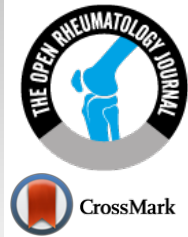# The Open Rheumatology Journal

RESEARCH ARTICLE

Association of Polymorphisms in the DNA Repair Genes XRCC1 and XRCC3 with Systemic Lupus Erythematosus

Cristhiane A. Leite Da Silva[1,5,*], Marcial F. Galera[2], Regiane R. Festi[3], Mariano M. Espinosa[4], Vander Fernandes[1], Paula H. Blaskievicz[1] and Eliane P. Dias[5]

[1]*Master Program in Environment and Health, University of Cuiabá, Av. Manoel José de Arruda, 3100 - Jardim Europa, Cuiabá-MT, 78025-190, Brazil*

[2]*Department of Pediatrics, School of Medicine Cuiaba, Federal University of Mato Grosso, Av. Manoel José de Arruda, 3100 - Jardim Europa, Cuiabá-MT, 78025-190, Brazil*

[3]*Department of Genetic, School of Medicine Cuiaba, University of Cuiabá, Av. Fernando Correa da Costa, 2.367 – Bairro: Boa Esperança CEP: 78060-900, Brazil*

[4]*Department of Statistics, Institute of Exact Sciences, Federal University of Mato Grosso, Av. Fernando Correa da Costa, 2.367 – Bairro: Boa Esperança CEP: 78060-900, Brazil*

[5]*Department of Pathology, School of Medicine, Federal Fluminense University, Rua Rua Marquês do Paraná, 303 Centro. CEP 24033 900, Brazil*

Abstract:

Background:

Evidence suggests that DNA damage is implicated in the development of Systemic Lupus Erythematosus (SLE).

Objective:

Investigate the possible association of polymorphisms in the DNA repair genes *XRCC1* and *XRCC3* with SLE and its clinical and laboratory features.

Methods:

This is a case-control study comparing the polymorphisms in the DNA repair genes *XRCC1* and *XRCC3* in SLE patients and control individuals. Genotyping for DNA repair genes was performed by polymerase chain reaction-restriction fragment length polymorphism in 76 patients and 82 healthy control individuals.

Results:

Our data indicated that the genotype frequencies in patients with the *XRCC1* Arg399Gln and *XRCC3* Thr241Met polymorphisms were similar to those observed in the control group (p > 0.05). However, the frequencies of the 399Gln allele (p = 0.023, OR = 0.58, 95% CI = 0.36–0.93) and 241Met allele (p = 0.0039, OR = 0.59, 95% CI = 0.36–0.98) were significantly lower in the patients than those in the control subjects.

Conclusion:

We demonstrated that 399Gln and 241Met alleles may play a protective role in SLE susceptibility.

Keywords: Genetic, DNA repair, Polymorphism, XRCC1, XRCC3, Systemic lupus erythematosus.

1. INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a complex, autoimmune and chronic inflammatory disease characterized

* Address correspondence to this Master Program in Environment and Health, University of Cuiabá, Av. Manoel José de Arruda, 3100 - Jardim Europa, Cuiabá - MT, 78025-190, Brazil; Email: cristhianeleite@hotmail.com

by T- and B-cell hyper-reactivity, autoantibody formation and immune complex deposition, which triggers inflammation and severe damage to organs and tissues [1 - 4]. SLE presents a wide spectrum of clinical and laboratory manifestations, with periods of exacerbation and remission [5, 7]. The estimated incidence ranges from 20 to 150 cases per 100,000 individuals and its prevalence varies with race/ethnicity, socioeconomic

factors and genetic susceptibility [6, 7]. Although of unknown origin, SLE can be considered a multifactorial disease since genetic susceptibility, hormonal and environmental factors can influence the immunological abnormalities observed in these patients [4]. Epstein–Barr virus (EBV) and cytomegalovirus (CMV) infections have been associated with SLE [4]. Ultra-violet B (UV-B) radiation on deoxyribonucleic acid (DNA) and reactive oxygen species (ROS) has also been demonstrated in experimental studies. Exogenous hormone use is associated with a high risk of SLE. Exposure to respirable silica dust and smoking have been defined as risk factors for SLE. Drugs are a major factor, and the common drugs implicated are hydra-lazine, D-penicillamine, minocycline and lithium. Defective immune regulatory mechanisms caused by genetic mutations or single nucleotide polymorphisms can dysregulate inflammatory cytokine production and the clearance of apoptotic cells or immune complexes [1, 4, 5, 8 - 10].

