Association of *c-Jun* Gene Polymorphism with Susceptibility to Systemic Lupus Erythematosus in a Chinese Population

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c-Jun has been proved as playing an important role in the pathogenesis of tumors, as a main component of Activator protein 1 and *c-Jun* gene polymorphisms are associated with colorectal cancer. However, the relationship between the *c-Jun* gene polymorphism and the susceptibility to systemic lupus erythematosus (SLE) has not been known. Our purpose is to evaluate whether the *c-Jun* gene polymorphism (SNP rs3748814) is associated with susceptibility to SLE in a Chinese population. In this study, we enrolled 502 SLE patients and 652 healthy controls. The *c-Jun* polymorphism (rs3748814) was specified from genomic DNA using the TaqMan genotyping assay on a 7300 real-time reverse transcription polymerase chain reaction system. We found that the frequency of the A/G genotype in SLE patients was lower than in healthy controls, whereas the frequency of the G/G genotype was significantly higher in SLE patients than in healthy controls (A/G vs. G/G $p=8.670\text{e-}08$, odds ratio [OR]=0.290, 95% confidence interval [CI]=0.184–0.456). In addition, the frequency of allele A in the patients group was significantly lower than in the control group (A vs. G $p=5.221\text{e-}09$, OR=0.308, 95% CI=0.212–0.466). The distribution of genotype and allele frequency in SLE patients with lupus nephritis (LN) compared with SLE patients without LN was not statistically significant (A/G vs. G/G $p=0.744$, OR=1.157, 95% CI=0.481–2.785; A vs. G $p=0.748$, OR=1.152, 95% CI=0.486–2.734; A/A + A/G vs. G/G $p=0.744$, OR=1.157, 95% CI=0.481–2.785). Furthermore, we did not find any significant association between other clinical features and genotypes. Our findings suggest that the *c-Jun* polymorphism (rs3748814) may be significantly associated with the susceptibility to SLE in a Chinese population.

Introduction

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is a prototypic multisystem autoimmune disorder that is characterized by the excessive production of autoantibodies, complement activation, and immune-complex deposition, resulting in tissue and organ damage (Mok and Lau, 2003; Font *et al.*, 2004; Yurasov *et al.*, 2005; Ruiz-Irastorza *et al.*, 2007). Although the etiology and pathogenetic mechanisms of SLE have not been fully understood, evidence has convinced us of a combination of genetic and environmental factors that might be associated with the pathogenesis of SLE (Criswell *et al.*, 2005; Liu *et al.*, 2009). Recently, genetic association studies, especially a genome-wide association study, have suggested that genetic predisposition might play a critical role in the pathogenesis of SLE (Harley *et al.*, 2008; Han *et al.*, 2009).

The transcription factor activator protein 1 (AP-1), including members of *Jun*, *Fos* and other activating transcrip-

tion factor proteins, is a key component in many signal transduction pathways and plays a critical role in cellular proliferation, differentiation, and apoptosis. It is expressed in many types of cells and can be activated by *c-Jun* N terminal kinase, transforming growth factor beta, or Wnt signaling pathway (Zenz *et al.*, 2008). Studies have demonstrated that AP-1 is involved in the pathogenesis of inflammatory bone diseases, autoimmune diseases, and tumors (Han *et al.*, 1998; Wagner and Eferl, 2005; Maritz *et al.*, 2011). Since it is the dominant component of AP-1, the human *Jun* gene is located on chromosome 1p31-p32, lacks introns, and encodes a protein with 331 amino-acid residues (Haluska *et al.*, 1988; Vogt, 2001). In mammals, *c-Jun* can either homodimerize with the Jun family members (*Jun*, *JunB*, *JunD*) or heterodimerize with the Fos family members (*Fos*, *FosB*, *Fra-1*, and *Fra-2*), and *c-Jun/c-Fos* heterodimer is the most predominant component of AP-1, which has a high AP-1 DNA binding affinity (Lee *et al.*, 2004). Furthermore, a basal level of *c-Jun* is

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required for maintaining normal cellular function (Hilberg *et al.*, 1993). *c-Jun* deficient fibroblasts displayed an obvious proliferation defect *in vitro*, and *c-Jun* deficient hepatocytes were severely impaired during liver regeneration *in vivo* (Zenz *et al.*, 2008). Lately, investigations have revealed that *c-Jun* may influence the susceptibility of diseases. For instance, Johnson *et al.* (1993) reported that a *c-Jun* null mutation could cause embryonic lethality and retard cell growth in mice, and Suto *et al.* (2004) demonstrated that a dominant-negative mutant of *c-Jun* had a significant antitumor effect on colorectal cancer both *in vitro* and *in vivo*. Moreover, *c-Jun* polymorphisms in the promoter regions have been discovered as being associated with colorectal cancer (Chen *et al.*, 2011).

