ASSOCIATION OF IKZF3 GENE POLYMORPHISM WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN THE GUIZHOU HAN POPULATION

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ABSTRACT

Introduction*: Genetic factors play an important role in the pathogenesis of SLE, several loci of the IKZF3 gene have a certain correlation with SLE. However, single nucleotide polymorphisms (SNP) have ethnic and regional differences, to investigate the correlation between zinc finger 3 gene polymorphism and patients with systemic lupus erythematosus (SLE) in the Guizhou Han population was our main aim.*

Materials and methods*: A total of 213 SLE patients and 187 healthy persons as control group in the Guizhou Han population, were registered to detect the SNP of the rs114509391, rs907091 and rs907092 loci in the IKZF3 gene by multiple SNaPshot techniques. Then genotype frequency, allele frequency, linkage disequilibrium and haplotype analysis were compared between the SLE group and the healthy control group. Statistical methods were performed using unconditional logistic regression analysis.*

Results*: The genotype and allele frequencies of the three SNPs (rs114509391, rs907091, rs907092) were not significantly different between the SLE group and the healthy control group (P>0.05). There were no difference in genotype frequencies between the SLE group and the healthy control group, in the dominant, recessive or cumulative genetic models of the three SNPs (P>0.05). Hierarchical analysis indicated that the C allele of rs114509391 may be a protective factor for light-nonsensitive SLE (P<0.05). No correlation was found between the rs907091 and rs907092 loci and the clinical phenotypes of SLE (P>0.05). Linkage disequilibrium analysis revealed linkage disequilibrium among the three SNPs. There were no significant differences in the distribution of six haplotypes in the SLE group and the healthy control group, and each haplotype was not associated with the risk of SLE (P>0.05).*

Conclusions*: The C allele of rs114509391 may be a protective factor for light-nonsensitive SLE. the specific protection mechanism needs to be further studied in large samples in the future.*

Keywords: *zinc finger 3 gene; polymorphism; systemic lupus erythematosus; SNP.*

DOI: 10.19193/0393-6384_2020_6_516

Received *June 30, 2019;* ***Accepted*** *August 20, 2020*

Introduction

SLE (systemic lupus erythematosus) is a chronic inflammatory autoimmune disease characterized by autoimmune antibody production, immune response dysfunction and immune complex deposition, which can be directed against almost any organ system in a heterogeneous array of clinical manifestations[(1)]. SLE predominantly occurs in young and middle-aged people with a female to male ratio of 9:1. At present, the global incidence of SLE is 20-150 per 100,000[(2)]. In Asia, the incidence is higher than Europe's, besides the symptoms of SLE are more serious, the serum autoantibody level is higher[(3-4)]. The etiology of SLE is unknown, and its development may be the result of multiple factors, such as genetic, environmental and immune system mutations[(5-6)]. Genome-wide association studies are identifying a growing list of gene contributing to SLE pathogenesis, IKZF3 is one of those related genes[(8-11)].

The IKZF3 gene is located in the 17q21 region of the chromosome and it contains 8 exons. Recent studies have shown that the IKZF3 gene is associated with a variety of immune-related diseases[12-16]. The pathogenesis of SLE is associated with the overexpression of Aiolos(8), and some studies suggest that multiple SNPs in the IKZF3 gene may be associated with SLE (9-11). These SNP sites have significant ethnic and geographical differences. A recent study has shown that the rs9913957, rs8076347 and rs8079075 of IKZF3 gene are polymorphic in European and African American, but not in Asian population[11]. The frequency of presence of the CC genotype and C allele of rs907091 in SLE patients presented a significant decrease in Chinese Han Population(10), but they were not significantly different between the SLE and the healthy control in Han ethnic group in southern China[9]. At present, there is no correlation between the IKZF3 gene polymorphism and SLE in the Guizhou Han population. In this study, we detected the distribution of IKZF3 gene (rs114509391, rs907091, rs907092) polymorphisms in SLE patients and healthy people in the Guizhou Han population and explored the influence of molecular genetic mechanisms and genetic factors on SLE and provided clues regarding the genetics to SLE in the Guizhou Han population.

