Single Nucleotide Polymorphism rs6445975 in the PXK Gene Is Correlated with Susceptibility and Clinical Characteristics of Systemic Lupus Erythematosus

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Abstract
Background: Recently, genome-wide association studies (GWAS) have discovered several single nucleotide polymorphisms (SNPs) and loci associated with the risk of systemic lupus erythematosus (SLE). rs6445975 (T>G; intronic variant) polymorphism in the PXK gene is one of these loci. However, there was an inconsistency between the results of replicative studies on European and Asia ancestry. This study aimed to assess the possible association between rs6445975 polymorphism with SLE risk in the Iranian population.

Methods: Genotype and allele distribution of rs6445975 polymorphism were investigated in 110 patients with SLE and 115 healthy controls in Isfahan University of Medical Sciences, Isfahan, Iran in 2019 via real-time PCR high resolution melting method (HRM).

Results: GG and TG genotypes, but not TT genotype, were associated with increased risk of SLE (GG vs TT; OR= 7.538; 95%CI[3.47, 17.066] and TG vs TT; OR=2.21; 95%CI[1.06, 4.72]). Inheritance analysis revealed that TG + GG was correlated with the increased risk of SLE disease in the dominant model (OR=3.928; 95%CI[2.056, 7.74]). Moreover, subjects with the G allele were more frequently affected with SLE than individuals with the T allele (OR= 3.55; 95%CI[2.37, 5.36]). The G allele in patients was correlated with serum concentration of CRP, ESR, anti-dsDNA antibody, C3, and C4 and presentation of some clinical manifestations such as kidney involvements and skin lesions (P<0.05).

Conclusion: Our findings suggest a substantial association between rs6445975 polymorphism in the PXK gene with susceptibility and clinical characteristics of SLE in the Iranian population.

Keywords: Systemic lupus erythematosus; Gene; Single nucleotide polymorphism; Autoimmune disease

Introduction

Systemic lupus erythematosus (SLE) is a chronic, progressive, and heterogeneous multisystem autoimmune disorder with multifactorial nature inherited in a polygenic manner (1, 2). SLE is char-
characterized by dysregulation in immune response and production of a high frequency of autoantibodies, which damage the internal organs such as kidneys.

The most common symptoms of SLE range from skin rashes, fatigue, oral ulcers, arthritis, anemia, anorexia, and weight loss to life-threatening symptoms such as renal failure, seizures, blood clots, and stroke (3, 4). SLE, similar to many of the autoimmune disorders, represents a striking sex imbalance in favor of females (9:1 female to male ratio) (5).

Genetic factors exert an imperative role in the incidence of SLE disease. The heritability of SLE is about 66% (6). Moreover, having a positive family history of SLE or related autoimmune diseases obviously increases the risk of developing SLE (7). Newly, with advances in genotyping and sequencing methods, studies have discovered several genetic risk loci correlated with SLE risk (8, 9). Over the past decade, genome-wide association studies (GWAS) have nominated more than 3 thousand single nucleotide polymorphisms (SNPs) and loci in various genes. These genes have immune and inflammatory functions, which can elevate the SLE risk (7, 10, 11). SNPs, as the most abundant form of allelic variations, exist once almost in every 300 nucleotides with appreciable frequency (>1%) and could be associated with disorders especially multifactorial autoimmune diseases such as SLE (12-14). rs6445975 (T>G), an intronic variant in the PXK gene, is one of these loci identified in a GWAS study. In their study, the G allele increases the risk of SLE in populations of European ancestry (15). Similarly, in the other GWAS study, this variant was also correlated with the risk of rheumatoid arthritis (RA) in the European population (16). Furthermore, some other replicative studies emphasized the association of this polymorphism with SLE risk and also some clinical features of the disease (17-19). The PXK gene is located in 3p14.3 and encodes a phox (PX) domain-containing protein. PXK is involved in synaptic transmission and ligand-induced internalization. However, the exact function of the PXK gene in the immune system, as well as the pathogenesis of autoimmune diseases, is unclear. Relevantly, the risk allele in rs6445975 was associated with higher expression of PXK in female SLE patients (20).

Regarding these data, for the first time, we intended to assess the possible association between rs6445975 polymorphism with the risk of SLE incidence and clinical characteristics of the disease in the Iranian population.

