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IL-17F GENE POLYMORPHISM (7488T/C, RS763780) IN EGYPTIAN PATIENTS WITH SLE

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Systemic Lupus erythematosus (SLE) is a worldwide autoimmune disease with different presentations. Genetic and environmental factors like infection and ultraviolet light are supposed to be responsible for the development of SLE. Disturbance in cytokines production may be involved in SLE pathogenesis. In this case-control study, we investigate the interleukin-17F (IL-17F) gene polymorphism (7488T/C, rs763780) in Egyptian SLE patients using polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP). There were no significant changes when both genotypes and alleles for patients and controls were compared with each other. According to the results, no association between the IL-17F gene polymorphism (7488T/C, rs763780) and SLE.

Keywords: *SLE, IL-17F, Cytokine, autoimmune.*

INTRODUCTION

Systemic Lupus erythematosus (SLE) is a historical chronic autoimmune disease with heterogeneous presentations. The immune system is activated against self-antigens that form immune complexes with autoantibodies and deposited in the vasculature of various organs like joints, kidney, lung, central nervous system, and skin which induce local inflammation and to the end lead to tissue damage [1, 2]. The exact etiology is still unclear; However, multifactorial etiology is supposed, involving genetic and environmental factors like infection, ultraviolet light, and medication[3]. The prevalence of SLE is 20-70/100000 person-year worldwide[4]. SLE affects mainly female in the childbearing period more than male with female to male ratio is 12:1[5]. The mortality rate per 1000 patients was different according to ethnicity, the highest was in Native American (27.52), and the lowest was in Asian (5.18) and Hispanic (7.12) while Caucasian and African American were (20.17) and (24.13), respectively[6]. In a cohort study on Egyptians with SLE, the mortality rate was about 4.4%, mainly due to cardiovascular complications and infection[7].

Cytokines are soluble factors released from immune cells like monocytes, macrophages, and dendritic cells and play a fundamental role in the differentiation, maturation, and functional regulation of different immune cells[8]. Disturbance in cytokines production has been identified in SLE both in vivo and in vitro[9]. The exact role of cytokines in SLE has not been detected. However, disruption in cytokines production reflects the disturbance in immune cells functions. The disturbance in the balance between T-Helper 1 (TH-1) and T-Helper 2 (TH-2) cytokines are associated with disease progression[9&10]. In the murine model for SLE, TH-1 cytokines were predominant in the early stage of the disease while TH-2 cytokines were increased in the later stages[11&12].

IL-17 is an inflammatory cytokine family, formed of 6 members (from IL-17A to IL-

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17F)[2,13-15]. IL-17A is known as cytotoxic T lymphocyte-associated antigen (CTLA)-8, and IL-17E is called IL-25[15&16]. IL-17 produces its effect through a distinct group of cytokines receptor family consisted of 5 members (IL17RA, B, C, D, and E)[17&18]. The members of the IL-17 family have molecular masses varying from 20–30 kDa, and at the C-terminal region, they have four cysteine residues[19&20]. Least homology has been detected between IL-17A and IL-17B, IL-17C and IL-17D and IL-17E, while IL-17A and IL-17F show a high degree of similarity of about 50%[13,20-22].

IL-17 genetic polymorphisms have been suggested to be associated with multiple disorders like osteoarthritis[23], asthma[24], gastric cancer[25], multiple sclerosis (MS)[26], autoimmune thyroid diseases (AITDs)[27], Hepatitis B virus infection[28], inflammatory bowel diseases (IBD)[29], childhood Henoch-Schoenlein purpura[30] and chronic immune thrombocytopenia (ITP)[31]. The IL-17F gene is found on chromosome 6p12, spans 7.86 kb, has three exons and two introns, and is related to the IL-17A gene[20,32]. There is growing evidence supporting the role of IL-17F in the pathogenesis of SLE[33,34]. In this study, we investigated the IL-17F gene polymorphism (7488T/C, rs763780) in Egyptian SLE patients. This polymorphism is responsible for substitution of G to A at position 7488 in exon 3 and for replacement of histidine (CAT) for arginine (CGT) in the newly-synthesized IL-17F protein, which leads to altering the structure, function, and activity of the protein.

SUBJECTS AND METHODS

Patients and controls

This study involved 100 unrelated Egyptian patients with active SLE attending the internal medicine outpatient clinic in the internal medicine department, Mansoura University Hospital, Egypt, in the period from July 2017 to August 2018. A specialist confirmed the disease status according to the revised criteria of the American Rheumatism Association for the classification of SLE[35]; eleven male and eighty-nine females with average age of 26.08 ± 8.16 years. One hundred unrelated age and sex-matched controls were involved (83 females and 17 males, mean ± SD age of 30.7 ±6.2 years). The patients and controls were from the same geographical area and had the same ethnic origin. They were recruited from a general outpatient clinic in the Internal Medicine Department, Mansoura University Hospital, Egypt, for a routine check-up without any history of SLE or any other autoimmune disease.

