Role of Three-prime Repair Exonuclease (*TREX1*) Variants in the Susceptibility to Systemic Lupus Erythematosus Patients

Original Article

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ABSTRACT

Background: The autoimmune disease systemic lupus erythematosus (SLE) is considered to have polygenic, multifactorial aetiology. *TREX1* mutations are under investigations for possible significant association with some SLE forms.
Objective: To find out the role of *TREX1* and its variants in the genetic susceptibility to SLE among Egyptian patients and to investigate its relation to the clinical manifestations, laboratory data and disease activity in SLE patients.
Methods: Fifty SLE patients, and 70 age and sex matched healthy controls were included in this study. History taking, clinical examination, laboratory investigations were recorded. Systemic Lupus Erythematosus Disease Activity Index was assessed, and *TREX1* gene polymorphisms were investigated.
Results: Patients in this study were 46 females (92%) and 4 males (8%), their mean age was 28.76±8.83 years, and disease duration 5.49±4.43 years. A synonymous *TREX1* variant c.531C>T (p.Y177Y) has been identified in 28/50 (56%) SLE cases, whereas in 23/70 (32.9%) of the control group (p= 0.01), with minor allele frequency of 0.28 in cases and 0.16 in controls. *TREX1* positive patients had more oral ulcers (p= 0.004), photosensitivity (p= 0.047), seizures (p= 0.029), neuropsychiatric systemic lupus erythematosus (NPSLE) (p= 0.045, OR=7.000, 95% CI=0.791-61.975), and chilblains (p= 0.059, OR= 10.532, 95% CI= 0.550-201.679). Thrombocytopenia was significantly more found in *TREX1* positive patients (p= 0.015).
Conclusion: *TREX1* variant (c.531C>T) was found at higher frequency in a sample of Egyptian lupus patients. *TREX1* positive patients had significantly more oral ulcers. However, no homozygous or heterozygous pathogenic variants were found among studied group of Egyptian lupus patients.

Key Words: Polymorphism, Systemic Lupus Erythematosus, TREX1; Variants .

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease with multifactorial etiologies contributed by genetic, epigenetic, and environmental factors (**Tsokos *et al.,* 2016**). A polygenic additive model has been proposed in the pathogenesis of SLE, supported by hereditary tendency of this disorder (similar familial conditions of either SLE cases or other autoimmune diseases) (**Fanouriakis *et al.,* 2021**). Most of these genes are known to be involved in three types of biological processes: the immune complex processing, the toll-like receptor function mediating type I interferon production processes, and the immune signal transduction in lymphocytes (**Harley *et al.,* 2009**).

Many gene mutations have been reported to increase the risk of developing SLE. *TREX1* is an example of a susceptibility gene for SLE (**Durcan *et al.,* 2019**). Mutations throughout the *TREX1* gene have been identified also in other human autoimmune diseases patients such as Aicardi–Goutières syndrome (AGS), a monogenic form of cutaneous lupus erythematosus entitled "familial chilblain lupus", retinal vasculopathy and cerebral leukodystrophy (**Kavanagh *et al.,* 2008; Lehtinen *et al.,* 2008**).

The *TREX1* enzyme is one of 3'→5' deoxyribonucleic acid (DNA) exonucleases that target DNA, acting 3-4 folds more efficiently on single stranded DNA (ssDNA) than on

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double stranded DNA (dsDNA) (**Lindahl *et al.,* 2009**) The ssDNA is released during DNA metabolism or repair as main endogenous substrate (**Wolf *et al.,* 2016**). *TREX1* also can degrade DNA fragments derived from exogenous viraL retroelements (**Thomas *et al.,* 2017**).

TREX1 enzyme deficient cells accumulate ssDNA species that are capable of triggering inappropriate innate autoimmunity (**Wang *et al.,* 2022**). Degrading endogenous DNA by *TREX1* can prevent type I IFN activation in an interferon regulatory factor 3 (IRF3) and type I IFN receptor (IFNAR1)-dependent manner (**Stetson *et al.,* 2008**). IFN α pathway has been identified as a central performer in SLE pathogenesis (**Lichtman *et al.,* 2012**). Clinical studies investigating *TREX1* mutations and/or variations in the perspective of SLE disease, and the relation to disease parameters are still insufficient. In this study we aimed to find out the role of *TREX1* and its variants in the genetic susceptibility to systemic lupus erythematosus (SLE) among Egyptian patients and to evaluate its relation with clinical manifestations and laboratory data in SLE patients with the genetic testing.

