RESEARCH ARTICLE

Association of Apurinic/Apyrimidinic Endonuclease Gene Polymorphism with Some Clinical Features in Systemic Lupus Erythematosus

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ABSTRACT

The Systemic Lupus erythematosus (SLE) is an autoimmune disease characterized by attack body cells by immune molecules, and the present study was conducted to estimate Apurinic/Apyrimidinic Endonuclease (APE 1) Gene Polymorphism in SLE and associated with clinical features. Deoxyribonucleic acid (DNA) extraction was implemented then allele-specific PCR was used to detect Asp148Glu (rs3136820) in study groups. The results show two alleles (T, G) and three genotyping's (TT, TG, GG), significant association APE1 with SLE disease (X^2 9.8609, P 0.019) and more frequent TT genotyping in patients, non-significant association with present oral ulcer (X^2 2.6207, P 0.453), non-significant association with malar rash (X^2 0.684, p 0.710), and non-significant correlation with painful (X^2 1.78, P 0.619). Finally, the association of APE1 with the number of oral ulcers (multiple and single) also non-significant differences (X^2 3.6771, P 2.98). the present study shows association APE1 with SLE disease but non-association with clinical features of SLE.

Keywords: Autoimmune disease, APE1 gene Polymorphism, DNA repair genes, Systemic lupus erythematosus.

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic relapsing autoimmune disease that primarily affects females. The disease coincides with the production of autoantibodies to molecules of nucleic acids and other cellular antigens, which leads to the formation of immune complexes and deposits in systemic organs, causing inflammation and damage to those organs.[1,2]

Furthermore, women are 9 times more likely than males to acquire lupus, and studies of monozygotic twin concordance and familial aggregation suggest that genetic predisposition plays a role in SLE.[3] Several genome-wide association studies have found over fifty common risk alleles linked to lupus; the bulk of them are caused by a faulty immune system.[4,5]

In human cells, the APEX gene encodes the major AP endonuclease enzyme, a DNA repair enzyme with apurinic/apyrimidinic (AP) activity. By spontaneous hydrolysis, DNA damaging agents, or DNA glycosylases that remove particular aberrant bases, such AP activity sites often appear in DNA molecules. The most common pre-mutagenic lesions that can inhibit normal DNA replication are AP sites. This gene has several splice variants, all of which encode the same protein. Disruptions in the biological processes connected to APEX have been linked to several different cancers and autoimmune disorders.[6]

The Base excision repair (BER) mechanism, which acts on tiny lesions such as reduced or oxidized bases, fragmented or nonbully adducts, also bases produced by methylating agents, is the most common route for oxidative DNA damage repair. APE1 plays a key role in BER.[7,8]

The fact that cells generated from SLE patients are unable to repair DNA damages as effectively as control cells raise the notion that DNA repair is linked to SLE, an old study deal with DNA repair relation with the autoimmune disease found that the lymphocytes have a major defect in the removal of O^6-Methylguanine after treatment with N-methyl-N-nitrosourea. The growth of SLE lymphocytes is significantly reduced in the presence of N-methyl-N-nitrosourea compared with controls.[9]

Other findings show that lymphoblastoid cells generated from SLE patients have poor DNA double-strand break (DSB) repair and that lymphocytes produced from a subgroup of SLE patients are extremely susceptible to hydrogen peroxide (H_2O_2),

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perhaps involving abnormal BER as an underlying cause.[10,11] The present study is one of the sequential investigations deal with repair genes with SLE in Iraqi patients.

MATERIAL AND METHODS

This study was conducted in the DNA lab at the University of Babylon's biology department, with 49 SLE patients (male) ranging in age from 30 to 65 years old and 20 healthy subjects (30 to 65 years old). All samples were collected with the approval of Iraq's environment and health ministry.

- Isolated DNA from white blood cells (WBCs) was extracted using a DNA extraction kit (Favorgen), and the DNA concentration of samples was measured using a spectrophotometer for both SLE patients and controls (Nanodrop).
- The primer of APE1 gene was used: F1: CCT ACG GCA TAG GTG AGA CC R1: TCC TGA TCA TGC TCC TCC F2 TCT GTT TCA TTT CTA TAG GCG AT R2 GTC AAT TTC TTC ATG TGC CA
- The PCR-CTPP amplicon size two allele, 236 bp, 167 bp and a 360 bp band for T allele, G allele and common band respectively, PCR experiments completed with annealing temperature reached to 60ºC for 20 seconds.
- The data were analyzed statically by Qi-Square analysis at a level of significance (0.05)

Figure 1: Electrophoreses pattern of DNA extracted from whole blood of SLE patient and control,1% Agarose, 75 v, 20 mA for 45 minutes, lane 1–10 DNA from the patient, lane 11-15 DNA from control.