However, we know little about *c-Jun* and SLE to date. Doníz-Padilla *et al.* (2011) detected a higher expression of *c-Jun* in peripheral blood mononuclear cells in SLE patients than in controls. Olferiev *et al.* (2007) found that *c-Jun* might play an important role in the transcriptional regulation of FCGR2B promoter activity, whereas FCGR2B had been demonstrated as being associated with the pathogenesis of SLE. These studies might imply that *c-Jun* is involved in the pathogenesis of SLE. Consequently, based on the current literature, where there is no report about the *c-Jun* gene polymorphism in SLE, this study examines whether the *c-Jun* gene polymorphism (SNP rs3748814 in UTR-5) is associated with the susceptibility to SLE in a Chinese population.

Materials and Methods

Patients and controls collection and SNPs selection

A case-control study was conducted that examines the association between the *c-Jun* gene polymorphism and SLE susceptibility. Five hundred two patients with SLE (37 men and 465 women, mean age 36.16 ± 11.99 years) were recruited from the first affiliated hospital of the Anhui Medical University and the Anhui Provincial Hospital. All the patients fulfilled at least four of the American College of Rheumatology (ACR) 1997 Revised Criteria for the classification of SLE (Tan *et al.*, 1982; Hochberg, 1997). Overall, 652 (249 men and 403 women, mean age 34.23 ± 16.44 years) healthy controls were enrolled in this study. Venous blood samples were collected from all the subjects for genomic DNA isolation.

The study was approved by the ethics committee of the Anhui Medical University, and informed consent was obtained from all the participants.

In this study, we selected single nucleotide polymorphisms from the international HapMap project databank (www.hapmap.org/) and the Genbank dbSNP database (www.ncbi.nlm.nih.gov), on the basis of a minor allele frequency (MAF) ≥ 0.05 in the Han Chinese population of Beijing, China. Then, we selected tagging SNP using haploview 4.2 software. Furthermore, SNPs located in the *c-Jun* functional domain, including UTR-3, UTR-5, synonymous, and nonsynonymous substitutions, were selected. Finally, 2 SNPs were possibly found in the *c-Jun* gene; we selected an SNP (rs3748814) with a higher MAF from the international HapMap project databank (www.hapmap.org/).

DNA samples and genotyping

The genomic DNA was extracted from peripheral blood leukocytes using Flexi Gene DNA kits (Qiagen) according to the manufacturer's instructions. Genotyping of SNP was carried out by a TaqMan allele discrimination assay (Applied Biosystems), using an assay-on-demand probe and primer (ID: C_27511276_10 for rs3748814). A polymerase chain reaction (PCR) was used to identify the genotype of the *c-Jun* (rs3748814) polymorphism. Amplification was performed in a 10 μ L reaction volume containing 5 μ L of TaqMan Genotyping master mix, 0.1 μ L of TaqMan Genotyping assay mix, and 4 μ L of genomic DNA using a 7300 real-time PCR system (ABI7300; Applied Biosystems). PCR analysis was carried out in 96-well plates on a programmable thermal cycler. The PCR cycling conditions consisted of initial denaturation at 95°C for 10 min, followed by 40 cycles at 95°C for 15 s and at 60°C for 1 min.