Materials and methods

Subjects

A total of 213 SLE patients consisting of 16 males and 197 females with an average age of 32.93±12.15 years (mean ± SD), and their age span is 8~68 years, were recruited from October 2014 to October 2017 in the Zunyi Medical University Hospital. The SLE classification and diagnostic criteria were revised by the American College of Rheumatology in 1997. A total of 187 healthy (16 males and 171 females) individuals without a history of SLE in our hospital were used as controls group, with an average age of 33.48±10.61 years (mean ± SD), aged from 12~69 years. There was no significant difference in age or gender composition between the normal and case groups (P>0.05). Clinical information for all patients was collected by physician specialists and was tabulated in the database. Experimental data were obtained from the clinic laboratory reports. All subjects were Han population in Guizhou, and they were not related. The study was approved by the ethics committee of the hospital, and all subjects signed informed consent.

SNP selection

20 SLE cases and 20 normal controls were selected randomly, we repeatedly sequenced their exons of the IKZF3 gene (completed by The Beijing Genomics Institute), 2 SNPs (rs114509391, rs907092) with MAF>0.05 were screened out. Finally, we selected the label SNP (rs114509391, rs907092, rs907091) in this study by combining the Aiolos gene signature of the Chinese population on the Hap-Map website and a literature review.

DNA extraction

Two milliliters of peripheral venous blood from SLE patients and healthy controls was collected. The genomic DNA was isolated from peripheral blood samples by standard procedures with a Magen whole-blood genome DNA isolation kit.

PCR amplification

The primer design for PCR was carried out using online Primer 3.0 software (http://primer3.ut.ee/), and the primers are presented in Table 1.

Site	Primer sequence 5'~3'	Product (bp)
rs114509391	Forward: CAGTTTAATGTGGCGGAGGAG Reverse:GTAAGTCTTAGGCTTGCCTTGAAAT	233
rs907092	Forward:CCAGGAAGAGGACGCGGCAGTGGTC Reverse:CGACTCCACGGACACTGACAGCAAC	236
rs907091	Forward:CTGTGAAGGGCAGAAGGGTGAG Reverse:TATTCGCAGGTCTAGCATATTATTA	256

Table 1: Primer sequences and product sizes at different sites of the IKZF3 gene.

Genotypes of the IKZF3 SNPs (rs907091, rs907092 and rs114509391) were analyzed by the multiple single nucleotide primer extension technique. Each assay (30 μl) for PCR amplification comprised 3 μl of 10* Ex Taq buffer, 2 μl of dNTP (2.5 mM each), 1 μl of MIX Primer (10p), 0.2 μl of Ex Taq (5U/μl), 20.8 of μl ddH2O, and 2.0 μl of template DNA. Reaction conditions included 35 cycles (96°C 2 min, 96°C 20 s, 55°C 10 s, 72°C 30 s); 72°C 2 min; 4°C. Then, 6 μl of PCR product was purified with 2 U shrimp alkaline phosphatase (SAP) and 2 U exonuclease I (ExoI) enzyme, then incubated at 37°C for 60 min, 75°C for 15 min to inactivate the SAP and ExoI enzyme.

Genotyping

The gene sequencing using SNaPshot detection, the extension primer sequences are shown in

Table 2. The system for the extension reaction was as follows: PCR product 1 μl, MIX Primer (5pM) 1 μl, SNaPshot MIX 0.5 μl, ddH20 0.5μl. The Reaction conditions were as follows: 95°C x 2 min, 95°C x 10 s, 50°C x 5 s, 65°C x 30 s; for 35 total cycles. Finally, 1 μl of extension product was sequenced using an ABI 3730XL sequencer after purification with SAP. To confirm the genotyping success, a random selection of samples were analyzed by direct sequencing, and the results were 100% concordant.