DNA has been considered the most important autoantigen target for autoantibodies in SLE, and the origin of these antibodies is uncertain [11, 12]. However, antigenicity might be enhanced by reactive oxygen species and drugs, among other agents, which cause altered DNA conformation or DNA base damage and breaks [10, 13]. Recently, deficiencies in the ability to repair DNA damage and consequent abnormal levels of apoptotic bodies, have been implicated as causative factors for SLE. The two important repair pathways for DNA damage are Base Excision Repair (BER) and Nucleotide Excision Repair (NER) [14]. DNA repair enzymes check the chromosomes to correct damaged nucleotides produced by methylation, oxidation, or oxidative damage [15, 16].

The gene X-ray cross-complementing defective repair in Chinese hamster cells 1 (XRCC1), mapped on the long arm of chromosome 19 (19q13.2), contains 17 exons and encodes a protein composed of 633 amino acids known by the same name. It is one of the most important proteins involved in repairing simple DNA breaks by BER [15, 17]. It has been reported that the XRCC1 polymorphisms Arg399Gln, Arg 194Trp, and Arg280His might play roles in an individual's susceptibility to SLE [18]. This DNA repair protein is responsible for the effective repair of DNA damage caused by active oxygen, ionization, and alkylating agents. Although the functional effects of these polymorphisms in repair proteins have not been understood, it is suggested that amino acid changes at preserved regions may alter the functions of these genes [18 - 22].

The gene X-ray repair complementing defective repair in Chinese hamster cells 3 (XRCC3) is located on the long arm of chromosome 14 (14q32.3), and it encodes a protein of the same name, which is involved in DNA repair by homologous recombination. In this process, the undamaged complementary strand is used as a template for the replacement of the damaged fragment. XRCC3 also participates in the last step of recombination, where it stabilizes the nucleoprotein complex and aids in heteroduplex DNA formation [16]. XRCC3 is required for the assembly of the Rad51 protein complex, and it also participates in the maintenance of chromosomal stability [17]. The major polymorphism in this gene is Thr241Met (exon 7) [16, 17].

As SLE is a heterogeneous disease, of unknown origin, the objective of this study was to investigate the possible association of XRCC1 and XRCC3 polymorphisms with SLE and it's clinical and laboratory features.

2. MATERIALS AND METHODS

2.1. Study Design, Patients and Control Subjects

This was an observational case-control analytical study. The studied population comprised of 76 women patients diagnosed with SLE who fulfilled the American College of Rheumatology Classification criteria [21, 23]. The included patients were already undergoing treatment for SLE and were followed from June 2010 to February 2014 at the General University Hospital (HGU/UNIC), Júlio Muller University Hospital (HUJM), University of Cuiabá (UNIC), and other health facilities in the city of Cuiabá/MT, Brazil (Table **1**).

As inclusion criteria, we considered patients with a confirmed diagnosis of SLE, aged 18 years or older and who agreed to participate in the study. As control subjects, we included 82 women clinically healthy, matched by age and ethnicity, who agreed to participate in the study. We excluded individuals having other autoimmune diseases and malignant neoplasms. This study was approved by the Local Ethics Committee of the University of Cuiabá (2010-062).

2.2. Demographic, Clinical and Laboratory Data

All demographic, clinical, and laboratory data were collected by a rheumatologist by filling out a clinical record, and this information was subsequently organized into a database for further analyses.

2.3. Molecular Analysis

DNA was obtained from peripheral leukocytes using a salting out procedure [20]. The presence of XRCC1 Arg 399Gln (exon 10) and XRCC3 Thr241Met (exon 7) poly-morphisms was identified by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). PCR was carried out using the following primers: (i) XRCC1 Arg399Gln (exon 10): F 5′-CCC CAA GTA CAG CCA GGT C-3′ and R 5′-TGC CCC GCT CCT CTG AGT AG-3′; (ii) XRCC3 Thr241Met (exon 7): F 5′-GGT CGA GTG ACA GTC CAA AC-3′ and R 5′-CCA CCT CCA GAC CGG C-3′ [16].