SUBJECTS AND METHODS:

Patients:

Fifty patients diagnosed with systemic lupus erythematosus (SLE), and 70 age & sex matched healthy controls were enrolled in the present study. The patients were recruited from the Rheumatology Department, Cairo University hospitals, and they were fulfilling 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (**Petri *et al.,* 2012**). An informed consent was obtained from all patients according to the world medical association declaration of Helsinki, and the study was approved by the medical research ethics committee of the National Research Centre (NRC 14097) and Faculty of medicine, Cairo University. All the patients were subjected to full history taking, clinical examination and laboratory investigations. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (**Bombardier *et al.,* 1992**).

Molecular analysis:

Genomic DNA was extracted from fresh peripheral blood samples of cases with SLE using standard QIA quick DNA Extraction Kit (Qiagen, Germany). The only coding exon of *TREX1* gene was amplified using two overlapping primers as described by (**Lee-Kirsch *et al.,* 2007**). PCR amplification was carried out in a total volume of 50ul. The PCR products were separated by electrophoresis through 2% agarose gels, purified by QIA quick PCR purification kit (Qiagen, Germany), directly sequenced in both directions using the Big Dye Termination kit (Applied Biosystems, Foster City, CA, USA) and was analyzed on the ABI Prism 310 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) according to manufacturer's instructions.

Statistical analysis:

All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006). Qualitative variables were presented as frequencies and percentages, while quantitative data as mean±SD or median and interquartile range. For comparing categorical data, Chi square (X^2) test was performed and Fisher exact test was used whenever an expected cell count was <5. Comparison of numerical variables was done using Independent *t* test or Mann whitney test for independent samples in 2 groups. Odds Ratio (OR) with the 95% confidence interval (95%CI) in relation to *TREX1* state were calculated when appropriate. Spearmen Correlation was performed. *P* values were considered significant at <0.05.

RESULTS

This study included 46 females (92%) and 4 males (8%), their mean age was 28.76±8.83 years. Concerning the control group, fifty nine females (84.3), 11 males (15.7) were included in the control group, and their mean age was 26.96±6.44 years. Twenty eight SLE patients had positive family history to autoimmune disease (Table 1). There were 21 patients (75%) having family history of SLE out of the 28 patients; and an identical twin was included. The disease duration in all SLE patients ranged from 3 months to 18 (5.49±4.43) years.

A synonymous *TREX1* variant c.531C>T (p.Y177Y) has been identified in 28/50 (56%) SLE cases, whereas in 23/70 (32.9%) of the control group (p= 0.01). The amplification of the *TREX1* gene is shown in (Figure 1), while (Figure 2) shows the sequencing electrophoregram showing the c.531C>T (p.Y177Y) polymorphism.

Clinical features of lupus patients are shown in (Table 2), and laboratory characteristics in (Table 3). *TREX1* positive polymorphism was found in 7 cases with history of consanguinity (25%) while in 4 SLE cases with negative consanguinity history (18.2%) (p= 0.734). The minor allele frequency between patients and controls was 0.28, 0.16 respectively (Table 4). In this studied group no homozygous or heterozygous pathogenic variants were detected.

Clinical characteristics of *TREX1* positive and negative SLE patients:

SLE patients positive for *TREX1* polymorphism showed more frequent oral ulcers, photosensitivity, seizures and NPSLE (p= 0.004, 0.047, 0.029 and 0.045) respectively (Table 5). Upon calculating odds ratio; Lupus cases with *TREX1* polymorphism were 7 folds more likely to develop neuropsychiatric manifestations (OR= 7.000, 95% CI= 0.791-61.975) and 10 folds more likely to have chilblains (OR= 10.532, 95% CI= 0.550-201.679). A

positive significant correlation was found between *TREX1* positivity and each of oral ulcers (r= 0.43, p= 0.002), photosensitivity (r= 0.29, p= 0.04), and seizures (r= 0.34, p= 0.02).

Laboratory parameters of the *TREX1* positive and negative lupus patients:

Difference between positive and negative *TREX1* polymorphism SLE cases as regards laboratory parameters and autoantibodies are shown in (Table 6).

Disease activity score, medications received and *TREX1* polymorphism:

No statistically significant difference was found regarding SLEDAI scores between *TREX1* positive and negative lupus patients (p >0.05).

Table 1: Demographic data of systemic lupus erythematosus patients and controls:

Demographic data	SLE patients (n=50)		Controls (n=70)		P value
	No.	%	No	%	
Gender					
Male	4	8	11	15.7	0.56
Female	46	92	59	84.3	
Age (years)					
Mean±SD	28.76±8.83		26.96±6.44		0.31
Family history of autoimmune diseases	28(56)		–		–
History of positive consanguinity	11(22)		–		–

SLE: systemic lupus erythematosus; SD: Standard deviation.

