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ORIGINAL RESEARCH

Contribution of Interleukin-1 Receptor-Associated Kinase 1 Gene Polymorphism to Systemic Lupus Erythematosus in Chinese Patients

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Introduction: Systemic lupus erythematosus (SLE) is a complex autoimmune condition distinguished by a wide range of clinical manifestations and numerous genetic predisposition factors. The aim of the current study was to analyze the association between the IRAK1 polymorphisms (rs3027898 and rs1059702) and SLE in a Chinese cohort.

Patients and Methods: A total of 150 SLE patients and 168 healthy controls of Chinese ethnicity were included in this study. The genotyping of IRAK1 was performed using sequence-specific primers (SSP)-polymerase chain reaction. Additionally, correlations between the SNPs and clinical manifestations of SLE were evaluated.

Results: In comparison to the wild genotype CC of rs3027898, the homozygous mutation AA exhibited a significant association with a reduced risk of SLE across homozygous (AA vs CC, OR = 0.270, 95% CI = 0.086–0.847, $p = 0.017$), dominant (CA+AA vs CC, OR = 0.601, 95% CI = 0.375–0.964, $p = 0.034$) and recessive models (AA vs CA+CC, OR = 0.301, 95% CI = 0.097–0.937, $p = 0.029$). The A allele of rs3027898 demonstrated a negative correlation with susceptibility to SLE (A vs C, OR = 0.580, 95% CI = 0.388–0.866, $p = 0.007$). Furthermore, rs3027898 and rs1059702 were found to be in strong linkage disequilibrium ($D' = 0.914$, $r^2 = 0.809$). The frequency of haplotype HT2 (A/G) was significantly lower in SLE patients compared to controls (OR = 0.465, 95% CI = 0.300–0.723, $p < 0.001$), while haplotype HT3 (C/G) was positively correlated with an increased susceptibility to SLE (OR = 3.838, 95% CI = 1.406–10.480, $p = 0.005$).

Conclusion: The findings suggest that polymorphisms in IRAK1 are associated with a reduced risk of SLE within a Chinese demographic. These genetic variations may serve as potential biomarkers for assessing SLE risk and offer novel perspectives on the molecular mechanisms that underpin the disease.

Keywords: SLE, IRAK1, single nucleotide polymorphism, haplotype, TLR signaling pathway

Introduction

Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune condition characterized by an aberrant immune response that results in the generation of autoantibodies and the deposition of immune complexes. This pathological process leads to both systemic and localized tissue damage, as well as dysfunction of various organs.[1] The etiology of SLE is multifaceted, involving intricate interactions between genetic predispositions and environmental factors that contribute to the onset and progression of the disease.[2] A multitude of studies have identified specific genetic loci

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associated with SLE, particularly those encoding proteins involved in immune signaling pathways, thereby highlighting the significant role of genetic determinants in the susceptibility to this disorder.

Interleukin-1 receptor-associated kinase 1 (IRAK1), a serine/threonine protein kinase, is integral to the modulation of immune responses mediated by toll-like receptors (TLRs).[3] Within the myeloid differentiation primary response 88 (MyD88)-dependent signaling pathway, IRAK1 promotes the activation of tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) and the nuclear factor-κB (NF-κB) signaling pathways.[4] Dysregulated activation of NF-κB has been linked to SLE, contributing to the heightened inflammatory responses and immune dysregulation observed in affected individuals.[5,6] Furthermore, aberrant IRAK1 activity has been correlated with a range of autoimmune disorders, indicating its significant role as a principal mediator of inflammation and autoimmunity.[4]

Single nucleotide polymorphisms (SNPs) within the IRAK1 gene have been identified as potential contributors to susceptibility to SLE, particularly among females, due to the gene's localization on the X chromosome.[7,8] Notably, the SNPs rs1059702 (A > G) and rs3027898 (C > A) have attracted considerable interest because of their possible functional implications.[9,10] The rs1059702 variant results in a nonsynonymous substitution that may modify IRAK1 kinase activity, potentially resulting in hyperactivation of the immune response, which is a characteristic feature of SLE.[9,11,12] Conversely, the rs3027898 variant may influence the binding of transcription factors, thereby modulating IRAK1-mediated inflammatory responses.[10] Collectively, these genetic variations are posited to play a role in the chronic immune activation and inflammation observed in SLE.