PCR-amplified fragments (242 bp) containing the XRCC1 Arg399Gln polymorphism were digested with the endonu-clease MspI (New England Biolabs, Ipswich, Massachusetts, USA). The XRCC1 399 Arg allele was cleaved into 378 bp and 131 bp fragments, whereas the XRCC1 399 Gln allele was not cleaved. The wild-type allele Arg was identified by the presence of two bands of 148 and 94 bp, and the mutant allele Gln by the uncut 242 bp product. The PCR-amplified fragments of 375 bp containing the XRCC1 Arg399Gln polymorphism were diges-ted with NlaIII (New England Biolabs) at 37 °C overnight. The wild-type allele Thr was identified by the presence of two bands of 141 and 234 bp, while the mutant allele Met was represented by bands of 141, 129, and 105 bp. The digested products of the evaluated polymorphisms were visualized on a 10% polyacrylamide gel stained with silver nitrate.

Table 1. Demographic characteristics of patients and controls.

Variable	–	Patients n=76 (%)	Controls n=82 (%)	p
Age [a] (variation in years)	–	40.3 (20-74)	41.2 (20-76)	0.9[b]
–	White	11 (14)	15 (18)	–
Ethnicity [c]	Mulatto	36 (48)	37 (45)	0.7
–	Black	29 (38)	30 (37)	–

[a] = Student's *t*-test; [b] = p-value of the Kolmogorov–Smirnov test; [c] = p-value of the chi-square test.

Table 2. Allelic and genotypic frequencies for the *XRCC1* Arg399Gln polymorphism in SLE patients and controls.

Polymorphism	Genotypics	Patients		Controls		OR	IC 95%	P
		n=76	(%)	n=82	(%)			
XRCC1	Arg/Arg	44	55.70	35	44.30	1.00	–	–
Arg399Gln	Arg/Gln	23	46.00	30	54.00	0.61	(0.30;1.22)	0.166
–	Gln/Gln	9	37.50	17	62.50	0.42	(0.17;1.04)	0.062
–	Arg/Gln + Gln/Gln	32	40.51	47	59.49	0.54	(0.29; 1.02)	0.056
–	Allelle frequency Arg	111	52.61	100	47.39	1.00	–	–
–	Allelle frequency Gln	41	39.05	64	60.95	0.58	(0.36; 0.93)	**0.023**

OR = Odds ratio; CI95% = 95% confidence interval; p = p-value of the chi-square test.

Table 3. Allelic and genotypic frequencies for the *XRCC3* Thr241Met polymorphism in patients and control subjects.

Polymorphism	Genotypes	Patients		Controls		OR	IC 95%	P
		n=70	(%)	n=82	(%)			
XRCC3	Thr/Thr	43	50.59	41	49.41	1.00	–	–
Thr241Met	Thr/Met	21	39.62	31	60.38	0.65	(0.32 ; 1.30)	0.219
–	Met/Met	6	35.29	10	64.71	0.57	(0.19 ; 1.72)	0.315
–	Thr/Met + Met/Met	27	38.57	41	61.43	0.63	(0.33 ; 1.20)	0.158
–	Allelle frequency Thr	107	47.98	113	52.02	1.00	–	–
–	Allelle frequency Met	33	37.93	59	62.07	0.59	(0.36 ; 0,98)	**0.0039**

OR = Odds ratio; CI95% = 95% confidence interval; p = p-value of the chi-square test.

2.4. Statistical Analysis

To verify the statistical significance between genotypic and allelic frequencies, Fisher's exact test was used in the total cohort of patients and controls. The Hardy–Weinberg Equilibrium (HWE) was calculated using the Genepop on the Web software, version 4.0, developed by Michel Raymond and François Rousset and available at http://genepop.curtin.edu.au/.

3. RESULTS

We evaluated 76 women patients and 82 control subjects from whom we could amplify XRCC1 and XRCC3. The mean ages and ethnicity of the patients and control individuals were similar (p = 0.9 and p = 0.7)as demonstrated in Table **1**. Regarding Hardy–Weinberg equilibrium, a balance in both patients and controls was observed for both XRCC1 and XRCC3 polymorphisms.