RESULT

The present study was a case and control deals with patients' systemic lupus erythematosus. This study involved 49 samples, additionally the healthy control group 28 samples. This study aims to estimate Apurinic/Apyrimidinic Endonuclease (APE 1) Gene Polymorphism in SLE and associated with clinical features as shown in Figure 1.

The result of the Polymerase chain reaction for APE1 gene showed two alleles (T, G) and three genotyping's (TT, TG, GG), significant association APE1 with SLE disease (X^2 9.8609, p 0.019), and more frequent of TT genotyping in patients. Non-significant association with present oral ulcer (X^2 2.6207, p 0.453). non-significant association with malar rash (X^2 0.684, p 0.710). non-significant correlation with pain (X^2 1.78, p 0.619). as shown in Figure 2 and Table 1.

DISCUSSION

The Apurinic/Apyrimidinic Endonuclease Gene (APE1) is one of the base excision repair in DNA, its helped the DNA-binding capability of activator protein-1 as a redox coactivator.[12] Previous investigations have found that individuals with systemic lupus erythematosus (SLE) (Table 2) have Impaired

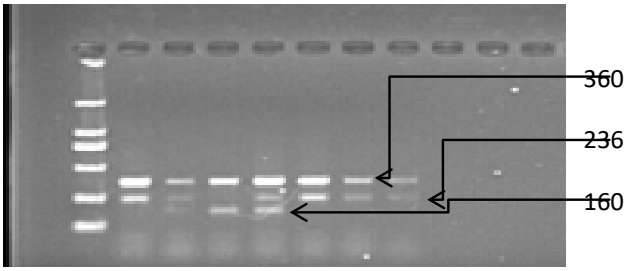

Figure 2: Electrophoresis pattern of PCR product for APE1 gene in study groups,these amplification productswere 360 bp, 236 bp, and 160 bp. 1% agarose, 75v, 20 mA for 45 minutes (5 µL in each well).

Table 1: Genotyping and allele frequency among study group

Genotypes	*TT*	*GG*	*TG*	*D*	X^2	*P*
P vs C						
Control	7(28%)	3(15)	14(56%)	1(4)	9.8609	0.019
Patients	24(53.33)	9(20)	9(20)	4(8.88)		
ulcer						
With oral ulcer	11(24.44)	6(13.33)	3(6.66)	4(8.88)	2.6207.	0.4538
Without ulcer	13(54.16)	3(6.66)	2(4.44)	0		
Malar rash						
With Malar rash	3(12.5)	2(8.33)	0	0	0.6849	0.710
Without malar rash	21(87.5)	7(29.16)	9(37.5)	0		
Painful						
With Paine	4(16.66)	3(12.5)	3(12.5)	2(8.33)	1.781.	0.619
Without Paine	7(29.16)	3(12.5)	0	2(8.33)		
Number oral ulcer						
Single	7(29.16)	1(4.166)	1(4.166)	2(8.33)	3.6771	0.298
Multiple	4(16.66)	5(20.83)	2(8.33)	2(8.33)		

DNA repair efficiency, particularly when it comes to oxidative damage repair.[13.]

Present output pointed that the APE1 Asp148Glu gene genotyping can be a risk factor for SLE incidence and our result agrees with the study conducted by Meas *et al*., 2017[14] pointed that the variant in APE1 gene can be associated with SLE incidence. Some DNA defects like the defect in NER and double-strand breaks repair were found in SLE, with lupus nephritis patients showing higher DNA damage levels than those with quiescent disease.[15] Because of the high level of oxidative damage, NER was less efficient in SLE patients than healthy controls.[16]

In this study, we found no association with presence of oral ulcer and malar rash, and this result disagrees with studies conducted by Warchoł *et al*., 2012[17] that found a significant elevation risk of malar rash or oral ulcer development and photosensitivity.

The link between faulty or abnormal repair of DNA and SLE development is novel. Because a defective or aberrant DNA repair system, resulting from mutations in DNA repair genes, may be led to several consequences changes like modification in antibody diversification, cell death, and SLE development, the mutations in these genes may be associated with an increased risk for lupus development.[18]

In conclusion, any defect in DNA repair gene will emerge as an important underlying mechanism of the development of autoimmune disease.

