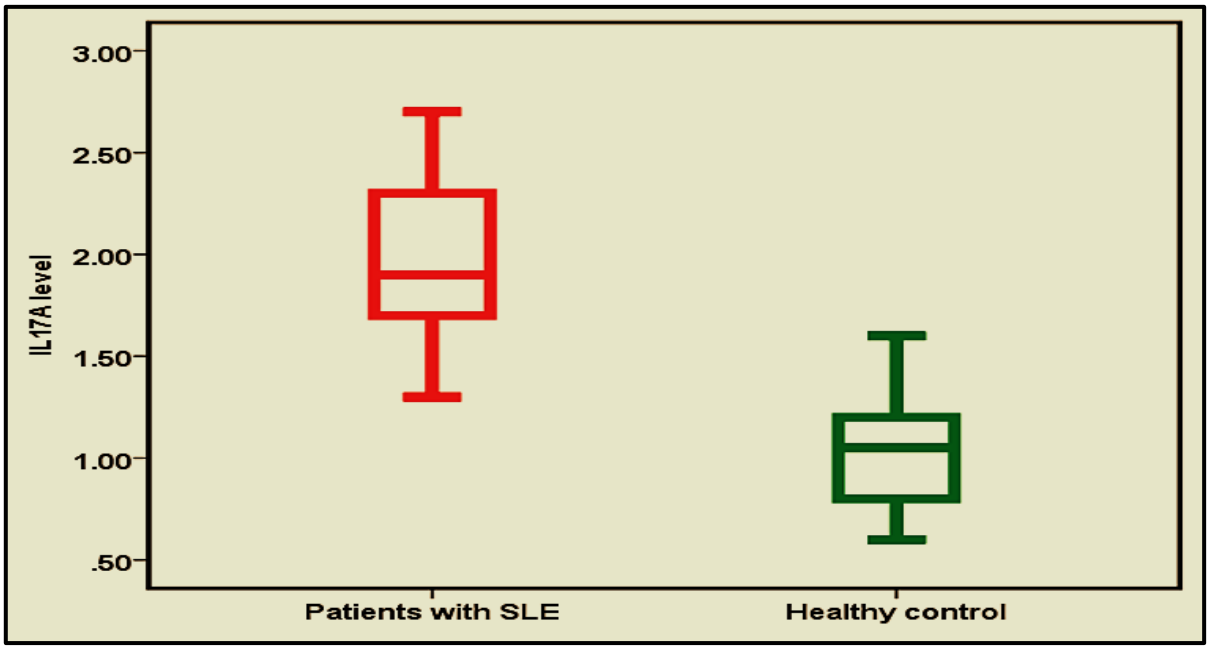

Figure (2): Comparison of the IL-17A concentration among SLE patients and control group.

Table (4): Correlation between soluble IL-17A levels and *IL-17A (rs2275913-G/A)* genotype in patients with SLE

IL-17A **levels**	***IL-17A (rs2275913-G/A)***			
	GG Genotype	***GA Genotype***	***AA genotype***	**P**
Mean	**1.5^{A}**	**2.2^{B}**	**2.4^{B}**	**0.013 † (S)**
Range	1.3 – 1.9	1.5 – 2.6	2.1 – 2.7	
SD	**0.56**	**0.61**	**0.32**	
N	**14**	**16**	**10**	
Different latters denote to the significant differences at p< 0.05				

n: number of cases; **SD**: standard deviation; †: one way ANOVA; **S**: significant at *P*< 0.05

DISCUSSION

The autoimmune illness known as systemic lupus erythematosus (SLE) is described by a range of clinical symptoms with an entirely unexpected course for flare-ups, as well as an enhanced generation of autoantibodies against self-antigens [(16)]. Even with significant progress in our understanding of the pathogenesis of SLE, patients remain at high risk of organ damage and death. Forecasting new instruments enables early SLE diagnosis, which in turn enables early disease activity monitoring and treatment selection [(17)]. The findings indicate that age and gender may have a role in the genesis of SLE. Age-wise, SLE is thought to primarily affect younger people rather than those who are middle-aged or older. According to the current data, the average age of SLE patients is 29.37 ± 3.9 years. These results align with the research conducted by Abd-Alrasool*et al.*,[(18)], who found that the majority of patients were female and that the mean of age of the patients was 33.6 years.Thus, it is thought that one of the main risk factors for SLE in adults is their younger age [(19)]. However, Elkoumi*et al.*,[(20)] data showed the mean age of 12.3 ± 2.8, which is lower than the mean age of the current results. The results revealed that the patients' ages varied from 19 to 40 years old. Additionally, the majority of SLE patients (55.0%) and the control group (60.0%) were both between 30 and 40 years old. This suggests that there was no screening program in place, which would have led to an early diagnosis. Regarding age, it is believed that middle-aged people are more likely to be affected by SLE than younger or older people. Consequently, the results of this investigation showed that the age of thirty is thought to be a significant risk factor. This is consistent with Ohta*et al.,* (21) finding that people between the ages of 20 and 39 are most prone to SLE.