A possible association of polymorphisms with SLE was evaluated by comparing the allelic and genotype frequencies of the patients with those of the controls. The genotype frequencies of the XRCC1 codon 399 polymorphism were similar in both the patients and control subjects (p > 0.05).

However, the frequency of the 399Gln allele polymorphism was significantly lower in the patients than in the control subjects (p = 0.023, OR = 0.58, 95% CI = 0.36–0.93), which suggested a protective effect. No statistically significant difference was observed in the genotype frequencies for the XRCC3 codon 241 polymorphism. The frequency of the 241Met allele was significantly lower in the patients than in the controls (p = 0.0039, OR = 0.59, 95% CI = 0.36–0.98), which also indicated a protective effect. The allelic and genotype frequencies for XRCC1 and XRCC3 observed in patients and controls are shown in Tables **2** and **3**.

In addition to the genotype frequencies, a comparison of the frequencies of non-polymorphic homozygotes (XRCC1: Arg/Arg and XRCC3: Thr/Thr) with the sum of polymorphic heterozygotes and homozygotes (XRCC1: Arg/Gln+Gln and XRCC3: Thr /Met+Met/Met) was performed between patients and control subjects, given the evidence shows that the latter have similar phenotypes. However, no statistically significant differences were observed, as shown in Tables **2** and **3**.

No statistically significant difference was observed in the genotype frequencies of patients and control subjects upon eva-

Table 4. Association of the *XRCC1* Arg399Gln polymorphism with clinical and laboratory variables.

–	–	Variable		–	–
Polymorphism	**Genotypes**	**Yes (%)**	**No (%)**	**P[a]**	**OR (IC 95%)[b]**
Anti-Dna(ds)	–	–	–	–	–
*XRCC1*códon 399 Arg→Gln	Arg/Arg	6	38	Reference	1
	Arg/Gln	6	17	0.31	2.23 (0.63-7.9)
	Gln/Gln	3	6	0.33	3.16 (0.62 – 16.20)
	Arg/Gln + Gln/Gln	9	23	0.15	2.47 (0.78 – 7.87)
Leukopenia	–	–	–	–	–
*XRCC1*códon 399 Arg→Gln	Arg/Arg	16	28	Reference	1
	Arg/Gln	9	14	1	1.12(0.40-3.18)
	Gln/Gln	5	4	0.46	2.19 (0.51 – 9.34)
	Arg/Gln + Gln/Gln	14	18	0.63	1.36 (0.54-3.45)
Cutaneous Lupus	–	–	–	–	–
XRCC1 codon 399 Arg→Gln	Arg/Arg	15	29	Reference	1
	Arg/Gln	4	19	0.17	0.41 (0.12 - 1.41)
	Gln/Gln	2	7	0.7	0.55 (0.10 – 2.99)
	Arg/Gln + Gln/Gln	6	26	0.19	0.45 (0.15 - 1.32)

[a]Fisher's test; [b]OR, odds ratio.

Table 5. Association of the *XRCC3* Thr241Met polymorphism with clinical and laboratory variables.

–	–	Variables		–	–
Polymorphism	**Genotypes**	**Yes (%)**	**No (%)**	**P[a]**	**OR (IC 95%)[b]**
Anti-Dna (ds)	–	–	–	–	–
XRCC3 codon 241 Thr→Met	Thr/Thr	8	35	Reference	1
	Thr/Met	5	16	0.74	1.37 (0.39 – 4.84)
	Met/Met	1	5	1	0.88 (0.90 – 8.56)
	Thr/Met + Met/Met	6	21	0.76	1.25 (0.38 – 4.10)
Leukopenia	–	–	–	–	–
*XRCC3*códon 241 Thr→Met	Thr/Thr	14	29	Reference	1.88 (0.65 – 5.48)
	Thr/Met	10	11	0.28	0.41 (0.04 – 3.89)
	Met/Met	1	5	0.65	1.42 (0.52 – 3.86)
	Thr/Met + Met/Met	11	16	0.61	
Cutaneous Lupus	–	–	–	–	–
*XRCC3*códon 241 Thr→Met	Thr/Thr	13	30	Reference	1
	Thr/Met	6	15	1	0.92 (0.29 – 2.91)
	Met/Met	1	5	0.66	0.46 (0.049 - 4.35)
	Thr/Met + Met/Met	6	21	0.58	0.66 (0.21 – 2.01)

[a]Fisher's test; [b]OR, odds ratio.

luating the frequency of the XRCC1 Arg399Gln polymorphism with respect to clinical and laboratory variables where apoptosis might be involved (Table **4**).