Site	Extension primer sequence
rs114509391	CCAGTGTAATCAGTGTGGGGCATCTTTTAC
rs907092	ATCCATCACCTCCCCTTCCTTGTTGATCACTTTGAC
rs907091	GGTTGATATATCTCAGAAAGAATGTTTCATATAGCACATCTC

Table 2: Extension primer sequence at different sites of the IKZF3 gene.

Statistical analysis

All statistical data analyzed with SPSS 17.0. The measurement data were expressed as the mean±SD. Differences in age between cases and healthy control groups were compared using Student's t-test, whereas differences in gender were evaluated by the $\varkappa^2$ test. Hardy-Weinberg equilibrium (HWE) was tested using $\varkappa^2$ test. Genotype and allele frequencies of IKZF3 were compared by the $\varkappa^2$ test too. Haplotype analysis was performed using SHEsis software (http://analysis.bio-x.cn/myAnalysis.php). The association of the three SNP polymorphisms and risk of SLE was evaluated by odds ratio (OR) with 95% confidence interval (95% CI). OR and 95% CI were adjusted based on age and gender using logistic regression. A value of P <0.05 was considered statistically significant.

Results

Clinical characteristics of the study subjects

The clinical characteristics of patients with SLE and the healthy controls are shown in Table 3. There was no significant difference between cases and controls in age (P=0.634) and gender (P=0.701).

Hardy-Weinberg balance test

Genotype distributions for SNP rs114509391, rs907092 and rs907092 were in the range of predicted HWE, no matter in the patient group or the control group (P>0.05).

Characteristics	SLE n =213 (%)	Control n =187 (%)	*P*
Male/Female	16 (7.5) / 197 (92.5)	16 (8.6) / 171 (91.4)	0.701
Age(median, years)	32.93±12.15	33.48±10.61	0.634
Abnormal blood system(+)	58 (27.2)		
Renal disorder(+)	116 (54.5)		
Malar rash(+)	143 (67.1)		
Discoid erythema(+)	9 (4.2)		
Photosensitivity(+)	106 (49.8)		
Complement depressed(+)	171 (80.3)		
Accelerated ESR(+)	67 (48.2)		
Anti-nuclear(+)	198 (93.0)		
Anti-SSA(+)	149 (70.0)		
Anti-SSB(+)	42 (19.7)		
Anti-RNP(+)	112 (52.6)		
Anti-Sm(+)	79 (37.1)		
Anti-dsDNA(+)	65 (30.5)		
Anti-nucleosome(+)	76 (35.7)		

Table 3: Clinical characteristics of the SLE patients and the healthy controls.

Polymorphisms in IKZF3 gene with SLE risk

Two genotypes were detected in the rs114509391 polymorphisms, and three genotypes were detected in the rs907091 and rs907092 polymorphisms. The genotype and allele distributions of rs907091, rs907092 and rs114509391 in SLE and controls are shown in Table 5. However, the genotypes and allele frequencies of rs907091, rs907092 and rs114509391 had no significant association with SLE risk (P>0.05). There was no significant difference in genotype frequency between SLE and healthy controls under 3 different genetic models (P>0.05) (Table 4).

Association of IKZF3 gene with clinical characteristics

We performed stratification analysis between IKZF3 gene and clinical characteristics of SLE, as well as compared allele frequencies of rs907091, rs907092 and rs114509391 between positive patients, negative patients and healthy controls in thirteen clinical characteristics.

The results showed an association between rs114509391 and photosensitivity in the distribution of allele frequencies (negative-control: P=0.0442, OR= 0.243, 95%CI 0.061-0.963, as shown in Table 5; positive-negative: P=0.018, OR=5.248,95% CI 1.324-20.804). This indicated the C allele may be a protective factor for light-nonsensitive SLE and a risk factors for light-sensitive SLE, and no correlation was found in other phenotypic analyses (P>0.05).

No correlation was found between rs907191 and rs907192 and SLE in the stratified analysis (P>0.05).