Methods

Study population
In this case-control study, 225 participants were selected amongst subjects referred to the Rheumatology Division of Alzahra Hospital, Isfahan, Iran, in 2019. Overall, 110 SLE cases met the diagnostic criteria created by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) for SLE (21). Overall, 115 controls were also selected from the same population with no signs and symptoms of SLE based on negative clinical and laboratory examination and without any personal and family history of SLE or other immunological and autoimmune disorders.

The study was confirmed by the Isfahan University of Medical Sciences Ethics board (IR.mui.med.rec.1397.284) and all subjects provided written informed consent.

Demographic and clinical characteristics data of all individuals were documented. These data were gender, age (age of onset and age at sampling time), blood pressure, height and weight to calculate body mass index (BMI, calculated as weight [kg] divided by height [m] squared), family history of SLE and other autoimmune conditions and clinical manifestations such as the presence of skin lesions, neurological disorders, hematological symptoms, oral mucosal ulceration, arthritis, and kidney diseases. Likewise, we collected laboratory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-dsDNA antibodies, complement component 3 (C3), and complement component 4 (C4), white blood cell (WBC) count, hemoglobin, blood urea nitrogen (BUN), platelet count test (PLT), creati-
nine, fasting blood sugar (FBS), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). These parameters were as previously described (22, 23).

**Genotyping of polymorphism**

After the collection of 3 ml of venous blood from all volunteers into Ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes, we stored samples at –20 °C for further processing. DNA was isolated from whole blood by PrimePrep Genomic DNA Isolation Kit (GeneNateBio, Korea) (24). The quality, quantity, and suitability of DNA for the polymerase chain reaction high-resolution melting (HRM) method was evaluated by spectrophotometry and agarose gel electrophoresis. The PCR was carried out for amplification of fragments that span the rs6445975 in the PXK gene. This method was performed via HOT FIREPol EvaGreen HRM Mix (no ROX) HRM PCR kit (Solis BioDyne, Tartu, Estonian) and analysis accomplished with Rotor-Gene 6000™ (Corbett Research, Mortlake, New South Wales, Australia) (25, 26) under the following conditions: 5 min at 95 °C for initial denaturation of the template DNA for the first cycle, 36 cycles of denaturation at 95 °C for the 20 sec, annealing at 60 °C for 30 sec and extension at 72 °C for 20 sec. In this system, polymorphism in the PCR product is distinguished by alterations in the shape of the melting curve compared to a known sample as reference. The melting curve is produced by the decrease in fluorescence with the concurrent increase in the temperature among 60 °C and 95 °C at 0.1 °C/sec; nucleotide changes result in different curve patterns. For utilizing reference sample genotypes in HRM analysis, some samples were subjected to direct Sanger sequencing and their correct genotypes were distinguished.

**Statistical analysis**

The SPSS 25 (IBM Corp., Armonk, NY, USA) was utilized for statistical analyses. Genotype frequencies in two groups of participants were tested for Hardy-Weinberg equilibrium using the χ² test (27). Logistic regression analysis was performed to examine the correlation between genotypes and SLE and compute specific odds ratios (ORs), 95% confidential intervals (CIs), and P-values. For demographic, clinical, and laboratory characteristics, P values were examined using the independent Pearson χ² test for categorical variables and t-test for continuous variables test with the significance level of <0.05.