Similarly, no statistically significant difference was observed in the genotype frequencies of patients and control subjects upon evaluating the frequency of the XRCC3 Thr 241Met polymorphism with respect to clinical and laboratory variables where apoptosis might be involved (Table **5**).

4. DISCUSSION

Although its origin is unknown, SLE can be considered a multifactorial disease. Currently, extensive investigations for understanding the etiology and genetic mechanisms involved in the pathophysiology of the disease are underway. Studies have shown that genetic susceptibility to SLE exists [1, 8, 9], and several genes have been associated [5, 10].

In SLE, the immune system responds to nuclear components such as DNA, histones, and ribonucleoproteins [11, 12],

which are usually protected inside the cell by nuclear and cellular membranes but are exposed to the immune system *via* apoptosis. In this study, we investigated polymorphisms in genes encoding DNA repair proteins as they can cause inefficient DNA damage repair, increasing the apoptotic rates observed in these patients.

The XRCC family of DNA repair genes is associated with ionizing radiation-induced DNA damage repair in mammalian cells [23, 24]. Ultraviolet (UV) radiation induces apoptosis in keratinocytes by direct DNA damage. Patients with SLE exhibit perturbations in the mechanisms *via* which apoptotic cells are eliminated, which serves as a continuous inflammatory stimulus [25]. Considering the high rates of UV radiation in the state of Mato Grosso, we selected this family of repair genes for studying genetic polymorphisms associated with SLE.

We did not observe any statistically significant difference in the genotype frequencies of the XRCC1 Arg399Gln and

XRCC3 Thr241Met polymorphisms among patients and control subjects. However, we demonstrated that the frequencies of the 399Gln allele and 241Met allele were significantly lower in SLE patients than in control individuals, which suggest a protective effect of these alleles in the susceptibility to SLE.

XRCC1 is required exclusively for repairing DNA damage by base excision in single-strand DNA breaks [16, 17, 26, 27], whereas XRCC3 is involved in DNA repair by homologous recombination [6, 28 - 30]. The amino acid substitutions associated with XRCC1 Arg399Gln and XRCC3Thr241Met polymorphisms are located in important interacting regions of these proteins, however, the precise effects of these polymorphisms on gene function are still not fully understood [31, 32]. Studies show that nucleoproteins and DNA damage caused by numerous factors such as exposure to UV radiation might produce immunogenic antigens that can induce the generation of autoantibodies [33]. Thus, the efficiency of DNA repair is animportant factor in the development of SLE.

Similar case control studies analysed the relationship between theXRCC1 Arg399Gln polymorphism and SLE in different populations [16 - 18, 26, 34]. Bassi *et al.*, 2008 in a Brazilian population, found no correlation between the XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms allele and genotypes frequency and SLE [16]. Lin *et al.* 2009 analysed the same polymorphism and suggest that people in the Taiwanese Han Chinese population with genotype A/G at codon 399 of XRCC1 have a higher risk of developing SLE disease [26]. Another study in a Chinese subpopulation also showed that theXRCC1 Arg399Gln polymorphism is a risk factor for SLE [18].Warchol *et al.*, 2012 in a polish population showed that XRCC1 Arg399Gln polymorphism may increase the risk of incidence of SLE and found a significantly higher frequency of the XRCC1 399 Gln allele in patients than in controls [17].

A similar study suggest that XRCC1 399 Arg/Gln heterozygous genotype may plays a protective role in SLE susceptibility, the frequency of Arg/Gln genotype was significantly lower in SLE patients than in a Iranian population [34]. These results are similar with those obtained in the present study, as we observed that the frequency of the Gln allele was significantly lower in Brazilian patients with SLE, suggesting the protective effect of this allele in SLE.

