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

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1. INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a complex, autoimmune and chronic inflammatory disease characterized 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 conditions, and geographic location [6].

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.

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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]. Ultraviolet 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 hydralazine, 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, Arg194Trp, 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 its 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 Arg399Gln (exon 10) and XRCC3 Thr241Met (exon 7) polymorphisms 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′-GTT CGA GTG ACA GTC C-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 endonuclease MspI (New England Biolabs, Ipswich, Massachusetts, USA). The XRCC1 399Gln allele was cleaved into 378 bp and 131 bp fragments, whereas the XRCC1 399Gln 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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients n=76 (%)</th>
<th>Controls n=82 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.3 (20-74)</td>
<td>41.2 (20-76)</td>
<td>0.9</td>
</tr>
<tr>
<td>White</td>
<td>11 (14)</td>
<td>15 (18)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Mulatto</td>
<td>36 (48)</td>
<td>0.7</td>
</tr>
<tr>
<td>Black</td>
<td>29 (38)</td>
<td>30 (37)</td>
<td></td>
</tr>
</tbody>
</table>

" = Student’s t-test; " = p-value of the Kolmogorov-Smirnov test; " = p-value of the chi-square test.

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

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

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.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Genotypes</th>
<th>Patients n=70 (%)</th>
<th>Controls n=82 (%)</th>
<th>OR</th>
<th>IC 95%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRCC3</td>
<td>Thr/Thr</td>
<td>43 50.59</td>
<td>41 49.41</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thr241Met</td>
<td>Thr/Met</td>
<td>21 39.62</td>
<td>31 60.38</td>
<td>0.65</td>
<td>(0.32;1.30)</td>
<td>0.219</td>
</tr>
<tr>
<td>–</td>
<td>Met/Met</td>
<td>6 35.29</td>
<td>10 64.71</td>
<td>0.57</td>
<td>(0.19;1.72)</td>
<td>0.315</td>
</tr>
<tr>
<td>–</td>
<td>Thr/Met + Met/Met</td>
<td>27 38.57</td>
<td>41 61.43</td>
<td>0.63</td>
<td>(0.33;1.20)</td>
<td>0.158</td>
</tr>
<tr>
<td>–</td>
<td>Allele frequency Thr</td>
<td>107 47.98</td>
<td>113 52.02</td>
<td>1.00</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>–</td>
<td>Allele frequency Met</td>
<td>33 37.93</td>
<td>59 62.07</td>
<td>0.59</td>
<td>(0.36;0.98)</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

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.

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

Fisher’s test; OR, odds ratio.

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

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

Fisher’s test; OR, odds ratio.

In evaluating 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 Thr241Met 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 XRCC3 Thr241Met 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 an important 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 an 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 the XRCC1 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.

FUNDING STATEMENT

This work was supported by the Foundation for Research Support of the State of Mato Grosso-FAPEMAT/CNPQ (EDITAL UNIVERSAL - MESTRE/FAPEMAT No. 009-201 - No. 755373/2011).

ETHICS APPROVAL AND CONSENT TO PARTICI-
PATE

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.
CONSENT FOR PUBLICATION
All patients gave an informed written consent when they were enrolled.

CONFLICT OF INTEREST
The authors declare no conflict of interest, financial or otherwise.

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