**Results**

**Demographic and Clinical characteristics**

Participants of this study composed of 110 SLE patients (25 males and 85 females with a mean age of onset: 26.22±10.84) and 115 SLE-free individuals (29 males and 86 females). The mean age at sampling time for case and control groups was 43.61± 13.41 and 45.37±12.95, respectively. The characteristics of individuals with SLE and healthy subjects are listed in Table 1. There was no considerable difference among the two groups in regards to age (P=0.319) and gender (P=0.755), demonstrating that for these factors matching was satisfactory. In the SLE patients group, 20 (18%) had a family history of SLE or other autoimmune diseases. Between case and healthy control groups of subjects, there was a noteworthy difference in terms of BMI and blood pressure (P<0.05). In detail, patients had significantly higher BMI compared with controls. Similarly, the systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients was higher than in the control group. Most of the patients had arthritis (98 patients, 89%), oral mucosal ulceration (84 patients, 76%), and skin manifestations (70 patients, 64%). Moreover, 56 patients (51%) had hematological symptoms and 48 subjects (44%) had renal involvements. Neurological symptoms were observed in 27 (25%) of patients.
Table 1: Baseline characteristics of SLE patients and control subjects who participated in the study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>110</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>Age at now (mean± SD)</td>
<td>43.61±13.41</td>
<td>45.37±12.95</td>
<td>0.319</td>
</tr>
<tr>
<td>Gender n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25(23%)</td>
<td>29(25%)</td>
<td>0.755</td>
</tr>
<tr>
<td>Female</td>
<td>85(77%)</td>
<td>86(75%)</td>
<td></td>
</tr>
<tr>
<td>Age of onset (mean± SD)</td>
<td>26.22±10.84</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>BMI (mean± SD)</td>
<td>25.75±2.33</td>
<td>24.29±3.24</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>SBP (mean± SD)</td>
<td>125.46±15.99</td>
<td>120.60±9.69</td>
<td>0.006*</td>
</tr>
<tr>
<td>DBP (mean± SD)</td>
<td>87.95±8.31</td>
<td>82.63±5.85</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Positive family history n (%)</td>
<td>20(18%)</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Neurological symptoms n (%)</td>
<td>27(25%)</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Skin manifestations n (%)</td>
<td>70(64%)</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Hematological manifestations n (%)</td>
<td>56(51%)</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Oral ulcers n (%)</td>
<td>84(76%)</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Arthritis n (%)</td>
<td>98(89%)</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Renal involvement n (%)</td>
<td>48(44%)</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>

*P-value<0.05. BMI: Body mass index; SD: Standard deviation; SLE: Systemic lupus erythematosus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

The results of laboratory tests discovered that the mean serum concentration of ESR, CRP, creatinine, BUN, and anti-dsDNA antibody was meaningfully higher in the SLE patients group than healthy controls (P<0.05). On the other hand, the serum concentration of hemoglobin, PLT, C3, and C4 levels was profoundly higher in controls than in patients’ subjects (P<0.05) (Table 2).

Table 2: Laboratory characteristics of patients with SLE and controls group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (110)</th>
<th>Controls (115)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm/h)</td>
<td>41.32±22.80</td>
<td>15.39±7.00</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>16.30±9.70</td>
<td>4.32±2.56</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>White blood cell (10⁹/1)</td>
<td>6820.90±1780.71</td>
<td>6500.17±1342.84</td>
<td>0.128</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.87±1.39</td>
<td>14.23±1.49</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PLT (10⁹/1)</td>
<td>225.90±63.28</td>
<td>249.59±66.95</td>
<td>0.007*</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.018±0.24</td>
<td>0.866±0.17</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BUN</td>
<td>19.58±11.87</td>
<td>16.04±4.14</td>
<td>0.003*</td>
</tr>
<tr>
<td>FBS</td>
<td>89.67±12.70</td>
<td>93.17±22.33</td>
<td>0.152</td>
</tr>
<tr>
<td>HDL</td>
<td>51.05±8.86</td>
<td>50.19±11.20</td>
<td>0.523</td>
</tr>
<tr>
<td>LDL</td>
<td>102.73±26.14</td>
<td>107.44±31.89</td>
<td>0.228</td>
</tr>
<tr>
<td>TG</td>
<td>157.22±46.49</td>
<td>156.51±60.92</td>
<td>0.922</td>
</tr>
<tr>
<td>Anti-dsDNA (IU/ml)</td>
<td>198.91±181.68</td>
<td>10.85±4.41</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>C3 level (mg/dl)</td>
<td>50.04±36.85</td>
<td>142.38±35.22</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>C4 level (mg/dl)</td>
<td>10.52±7.15</td>
<td>20.03±5.89</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

* P-value<0.05. Data are mean ± SD; SD: Standard deviation; SLE: Systemic lupus erythematosus; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; BUN: Blood urea nitrogen; PLT: Platelet; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; FBS: Fasting blood sugar; C3: Complement component 3; C4: Complement component 4; dsDNA: Double-stranded DNA
**Genotype and allele distribution**

Genotype distribution in the present study indicated that homozygous variant (GG) and heterozygous genotype (TG) were significantly higher in the SLE patients group compared with control subjects (P<0.001 and P= 0.026, respectively). The frequency of GG genotype in case and control group was, respectively, 51% and 18% and frequency of TG genotype in case and control group was 32% and 37%, respectively. The comparison of combined genotypes i.e. TG + GG genotypes, compared with the TT genotype was significantly different between case and control groups (P= 0.017). Additionally, the frequencies of T and G alleles were 33% and 67% in cases, and 64% and 36% in the control group, respectively. There was a statistically substantial difference between SLE patients and healthy participants regarding allele frequency (P<0.001). The genotype and allele distribution of rs6445975 polymorphism are summarized in Table 3.