A recent meta-analysis study showed no significant association of XRCC1 Arg399Gln polymorphism with SLE in all genetic models when all study subjects were considered together. After stratification by ethnicity, significant association between the Arg399Gln polymorphism and SLE in Caucasians and Asians were observed. These findings suggested that the Arg399 allele may be a risk factor for SLE in Asians, while the Arg399 allele may be a protecting factor for SLE in Caucasians [35].

Previous studies found different associations of XRCC1 Arg399Gln polymorphism genotypes and allele frequency with clinical presentation and laboratory features. Photosensitivity and malar rash were associated with Gln allele in a polish population [17] and genotype A/G in Chinese population [26].

The XRCC1 Gln/Gln or Arg/Gln genotypes were associated with the presence of anti-dsDNA antibody in a Brazilian population study [16].

In this study we focused on evaluate the association between theXRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms in Brazilian patients with SLE, stratified according to clinical presentation and laboratory features. Where apoptosis might be involved and no statistically significant difference was observed in the genotype frequencies of patients and control subjects.

In this study, the frequency of 241Met allele was significantly lower in patients with SLE and suggests a protective effect of this polymorphism for SLE in the population analysed. The same Met allele has been found to confer SLE risk in a Chinese population [36] and XRCC3 Thr241Met polymorphism was more frequent in patients with antiphospholipid antibody syndrome in a Brazilian population previous study [16].

The reasons for these different findings reveal that the same polymorphism plays different roles in different ethnic groups. Autoimmune diseases are complex and multifactorial, caused by the interaction of genetic and environmental factors which are not the same in different populations and may explain why XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms play different roles in SLE patients, but the clear mechanism still remains to be elucidated [35].

CONCLUSION

In conclusion, frequencies of the XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms were similar observed in patients and controls group (p > 0.05). However, the frequencies of the 399Gln allele (p = 0.023, OR = 0.58, 95% CI = 0.36–0.93) and 241Met allele (p = 0.0039, OR = 0.59, 95% CI = 0.36–0.98) were significantly lower in the patients than those in the control subjects. There was no association between XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms, but 399Gln and 241Met alleles may play a protective role in SLE susceptibility.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee in Research of the University General Hospital, University of Cuiaba, under registration No. 081/UNIC, Protocol 2010-062.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

REFERENCES

[1]   Harley JB, Kelly JA, Kaufman KM. Unraveling the genetics of systemic lupus erythematosus. Springer Semin Immunopathol 2006; 28: 119-30.

[2]   Moser KL, Kelly JA, Lessard CJ, Harley JB. Recent insights into the genetic basis of systemic lupus erythematosus. Genes Immun 2009; 10(5): 373-9.
[http://dx.doi.org/10.1038/gene.2009.39] [PMID: 19440199]

[3]   Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med 2008; 358(9): 929-39.
[http://dx.doi.org/10.1056/NEJMra071297] [PMID: 18305268]

[4]   Rose T, Dörner T. Drivers of the immunopathogenesis in systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2017; 31(3): 321-33.
[http://dx.doi.org/10.1016/j.berh.2017.09.007] [PMID: 29224674]

[5]   Fortuna G, Brennan MT. Systemic lupus erythematosus: epidemiology, pathophysiology, manifestations, and management. Dent Clin North Am 2013; 57(4): 631-55.
[http://dx.doi.org/10.1016/j.cden.2013.06.003] [PMID: 24034070]

[6]   Goulielmos GN, Zervou MI, Vazgiourakis VM, Ghodke-Puranik Y, Garyfallos A, Niewold TB. The genetics and molecular pathogenesis of Systemic Lupus Erythematosus (SLE) in populations of different ancestry. Gene 2018; 668: 59-72.
[http://dx.doi.org/10.1016/j.gene.2018.05.041] [PMID: 29775752]

[7]   Falasinnu T, Chaichian Y, Bass MB, Simard JF. The representation of gender and race/ethnic groups in randomized clinical trials of individuals with systemic lupus erythematosus. Curr Rheumatol Rep 2018; 20(4): 20-31.
[http://dx.doi.org/10.1007/s11926-018-0728-2] [PMID: 29550947]