Table 2: Clinical features of systemic lupus erythematosus patients:

Variable n(%)	SLE patients (n=50)
Oral ulcers	32(64)
Malar rash	28(56)
Photosensitivity	22(44)
Discoid lesions	7(14)
Chilblains	5(10)
Mucocutaneous manifestations	42(84)
Musculoskeletal manifestations	44(88)
Serositis	17(34)
Lupus nephritis	29(58)
Seizures	10(20)
Neuropsychiatric lupus (other than seizures)	8(16)
Neuropsychiatric lupus (seizures included)*	12(24)
Vasculitic skin ulcers	6(12)
Venous thrombosis	6(12)

*: Six patients had seizures besides to other NPSLE manifestation, 4 patients had seizures only, and 2 had NPSLE other than seizures.

Table 3: Laboratory characteristics and medications received by systemic lupus erythematosus patients:

Variable mean±SD(range) median(IQR) or n(%)	SLE patients (n=50)
Positive *TREX1* polymorphism	28(56)
ESR(mm/1st hour)	58.22±33.73
Hb(gm/dl)	11.12±1.79
WBC(x10^3/mm^3)	9.04±1.00
Platelets(x10^3/mm^3)	262.62±103.85
Serum albumin(gm'/dl)	3.81±0.41
Creatinine(mg/dl)	0.86±0.59
Protein in urine (g/24 hour)	0.90±1.43
Consumed C3	18(36)
Consumed C4	13(26)
positive ANA (n=50)	49(98)
Positive anti ds- DNA (n=43)	32/43(74.4)
SLEDAI mean±SD(range) Median(IQR)	7.04±4.99 6(2-10)

TREX1: Three prime repair exonuclease; ESR: Erythrocyte sedimentation rate; Hb: Hemoglobin; WBC: White blood cells; ANA: Antinuclear antibody; anti ds-DNA: anti double stranded deoxyribonucleic acid; SLEDAI: Systemic lupus erythematosus disease activity index.

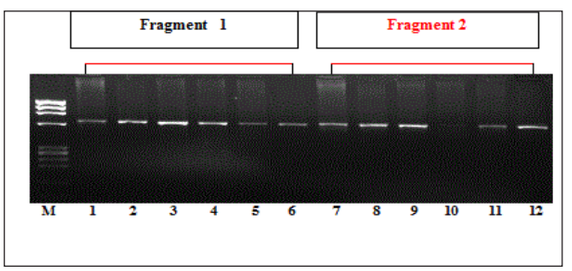

Figure 1: 2% agarose gel illustrating the amplification of *TREX1* gene using two primers in 6 patients with SLE. M: Size Marker (PhiX DNA Ladder), 1-6: Amplified PCR product of Fragment 1 in 6 patients (618 bp), 7-12: Amplified PCR product of Fragment 2 in the same 6 patients (670 bp).

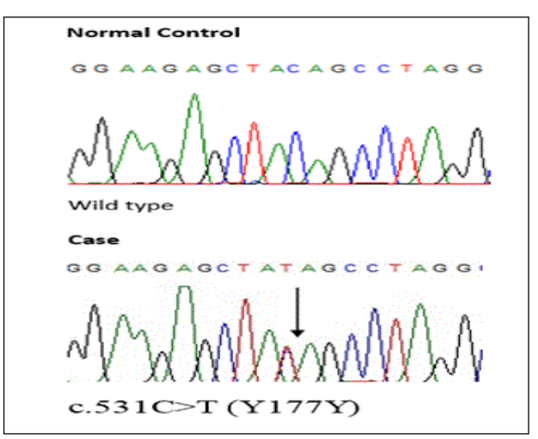

Figure 2: Portion of the sequencing electrophoregram showing the c.531C>T (p.Y177Y) polymorphism identified in our SLE patients. Arrow indicates the site of the polymorphism.

Table 4: Allele and genotype frequency of the c.531 C>T allele of the *TREX1* gene in systemic lupus erythematosus cases and controls:

Genotype	*CC	CT	TT	CC (%)	CT (%)	Allele frequency C (major allele)	Allele frequency T (minor allele)
SLE patients (*N*=50)	22	28	_	0.44	0.56	0.72	0.28
Controls (*N*=70)	47	23	_	0.67	0.33	0.84	0.16

C: Cytosine; T: Tyrosine.