G*power software 3.1.9.7 was used to determine the sample size[36]. Each group's minimum sample size was 64 individuals. The following software parameters were changed: the effect size was set to 0.5, the power level was set to 0.8, and the alpha error probability was set to 0.05 (two-tailed). To prevent missing values, we wanted to raise the sample sizes for both groups.

Ethical Issue

Written consent was obtained from both patients and controls. Approval for the study was obtained from the Local Ethical Committee.

Samples

Three ml of venous blood was collected from both patients and controls by plastic syringe using aseptic venipuncture technique; then the blood was delivered into 5.0 ml EDTA tube. Samples were mixed thoroughly with anticoagulant by gentle inversion from about 3 to 6 times end-over-end.

Genotyping

DNA was extracted from whole blood EDTA samples by using Gene JET Whole Blood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific, Waltham, MA, Cat No K0781, Lithuania). The extracted DNA samples were stored in – 20 C° until used. The genotyping for IL-17F rs763780 was done by using the polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP)[37&38]. The sequence of forwarding primer was GTGTAGGAACTTGGGCTGCATCAAT while that for reverse primer was AGCTGGGAATGCAAACAAAC. The reaction involved 5µl of extracted DNA, 15 µl master mix (Thermo Fisher Scientific, Waltham, MA, Cat No K1081, Lithuania), 0.5 µl forward primer, 0.5 µl reverse primer and 4.0 µl H2O. The final reaction volume was 25.0 µl. The cycling conditions for the PCR reaction were as the following: initial denaturation at 94° C for 5 minutes followed by 35 cycles of denaturation at 94° C for 30 seconds (s), annealing at 55.2° C for 60 s, extension at 72° C for 60 s and a final extension at 72° C for 10

minutes. Before incubation with the restriction enzyme, PCR products were checked by mixing five µI of products with two µI of loading buffer and migrated on 2% agarose gel. The PCR products were checked at 470 bp. The PCR products were digested by using NlaIII restriction enzyme, cleavage site for the enzyme is

5'		C	A	T	G ↓	3'
3'	↑	G	T	A	C	5'

(Thermo Fisher Scientific, Waltham, MA, Cat No ER1831). The reaction volume formed of PCR products (10 µl), restriction enzyme (1 µl), nuclease-free water (17 µl) and green buffer (2.0 µl) and the final volume was 30 µl. The reaction mixture was incubated for 10 minutes at 37°C then at 65°C for 10 minutes. DNA fragments were loaded in 2.5% agarose gel. The final genotypes for rs763780 were AA (288, 130, 52 bp), GA (418, 288, 130, 52 bp) and GG (418, 52 bp) (Figure 1)