[8]   Criswell LA. The genetic contribution to systemic lupus erythematosus. Bull NYU Hosp Jt Dis 2008; 66(3): 176-83.
[PMID: 18937628]

[9]   Ramos PS, Brown EE, Kimberly RP, Langefeld CD. Genetic factors predisposing to systemic lupus erythematosus and lupus nephritis. Semin Nephrol 2010; 30(2): 164-76.
[http://dx.doi.org/10.1016/j.semnephrol.2010.01.007] [PMID: 20347645]

[10] Ali A, Sayyed Z, Ameer MA, *et al.* Systemic lupus erythematosus: An overview of the disease pathology and its management. Cureus 2018; 10(9): e3288.
[http://dx.doi.org/10.7759/cureus.3288] [PMID: 30443458]

[11] Stollar BD. Antibodies to DNA. CRC Crit Rev Biochem 1986; 20(1): 1-36.
[http://dx.doi.org/10.3109/10409238609115899] [PMID: 3514122]

[12] Takeda Y, Dynan WS. Autoantibodies against DNA double-strand break repair proteins. Front Biosci 2001; 6: D1412-22.
[http://dx.doi.org/10.2741/A690] [PMID: 11689355]

[13] Thomas TJ, Messner RP. Effects of lupus-inducing drugs on the B to Z transition of synthetic DNA. Arthritis Rheum 1986; 29(5): 638-45.
[http://dx.doi.org/10.1002/art.1780290508] [PMID: 3718555]

[14] Svilar D, Goellner EM, Almeida KH, Sobol RW. Base excision repair and lesion-dependent subpathways for repair of oxidative DNA damage. Antioxid Redox Signal 2011; 14(12): 2491-507.
[http://dx.doi.org/10.1089/ars.2010.3466] [PMID: 20649466]

[15] Thacker J, Zdzienicka MZ. The XRCC genes: Expanding roles in DNA double-strand break repair. DNA Repair (Amst) 2004; 3(8-9): 1081-90.
[http://dx.doi.org/10.1016/j.dnarep.2004.04.012] [PMID: 15279796]

[16] Bassi C, Xavier Dj, Palomino G, *et al.* Efficiency of the DNA repair and polymorphisms of the XRCC1, XRCC3 and XRCC4 DNA repair genes in systemic lupus erythematosus. Lupus 2008; 17(11): 988-95.
[http://dx.doi.org/10.1177/0961203308093461] [PMID: 18852222]

[17] Warchoł T, Mostowska A, Lianeri M, Lącki JK, Jagodziński PP. XRCC1 Arg399Gln gene polymorphism and the risk of systemic lupus erythematosus in the Polish population. DNA Cell Biol 2012; 31(1): 50-6.
[http://dx.doi.org/10.1089/dna.2011.1246] [PMID: 21682595]

[18] Zhang MM, Qi M, Che DF, *et al.* Correlation between single nucleotide polymorphism of the DNA repair gene XRCC1 and systemic lupus erythematosus. Chin J Clin Lab Sci 2011; 29: 115-7.

[19] Trabulus S, Guven GS, Altiparmak MR, *et al.* DNA repair XRCC1 Arg399Gln polymorphism is associated with the risk of development of end-stage renal disease. Mol Biol Rep 2012; 39(6): 6995-7001.
[http://dx.doi.org/10.1007/s11033-012-1529-8] [PMID: 22302399]

[20] Miller SA, Dykes DDE, Polesky HFA. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988; 16(3): 1215.
[http://dx.doi.org/10.1093/nar/16.3.1215] [PMID: 3344216]

[21] Tan EM, Cohen AS, Fries JF, *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25(11): 1271-7.
[http://dx.doi.org/10.1002/art.1780251101] [PMID: 7138600]

[22] Relton CL, Daniel CP, Hammal DM, Parker L, Janet Tawn E, Burn J. DNA repair gene polymorphisms, pre-natal factors and the frequency of somatic mutations in the glycophorin-A gene among healthy newborns. Mutat Res 2004; 545(1-2): 49-57.
[http://dx.doi.org/10.1016/j.mrfmmm.2003.09.007] [PMID: 14698416]

[23] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40(9): 1725.
[http://dx.doi.org/10.1002/art.1780400928] [PMID: 9324032]