REFERENCES

1. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, Bruce IN, Isenberg D, Wallace DJ, Nived O, Sturfelt G. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis & Rheumatism. 2012 Aug;64(8):2677-2686.
2. Kadhum AM, Al-Saadi AH. Genetic Polymorphisms of ATP6 Gene in Systemic Lupus Erythematosus (SLE).
3. Alarcón-Segovia D, Alarcón-Riquelme ME, Cardiel MH, Caeiro F, Massardo L, Villa AR, Pons-Estel BA, Grupo Latinoamericano de Estudio del Lupus Eritematoso (GLADEL). Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. Arthritis & Rheumatism. 2005 Apr;52(4):1138-1147.
4. Ghodke-Puranik Y, Niewold TB. Immunogenetics of systemic lupus erythematosus: a comprehensive review. Journal of autoimmunity. 2015 Nov 1;64:125-136.
5. Alqaim ZH, Al-Jboori MJ, Al-Terehi MN. Major Histocompatibility Complex gene Polymorphism in Systemic Lupus Erythematosus Patients. Indian Journal of Forensic Medicine & Toxicology. 2020 Oct 1;14(4):1671.
6. Shah F, Goossens E, Atallah NM, Grimard M, Kelley MR, Fishel ML. APE 1/Ref-1 knockdown in pancreatic ductal adenocarcinoma–characterizing gene expression changes and identifying novel pathways using single-cell RNA sequencing. Molecular oncology. 2017;11(12):1711-17323
7. Lu AL, Li X, Gu Y, Wright PM, Chang DY. Repair of oxidative DNA damage. Cell biochemistry and biophysics. 2001;35(2):141-170.
8. Warkentin MT, Morris D, Bebb G, Brenner DR. The role of DNA repair capacity in lung cancer risk among never-smokers: a systematic review of epidemiologic studies. Cancer Treatment and Research Communications. 2017;13:13-24.
9. Davies RC, Pettijohn K, Fike F, Wang J, Nahas SA, Tunuguntla R, Hu H, Gatti RA, McCurdy D. Defective DNA double-strand break repair in pediatric systemic lupus erythematosus. Arthritis & Rheumatism. 2012 Feb;64(2):568-578.
10. McCurdy D, Tai LQ, Frias S, Wang Z. Delayed repair of DNA damage by ionizing radiation in cells from patients with juvenile systemic lupus erythematosus and rheumatoid arthritis. Radiation research. 1997 Jan 1;147(1):48-54.
11. Meas R, Burak MJ, Sweasy JB. DNA repair and systemic lupus erythematosus. DNA repair. 2017 Aug 1;56:174-182.
12. Sweasy JB, Senejani AG, Kidane D, McNiff J, Zeiss C, Kashgarian M, and Maher S. DNA Repair and Lupus. In Environmental and Molecular Mutagenesis. 2015, August;56: S32-S32. 111 River St, Hoboken 07030-5774, NJ USA: Wiley-Blackwell.
13. Bassi CL, Xavier DJ, Palomino GM, Nicolucci P, Soares CP, Sakamoto-Hojo ET, Donadi EA. Efficiency of the DNA repair and polymorphisms of the XRCC1, XRCC3 and XRCC4 DNA repair genes in systemic lupus erythematosus. Lupus, 2008; 17(11):988-995.
14. Meas R, Burak MJ, Sweasy JB. DNA repair and systemic lupus erythematosus. DNA repair. 2017;56:174-182.
15. Souliotis VL, Vougas K, Gorgoulis VG, Sfikakis PP. Defective DNA repair and chromatin organization in patients with quiescent systemic lupus erythematosus. Arthritis research & therapy, 2016;18(1):1-12.
16. Gong F, Kwon Y, Smerdon MJ. Nucleotide excision repair in chromatin and the right of entry. DNA repair. 2005;4(8):884-896.
17. Warchoł T, Mostowska A, Lianeri M, Łącki JK., and Jagodziński, XRCC1 Arg399Gln gene polymorphism and the risk of systemic lupus erythematosus in the Polish population. DNA and cell biology. 2012;31(1):50-56.
18. Baute J, Depicker A. Base excision repair and its role in maintaining genome stability. Critical reviews in biochemistry and molecular biology. 2008;43(4):239-276.