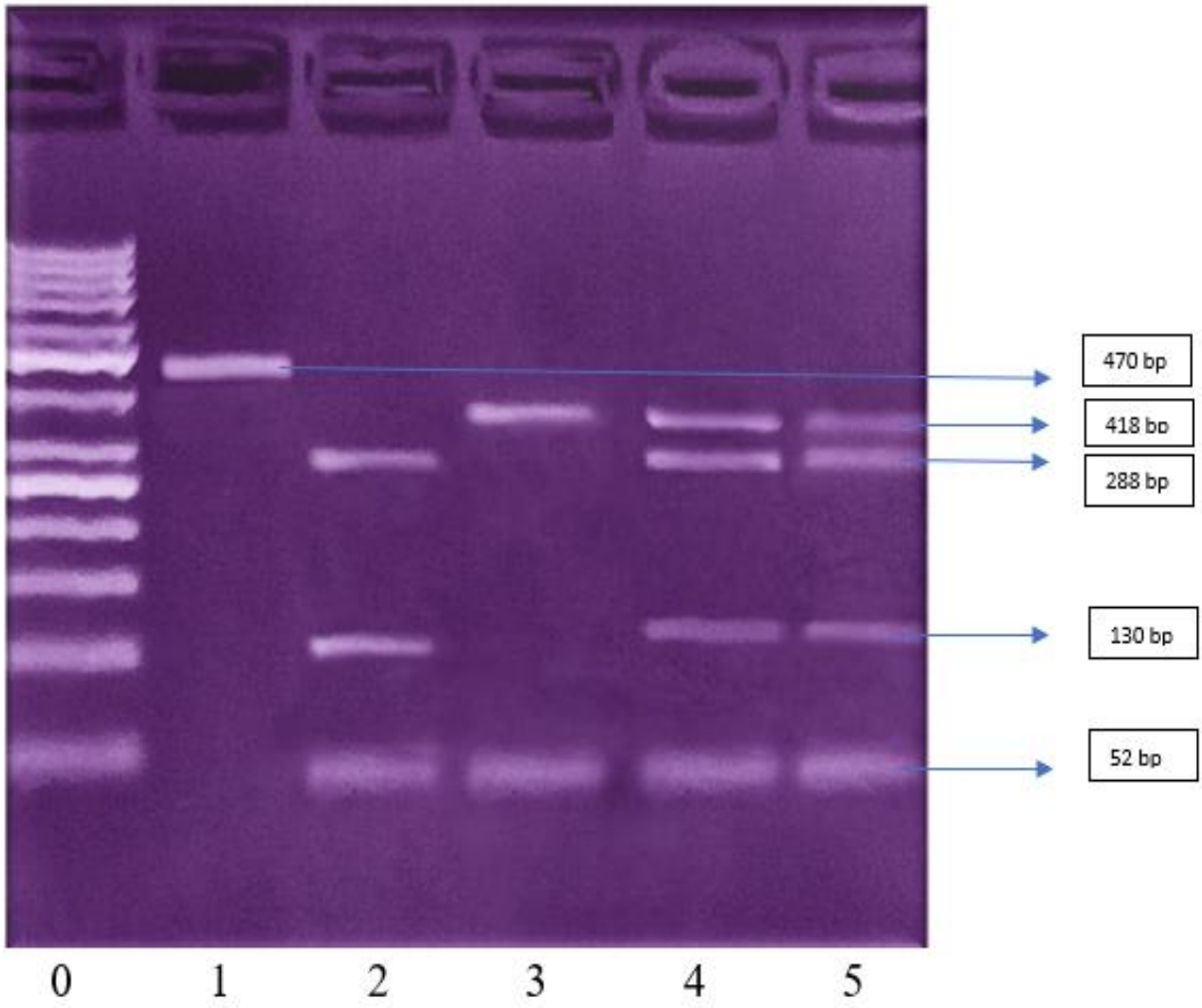

Fig. 1: PCR- RFLP with FastDigest NlaIII (Hin1II) restriction enzyme.

- Lane 0 gene ruler 50 bp ladder thermo scientific.
- Lane 1 PCR amplified product at 470 bp.
- Lane 2 AA genotypes (three bands at 288, 130, 52 bp).
- Lane 3 GG genotype (two bands at 418 and 52 bp).
- Lane 4,5 GA genotype (four bands at 418, 288, 130 and 52 bp).

Statistical analysis

Microsoft office 2013 was used for data entry. The study of data was done by using and the statistical package of social science (IBM-SPSS) version 20 (Chicago, IL, USA). The quantitative data were presented as mean and standard deviation. Chi-square test was used to compare groups. Mann-Whitney U test and the Kruskal-Wallis test were used to estimate the differences in continuous nonparametric variables. Odd's ratio and 95% confidence interval were calculated. P Value below 0.05 is considered statistically significant.

RESULTS AND DISCUSSION

Results

The clinical and demographic data are presented and tabulated in Table 1. No statistically significant difference was found in IL-17F rs763780 genotypes and alleles between SLE patients and controls (Table 2). There was no significant change of AA genotype in the patient group compared to control (OR= 0.3, 95% CI =0.01-3.7, P= 0.6). Additionally, there was no significant change of AG genotype in the control group compared to patients (OR= 0.28, 95% CI=0.01- 3.6, P=0.3). When the two study groups were compared to one another, neither the A allele nor the G allele displayed any significant changes (OR=0.95, 95% CI= 0.48- 1.87, P= 0.87).

Table 1: Demographic and clinical data of SLE patients**.**

	Value
Age years (M±SD)	26.08 ±8.16
Gender: Male/female	13/87
Polyarthritis	60
Myalgia	51
Seizures	8
Neuropathy	3
Malar rash	59
Alopecia	31
Serositis	44
Oral ulcers	20
Pericardial effusion	8
Proteinuria	34
Hematuria	33
Anemia	69
Thrombocytopenia	19
Leucopenia	26
Positive ANA	96
Positive Ds-DNA	76
Activity index; median (range)	6.5 (0.0–22)
Chronicity index; median (range)	1.9 (0.0–5.0)

M±SD: Mean ± Standard deviation, ANA: Antinuclear Antibody, Ds-DNA: double stranded-DNA.