Moreover, research has established associations between IRAK1 polymorphisms and the predisposition to various autoimmune disorders, including multiple sclerosis, rheumatoid arthritis, and neuromyelitis optica spectrum disorder (NMOSD), highlighting the broader implications of these genetic variations in the regulation of immune responses.[13–17] Notwithstanding the considerable body of research, the influence of IRAK1 SNPs on susceptibility to SLE across diverse ethnic groups remains inadequately elucidated. This research investigates the role of polymorphisms in the IRAK1 gene, specifically rs1059702 and rs3027898, in the susceptibility to SLE among Chinese patients. By analyzing the relationship between these SNPs and the risk of developing SLE, the study seeks to enhance the understanding of the genetic underpinnings of SLE within this demographic. This may further elucidate the pathogenesis of the disease and highlight potential pathways for the development of personalized therapeutic interventions.

Materials and Methods

Patients and Controls

A total of 318 participants, comprising Han Chinese individuals from northern China, were enrolled in this study. Among these, 150 subjects diagnosed with SLE were exclusively female, with a mean age of 36.5 ± 11.8 years. The healthy control (HC) group consisted of 168 women, with a mean age of 36.3 ± 12.6 years. The diagnosis of SLE in patients was established in accordance with the 1997 revised criteria set forth by the American College of Rheumatology (ACR).[18] The exclusion criteria included individuals with concurrent autoimmune or infectious diseases, recent cancer diagnoses, and those who were pregnant or lactating. The control group consisted of healthy volunteers who were matched for age and sex, with the stipulation that they had no previous history of autoimmune disease. The study received ethical approval from the Ethics Committees of the First Affiliated Hospital of Henan University of Science and Technology (2023–03-K0049). Peripheral blood samples were collected from all participants following the acquisition of written informed consent. The study incorporated clinical characteristics and physical/physiological attributes associated with SLE, including malar rash, arthritis, serositis, and nephritis. Clinical data were gathered from patients diagnosed with SLE, encompassing measurements of anti-dsDNA antibodies, anti-nuclear antibodies (ANA), complement components C3 and C4, high sensitivity C-reactive protein (hs-CRP), and erythrocyte sedimentation rate (ESR).

Genomic DNA Extraction

Genomic DNA was extracted from approximately 2 mL anti-coagulated whole blood collected in Ethylenediaminetetraacetic acid (EDTA) tubes from both patients and healthy controls, utilizing the Blood Genomic

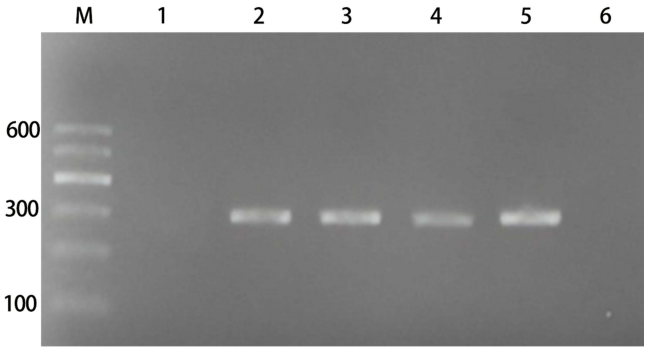


Figure 1 Representative genotyping of IRAK1 rs1059702 by PCR-SSP. A 307 bp band indicated the presence of the allele; amplification failure indicated the absence of the allele; Lane (M) marker; Lane 1, 2: GG genotype; Lane 3, 4: AG genotype; Lane 5, 6: AA genotype.

DNA Extraction Kit (Solarbio, China). DNA quality and concentration were assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA). Samples were stored at −80°C until further analysis.