The present study revealed higher prevalence of SLE in female 26 (65.0 %) than male 14 (35.0%), and there was no significant difference in the frequency distribution of patients control according to gender (P= 0.816), table (1).The majority of research concurs that women are more likely than men to develop SLE [(22)]. The gender gap that has been shown may arise from the interplay of genetics, environment, and sex hormones during a person's development; additionally, all cases were adult cases, which is consistent with earlier studies that showed that after puberty, females with SLE are more common than males due to elevated levels of circulating estrogen [(23)]. The increased incidence of SLE in women could perhaps be brought about by variations in gonadotropin-releasing hormone (GnRH) or sex hormone metabolism [(24)]. The findings suggested that the higher frequency of SLE in females than in males may be due to hormonal differences and their effect on the immune response. Because these cells act as stimulators, women produce more helper T cells, which may aid in the development of autoimmunity [(25)].

In its early stages, SLE is typically believed to be a Th2-mediated disorder. However, Th1 circumvents the Th2 pathway, assuming control of SLE progression to the point of active nephritis[(26)]. Researchers discovered that the SLE patients had greater concentration of IL-17, a pro-inflammatory cytokine that plays a significant role in autoimmune illnesses. This finding suggests that IL-17 plays a role in the development and activity of the disease [(27)]. Human CD4+ T cells that belong to the Th17 fraction produce IL-17. Furthermore, neutrophils and CD8+T cells all produce it[(28)]. The purpose of this study was to determine how Il-17 functioned as a biomarker in SLE. Other cytokines, including IL-1, IL-6, and TNF-a, can also be produced in response to IL 17. Granulocyte colony stimulating factor and local chemokines are induced by

IL-17A signaling, which attracts monocytes and neutrophils [29]. Additionally, IL-17A engages in a complex network of interactions with IL-23 and other Th-17-related cytokines, including IL-17 F, IL-22, and IL-21, to enhance tissue damage caused by SLE and promote inflammation [30]. Furthermore, in SLE patients, IL-17 promotes autoantibody overproduction, indicating a special function for it in triggering autoimmunity and tolerance disruption[31].

In the present investigation, IL-17A levels was assessed in SLE patients and healthy controls, and additional correlation analyses were carried out to clarify the relevance of the study's findings. When comparing the median of IL-17A between patients with SLE and healthy individuals, it was discovered that the former had a significantly higher level than the latter, at 1.9 (0.7) vs 1.05 (0.48), respectively. This finding is consistent with Zickert *et al.,* (32), finding that Th17 were elevated in the tissues and sera of patients with lupus nephritis (LN). According to a different study, elevated serum IL-23 in SLE patients leads to the formation of pathogenic Th17 cells, which produce IL-17 and draw neutrophils to regions implicated in the pathophysiology of the disease[33]. By preventing the development and function of Treg cells, IL-17 may worsen SLE. Treg cells' capability to regulate the secretion and growth of proinflammatory cytokines in ESL's effector immune cells appears to be aberrant, either qualitatively or quantitatively [34]. Reduced IL-2 and increased IL-6 concentrations lead to the development of Th17 cells. Environmental factors that cause oxidative stress and increased production of IL-6, such UV rays, infections, and cigarette smoking, may be the primary cause of Tregreduction in SLE [35]. IL17 advances clinical SLE symptoms in the central nervous system [36].Along with the current findings, previous research revealed that SLE patients had greater plasma IL17 levels and circulating Th17 cells than did healthy individuals [6]. Additionally, a number of colleagues reported a favorable correlation between disease activity and serum levels of IL-17 [37, 38].

Research has demonstrated that administering anti-IL-17 antibodies to animal models of autoimmune illnesses can lessen the severity of the disease. When IL-2 was given to animals at risk for lupus, the T cells that produce IL-17 were inhibited and renal tissue damage was prevented. Thus, it is possible that IL-17 is the primary effector cytokine found in the inflammatory kidneys of mice at risk for lupus [39]. Dong et al. [40] showed that in patients with lung cancer, IL-17A might cause autoantibody overproduction and peripheral blood mononuclear cells (PBMCs) to overexpress IL-6.