[24] Ladiges W, Wiley J, MacAuley A. Polymorphisms in the DNA repair gene XRCC1 and age-related disease. Mech Ageing Dev 2003; 124(1): 27-32.
[http://dx.doi.org/10.1016/S0047-6374(02)00166-5] [PMID: 12618003]

[25] Bijl M, Kallenberg CG. Ultraviolet light and cutaneous lupus. Lupus 2006; 15(11): 724-7.
[http://dx.doi.org/10.1177/0961203306071705] [PMID: 17153842]

[26] Lin YJ, Wan L, Huang CM, *et al.* Polymorphisms in the DNA repair gene XRCC1 and associations with systemic lupus erythematosus risk in the Taiwanese Han Chinese population. Lupus 2009; 18(14): 1246-51.
[http://dx.doi.org/10.1177/0961203309345777] [PMID: 19880550]

[27] Hung RJ, Hall J, Brennan P, Boffetta P. Genetic polymorphisms in the base excision repair pathway and cancer risk: a HuGE review. Am J Epidemiol 2005; 162(10): 925-42.
[http://dx.doi.org/10.1093/aje/kwi318] [PMID: 16221808]

[28] Kurumizaka H, Ikawa S, Nakada M, *et al.* Homologous-pairing activity of the human DNA-repair proteins Xrcc3.Rad51C. Proc Natl Acad Sci USA 2001; 98(10): 5538-43.
[http://dx.doi.org/10.1073/pnas.091603098] [PMID: 11331762]

[29] Pierce AJ, Johnson RD, Thompson LH, Jasin M. XRCC3 promotes homology-directed repair of DNA damage in mammalian cells. Genes Dev 1999; 13(20): 2633-8.
[http://dx.doi.org/10.1101/gad.13.20.2633] [PMID: 10541549]

[30] Griffin CS, Simpson PJ, Wilson CR, Thacker J. Mammalian recombination-repair genes XRCC2 and XRCC3 promote correct chromosome segregation. Nat Cell Biol 2000; 2(10): 757-61.
[http://dx.doi.org/10.1038/35036399] [PMID: 11025669]

[31] Jiao L, Hassan MM, Bondy ML, *et al.* XRCC2 and XRCC3 gene

polymorphism and risk of pancreatic cancer. Am J Gastroenterol 2008; 103(2): 360-7.
[http://dx.doi.org/10.1111/j.1572-0241.2007.01615.x] [PMID: 1798 6315]

[32]   Matullo G, Palli D, Peluso M, *et al.* XRCC1, XRCC3, XPD gene polymorphisms, smoking and (32)P-DNA adducts in a sample of healthy subjects. Carcinogenesis 2001; 22(9): 1437-45.
[http://dx.doi.org/10.1093/carcin/22.9.1437] [PMID: 11532866]

[33]   Hanssen-Bauer A, Solvang-Garten K, Akbari M, Otterlei M. X-ray repair cross complementing protein 1 in base excision repair. Int J Mol Sci 2012; 13(12): 17210-29.
[http://dx.doi.org/10.3390/ijms131217210] [PMID: 23247283]

[34]   Salimi S, Mohammadoo-Khorasani M, Tabatabai E, Sandoughi M, Zakeri Z, Naghavi A. XRCC1 Arg399Gln and Arg194Trp polymorphisms and risk of systemic lupus erythematosus in an Iranian population: A pilot study. BioMed Res Int 2014; 2014: 492956.
[http://dx.doi.org/10.1155/2014/492956] [PMID: 24971336]

[35]   Zhang MY, Yang XK, Ly TT, *et al.* Meta-analysis of associations between XRCC1 gene polymorphisms and susceptibility to systemic lupus erythematosus and rheumatoid arthritis. Int J Rheum Dis 2017.

[36]   Chen YT, Chen SY, Lin YJ, Huang CM, Chang YY, Tsai FJ. Association between XRCC3 Thr241Met SNP and systemic lupus erythematosus in Han Chinese patients in Taiwan, and a meta-analysis of healthy populations. J Clin Lab Anal 2014; 28(2): 118-23.
[http://dx.doi.org/10.1002/jcla.21654] [PMID: 24395651]