IRAK1 Genotyping

The SNPs rs3027898 and rs1059702 were determined by sequence-specific primers (SSPs)-polymerase chain reaction. For the genotyping of rs3027898, the following primers were employed: 5′-CCTGGACGCTCAAGAACCC-3′ (forward), 5′-CCTGGACGCTCAAGAACCA-3′(forward) and 5′-GCCACTACCCAAGGTCTAGC-3′ (reverse). In the case of rs1059702, the primers used were: 5′- GGGGCCAGCAAAACGGAA-3′ (forward), 5′-GGGGCCAGCAAAACGGAG -3′ and 5′- CAAGCCCTGCTTCCCTGTG −3′ (reverse). The PCR was conducted in a total reaction volume of 20 μL, which included 10 μL of 2× San Taq PCR Master Mix (with Blue Dye) (Sangon Biotech, China), 0.8 μL of gene-specific primers (10 μM of each, Sangon Biotech, China), 7.4 μL of DNase-RNase free water, and 1μL of template DNA (50 ng/μL). Amplification was performed using a 9600 thermal cycler (Hema, China) under the following conditions: an initial cycle at 94°C for 3 min, followed by 30 cycles consisting of denaturation at 94°C for 30s, annealing at 62°C for 30s, and extension at 72° C for 40s, concluding with a final extension of 72°C for 5 min. The resultant PCR products were analyzed via 2% agarose gel electrophoresis and visualized under ultraviolet light. The expected product sizes were 404 bp for the C and the A alleles of the IRAK1 rs3027898 polymorphism, and 307 bp for the A and the G alleles of the rs1059702 polymorphism (Figure 1, Supplemental Figure 1). To ensure quality control, randomly selected samples from both cases and controls, representing all IRAK1 genotypes, were reevaluated using Sanger sequencing, and the sequencing data were analyzed using Chromas version 2.6.6 (Technelysium Pty Ltd, South Brisbane, Queensland, Australia).

Statistical Analysis

The genotypes of the control group were evaluated for Hardy-Weinberg equilibrium through application of the chi-square ($\chi 2$) test. This statistical test was utilized to assess the potential association between alleles and genotypes among the individuals and the control group. The analysis was conducted using SPSS software version 17.0 to ascertain the presence of any associations. The relationship with susceptibility to SLE was examined by calculating the odds ratio (OR) along with 95% confidence intervals, with *P* values below 0.05 deemed statistically significant. Statistical power analysis was conducted using G*Power 3.1. Additionally, the construction of haplotype block patterns and the analysis of linkage disequilibrium (LD) were carried out using Haploview 4.2. Pairwise r^2 values were computed based on the genotypes of 151 healthy controls, and haplotype frequencies along with association tests were also performed using the same software. To explore the relationship between the IRAK1 SNPs and specific clinical phenotypes of SLE, the SLE patients were further stratified based on clinical features such as lupus nephritis, cutaneous involvement, neuropsychiatric manifestations, and autoantibody profiles. Associations between the IRAK1 SNPs and these clinical manifestations were analyzed using the chi-square test to identify genotype-phenotype correlations.

Results

Demographic and Clinical Characteristics of Subjects

Table 1 displays the demographic and clinical traits of all SLE patients as well as healthy controls. The average age of SLE patients was 35.0 ± 13.5 years, and that of HCs was 36.3 ± 12.6 years, with no significant differences between the two groups on the distribution of age and gender ($p > 0.05$). In addition, 36.0% of patients were positive for anti-dsDNA antibodies, 74.7% were positive for ANA, 30.0% had decreased C3, 50.7% had decreased C4, 38.0% had increased ESR, 13.3% had increased hs-CRP, 56.6% had rash, and 51.6% had nephritis.

Genotyping and HWE

In the present study, we assessed all the SNPs for Hardy-Weinberg equilibrium (HWE) within control group. The genotypic distributions for all loci conformed to Hardy-Weinberg equilibrium ($p > 0.05$ for all), indicating that the selected sample population was representative (Table 2).

Table 2 presents the distributions of alleles and genotypes for the IRAK1 polymorphisms rs3027898 and rs1059702 among both patients and controls. Notably, there were significant differences in the distribution of genotype and allele frequencies for the rs3027898 polymorphism between the patient and control groups ($p = 0.032$, $p = 0.007$). Power analysis showed that the statistical power of this effect was 76.9%. Conversely, the allele and genotype distributions for the rs1059702 polymorphism did not exhibit significant differences between patients with SLE and healthy controls ($p = 0.052$, $p = 0.146$).

