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Determination of estrogen receptor alpha gene (ESR1) polymorphism and its relation to systemic lupus erythematosus disease status

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease with variable clinical manifestations that can affect various organs and tissues. Estrogen is an important element that performs a vital role in the pathology of SLE. It acts on target cells through binding to estrogen receptors (ERs). This study aimed to assess the effect of ER alpha gene polymorphism on SLE disease activity and clinical manifestations. This study included 30 SLE female patients and 20 healthy subjects as controls. ERα gene ***(pvull*** and ***xbal)*** polymorphisms were genotyped using the real-time polymerase chain reaction (RT-PCR) and correlated with clinical and laboratory manifestations of SLE as well as the activity and severity scores.

Results: Regarding ERα (*rs1 2234693 Pvull*) polymorphism, the *TC* and *CC* genotypes were mainly associated with SLE patients, with a high frequency of the mutant *C* allele. The *TT* genotype was found mainly in the control group. Concerning *rs2 9340799 Xbal* polymorphisms, the *AG*, *AA*, and *GG* genotypes frequencies were not significantly different between patient and controls. The *TC/AA*, *CC/GG*, and *CC/GG* genotypes were the most prevalent combinations among SLE patients, while the later combination is completely absent from the control group. There was a significant statistical association with the *AA* genotype with the neurological disorders and/or hematological affection in SLE patients. The *TC* genotype was more related to serositis, leucopenia and pyuria, while the *AA* polymorphism was associated only with leucopenia.

Conclusions: We conclude that the study offers a clue to the associations of ERα gene polymorphisms in SLE disease, and the combinations relevant to certain clinical manifestations. Estrogen level itself does not affect SLE susceptibility or activity but the mutations in its receptors are the main pathogenic factor.

Keywords: Systemic lupus erythematosus, Estrogen receptors, Estrogen receptor alpha gene polymorphism, Systemic Lupus Erythematosus Activity Index

Background

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease with a wide range of clinical manifestations that predominantly affect women [1]. Immunologic abnormalities, particularly the production of a range of autoantibodies were considered as the main cause of SLE [2].

Many aspects of SLE disease pathogenesis are still unclear [1]. There is prominent evidence that the development of SLE is dependent on environmental and genetic factors [3].

There is a female sex bias observed in SLE, which thought to be partially due to estrogen [4]. The fact that SLE is more frequent during pregnancy and decrease after menopause strengthens the hypothesis that this

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disease onset is estrogen-dependent [5]. Estrogen, is an important element in the pathogenesis of SLE [6]. It binds two types of receptors, which were named nuclear receptors (ERα and ERβ) and cell membrane receptors [G protein-coupled estrogen receptor 1 (GPER1) and ER-X], to trigger direct and indirect responses within the cell [7].

Estrogen-mediated signaling is a result of balance between ERα and ERβ that are encoded by *ESR-1* and *ESR-2* genes expressed on the human chromosomes 6 and 14, respectively [8]. ESR1, comprise eight exons and seven entrons, several single nucleotide polymorphisms (SNPs) have been identified in ESR1, among these identified polymorphisms, only a few have been extensively studied in relation to health outcomes [9].

There are two single-nucleotide polymorphisms (SNP) located in introne1 of ERα gene: The *T/C* transition (*pvull* polymorphism, also known as *c.454-397T/C* or *rs2234693*) and the *A/G* transition (*Xbal* polymorphism, known as *c.454-351A/G* or *rs9340799*) [6].

Many studies aimed to assess the relation between Polymorphisms in the ERα gene and SLE [10] and found significant associated with the development of disease and disease features and severity [11], but the results were conflicting. Therefore, the current study was performed to investigate the effect of two types of this gene polymorphism on the activity and severity and find their predictive value for specific clinical manifestations.

Methods

Study design

This case-control prospective study was carried out between January 2020 and January 2021. It included 30 female patients and 20 control subjects.

Inclusion criteria

1. Female patients with SLE in the child bearing period fulfilling the 2012 Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC) [12].
2. Healthy female volunteers and relatives of the other patients were included as a control group.

Both patients and control groups were selected from the out-patients' clinic and the in-patient of the Department of Rheumatology, Rehabilitation and physical medicine, XXX University Hospital.

Exclusion criteria

1. Patients and healthy females taking hormonal replacement therapy or oral contraceptive bills.
2. Patients with other autoimmune diseases were excluded.
3. Patients with end stage renal disease.