Polymorphisms	SLE n (%)	controls n (%)	*P*	OR (95%CI)
rs114509391				
A	414 (97.2)	360 (96.3)	0.461	1.342 (0.614-2.933)
C	12 (2.8)	14 (3.7)		
AC	12 (5.6)	14 (7.5)	0.453	0.738 (0.333-1.633)
CC	0 (0)	0 (0)	/	/
AA	201 (94.4)	173 (92.5)		1
Recessive mode				
CC vs(AC+AA)	0/213	0/187	/	/
Dominant mode				
(CC+AC) vs AA	12/201	14/173	0.453	0.803 (0.368-1.755)
Cumulative mode				
AC vs AA	12/201	14/173	0.453	
Rs907092				
A	123 (28.9)	99 (26.5)	0.449	1.128 (0.826-1.541)
G	303 (71.1)	275 (73.5)		
AG	93 (43.7)	75 (40.1)	0.426	1.181 (0.784-1.779)
AA	15 (7.0)	12 (6.4)	0.672	1.190 (0.533-2.658)
GG	105 (49.3)	100 (53.5)		1
Recessive mode				
AA vs(AG+GG)	15/198	12/175	0.804	1.105 (0.504-2.425)
Dominant mode				
(AA+AG) vs GG	108/105	87/100	0.404	1.182 (0.798-1.751)
Cumulative mode				
AG vs AA vs GG	93/15/105	75/12/100	0.706	
Rs907091				
C	127 (29.8)	102 (27.3)	0.363	1.153 (0.848-1.567)
T	299 (70.2)	277 (74.1)		
CT	95 (44.6)	78 (41.7)	0.481	1.158 (0.770-1.741)
CC	16 (7.5)	12 (6.4)	0.559	1.268 (0.571-2.816)
TT	102 (47.9)	97 (51.9)		1
Recessive mode				
CC vs(CT+TT)	16/197	12/175	0.669	1.184 (0.546-2.567)
Dominant mode				
(CC+CT) vs TT	111/102	90/97	0.427	1.173 (0.791-1.738)
Cumulative mode				
CC vs CT vs TT	16/95/102	12/78/97	0.712	
Note:"/"is the place where *P*, OR or 95% CI can not be calculated.				

Table 4: Distribution of polymorphisms of IKZF3 gene in SLE and controls.

Haplotype analysis of the IKZF3 gene

Haplotype analysis was performed by online SHEsis software and the possible haplotype frequencies are shown in Table 6. The maximum haplotype (AGT) accounted for 67.1% and 69% in the SLE and the controls, respectively. No haplotypes was associated with the risk of SLE (P>0.05).