Table 2: Comparison of gene distribution and allele among studied groups**.**

	Cases n =100	Contro N=100	P value	OR (95%CI)
	NO (%)	NO (%)		
AA	81(81.0)	80(80)	0.60	0.30(0.01-3.7)
AG	16(16.0)	19(19)	0.30	0.28(0.01-3.6)
GG (r)	3(3.0)	1(1.0)	1	
Allele				
A	178(89)	179(89.5)	0.87	0.95(0.48-1.87)
G(r)	22(11)	21(10.5)	1	

OR: Odd's Ratio, CI: Confidence Interval.

There was no significant association between genotype distribution in the patient group and found in different laboratory tests (Hb, WBC count, platelets count, creatinine, dsDNA and C3) ($p > 0.05$ for each) (Table 3).

There was no significant association between genotype distribution in the patient group and clinical presentations (p>0.05 for each), except that for photosensitivity (p=0.02). AA genotype consider as risky genotype for photosensitivity, frequency of cases with AA genotype has photosensitivity is 72.8% (Table 4).

Table 3: Laboratory markers according to gene distribution among the studied group**.**

	AA n=81	AG n=16	GG n=3	P value
HB Mean (sd)	9.9 (1.8)	9.7(1.7)	10.5(1.6)	0.7
WBCs mean (sd)	5.6(2.4)	6.06(2.04)	3.4(0.5)	0.2
Platelets mean (sd)	230.3(104.4)	185.0(71.5)	154.3(54.8)	0.1
Creatinine mean (sd)	1.06(0.7)	1.03(0.7)	0.8(0.2)	0.8
Ds DNA antibodies mean (sd)	n=64 70.9(18.2)	n=11 68.9(18.7)	n=1 60.0	0.8
C3 mean (sd)	n=81 1.09(0.4)	n=16 0.9(0.4)	n=3 1.2(0.1)	0.2

HB: Hemoglobin, Sd: Standard deviation, WBCs: White Blood Cells, Ds DNA: Double stranded DNA, C3: Complement 3.

Table 4: Gene distribution according to different clinical presentations**.**

	AA n=81	AG n=16	GG n=3	P value
	n (%)	n (%)	N (%)	
Polyarthritis	49 (60.5)	9(56.2)	2 (66.7)	0.9
Myalgia	38 (46.9)	10 (62.5)	3 (100)	0.1
Seizures	7 (8.6)	1 (6.2)	0 (0)	0.8
Neuropathy	3 (3.7)	0(0)	0 (0)	0.6
Photosensitivity	59 (72.8)	10(62.5)	0(0)	0.02*
Malar rash	48(59.3)	9(56.2)	2 (66.7)	0.9
Alopecia	26(32.1)	4(25.0)	1 (33.3)	0.8
Serositis	38(46.9)	5(31.2)	1 (33.3)	0.4
Oral ulcers	14(17.3)	4(25.0)	2 (66.7)	0.09
Pericardial effusion	6(7.4)	2(12.5)	0 (0)	0.6
Proteinuria	27 (33.3)	6 (37.5)	1 (33.3)	0.9
Hematuria	29 (35.8)	4 (25.0)	0(0)	0.3

Discussion

The IL-17F is the most recently discovered member of the IL-17 family[19]. It was released by different immune cells like CD4 T cells, γδ T cells[39], NKT cells[40], CD8 T cells[41], lamina propria T cells[39], memory CD 4 T cell[39] and TH 17 cells[42]. mRNA of IL-17F was also found in mast cells, monocytes, and basophil[22&43]. The crystallographic structure of IL-17F was the first to be described in this family[21]. The function of IL-17F is closely related to IL-17A; both of them are proinflammatory cytokines, and protect against infection, which affects mucosal surfaces like skin, intestine, and lungs[44&45]. It has been proposed that IL-17F plays a role in angiogenesis by inducing TGF-β and IL-2 production in venous endothelial cells[43]. In a bronchial epithelial cell, IL-17F can enhance expression of ICAM-1 and GM-CSF[22,46]. The same effect was also observed in fibroblast and epithelial cells, but for CXCL1 and IL6[47]. IL-17F has a synergistic effect with other cytokines. IL23 and IL-17F enhance inflammatory cytokines (IL6) from eosinophil[48]. TNFα with IL-17F induces G-CSF production[49]. The exact synergistic mechanism of IL-17F is still undetermined[19]. IL-17F binds to IL-17RA but with a much lower affinity than IL-17A[47,49]. However, it can bind with higher affinity to IL-17RC[50].