Written informed consent was obtained from all the patients and control according to the protocol approved by local ethics committee of XXX Faculty of Medicine.

- The demographic characteristic of the patients and controls were recorded.
- Baseline clinical characteristics of the SLE patients were obtained by a careful and detailed clinical examination.
- Routine laboratory tests and the autoimmune profile were checked as well as urine culture for exclusion of urinary tract infection.
- Results of renal biopsy that previously done within two months before or during the period of the study were obtained.
- Assessment of the SLE disease activity was done using the Systemic lupus erythematosus disease activity index (SLEDAI) Score [13]. The SLE disease severity was done using the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage index (SLICC/ACR DI) Score [14].
- Peripheral venous blood samples (2 cm) were obtained for the measurement of serum estrogen level and the molecular assay of the estrogen receptor alpha (ESRα) gene polymorphism [11]:
- Total DNA extraction from the whole blood samples using the Quick-DNA Miniprep kits supplied by (ZYMO RESEARCH). After extraction, 10 µl of predesigned TaqMan genotyping assay (TaqMan Gene Expression Master Mix, USA) were added to 0.5 µl of the single-nucleotide polymorphism (SNP) assay, 6.5 µl of H_2O and 3 µl of DNA (total = 20 µl) in real-time polymerase chain reaction (RT-PCR).
- Amplification and genotyping of the ESRα gene polymorphism were done using the SNP (*rs1 2234693)* for genotyping of ESRα *Pvull* (*T* and *C* alleles) and the SNP (*rs2 9340799)* for ESRα *Xbal* (*A* and *G* alleles).

Statistical analysis

All the data were recorded and analyzed using the Statistical Package of Social Sciences (SPSS) version 17.0 and Microsoft Excel XP. The results were shown as mean ± SD in normally distributed data. Qualitative data were shown as percentages and numbers. Comparisons between of the frequencies of the three genotypes of both polymorphisms in SLE patients regarding different

systems affected were done using the Fisher's exact test. The strength of associations between variables were assessed by the odds ratio (OR) with 95% confidence interval (CI). A p value ≤ 0.05 was considered statistically significant.

Sample size calculation

The sample size was calculated using PASS software program of power analysis and sample size, based on previous studies [15], a total sample size of 40 was required, 20 in each group with a power of 0.8.

Results

The ages of the patients ranged from 17 to 40 years with mean ± SD = 27.6 ± 7.7 years while the ages of controls ranged from 19 to 39 years with mean ± SD = 26.3 ± 7.26 years, with non-significant difference of $p = 0.66$. The mean age at the SLE disease onset was 20.10 ± 5.99 years, and the mean disease duration was 7.5 ± 4.3 years. There was no significant difference ($P > 0.05$) between patients and controls regarding the mean serum estrogen level (182.78 ± 91.27 pg/ml and 170.80 ± 92.94 pg/ml respectively).

Twenty patients (66.7 %) had no renal histopathological changes, while 10 patients (33.3%) had different histopathological grades in renal biopsy from II to V.

Clinical manifestations, laboratory parameters, and the immune profile of the SLE patients included in the study are shown in Table 1.

A flow chart illustrates ESRα gene polymorphism distribution among the studied groups (Fig. 1).

There was a high statistically significant possession of ***TC*** ($p = 0.01$) and ***CC*** ($p = 0.003$) genotypes in the SLE patients compared to the control group who had lower frequencies of ***TC*** and ***CC*** genotypes. The frequency of the mutant ***C*** allele was highly significantly ($p = 0.001$) associated with SLE disease, whereas no significant association was noticed with the *T* allele (Table 2).

There were no statistical significant associations of the *rs2* genotyping (alleles and genotypes) with either the SLE patients or the control group. Higher odds ratio (OR) to the *GG* genotyping was observed in patients' group (Table 3).

The *TC/AA* was the most prevalent combination in the SLE disease, occurring in 26.7% of the patients. The *CC/AG* genotypes were absent in the controls, meanwhile they were present in 20% of patients. The combinations of *TC/AA* or *CC/AG* or *CC/GG* genotypes were significantly more frequent in SLE patients' group with p value (0.04, 0.04, and 0.03 respectively). These combinations were associated with 10, 28.6, and 17.5 higher occurrence of SLE (Table 4).