Clinical features		Allele n(%)		*P*	OR (95%CI)
		C	A		
Abnormal blood system	Positive	2 (1.72)	114 (98.28)	0.4411*	0.451 (0.059-3.423)*
	Negative	10 (3.26)	300 (96.77)	0.7142#	0.857 (0.375-1.958)#
	Control	14 (3.74)	360 (96.26)		1
Renal disorder	Positive	7 (3.02)	225 (96.98)	0.6351*	0.800 (0.319-2.007)*
	Negative	5 (2.58)	189 (97.42)	0.4642#	0.680 (0.242-1.908)#
	Normal	14 (3.74)	360 (96.26)		1
Malar rash	Positive	10 (3.50)	276 (96.50)	0.8671*	0.932 (0.408-2.126)*
	Negative	2 (1.43)	138 (98.57)	0.2892#	0.373 (0.060-2.309)#
	Normal	14 (3.74)	360 (96.26)		1
Discoid erythema	Positive	0 (0)	18 (100)	11*	/
	Negative	12 (2.94)	396 (97.06)	0.5322#	0.779 (0.356-1.704)#
	Normal	14 (3.74)	360 (96.26)		1
Photosensitivity	Positive	10 (4.72)	202 (95.28)	0.5681*	1.273 (0.557-2.912)*
	Negative	2 (0.93)	212 (99.07)	0.0442#	0.243 (0.061-0.963)#
	Normal	14 (3.74)	360 (96.26)		1
Complement depressed	Positive	11 (3.22)	331 (96.78)	0.7011*	0.855 (0.384-1.904)*
	Negative	1 (1.19)	83 (98.81)	0.3962#	0.310 (0.021-4.638)#
	Normal	14 (3.74)	360 (96.26)		1
Accelerated ESR	Positive	2 (1.49)	132 (98.51)	0.3211*	0.390 (0.061-2.507)*
	Negative	2 (1.39)	142 (98.61)	0.2702#	0.362 (0.060-2.198)#
	Normal	14 (3.74)	360 (96.26)		1
Anti-nuclear	Positive	12 (3.03)	384 (96.97)	0.5841*	0.804 (0.368-1.755)*
	Negative	0 (0)	30 (100)	0.5762#	/
	Normal	14 (3.74)	360 (96.26)		1
Anti-SSA	Positive	10 (3.36)	288 (96.64)	0.7881*	0.893(0.391-2.041)*
	Negative	2 (1.56)	126 (98.44)	0.3572#	0.408 (0.061-2.750)#
	Normal	14 (3.74)	360 (96.26)		1
Anti-SSB	Positive	2 (2.38)	82 (97.62)	0.7751*	0.627 (0.026-15.307)*
	Negative	10 (2.92)	332 (97.08)	0.5432#	0.775 (0.341-1.762)#
	Normal	14 (3.74)	360 (96.26)		1
Anti-RNP	Positive	8 (3.57)	216 (96.43)	0.9141*	0.952 (0.395-2.295)*
	Negative	4 (1.98)	198 (98.02)	0.2462#	0.519 (0.171-1.571)#
	Normal	14 (3.74)	360 (96.26)		1
Anti-Sm	Positive	6 (3.95)	152 (96.20)	0.9761*	1.015 (0.403-2.554)*
	Negative	6 (2.24)	262 (97.76)	0.2792#	0.589 (0.226-1.536)#
	Normal	14 (3.74)	360 (96.26)		1
Anti-dsDNA	Positive	2 (1.54)	128 (98.46)	0.3451*	0.402 (0.061-2.661)*
	Negative	10 (3.38)	286 (96.62)	0.8012#	0.899 (0.394-2.051)#
	Normal	14 (3.74)	360 (96.26)		1
Anti-nucleosome	Positive	2 (1.32)	150 (98.68)	0.2341*	0.343 (0.059-2.000)*
	Negative	10 (3.65)	264 (96.35)	0.9502#	0.974 (0.431-2.204)#
	Normal	14 (3.74)	360 (96.26)		1
Note: "/"is the place where P, OR or 95% CI can not be calculated;					

Table 5: Association of allele frequencies in rs114509391 with clinical features in SLE patients.

haplotype	SLE 2n=426	Controls 2n=374	OR (95%CI)	*P*	χ2
AAC	122 (28.6)	99 (26.5)	1.125 (0.824-1.537)	0.458	0.550
AGC	5 (1.2)	3 (0.8)	-	-	-
AGT	286 (67.1)	258 (69)	0.934 (0.691-1.263)	0.656	0.198
CAC	0 (0)	0 (0)	-	-	-
CGT	12 (2.8)	14 (3.7)	0.753 (0.343-1.650)	0.477	0.506
AAT	1 (0.2)	0 (0)	-	-	-
Note: "/"is the place where *P*, OR or 95% CI can not be calculated; in the data analysis, major haplotype - haplotype with frequency less than 3% will not be considered in the statistical analysis.					

Table 6: Haplotype analysis of the IKZF3 polymorphisms with risk of SLE.

Linkage disequilibrium of the IKZF3 gene

Linkage disequilibrium analysis was performed by online SHEsis software. There was linkage disequilibrium between 3 SNPs, rs114509391 and rs907192 (D'=0.998, r2=0.013), rs114509391 and rs907191 (D'=0.998, r2=0.013), rs907092 and rs907091 (D'=0.994, r2=0.946) had strong linkage disequilibrium (Table 7, fig 1-2).