### Table 3: Association between genotypes and allele frequency of rs6445975 polymorphism with SLE risk

<table>
<thead>
<tr>
<th>Genotype group</th>
<th>Patients (n=110) n (%)</th>
<th>Controls (n=115) n (%)</th>
<th>OR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>19(17)</td>
<td>52(45)</td>
<td>Reference</td>
<td>---</td>
</tr>
<tr>
<td>TG</td>
<td>35(32)</td>
<td>43(37)</td>
<td>2.21 (1.06, 4.72)</td>
<td>0.026*</td>
</tr>
<tr>
<td>GG</td>
<td>56(51)</td>
<td>20(18)</td>
<td>7.538 (3.47, 17.066)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Combined Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>19(17)</td>
<td>52(45)</td>
<td>Reference</td>
<td>---</td>
</tr>
<tr>
<td>TG+GG</td>
<td>91(83)</td>
<td>63(55)</td>
<td>3.928(2.056, 7.74)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>73(33)</td>
<td>147(64)</td>
<td>Reference</td>
<td>---</td>
</tr>
<tr>
<td>G</td>
<td>147(67)</td>
<td>83(36)</td>
<td>3.55(2.37, 5.36)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*P-value<0.05

Our evaluations demonstrated that patients with TT, TG, and GG genotypes had 32.89±11.76, 27.71±11.54, and 23.03±8.84 mean age of onset, respectively. The G allele was correlated with lower age of onset (P=0.001). Besides, patients with different genotypes had a significantly different mean serum concentration of CRP, ESR, C3, C4, anti-dsDNA, and creatinine (P<0.05). Patients with the G allele had a higher concentration of CRP, ESR, anti-dsDNA antibody, and creatinine, and a lower concentration of C3, C4. Moreover, patients with different genotypes had significant differences in some clinical presentations. In this context, the presence of the G allele in patients was expressively correlated with the presentation of skin manifestation, and renal involvement (P<0.05). The frequency of skin lesions in TT, TG, and GG genotypes was 47.36%, 45.71%, and 80.35%, respectively. Similarly, the frequency of renal involvements was 10.52%, 57.17%, and 60.71%, respectively. Nevertheless, there was no significant relationship between the stratification of the hematological manifestation, neurological symptoms, oral ulcers, and arthritis with different genotypes of this polymorphism (P>0.05). Furthermore, there was no significant correlation between hemoglobin concentration with this variant (P=0.496) (Table 4).
Table 4: Association of rs6445975 polymorphism with various parameters of SLE (110 Patients)

<table>
<thead>
<tr>
<th>Genotype group</th>
<th>TT (n =19)</th>
<th>TG (n =35)</th>
<th>GG (n =56)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>32.89±11.76</td>
<td>27.71±11.54</td>
<td>23.03±8.84</td>
<td>0.001*</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>29.57±14.28</td>
<td>40.42±18.85</td>
<td>45.87±25.98</td>
<td>0.024*</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>10.57±6.35</td>
<td>15.80±8.61</td>
<td>18.55±10.52</td>
<td>0.007*</td>
</tr>
<tr>
<td>C3 level (mg/dl)</td>
<td>89.00±23.01</td>
<td>56.42±40.85</td>
<td>32.83±25.18</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>C4 level (mg/dl)</td>
<td>16.48±7.59</td>
<td>11.51±6.63</td>
<td>7.87±5.94</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Anti-dsDNA (IU/mL)</td>
<td>34.10±58.54</td>
<td>102.30±92.99</td>
<td>315.20±172.80</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.86±0.16</td>
<td>1.00±0.23</td>
<td>1.07±0.24</td>
<td>0.002*</td>
</tr>
<tr>
<td>Hemoglobin (HB)</td>
<td>11.83±1.26</td>
<td>11.66±1.18</td>
<td>12.01±1.55</td>
<td>0.496</td>
</tr>
<tr>
<td>Neurological symptoms n (%)</td>
<td>2(10.52%)</td>
<td>6(17.14%)</td>
<td>19(33.92%)</td>
<td>0.057</td>
</tr>
<tr>
<td>Skin manifestations n (%)</td>
<td>9(47.36%)</td>
<td>16(45.71%)</td>
<td>45(80.35%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Hematological manifestations n (%)</td>
<td>8(42.10%)</td>
<td>22(62.85%)</td>
<td>26(46.42%)</td>
<td>0.219</td>
</tr>
<tr>
<td>Oral ulcers n (%)</td>
<td>13(68.42%)</td>
<td>31(88.57%)</td>
<td>40(71.42%)</td>
<td>0.116</td>
</tr>
<tr>
<td>Arthritis n (%)</td>
<td>16(84.21%)</td>
<td>31(88.57%)</td>
<td>51(91.07%)</td>
<td>0.704</td>
</tr>
<tr>
<td>Renal involvement n (%)</td>
<td>2(10.52%)</td>
<td>12(33.31%)</td>
<td>34(60.71%)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Data are mean ± SD, or n (%). *P-value<0.05. ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; dsDNA: Double-stranded DNA