IL-17 is involved in the pathogenesis of SLE as a proinflammatory cytokine[51-53]. The serum level of IL-17A is increased in patients with SLE compared to healthy control and is considered as a marker for poor outcome in patients with lupus nephritis[54]. Moreover, neurological manifestations of SLE are associated with increased IL-17A levels[55].

The role of IL-17F rs763780 has been studied in many diseases, including autoimmune disorders, with contradictory results. In rheumatoid arthritis, no association was detected[56&57]. In contrast, IL-17F gene polymorphism is linked to inflammatory bowel disease[29,58], asthma[24], MS[59], ITP[60], recurrent pregnancy loss[61] and AITDs[27].

In the present study, no association was found between IL-17F rs763780 and SLE susceptibility in the population involved in this study. The genotypes and alleles distribution of this single nucleotid polymorphism (SNP) were compared between the patients and the control group, and there was no statistically significant difference. Also, no associations were found between gene polymorphism and clinical and demographic data.

To the best of our knowledge, this is the first time to study this polymorphism involving adult patients with SLE from Egypt. However, it was studied earlier on Egyptian patients with different disorders like periodontal disease[62], ITP[63], MS[64] and juvenile SLE[2].

Our findings were in agreement with Sharifzadeh *et al.,* (2018). His case-control study involved 102 SLE patients and 141 healthy control subjects. No association were observed between the IL-17F rs763780 gene polymorphism and the risk of SLE ($P > 0.05$)[65]. Hammad *et al.,* (2015), found no relation between this gene polymorphism and the development of lupus nephritis, disease activity, or overall survival in pediatric patients, but the GGAGAA combined genotype and the GGA haplotype of IL-17A rs2275913, IL-17F rs763780, and rs2397084 can be considered risk factors for the development of SLE in Egyptian children[2].

Yan *et al.,* (2012), on the other hand, investigated the relationship between different IL-17 gene polymorphisms and their association with AITDs and discovered that the IL-17 rs763780 polymorphism increases the risk of developing AITDs in the Chinese Han population[27]. Bogunia-Kubik et al., (2015) found an association between this SNP and the development of rheumatoid arthritis[66].

This study has several limitations that may result in false negative results: all patients and controls were from the same locality in Egypt; SLE is a multifactorial disease with multiple cytokines involved, but only IL-17F was investigated in this study; the number of selected samples was relatively small, which may affect statistical power; there was no specific disease category to find its relationship with the selected SNP; and the limitations of the choice of SNP. However, to overcome these constraints, it is recommended to involve patients from numerous centers not only from Mansoura but also from different governments all across Egypt. Also, a wide sample size with varied age groups should be examined for a more reliable outcome. Different cytokines associated with SLE pathogenesis should be researched, including the IL-17 family, not only the gene polymorphism but also the serum level. Alternative manifestations of SLE disease (cardiovascular, renal, neurological, and

dermatological) should be considered carefully in connection to the investigated cytokine.

Abbreviations

- SLE: Systemic Lupus erythematosus
- IL: interleukin
- PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism
- TH-1: T-Helper 1
- TH-2: T-Helper 2
- MS: multiple sclerosis
- ITP: immune thrombocytopenia
- AITDs: autoimmune thyroid disorders
- IBD: inflammatory bowel diseases
- SNP: single nucleotid polymorphism

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التعد الجينى للانتليوكين السابع عشرF- فى المرضى المصريين المصابين بالزئبة الحمراء

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مرض الذئبة الحمراء هي أحد أمراض المناعة الذاتية في جميع أنحاء العالم وتتميز بتباين الأعراض حيش انها ذات تأثير متباين على جميع أجهزة الجسم. من المفترض أن تكون العوامل الوراثية والبيئية مثل العدوى والأشعة فوق البنفسجية مسؤولة عن تطور مرض الذئبة الحمراء و قد يكون للاضطراب في إنتاج السيتوكينات دور في التسبب في مرض الذئبة الحمراء. ومن خلال ما تقدم ، قمنا بالتحقيق في تعدد الأشكال الجيني للإنترلوكين السابع عشر(IL-17F)(٧٤٨٨ T/C, rs٧٦٣٧٨٠) في المرضى المصريين المصابين بالزئبة الحمراء باستخدام تفاعل البلمرة المتسلسل (PCR – RFLP). وبعد اجراء الدراسة والتحليل الاحصائى تبين أنه لم تكن هناك تغييرات كبيرة عند مقارنة كل من الأنماط الجينية للمرضى والأشخاص الأصحاء. وفقًا للنتائج ، لا يوجد ارتباط بين التعدد الأشكال الجيني محل الدراسة ومرض الزئبة الحمراء.