Site	rs114509391	rs907092	rs907091
rs114509391	-	0.998	0.998
rs907092	0.013	-	0.994
rs907091	0.013	0.946	-
Note: The upper right triangle is D'- chain unbalance coefficient; The lower left triangle is r^2- correlation coefficient.			

Table 7: Linkage disequilibrium of the IKZF3 with SLE(r2/D').

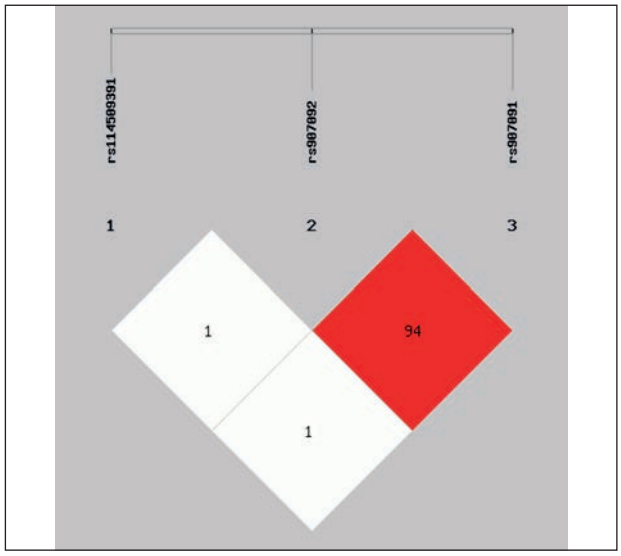

Fig. 1: Chain imbalance D 'value of SLE.

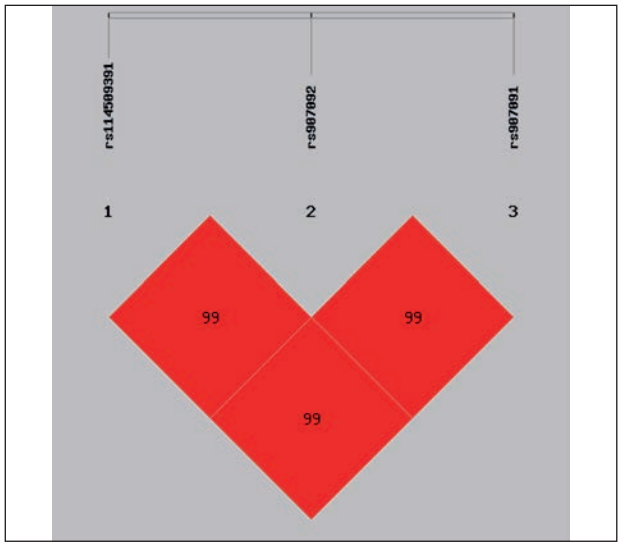

Fig. 1: Chain imbalance D 'value of the healthy control.

Discussion

IKZF3 (Aiolos), Ikaros (IKZF1) and Helios belong to the Ikaros family, they have the zinc finger structure, which mainly expressed in lymphoid tissues and are involved in the regulation of lymphocyte development, differentiation, function maintenance and apoptosis[17]. The product IKZF3 expresses highly in mature peripheral B cells, and also detected in B and T cell precursors. The IKZF3 gene not only participates in chromatin remodeling and histone deacetylation, but also is an important transcription factor, and inhibit B cell proliferation and differentiation[18]. The protein encoded by IKZF3 gene could induce the expression of immunosuppressive enzymes[19]. Current studies have shown that SNPs of the IKZF3 gene is related to diabetes, Graves' disease, rheumatoid arthritis (RA) and asthma, multiple myeloma[12-16], which indicate it is involved in the occurrence of autoimmune diseases. Studies by Sun J have shown that mice lacking the IKZF3 gene can produce anti-ds-DNA antibodies that cause systemic lupus erythematosus and immune complex-mediated nephritis[20]. Our previous study suggests that the mRNA and protein of the IKZF3 gene significantly reduced in SLE patients and have a certain correlation with the SLE activity[21-23].