Table 1 Clinical and laboratory data of SLE patients

Parameters	***Patients group n = 30*** ***N (%)***
Mucocutaneous manifestations (photosensitivity, malar rash, chronic cutaneous rash, non-scarring alopecia, nasal or oral ulcers)	19 (63.3%)
Hematological disorders (thrombocytopenia, leucopenia, lymphopenia, hemolytic anemia)	18 (60%)
Renal disorders (hematuria, proteinuria, pyuria, casts)	17 (56.6%)
Neurological disorders (seizure, psychosis, cerebrovascular accident, peripheral neuropathy, lupus headache)	11 (36.6%)
Arthritis	10 (33.3 %)
Serositis	8 (26.6 %)
Cardiac involvement (pericardial effusion, valvular affection)	6(20%)
Pulmonary disorders (pleurisy, pulmonary hypertension, pneumonitis)	5 (16.7 %)
Positive ANA	30 (100%)
Positive anti-dsDNA	19 (63.3%)
Positive APL antibodies	6 (20%)
SLEDAI (mean ± SD)	11.1 ± 5.2
SLICC/ACR (mean ± SD)	1.2 ± 0.99

ANA anti-nuclear antibody, *Anti-dsDNA* anti-double strand antibody, *APL* anti-phospholipid antibodies. *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *SLICC/ACR* The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage index. Data are represented as number (%) or mean ± SD