In SLE, Raymond *et al.,*[5] did not find an increase in IL-17 levels. They discovered that IL-17 level might not accurately reflect endogenous synthesis, that IL-17 may occasionally be restricted to inflammatory tissue like the brain, and that blood IL-17 levels might not accurately reflect the total amount of IL-17 produced. The variability of diseases may account for these disparate results. The ELISA test's sensitivity, confident studies' use of little sample volumes, and differences in the principles, and uncontrolled other factor as immune-suppressive medications could be important indicators of sera IL-17 concentrations could all have an impact on the disease's expression, which might difference among patients in terms of the involvement of significant organ involvement that possibly had an effect on this result[41].

The debate surrounding the relationship between IL-17A variation and critical to various human illness should be explained by a number of factors. Regarding the discrepancy shown between IL-17A variation and the likelihood of various human illnesses in multiple population, it is widely acknowledged that genetic variants typically have unique effects on various human disease types, particularly in diverse ethnic groups. The *rs2275913* polymorphism of the IL-17A promoter region. The current data demonstrate that the SLE group's (45.0%) frequency of the *rs2275913 A* allele was significantly greater than that of the healthy groups (26.2%) and related to a significantly risk of developing SLE in comparison to the control group (OR = 2.29, 95% CI, 1.18~4.46, P= 0.013).Additionally, it was demonstrated that, when comparing the *rs2275913 GG* genotype between cases and controls, the rs2275913 GA and AA genotypes were linked to non-significantly higher odds of SLE. The results of this investigation agree with those of Elkoumi *et al.,*[20], who discovered that patients had higher levels of the *IL-17 rs2275913 A* alleles and A/A genotype than control subjects. They also identified the A allele and A/A genotype as risk factors for lupus development. The current findings are also in line with those of Pasha *et al.,*[13], who found that patients had a higher AA genotype frequency than controls, although this difference was not statistically significant. Additionally, they detected a borderline significant elevation in A allele frequency of patients when compared to controls. Gunawan *et*

al.,[42] published the identical findings. They found that the GA and AA genotypes of the case group were higher than those of the control group, even though there was no statistically significant difference. Furthermore, the current results showed that healthy controls had a higher frequency of allele G than did SLE patients. Also revealed that the (GG) genotypes frequency was decreased in patients (35.0%) than in healthy control (57.5%). These results agree with those of Elkoumi and colleagues[20], who discovered that the (GG) genotype frequency was decreased in patients (47%) than in controls (48%). Thus, the G allele and GG genotype may be thought of as a preventative component that provides protection against SLE.

On the other hand, according to Sharifzade*et al.* (43), the IL-17 rs2275913 In the Iranian populations, an allele may provide protection against SLE.Additional research by Hammad et al., [44], who studies the IL-17 A rs2275913 SNP in 115 Egyptian SLE children compared to 259 well-matched healthy groups. The analysis by the researchers revealed that the haplotype GGA of the analyzed IL-17A and IL-17F SNPs constitutes a risk factors for pediatric beginning SLE, however they noted that the IL-17 A rs2275913 SNP had no association with the risk to juvenile-onset SLE. This divergence could be explained by differences in the examined age group and cohort size, as well as ethnic background or gene-environment interactions.
More significantly, the current findings revealed a connection between aberrant IL-17A expression and the *rs2275913 polymorphism.* When compared to patients with the rs2275913 GG genotype, those with *the rs2275913 GA or AA* genotype have greater serum IL17A levels. When combined, these findings suggest the *rs2275913 variation* could be used as a risk issue for prediction the likelihood of developing SLE, most likely by up-regulating the IL-17A gene's protein expression. Based on the results that showed that the G to A switch at –197position was linked to elevated IL-17 concentration and that the A/A, G/G, and G/A were linked to low, intermediate, and high IL-17A concentration in SLE patients, the current study postulates that altered IL-17 transcription and mRNA expression is the cause of the IL-17 G/A rs2275913 SNP's result. These findings support and expand upon those of Espinoza et al. [45], who observed that peripheral blood mononuclear cells with 197A allele positive genotypes secreted higher IL-17A in comparison to those with A allele negative genotype. The *IL-17 G/A rs2275913* SNP aligns to inside a binding motif for the nuclear factor activated T-cell (NFAT), which is a key transcriptional regulator of the IL-17 gene, according to Liu *et al.*[46]. Furthermore, compared to the G allele at the same location, the A allele showed a stronger relationship for the transcriptional factors. Our findings are consistent with the findings of numerous other studies[47-52] that found that SLE patients with the AG and AA genotypes of the IL-17A gene had much higher serum levels of the gene than SLE patients with the GG genotype[13].

CONCLUSIONS

IL-17 concentration was higher in SLE patients than healthy, which may have contributed to the etiology of the disease. The susceptibility to SLE was influenced by the polymorphisms of the IL-17A 197 genes. Moreover, show a strong relationship between serum IL-17 levels and polymorphisms in the IL-17A 197 gene.

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