Table 1 The Clinical Characteristics of Patients with SLE

Characteristics		SLE, n (%)
Rash		69(56.6%)
Photosensitivity		28(23.0%)
Oral ulcer		12(9.8%)
Alopecia		19(15.6%)
Leukopenia		34(27.9%)
Arthritis		18(14.8%)
Nephritis		63(51.6%)
Serositis		16(13.1%)
Anti-dsDNA Ab	Positive	54(36.0%)
	Negative	68(45.3%)
ANA	Positive	112(74.7%)
	Negative	10(6.7%)
C3	Normal	73(48.7%)
	Decreased	45(30.0%)
C4	Normal	42(28.0%)
	Decreased	76(50.7%)
hs-CRP	Normal	102(68.0%)
	Increased	20 (13.3%)
ESR	Normal	65 (43.3%)
	Increased	57 (38.0%)

Abbreviations: Anti-dsDNA, double-stranded DNA antibody; ANA, anti-nuclear antibody; C3, complement 3; C4, complement 4; hs-CRP, high sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 2 Genotype and Allele Frequencies of the IRAK1 and Hardy-Weinberg Equilibrium Test

Genotype/Allele	Case (n = 150)	Control (n = 168)	*P*-value	*P*/HWE
rs3027898				
CC	108(72.0%)	102(60.7%)	**0.032**	0.057
CA	38(25.3%)	52(31.0%)		
AA	4(2.7%)	14(8.3%)		
C	254(84.7%)	256(76.2%)	**0.007**	
A	46(15.3%)	80(23.8%)		
rs1059702				
AA	104(69.4%)	103(61.3%)	0.146	0.088
AG	41(27.3%)	52(31.0%)		
GG	5(3.3%)	13(7.7%)		
A	249(83.0%)	258(76.8%)	0.052	
G	51(17.0%)	78(23.2%)		

Note: Bold values represent statistically significant, $p < 0.05$.
Abbreviation: HWE, Hardy-Weinberg equilibrium.

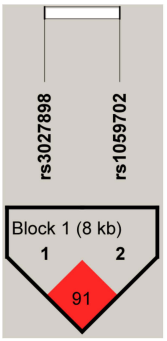
Correlation Analysis between rs3027898 or rs1059702 and the SLE Risk in Different Models

In the present investigation, we employed five genetic models to examine the association between SNPs within the IRAK1 gene and the risk of SLE. These models included heterozygous, homozygous, dominant, recessive and allelic configurations (Table 3). Specifically, for the rs3027898 variant, the homozygous AA genotype demonstrated a significant correlation with SLE diagnosis when compared to the CC genotype (AA vs CC, OR = 0.270, 95% CI = 0.086–0.847, $p = 0.017$). Additionally, both the AA and CA genotypes of rs3027898 were associated with a reduced risk in compared to the wild-type CC genotype (CA+AA vs CC, OR = 0.601, 95% CI = 0.375–0.964, $p = 0.034$). The analysis of recessive genetic model revealed a significant difference in the frequency of AA genotypes versus CA+CC genotypes within the SLE and control groups (AA vs CA+CC, OR = 0.301, 95% CI = 0.097–0.937, $p = 0.029$). Furthermore, the allelic model indicated that the presence of the A allele was significantly associated with SLE diagnosis (A vs C, OR = 0.580, 95% CI = 0.388–0.866, $p = 0.007$). Conversely, the rs1059702 polymorphism did not exhibit a significant correlation with SLE risk across any of the five genetic models.

Table 3 Distribution of IRAK1 rs3027898 and rs1059702 Genotypes and Allelic Frequencies in Five Genetic Models

Polymorphisms	Genetic Model	Genotype	OR (95% CI)	*P*-value
rs3027898	Heterozygous	CA vs CC	0.690(0.419–1.136)	0.144
	Homozygous	AA vs CC	0.270(0.086–0.847)	**0.017**
	Dominant	CA+AA vs CC	0.601(0.375–0.964)	**0.034**
	Recessive	AA vs CA+CC	0.301(0.097–0.937)	**0.029**
	Allele	A vs C	0.580(0.388–0.866)	**0.007**
rs1059702	Heterozygous	AG vs AA	0.781(0.478–1.277)	0.324
	Homozygous	GG vs AA	0.381(0.131–1.107)	0.067
	Dominant	AG+GG vs AA	0.701(0.440–1.117)	0.134
	Recessive	GG vs AG+AA	0.411(0.143–1.182)	0.090
	Allele	G vs A	0.677(0.457–1.044)	0.052

Note: Bold values represent statistically significant, $p < 0.05$.
Abbreviations: OR, odds ratio; CI, confidence interval.