Table 5: Comparison between demographic features and clinical characteristics of systemic lupus erythematosus patients with *TREX1* polymorphism versus those with no polymorphism:

Variable mean±SD, (range) or *n*(%),	Positive *TREX1* polymorphism *No*= 28	Negative *TREX1* polymorphism *No*=22	*P* value	OR	95% of CI OR
Sex					
Males	1(3.6)	3(13.65)	0.31	–	–
Females	27(96.4)	19(86.4)			
Age	28.6±8.6	28.95±9.3	0.89	–	–
Family history of autoimmune diseases	16(57.1)	12(54.5)	1.00	–	–
Positive consanguinity	7(25)	4(18.2)	0.73	–	–
Clinical manifestations					
Oral ulcers	23(82.1)	9(40.9)	0.004*	6.64	1.83-24.08
Malar rash	19(67.9)	9(40.9)	0.09	3.05	0.95-9.75
Photosensitivity	16(57.1)	6(27.3)	0.047*	3.56	1.07-11.8
Discoid lesions	4(14.3)	3(13.6)	1.00	1.06	0.21-5.23
Chilblains	5(17.9)	0	0.059	10.53	0.55-201.68
Mucocutaneous manifestations	26(92.9)	16(72.7)	0.06	4.88	0.88-27.15
Musculoskeletal manifestations	24(85.7)	20(90.9)	0.68	0.6	0.09-3.62
Serositis	12(42.9)	5(22.7)	0.23	2.55	0.73-8.87
Lupus nephritis	17 (60.7)	12(54.5)	0.78	1.29	0.42-3.99
Seizures	9(32.1)	1(4.5)	0.029*	9.95	1.15-86.01
NPSLE (other than seizures)	7(25)	1(4.5)	0.06	7.00	0.79-61.98
NPSLE (seizures included)	10(35.7)	2(9.1)	0.045*	5.56	1.07-28.82
Vasculitic skin ulcers	2(7.1)	4(18.2)	0.39	0.35	0.06-2.09
Venous thrombosis	5(17.9)	1(4.5)	0.21	4.57	0.49-42.23

TREX1: Three prime repair exonuclease; NPSLE: Neuropsychiatric systemic lupus erythematosus; *: *p* value is significant at <0.05.

DISCUSSION

In the present study, upon direct sequencing of the coding exon of *TREX1* gene in 50 SLE patients and 70 healthy controls; a synonymous mutation rs11797 (c.531C>T, cytosine to tyrosine at codon 177 of the *TREX1* gene) was found in a significantly higher rate in SLE cases (p= 0.01). In support to the present results; (**Barizzone *et al.*, 2013**) reported that they found the same variant (rs11797) in 110 out of 210 (52.3%) studied Italian SLE patients, in addition to other variants. Moreover; (**Fredi *et al.*, 2015**) identified the SNP rs11797 (c.531C>T) in 33 patients out of 51 studied SLE patient (64.7%). Minor allele frequency in the present study was found in 28 (56%) of the *TREX1* variants among the cases and in 16 (32%) of controls in the investigated cohort. This can be compared to a study conducted by (**Namjou *et al.*, 2011**); as they recruited 1527 African SLE cases, and minor allele frequency of 0.27 was observed. However, (**Fredi *et al.*, 2015**) estimated the minor allele frequency of the SNP rs11797 as 39.2% among Italian SLE patients and 39.6% among the controls.

No other *TREX1* variants could be revealed in the present study. Unlike this study (**De Vries *et al.*, 2010**) reported that on the sequencing of the genomic DNA of 60 European lupus patients, they detected the *TREX1* pathogenic variant R128H, and it wasn't found in any of the 400 control chromosomes.

In the current study, *TREX1* (c.531C>T) positive lupus patients showed higher percentage of oral ulcers (p= 0.004), photosensitivity (p= 0.047), seizures (p= 0.029) and NPSLE (P= 0.045). In support to our results, (**Fredi *et al.*, 2015**) reported that among the 8 patients with neuropsychiatric manifestations; two were in heterozygosity form for the mutated version., and the majority of them (5 out of 8) had the SNP mutation in homozygosis (p= 0.002). Similarly,

Table 6: Comparison between laboratory parameters and medications received between systemic lupus erythematosus patients with *TREX1* polymorphism and those without:

Laboratory features mean±SD (range) median(IQR) or no (%),	Positive *TREX1* polymorphism *N*=28	Negative *TREX1* polymorphism *N*=22	*P* value
ESR mm/hour	55.79±32.684(10-130) 44(30-78.75)	61.32±35.54(2-120) 50(31.5-95.25)	0.53
Hemoglobin (gm/dl)	10.9±1.74(6.5- 14) 9.43(10.95-12.75)	11.4±1.87(7-15.4) 11.10(9.98-13.03)	0.29
WBC ($x10^3/mm^3$)	8.98±1.12(5.9- 10.3) 9.4(8.48-9.78)	9.1±0.85(6.6 -10.1) 9.2(8.9-9.7)	0.92
Platelets ($x10^3/mm^3$)	232.46±94.98(71-542) 212.5(178.5-297.75)	301±103.97(186-605) 271(237-307.75)	0.015*
Serum creatinine (mg/dl)	0.95±0.75(0.5-3.7) 0.78(0.6-0.9)	0.75±0.23(0.2-1) 0.8(0.6-1.00)	0.79
24 hour urinary proteins (gm/day)	0.7±0.78(0.01-2.8) 0.4(0.2-0.96)	1.15±1.97(0.2-9.4) 0.5(0.29-1.27)	0.36
Serum albumin (gm/dl)	3.88±0.33(3.3-4.7) 4.00(3.6-4.08)	3.74±0.48(2.8-4.5) 3.8(3.38-4.03)	0.32
Consumed C3	8(28.6)	10(45.5)	0.25
Consumed C4	8(28.6)	5(22.7)	0.75
ANA (no= 50)	27/28(96.4)	22/22(100)	1.00
Anti ds- DNA(no=43) positive (n=32/43)	16/23(69.6)	15/20(75.0)	1.00
SLEDAI median(range)	6.5(2.25-10.00)	6(2.00-9.25)	0.55

TREX1: Three prime repair exonuclease; ESR: Erythrocyte sedimentation rate, WBC: White blood cells; ANA: Antinuclear antibody; DNA: Deoxyribonucleic acid; *: *p* value is significant at <0.05.

(**Namjou *et al.,* 2011**) found that 58% of lupus cases with seizures harbored the *TREX1* risk allele (rs11797) compared to 45% in normal controls.

Interestingly in this study; we found that all the 5 SLE cases (17.9%) presented with chilblain lupus associated with the *TREX1* variant (c.531C>T) (*p*= 0.059). On the other hand, (**Rice *et al.,* 2007**) revealed that all three affected individuals with chill blains carried a c.375 dup T and a c.50 T >C transitions that resulted in the replacement of a phenylalanine with a serine at position 17 (p.F17S). In other studies *TREX1* associated familial chilblain lupus has been attributed to the dominant Asp18Asn mutation (**Abe *et al.,* 2013; Tungler *et al.,* 2012; Lee-Kirsch *et al.,* 2006; Yamashiro *et al.,* 2013**).

On calculating odds ratio regarding neuropsychiatric manifestations; the SLE patients harboring the *TREX1* variant tended to develop neuropsychiatric manifestations 7 folds more than those with negative variant (OR= 7.000, 95% CI= 0.791-61.975), and an increase about 10 folds to develop chilblains was more observed in *TREX1* positive variant patients (OR= 10.532, 95% CI= 0.550-201.679). (**Namjou *et al.,* 2011**) reported 1.73 fold increased risk among cases with NPSLE (OR= 1.73, 95% CI= 1.25-2.39).

Thrombocytopenia was one of the recorded features of Aicardi–Goutières syndrome (AGS) syndrome (**Crow *et al.,* 2015; Abraham *et al.,* 2021**). This coincides with the significantly increased frequency of reduced platelets count in *TREX1* positive lupus patients in the present study, taking into consideration that; both of AGS and SLE may share some were frequently associated with *TREX1* positive variants (and/or) mutations (**Kavanagh *et al.,* 2008; Lehtinen *et al.,* 2008; Durcan *et al.,* 2019**).

In the current study no significant difference could be detected regarding SLEADI scores between *TREX1* positive and negative patients. This can be explained by the small size of the studied patient groups.

CONCLUSION

A recurrent *TREX1* variant rs11797 (c.531C>T) was found more frequently in lupus patients when compared to healthy controls (*p*= 0.01), with minor allele frequency of 0.28 in cases and 0.16 in controls. *TREX1* positive patients had more oral ulcers, photosensitivity and seizures. However, no homozygous or heterozygous pathogenic mutations were found among this cohort of Egyptian patients. *TREX1* gene variant may play a role in the genetic susceptibility to SLE in the present cohort.

Among limitations to the current study: The study was cross sectional, whereas the effect of gene variants or mutants on the phenotype of patients can be revealed at

different points of lifetime. Hence a longitudinal study on larger study population with disease damage data can be much informative.

STATEMENT OF ETHICS

This study was approved by the Medical Research Ethics Committee (MREC) of the National Research Centre, Egypt (NCR 14097) and was performed in accordance with the principles of Declaration of Helsinki.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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