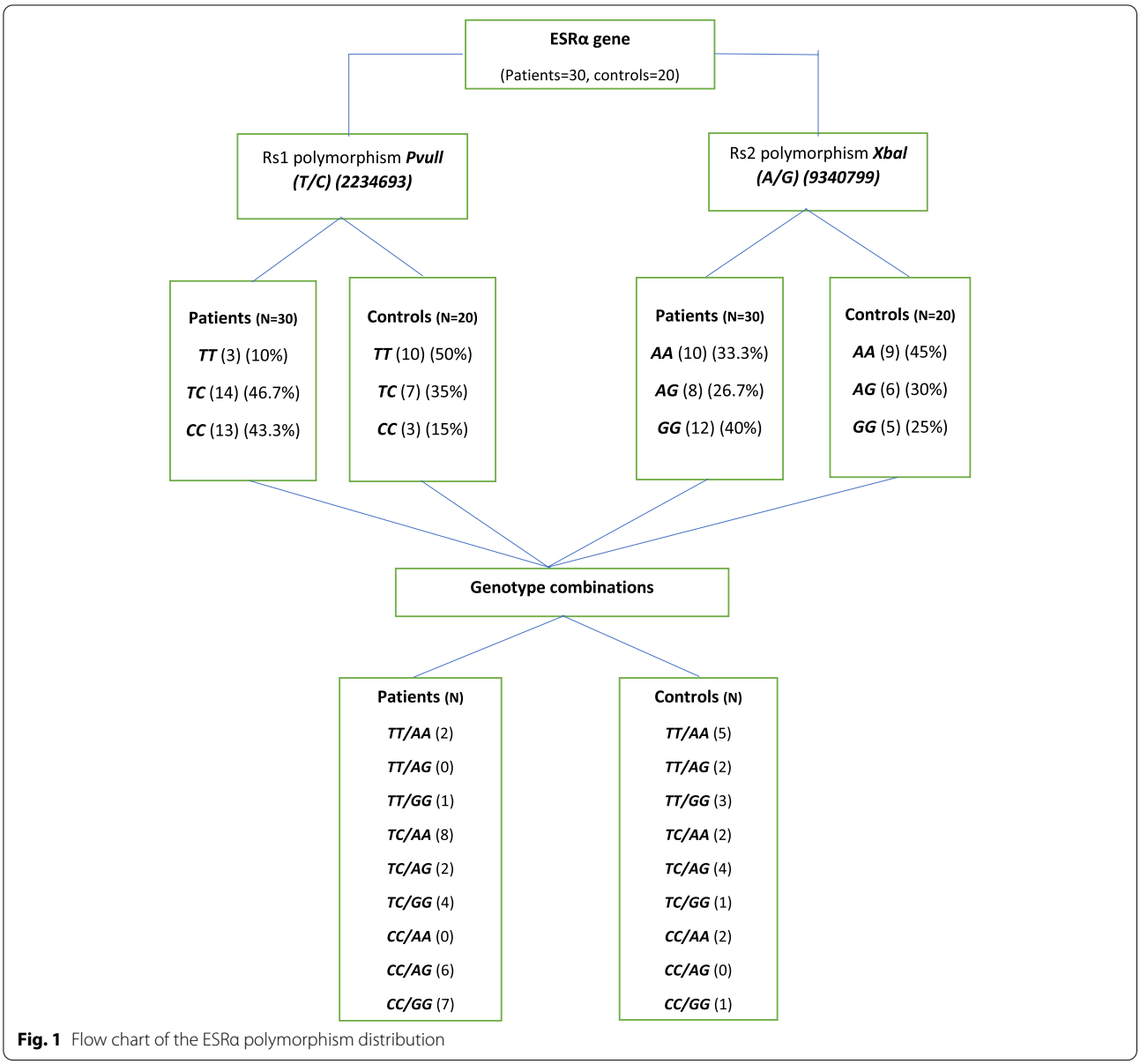

Fig. 1 Flow chart of the ESRα polymorphism distribution

There was no statistical significant difference among the three genotypes of *rs 2234693* and *rs 9340799* regarding the age at SLE disease onset, disease duration, disease activity, and damage scores.

Considering the relation between the ***rs1*** genotyping and systemic affection in SLE, there was no statistically significant difference regarding the association with any genotype with a specific system. However, it was found that the ***TC*** genotype was associated with some clinical manifestations as the presence of serositis ($p = 0.03$), leucopenia ($p = 0.045$), and pyuria ($p = 0.008$) (Table 5).

There was no statistical significant difference among the ***CT***, ***TT,*** and ***CC*** genotypes as regards to renal biopsy grades ($p = 0.32$).

As regards to the relation between the systems affected and *rs2* genotyping there was a significant statistical association of the *AA* genotype with neurological disorders ($p = 0.02$) and hematological disorders ($p = 0.003$) where leucopenia showed the higher significant association ($p = 0.01$). There was no systems association for *AG* and *GG* genotypes (Table 6).

There were no statistically significant differences among the *GG*, *AG*, and *AA* genotypes as regards to renal biopsy grades ($p = 0.32$).

Table 2 Comparisons of the allele and genotype frequency distribution of the ESR-α (*rs 2234693*) in SLE patients and the control subjects

ESR-α rs 2234693	SLE patients (*n* = 30) (%)	Control subjects (*n* = 20) (%)	OR	95% CI	*P* value
T allele	20 (33.3%)	27 (67.5%)	1	Reference	
C allele	40 (66.7%)	13 (32.5%)	4.1	1.7-9.7	**0.001***
TT	3 (10)	10 (50%)	1	Reference	
TC	14 (46.7%)	7 (35%)	6.6	1.3-32.2	**0.01***
CC	13 (43.3%)	3 (15%)	14.4	2.3-87.4	**0.003***

Data are represented as number (%)

Data were analyzed using odds ratio (**OR**) and 95% **CI**: Confidence interval

*Significant difference at $P \leq 0.05$

Table 3 Comparisons regarding the distribution frequencies of genotypes and alleles of the ESRα (*rs 9340799)* between SLE patients and control subjects

rs 9340799	*SLE* patients (*n* = 30) (%)	Control subjects (*n* = 20) (%)	OR	95% CI	*P* value
A allele	28 (46.7%)	24 (60%)	1	Reference	
G allele	32 (53.5%)	16 (40%)	1.7	0.7–3.8	0.19
AA	10 (33.3%)	9 (45%)	1	Reference	
AG	8 (26.7%)	6 (30%)	1.2	0.29–4.81	0.7
GG	12 (40%)	5 (25%)	2.16	0.54–8.5	0.27

Data are represented as number (%)

Data were analyzed using the odds ratio (OR) and *95% CI* confidence interval.

*Significant difference at $p \leq 0.05$

Discussion

SLE is an autoimmune disease affects women more than men [16]. This observation raises the possibility that variations in estrogen-related genes may be determinants of SLE risk [17]. The function of polymorphisms is unknown, but some studies suggest that specific alleles in these polymorphisms cause upregulation of ERα expression, leading to a higher response to estrogen [11]. Estrogen receptor alpha polymorphisms have been described as being associated with SLE, and the association of *pvull C/T* and *xbal A/G* polymorphisms with SLE susceptibility and clinical manifestations have been reported in many studies [18].

In the current study, the presence of ESRα polymorphism (*rs1 2234693 Pvull/TC* and *CC* genotypes) were mainly associated with SLE patients and that the frequency of the mutant *C* allele 5was highly associated with SLE disease, Meanwhile, ESRα polymorphisms (*rs2 9340799 Xbal/ AG*, *AA*, and *GG* genotypes) frequencies were not significantly different between patients and control groups.