In this study, the SNPs in the exons of IKZF3 gene were screened by resequencing, and three SNPs (rs114509391, rs907091, rs907092) were found (MAF>0.05). To investigate the relationship between the IKZF3 gene and SLE in the Guizhou Han population, the SNaPshot technique was used for genotyping. There was no significant difference in the genotypes and allele frequencies of the three SNPs (rs114509391, rs907091, rs907092) between the SLE and healthy controls. An unconditional logistic regression model analysis showed that the three SNPs has no significant differences in the genotype frequencies between the SLE and the healthy controls under the dominant, recessive and cumulative genetic models. Linkage disequilibrium analysis revealed linkage disequilibrium between the three SNPs. there were no significant differences in the distribution of six haplotypes (AACG, ACCA, GCCG, GCTG, GCTG, ACTA) in the SLE group and the healthy control group, and each haplotype was not associated with the pathogenesis of SLE. In our study, rs114509391 was correlated with the clinical characteristics of photosensitivity, The C allele frequency in the photonegative SLE was lower than healthy controls, and the difference was statistically significant, suggesting that the C allele may be a protective factor for photonegative SLE, The C allele was associated with photosensitivity of SLE. Ye[9] found that the C allele of rs114509391 was statistically lower in SLE patients than healthy controls and the rs114509391 was related to the SLE clinical characteristics in southern China Han population.

We take the Guizhou Han population as the study subjects and found that the rs114509391 locus was only related to the photosensitivity of SLE, and there was no difference in genotypes and alleles between SLE and healthy control. For the 907091 locus, Cai[10] found that it was related to SLE in the Chinese Han population , the frequency of C allele was significantly lower in the SLE than the healthy control. In another study, the rs907091 had no significant association with SLE risk in genotype and allele frequency, only in ds-DNA antibodies and kidney damage; In our study, the frequency of the C allele of rs907091 was slightly higher than the normal, but the difference was not statistically significant, there was no significant difference in genotype and allele frequency frequency and clinical characteristics between SLE and healthy controls too; the results in the three regions were different. The rs907092 loci has been found to be significantly related to asthma(13), and there are relatively few studies related to SLE. In our study, we found the rs907092 had no correlation with SLE in Guizhou Han population, which is consistent with Cai's study[23].

We analyzed this result for the following reasons:

• The sample size in this study was limited, the difference of the genotypes and allele frequencies of subjects was very small, which may result in the difference not be presented and negative result;

• the collected subjects were all from Guizhou Province, and the regional limitations may interfere with the results;

• Only three SNPs in the exon region were analyzed in this study, whose MAF>0.05, we did not screen SNP sites in regulatory regions and intron regions. The association of a low frequency SNP with disease requires a larger sample size to perform a genetic association study; 4) in linkage and association analysis, one or more negative genetic results can not be used as a basis to exclude the site as a disease-related site, one or more positive genetic markers also not show that the site is a related site. In the future, Gene-gene interaction studies still need to be further developed, not only a single locus is analyzed for association analysis.

Conclusion

The rs114509391 locus has a certain correlation with the clinical phenotype of SLE in the Guizhou Han population and the C allele may be a protective factor for light-nonsensitive SLE. The protection mechanism should be explored to provide new clues for SLE treatment at the molecular level. However, there is no significant correlation between rs907091 and rs907092 of IKZF3 gene and SLE in the Guizhou Han population.

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Acknowledgement

This study was supported by Zunyi Science and Technology Bureau (Zunshi Keheshezi (2014) No. 84),The Science and Technology Fund of Guizhou Provincial Health Commission(gzwjkj2017-1-040) and Joint Fund of Guizhou Provincial Department of Science and technology(Qian Kehe LH word [2015] No. 7474).

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