Discussion

Over the past decade, several GWAS studies have identified numerous variants in many different genes associated with autoimmune diseases, especially SLE susceptibility (28-30). PXK gene is one of these loci which for the first time was reported in a GWAS study on women of European ancestry with SLE. The rs6445975 (T>G) variant located in intron 4 of the PXK gene is correlated with an increased risk of SLE (15). Another GWAS study carried out in the same ancestry revealed that this variant is also associated with RA (16). Recently, the G allele in this polymorphism is associated with increased expression of PXK in women with lupus but not in male patients (20). This gene is expressed in various tissues and can encode 5 isoforms which PXK_3 is only expressed in leukocytes (31). However, the role of this gene in SLE pathogenesis is still not completely understood.

To the best of our knowledge, the current study is the first report in the Iranian population that assesses the possible correlation between rs6445975 polymorphism in the PXK gene with SLE disease risk. Logistic regression analysis demonstrated that homozygous GG and heterozygous TG genotype compared with the TT genotype increase the risk of SLE (GG vs. TT; OR=7.538; 95%CI [3.47, 17.066] and TG vs TT; OR=2.21; 95%CI [1.06, 4.72]). Inheritance analysis revealed that TG + GG increased the risk of SLE disease in the dominant model (OR=3.928; 95%CI [2.056, 7.74]). Besides, individuals with allele G were more frequently affected with SLE than subjects with T allele (OR= 3.55; 95%CI [2.37, 5.36]) (Table 3). Our finding was in concordance with the GWAS study, although in their analysis only female patients were evaluated (15). Likewise, in a case-control study, this polymorphism was associated with the risk of SLE in a population with European ancestry (19).

Contrarily, in the other case-control study in a Chinese population, the rs6445975 variant was not correlated with the risk of SLE but the minor allele (G) was considerably correlated with autoantibody (such as anti-Smith, anti-Ro, and anti-La), C3, and C4 production in SLE patients (18).

In a similar study in a Korean population, rs6445975 in the PXK gene was not correlated...

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with SLE susceptibility, but displayed a positive association with anti-Sm antibody production and also photosensitivity in SLE patients (32). In a Chinese study, this polymorphism was not correlated with SLE risk (33). The results from these two studies from Asian ancestry about the correlation of rs6445975 with the production of some serum protein biomarkers were in agreement with our finding. In our analysis, the G allele was correlated with increased levels of CRP, ESR, and anti-dsDNA antibody, as well as, there was a negative correlation with C3 and C4 levels. On the other hand, a positive association between this risk allele and skin lesions and renal involvement was observed (Table 4).

Considering the different results of studies from European and Asian ancestry, PXK locus (rs6445975) has a different impact on SLE in these two ancestries. This might emanate from the existence of different genetic backgrounds. However, our finding disclosed that the effect of this specific locus on SLE susceptibility could be similar to the European population.

Conclusion

The current study disclosed a significant association between rs6445975 polymorphism with SLE risk in the Iranian population. Moreover, this variant is correlated with increased production of serum proteins, which are indicators of severe disease activity of SLE. Besides, the risk allele (G) in this polymorphism was correlated with some clinical presentations such as skin manifestations and renal damages. In this work, probably, some possible limitations in the statistical validity of our results such as small population size exist, so further association studies in a larger sample size would help to confirm the suggested correlations.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

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Conflict of interest

The authors declare that there is no conflict of interest.

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