Several studies reported similar results. In 2018, Salimi et al. [5] found that the frequencies of *TC* and *CC* genotypes of ERα polymorphism in SLE Iranian female patients were higher than the *TT* genotype with no statistically significant difference and the frequency of the *CC* allele was 50%. In 2010, Wang et al. [10] also found significant association between *Pvull PP(CC)* genotype and SLE disease, but in contrast to our study they found a significant association with the *GG* genotyping also. Lee et al. [19] documented that *Pp(TC)* genotype was more frequent in SLE patients.

Drehmer et al. [11] stated that these results may confirm the hypotheses that the ***C*** allele is believed to create a binding site for the transcription factor B-myb. Thus,

Table 4 Comparison among SLE patients and controls regarding the frequency of Combinations of the *rs1(2234693)* and *rs2 (9340799)* genotypes

rs 2234693	rs 9340799	SLE patients (*n* = 30) (%)	Control subjects (*n* = 20) (%)	OR	95% CI	*P* value
TT	**AA**	2	5	1	reference	
TT	**AG**	0	2	0.4	0.01–12.9	0.63
TT	**GG**	1	3	0.83	0.05–13.6	0.89
TC	**AA**	8	2	10	1.04–95.4	**0.04***
TC	**AG**	2	4	1.25	0.11–13.2	0.85
TC	**GG**	4	1	10	0.64–154.4	0.09
CC	**AA**	0	2	0.4	0.01–12.9	0.63
CC	**AG**	6	0	28.6	1.1–731.5	**0.04***
CC	**GG**	7	1	17.5	1.2–250.3	**0.03***

Data are represented as number (%)

Data were analyzed using odds ratio (OR) and 95% CI: Confidence interval

*Significant difference at $P \leq 0.05$

Table 5 Comparisons of the frequencies of the three genotypes of *rs 2234693* in SLE patients regarding different systems affected

Features	*TT (n = 3)*	*TC (n = 14)*	*CC (n = 13)*	*P* value
Mucocutaneous affection	2	9	8	0.79
Arthritis	1	4	5	0.85
Neurological disorders	1	5	5	0.65
Pulmonary disorders	0	3	2	0.9
Cardiac affection	0	3	3	0.9
Hematological disorders	2	10	6	0.37
Renal disorders	2	9	6	0.57

Data were analyzed using the Fisher's exact test

*Significant difference at $P \leq 0.05$

Table 6 Comparisons of the frequencies of the three genotypes of *rs 9340799* in SLE patients regarding different systems affected

Features	*AA (n = 10)*	*AG (n = 8)*	*GG (n = 12)*	*P* value
Mucocutaneous affection	6	5	8	0.82
Arthritis	3	4	3	0.55
Neurological disorders	7	3	1	**0.02***
Pulmonary affection	2	2	1	0.58
Cardiac affection	1	3	2	0.53
Hematological disorders	10	3	5	**0.003***
Renal disorders	6	5	6	0.8

Data were analyzed using the Fisher's exact test

*Significant difference at $P \leq 0.05$

C allele could lead to the upregulation of the expression of ERα leading to higher response to estrogens in SLE patients than others.

In contrast, Johansson et al. [20] and Drehmer et al. [11] in their studies on SLE patients found no significant differences between patients and controls as regards to genotypes and allele frequency.

In our study, the combinations of *TC/AA*, *CC/AG*, and *CC/GG* genotyping were more frequent in SLE patients than in the control group, these combinations were associated with a higher occurrence of SLE.

Salimi et al. [5] also reported more frequent combinations of *TC/AA* and *CC/GG* genotypes in SLE patients than the control group, these combinations were associated with 3 and 2.6-fold higher risk of SLE, but in contrast Johansson et al. [20] found no significant difference between SLE patients and controls regarding genotype combinations.

In our work, there were no statistically significant difference between both *rs1, rs2* genotypes regarding the mean patient's age at disease onset or the mean disease duration, that agreed with Drehmer et al. [11]. Johansson et al. [20] found an association between the *CC* genotype and later onset of the SLE disease, while Lee et al. [19] found that *TC* and *CC* alleles *(Pvull* genotype) associated the earlier onset of SLE.

Our results showed no statistical significant relation of *rs1* or *rs2* genotypes with the SLICC/ACR damage index score or with the SLEDAI score.

Johansson et al. [20] on the contrary found that individuals carrying the *XbaI GG* genotype had a lower SLICC damage index value, unrelated to the disease duration. This could indicate that carriage of these alleles results in a milder form of the disease.