Statistical analysis

All data were analyzed by Plink 1.06 and SPSS10.01 software (SPSS Inc., 2000). Genotype and allele frequency were compared between the SLE patients and healthy individuals using the chi-square test. The odds ratio (OR) and 95% confidence interval (95% CI) from the genotype and allele frequency were also calculated. The power analysis was

TABLE 1. ANALYSIS OF C-JUN (rs3748814) GENOTYPE, ALLELE FREQUENCY BETWEEN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS AND HEALTHY CONTROLS

c-Jun (rs3748814)	SLE patients n=502 (%)	Healthy controls n=652 (%)	p-value	OR (95% CI)
Genotype				
G/G	473 (94.2)	542 (83.1)		reference
A/G	29 (5.8)	105 (16.1)	8.670e-08	0.290 (0.184–0.456)
A/A	0 (0.0)	5 (0.8)	0.999	NA
Allele frequency				
G	975 (97.1)	1189 (91.2)		reference
A	29 (2.9)	115 (8.8)	5.221e-09	0.308 (0.212–0.466)
Dominant model				
G/G	473 (94.2)	542 (83.1)		reference
A/A+A/G	29 (5.8)	110 (16.9)	4.011e-08	0.302 (0.197–0.463)
Recessive model				
A/A	0 (0.0)	5 (0.8)		reference
G/G+A/G	502 (100.0)	647 (99.2)	0.999	NA

NA, not available; SLE, systemic lupus erythematosus; OR, odds ratio; CI, confidence interval.

TABLE 2. DISTRIBUTION OF GENOTYPE AND ALLELE FREQUENCY OF *c-JUN* (rs3748814) IN LUPUS NEPHRITIS PATIENTS AND SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS WITHOUT LUPUS NEPHRITIS

<i>c-Jun</i> (rs3748814)	Patients with LN n=109 (%)	SLE without LN n=393 (%)	p-value	OR (95% CI)
Genotype				
G/G	102 (93.6)	371 (94.4)		reference
A/G	7 (6.4)	22 (5.6)	0.744	1.157 (0.481–2.785)
A/A	0 (0.0)	0 (0.0)	NA	NA
Allele frequency				
G	211 (96.8)	764 (97.2)		reference
A	7 (3.2)	22 (2.8)	0.748	1.152 (0.486–2.734)
Dominant model				
G/G	102 (93.6)	371 (94.4)		reference
A/A+A/G	7 (6.4)	22 (5.6)	0.744	1.157 (0.481–2.785)
Recessive model				
A/A	0 (0.0)	0 (0.0)		reference
G/G+A/G	109 (100.0)	393 (100.0)	NA	NA

LN, lupus nephritis.

performed using the statistical program G*Power (Faul *et al.*, 2009). All tests were two tailed, and a *p*-value <0.05 was regarded as the level of statistical significance.

Results

The genotype distribution of healthy controls was in accordance with the Hardy–Weinberg equilibrium. The genotype and allele frequency of *c-Jun* (rs3748814) in the SLE patients and healthy controls is shown in Table 1. In the patients group, none of them had the A/A genotype, 29 patients (5.8%) had the A/G genotype, and 473 patients (94.2%) had the G/G genotype, the control groups were 5 (0.8%), 105 (16.1%), 542 (83.1%), respectively. The frequency of the A/G genotype was lower in the patients group than in the healthy controls, whereas the frequency of the G/G genotype was significantly higher in the patients group than in healthy controls (A/G *vs* G/G *P*=8.670e-08, OR = 0.290, 95% CI = 0.184–0.456). In addition, the patients group showed a decrease in the A allele frequency compared with the controls group (A *vs* G *p*=5.221e-09, OR=0.308, 95% CI=0.212–0.466). We also analyzed the genotype using a dominant and recessive model, and the results showed statistical significance between the patients and controls group (A/A+A/G *vs* G/G *p*=4.011e-08, OR=0.302, 95% CI=0.197–0.463).

Overall, 502 SLE patients were enrolled in the current study, 109 of whom were patients with lupus nephritis (LN). The distribution of genotype and allele frequency in the SLE

patients with LN and the SLE patients without LN was compared. The results are shown in Table 2. No statistical significance was found in the SLE patients with LN compared with the SLE patients without LN (A/G *vs* G/G *p*=0.744, OR=1.157, 95% CI=0.481–2.785; A *vs* G *p*=0.748, OR=1.152, 95% CI=0.486–2.734; A/A+A/G *vs* G/G *p*=0.744, OR=1.157, 95% CI=0.481–2.785). The distribution of the genotype of main clinical characteristics in the SLE patients is shown in Table 3. Nevertheless, no significant association between the other clinical features of SLE and any genotypes was discovered.