L1	L2	D′	r^2
rs3027898	rs1059702	0.914	0.809

Haplotype		Frequency (%)
HT1	C/A	0.747
HT2	A/G	0.217
HT3	C/G	0.015
HT4	A/A	0.021

Figure 2 Haplotype and linkage disequilibrium (LD) coefficients among two SNPs in IRAK1 gene. Estimates of LD between SNPs were determined by calculating pair-wise Lewontin's /D′/ and r^2 statistics in unrelated individuals.

Linkage Disequilibrium and Haplotype Analysis

The haplotype analysis indicated a strong linkage disequilibrium between rs3027898 and rs1059702, with D′ = 0.914 and r^2 = 0.809, as illustrated in Figure 2. The distribution of IRAK1 haplotypes of rs3027898 and rs1059702 among patients with SLE and control subjects is presented in Table 4. An association was identified between the HT3 (C/G) haplotype and SLE (OR = 3.838, 95% CI = 1.406–10.480, $p = 0.005$), suggesting an elevated risk for SLE. Conversely, the HT2 (A/G) haplotype demonstrated a protective effect in SLE patients (OR = 0.465, 95% CI = 0.300–0.723, $p < 0.001$) (Table 4).

Associations Between SLE Phenotype and SNPs

To further explore the relationship between IRAK1 SNPs and specific SLE clinical manifestations, the SLE patients were stratified based on clinical features, including anti-dsDNA, antinuclear antibodies (ANA), complement 3 (C3), complement 4 (C4), hypersensitive C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR). The results indicated that there were no statistically significant differences in genotype frequencies (Table 5).

Table 4 Haplotype Frequencies of IRAK1 Gene in Case and Control Groups

Haplotype	rs3027898	rs1059702	Case (freq.)	Control (freq.)	*P*-value	OR (95% CI)
HT1	C	A	237(79.1%)	251(74.7%)	0.188	1.283(0.885–1.859)
HT2	A	G	34(11.4%)	73 (21.7%)	**<0.001**	0.465(0.300–0.723)
HT3	C	G	17(5.6%)	5(1.5%)	**0.005**	3.838(1.406–10.480)
HT4	A	A	12(3.9%)	7(2.1%)	0.181	1.887(0.733–4.858)

Note: Bold values represent statistically significant, $p < 0.05$.
Abbreviations: OR, odds ratio; CI, confidence interval.

Table 5 Association of IRAK1 rs3027898 and rs1059702 with Clinical Characteristics of Patients with SLE

Characteristics	rs3027898 (C>A)			rs1059702 (A>G)		
	CC	CA, AA	*p* value	AA	AG, GG	*p* value
	n = 84 (68.8%)	n = 38 (31.2%)		n = 80 (65.5%)	n = 42 (34.5%)	
Anti-dsDNA (+)	40(47.6%)	14(36.8%)	0.267	39(48.8%)	15(35.7%)	0.168
ANA (+)	78(92.9%)	34(89.5%)	0.784	74(92.5%)	38(90.5%)	0.968
Decreased C3	31(36.9%)	14(36.8%)	0.949	27(33.8%)	18(42.9%)	0.347
Decreased C4	50(59.5%)	26(68.4%)	0.146	48(60.0%)	28(66.7%)	0.239

(*Continued*)

Table 5 (Continued).

Characteristics	rs3027898 (C>A)			rs1059702 (A>G)		
	CC	CA, AA	*p* value	AA	AG, GG	*p* value
	n = 84 (68.8%)	n = 38 (31.2%)		n = 80 (65.5%)	n = 42 (34.5%)	
Increased hs-CRP	14(16.7%)	6(15.8%)	0.904	13(16.3%)	7(16.7%)	0.953
Increased ESR	41(48.8%)	16(42.1%)	0.492	39(48.8%)	18(42.9%)	0.535
Rash	45(53.6%)	24(63.2%)	0.323	43(53.8%)	26(61.9%)	0.388
Nephritis	43(51.2%)	20(52.6%)	0.833	38(47.5%)	25(59.5%)	0.207
Serositis	9(10.7%)	7(18.4%)	0.243	10(12.5%)	6(14.3%)	0.781

Note: + means positive.
Abbreviations: Anti-dsDNA, double-stranded DNA antibody; ANA, antinuclear antibodies; C3, complement 3; C4, complement 4; hs-CRP, hypersensitive-c-reactive-protein; ESR, erythrocyte sedimentation rate.