As regards to the relation between *rs1* and *rs2* polymorphisms and clinical manifestations, our results showed that the *TC* genotype had a higher association with serositis, leucopenia and pyuria, while *AA* was associated with leucopenia, neurological disorders and hematological affection.

Johansson et al. [20] found that serositis is associated with the *XbaI AA* genotype, and the *TT* and *AA* genotypes were significantly associated with cognitive impairment, they agreed with Lee et al. [19] who found no association between *Xbal* or *Pvull* polymorphisms and hematological disorders in SLE, and also consistent with Yaffe et al. [21] who found a higher risk of developing cognitive impairment in those who carried *Pvull T* allele.

This could indicate that the carriage of *TT* and *AA* alleles results in an aggressive form of the SLE disease with renal and CNS manifestations, while the carriage of *TC* allele results in a milder form of the disease.

There were no statistically significant differences among the *GG*, *AG*, and *AA* genotypes as well among the *CT*, *TT*, and *CC* genotypes as regards to renal biopsy grades or renal disorders. Liu et al. [22] studies carried out on biopsy proven lupus nephritis (LN) patients, found a strong association between the ***TC*** genotype and LN, while Drehmer et al. [11] found that renal involvement was associated with the presence of the ***CC*** genotype.

In the current study, we found non-significant association of mucocutaneous manifestations or arthritis with *Pvull* or *Xbal* genotypes discordantly with Lee et al. [19] who found oral ulcers to be associated with the presence of the ***CC*** genotype and discoid rash to be associated with the presence of the *GG* genotype. Liu et al. [22] also found a strong association between *TC/GA* genotypes and the presence of skin rash and arthritis, while Johansson et al. [20] found association between the *CC* alleles and malar rash, and the *G* allele with photosensitivity. Drehmer et al. [11] found a link between the *CC* alleles and the SLE discoid rash.

Shuit et al. [23] and Johansson et al. [20] reported a relation between carriers of the *AA* and *TT* alleles with an increased risk of myocardial infarctions, ischemic heart disease, and angina/coronary artery bypass surgeries. This was not confirmed in our results with either the *Pvull* or *Xbal* genotypes.

The level of estrogen in our SLE patients was non-statistically significantly different between the patients and controls, and these results coincided with the findings of Abdelaziz et al. [24] who informed that the estrogen level had a non-significant correlation with the SLE activity index score; moreover, 80% of their patients with low estrogen levels had a high SLE disease activity.

These conflicting results between studies might be due to the diversity in patient diagnostics and characterization techniques or true differences caused by the genetic and environmental variants.

The discrepancy between the results of the present study and other studies, could be due to the variations in sample size and ethnicity, as most of the studies were done on Caucasian and Asian patients selected from both genders.

The limitations of this study are the small sample size, the unequal numbers of the two study groups and the inclusion of female patients only.

Conclusions

We conclude that the study offers a clue to the associations of ERα gene polymorphisms in SLE disease, and the combinations relevant to certain clinical manifestations. Estrogen level itself does not affect SLE susceptibility or activity but the mutations in its receptors is the main pathogenic factor. More studies including larger numbers of SLE patients from many centers and from both genders are needed to clarify the influence of genetic polymorphism on the pathogenesis of SLE and/or specific clinical manifestations.

Abbreviations

SLE: Systemic lupus erythematosus; ESR1: Estrogen receptor alpha gene 1; ERs: Estrogen receptors; RT-PCR: Real-time polymerase chain reaction; GPER1: G protein-coupled estrogen receptor 1; SNPs: Single nucleotide polymorphisms; SLEDAI: SLE Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics Classification Criteria; SLICC/ACR DI: Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage index; Anti-ds-DNA: Anti-double strand antibody.

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Authors' contributions

All authors have read and approved the final manuscript. Idea suggestion and study design: Samia M. Abdel Moneam, Abdel Wahab Sh.E. El-Brashy, Waleed A. Hassan, and Dalia H.Almallah. Data collection and analysis: Omnia A. Abdullah and Dalia H.Almallah. Manuscript writing and final revision: Samia M. Abdel Moneam, Abdel Wahab Sh.E. El-Brashy, Waleed A. Hassan and Dalia H. Almallah. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

An informed written consent was taken from all patients and subjects' participating in this study and the protocol was approved by the ethical committee of Benha Faculty of Medicine reference number: MS 310-2017, date: 3-10-2017

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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