Power calculation was performed to assume the sample size for the SLE patients and controls at the 0.05 level of significance. On the basis of these assumptions, we estimated that our study had a statistical power of 92.5%, to detect a true-positive association.

Discussion

In the present study, we investigated the relationship between the *c-Jun* gene polymorphism and the susceptibility to SLE in a Chinese population. The results showed that the *c-Jun* polymorphism (rs3748814) was significantly associated with the susceptibility to SLE. The frequency of the A/G genotype was lower in the patients group than in healthy controls, whereas the frequency of the G/G genotype was significantly higher in the patients group than in healthy controls (A/G *vs* G/G *p*=8.670e-08, OR=0.290, 95% CI=0.184–0.456). In addition, the frequency of allele A was

TABLE 3. COMPARISON OF OTHER CLINICAL CHARACTERISTICS BETWEEN *c-JUN* (rs3748814) GENOTYPES

	<i>c-Jun</i> (rs3748814) A/G			p-value	OR (95% CI)
	Total n=502	A/G n=29	G/G n=473		
Malar rash, %	41.4	55.2	40.6	0.122	0.555 (0.261–1.181)
Discoid, %	7.4	0.0	7.8	0.118	—
Photosensitivity, %	10.2	17.2	9.7	0.193	0.517 (0.188–1.420)
Ulcers, %	11.6	6.9	11.8	0.419	1.813 (0.951–1.172)
Arthritis, %	40.2	41.4	40.2	0.897	0.951 (0.444–2.037)

significantly lower in the patients group than in the controls group (A vs. G $p=5.221e-09$, OR=0.308, 95% CI=0.212–0.466). These findings suggest that the allele A of *c-Jun* (rs3748814) may be a protective allele against SLE. Since LN is described as being the most serious complication of SLE (Mahmoud *et al.*, 2012), we have attempted to find whether the distribution of the genotype of the *c-Jun* gene polymorphism (rs3748814) influences SLE severity. The results showed that there was no statistical significance between the patients with LN and the patients without LN (A/G vs. G/G $p=0.744$, OR=1.157, 95% CI=0.481–2.785; A vs. G $p=0.748$, OR=1.152, 95% CI=0.486–2.734; A/A+A/G vs. G/G $p=0.744$, OR=1.157, 95% CI=0.481–2.785). Furthermore, we did not find any significant association between other clinical features and genotypes. These findings indicated that the genotype distribution of *c-Jun* (rs3748814) might not influence the SLE clinical characteristics.

As we know, autoimmune diseases, such as rheumatoid arthritis and SLE, are considered chronic inflammatory diseases caused by abnormally activated T cells (Goronzy and Weyand, 2004; Charles *et al.*, 2010). More and more studies have indicated that the *c-Jun* protein may play a key role in T-cell development (Gao *et al.*, 2004; Riera-Sans and Behrens, 2007). However, the influence of the *c-Jun* polymorphism (rs3748814) on the expression and function of the *c-Jun* protein has not been studied. In fact, the *c-Jun/c-Fos* heterodimer is the most predominant component of AP-1 in mammalian cells, and it has a high AP-1 DNA binding affinity (Lee *et al.*, 2004). *c-Jun* can dimerize through their leucine-zipper domains, which is the key component for activating AP-1, where AP-1 has been substantiated related to the pathogenesis of SLE. In this study, we demonstrate that the *c-Jun* polymorphism (rs3748814) is associated with the SLE susceptibility. Therefore, genetic variations of *c-Jun* may influence the ability for *c-Fos* and AP-1 DNA binding affinity, and AP-1 function. However, other studies are needed to verify this relationship in order to further clarify the mechanism of *c-Jun* in the pathogenesis of SLE.

In summary, we investigated the *c-Jun* polymorphism (rs3748814) and its susceptibility to SLE in a Chinese population based on a case-control study. Our results imply a major influence of *c-Jun* (rs3748814) on the genetic susceptibility to SLE.

Conclusion

Our findings suggest that the *c-Jun* polymorphism (rs3748814) may be significantly associated with the susceptibility to SLE in a Chinese population.

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Disclosure Statement

No competing financial interests exist.

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