Table 6 Clinical Characteristics According to the Haplotype of IRAK1 Gene in SLE

Characteristics	HT1 (C/A)			HT2 (A/G)			HT3 (C/G)		
	+/+	+/–, –/–	*p* value	+/+	+/–, –/–	*p* value	+/+	+/–, –/–	*p* value
	n = 73 (59.8%)	n = 49 (40.2%)		n = 3 (2.4%)	n = 119 (97.6%)		n = 4 (3.3%)	n = 118 (96.7%)	
Anti-dsDNA (#)	37(50.7%)	14(28.6%)	**0.015**	1(33.3%)	107(89.9%)	>0.999	2(50.0%)	52(44.1%)	>0.999
ANA (#)	68(93.2%)	20(40.8%)	**<0.001**	3(1.0)	109(91.6%)	>0.999	4(1.0)	108(91.5%)	>0.999
Decreased C3	25(34.2%)	20(40.8%)	0.513	2(66.7%)	43(36.1%)	0.668	0(0)	45(38.1%)	0.283
Decreased C4	43(58.9%)	33(67.3%)	0.184	2(66.7%)	74(62.2%)	>0.999	2(50.0%)	74(62.7%)	0.935
Increased hs-CRP	11(15.1%)	9(18.4%)	0.629	1(33.3%)	19(16.0%)	0.418	1(25.0%)	19(16.1%)	0.516
Increased ESR	36(49.3%)	21(42.9%)	0.483	0(0)	114(95.8%)	**<0.001**	1(25.0%)	56(47.5%)	0.707
Rash	38(52.1%)	31(63.3%)	0.221	2(66.7%)	67(56.3%)	>0.999	3(75.0%)	66(55.9%)	0.632
Nephritis	37(50.7%)	26(53.1%)	0.797	2(66.7%)	61(51.3%)	>0.999	2(50.0%)	61(51.7%)	>0.999
Serositis	9(12.3%)	7(14.3%)	0.754	0(0)	16(13.4%)	>0.999	1(25.0%)	15(12.7%)	0.434

Notes: + means having a HT, − means not having a HT, # means positive. Bold values represent statistically significant, $p < 0.05$.
Abbreviations: HT, haplotype; Anti-dsDNA, double-stranded DNA antibody; ANA, antinuclear antibodies; C3, complement 3; C4, complement 4; hs-CRP, hypersensitive-c-reactive-protein; ESR, erythrocyte sedimentation rate.

The clinical characteristics associated with the identified haplotypes are summarized in Table 6. Among the three haplotypes analyzed for these polymorphisms, patients with haplotype HT1 (C/A) exhibited significantly higher frequencies of anti-dsDNA antibodies and ANA ($p = 0.015$ and $p < 0.001$, respectively). Additionally, patients with haplotype HT2 (A/G) demonstrated a significantly elevated frequency of ESR ($p < 0.001$). Conversely, no statistically significant differences were noted for haplotype HT3 (Table 6).

Discussion

SLE is a complex autoimmune inflammatory disorder that exhibits a notably high incidence among young women. The exact etiology of SLE is not fully elucidated; however, it is widely accepted that a combination of genetic predisposition and environmental factors plays a crucial role in its pathogenesis.[19] Among the genetic components implicated, IRAK1 is recognized as a significant regulator of immune responses. As a key mediator in TLR signaling pathways, IRAK1 activates downstream signaling cascades, including NF-κB and mitogen-activated protein kinase (MAPK), which are essential for the regulation of inflammatory cytokine production and immune responses.[20] These pathways are also associated with various autoimmune and inflammatory diseases, such as diabetes and atherosclerosis.[21,22] SNPs represent one of the most prevalent forms of genetic variation that can affect susceptibility to diseases, including autoimmune disorders like SLE. Within the context of IRAK1, specific SNPs, such as rs1059702 (A > G) and rs3027898 (C > A), are

particularly noteworthy.[9,10] The SNP rs1059702 may result in a nonsynonymous substitution that could alter the structure or function of the IRAK1 protein, potentially leading to hyperactivation of the immune system.[9,11] Similarly, SNP rs3027898 may affect IRAK1 expression by influencing the binding of transcription factors, thereby modulating the inflammatory response.[10] Both polymorphisms have been associated with SLE, especially in females, given that IRAK1 is located on the X chromosome.[8,23]

Recent research has indicated abnormal expression levels of IRAK1 in various autoimmune conditions, including SLE and RA.[23,24] Notably, Zhou et al reported that IRAK1 transcript levels are significantly elevated in CD4+ T cells from SLE patients and show a positive correlation with disease activity.[23] Additionally, elevated IRAK1 expression has been observed in $CD8^+$ T cells and Tregs from individuals with SLE, with a pronounced increase noted in Tregs.[25] Interestingly, the expression levels of IRAK1 in Tregs correlate positively with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores and negatively with serum C3 levels, suggesting a potential role in the severity of the disease. The dysregulation of Tregs is a contributing factor to the immune homeostasis disruption observed in SLE. These findings suggest that IRAK1, through its genetic variations and expression levels, may significantly impact the equilibrium between immune activation and tolerance, thereby contributing to the pathogenesis of SLE.[26]

This research examined the relationship between IRAK1 polymorphisms and the susceptibility to SLE, revealing significant differences in the distribution of genotypes and alleles between SLE patients and control subjects. The findings indicated that the minor allele A of rs3027898 exhibited protective effects against SLE, whereas the major allele C of rs3027898 was linked to an elevated risk of developing the condition. Nonetheless, there was no significant correlation was observed between IRAK1 SNPs and the clinical characteristics of SLE. To our knowledge, this study provides evidence that IRAK1 polymorphisms are associated with SLE risk, offering insights into the molecular mechanisms underlying SLE and aiding in the identification of potential therapeutic targets.

The IRAK1 rs3027898 (C > A) variant is situated in the 3′-flanking region of the IRAK1 gene, positioned 68 base pairs from the transcription end site, in proximity to the binding site of the posttranscriptional regulator miR-146a.[27] This intronic variant may potentially influence the proper folding of the 3′-untranslated region (3′-UTR) of IRAK1 mRNA or interact with other unidentified variants within the IRAK1 sequence, thereby affecting protein expression. Research has indicated that the minor allele A of rs3027898 is linked to a decreased susceptibility to NMOSD, whereas the major allele C is associated with an increased risk of developing SLE.[28] Our findings reveal that in a cohort of Chinese patients with SLE, there are significant differences in genotype and allele frequencies of the IRAK1 rs3027898 polymorphism when compared to a healthy control group, which aligns with observations in the Indian population.[13] Furthermore, the A allele of rs3027898 demonstrates a negative correlation with susceptibility to SLE, which consistent with previous findings reported in the Chinese population.[29]

The rs1059702 polymorphism, which results in a serine to phenylalanine substitution at position 196, alters the structural and functional properties of the resultant protein products. Zhai et al[29] reported an association between rs1059702 and SLE within the Chinese Han population from Anhui province. Conversely, our study did not identify any significant association between rs1059702 and the risk of SLE. This lack of correlation may be attributed to the distinct genetic backgrounds present in different populations, as well as the possibility of a limited sample size in our research. The previous research findings regarding the rs1059702 polymorphism suggest an elevated risk of RA in both pooled analyses and predominantly in Caucasian populations across various genetic models, including homozygous, heterozygous, and allele comparison models.[17] The GG genotype of rs1059702 has been associated with increased susceptibility to autoimmune thyroid disease (AITD), specifically Hashimoto's disease (HD), in female, particularly in the absence of thyroid-associated ophthalmopathy (TAO).[30]

Evidence suggests that complement activation plays a significant role in tissue inflammation and damage, which is a critical factor in the pathogenesis of SLE.[31] Early complement components are essential for the clearance of immune complexes and apoptotic debris; deficiencies in complement components, such as C4 and C1q, are commonly associated with the onset of SLE.[32] Consequently, to examine the relationship between IRAK1 polymorphisms and the clinical characteristics of SLE, we conducted an analysis of anti-dsDNA, ANA, C3, C4, hs-CRP and ESR at disease onset, stratified by the genotypes of rs3027898 and rs1059702. Our findings did not reveal a significant association between IRAK1 SNPs and the clinical features of SLE. In contrast, Li et al reported a modest association between rs1059702 and

the presence of anti-dsDNA antibodies and serositis, which diverges from our findings.[33] Therefore, we cannot dismiss the potential influence of IRAK1 gene mutations on the immune system in SLE. This lack of association may be attributed to the limited number of studies included in our analysis. To further investigate the correlation between rs3027898 and rs1059702 with immune indicators, a larger sample size is necessary for more comprehensive exploration.

To enhance our understanding of the impact of IRAK1 variation on SLE, we conducted an analysis of the linkage disequilibrium between two SNPs. Our findings indicate that the polymorphisms rs3027898 and rs1059702 exhibit a strong linkage disequilibrium within the Chinese population. Furthermore, we explored the relationship between the haplotype structures of the rs3027898 and rs1059702 variants and their association with SLE susceptibility. Specifically, haplotype HT2, which has been previously linked to a reduced risk of SLE, was found to decrease susceptibility to lupus by a factor of 0.4, thereby demonstrating a protective effect on SLE. Conversely, haplotype HT3 was associated with an increased susceptibility to SLE, elevating the risk by 3.8-fold. These results suggest potential interactions between these SNPs and other genetic variations that may contribute to the pathogenesis of SLE. Additionally, we observed several clinical manifestations correlated with the haplotypes of IRAK1, including the presence of anti-dsDNA antibodies and ANA associated with HT1, and elevated ESR linked to HT2. Notably, patients with HT1 exhibited a significantly higher frequency of anti-dsDNA antibodies and ANA, while those with HT2 showed a marked increase in ESR. Thus, the polymorphisms rs3027898 and rs1059702 in IRAK1 may play a critical role in the development of lupus.

In addition to the distinct function of IRAK1 in immune signaling, it is noteworthy that the IRAK1 gene is situated in close proximity to the MECP2 gene on the X chromosome (Xq28), creating a locus that has been consistently linked to autoimmune disorders, including SLE.[34] The MECP2 gene encodes methyl-CpG-binding protein 2, which is integral to transcriptional regulation and the epigenetic modulation of gene expression, particularly within immune cells. As emphasized in the research conducted by Jacob et al[34] the genetic association signals identified in this region may represent the influence of IRAK1, MECP2, or a combination of both genes, owing to their strong linkage disequilibrium. This indicates that the susceptibility to SLE associated with the variant rs3027898 may also be partially influenced by regulatory mechanisms involving MECP2. Investigations have revealed a notable correlation between the X chromosome region containing MECP2 and the incidence of SLE.[35] The intricate nature of this locus underscores the necessity for fine-mapping and functional investigations to clarify the respective roles of IRAK1 and MECP2 in the pathogenesis of SLE, particularly in female patients, where X-chromosome-linked genes may have more significant effects due to incomplete X–inactivation or gene dosage imbalances.

The current investigation is constrained by several limitations. Primarily, it was conducted within a single patient cohort without subsequent replication. Additionally, power analysis demonstrated 76.9% statistical power to detect this effect size (OR=0.58) at α=0.05 with the current sample size, suggesting that the finding is moderately reliable, but a larger sample size is needed for further validation. While associations between IRAK1 polymorphisms and SLE were established, this study did not consider the epigenetic and environmental factors that could potentially influence gene expression. Therefore, further research involving larger cohorts is essential to corroborate these findings. Future studies should aim to clarify the specific molecular mechanisms through which IRAK1 SNPs contribute to the pathogenesis of SLE. This may include investigating their role in sex-based differences in the prevalence and severity of SLE, given that IRAK1 is located on the X chromosome.[8] Moreover, broadening the scope of this research to encompass diverse ethnic groups would enhance the understanding of IRAK1's involvement in SLE across various populations.

Conclusions

In summary, the present study provides evidence indicating a possible correlation between the IRAK1 polymorphisms rs3027898 (C > A) and the susceptibility to SLE. These findings underscore the significance of genetic variations within the IRAK1 signaling pathway in the development of SLE, suggesting that these SNPs may function as potential biomarkers or therapeutic targets for disease management. Nevertheless, further research is necessary to elucidate the role of IRAK1 variants in the pathogenesis of SLE and to investigate the underlying molecular mechanisms involved.

Data Sharing Statement

The data presented in this study are available on request from the corresponding author.

Institutional Review Board Statement

The research was carried out in compliance with the Declaration of Helsinki and received approval from the Ethics Committee of The First Affiliated Hospital, Henan University of Science and Technology (2023-03-K0049).

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Disclosure

The authors declare no competing interests in this work.

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