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IκBα Promoter Polymorphisms in Patients with Systemic Lupus Erythematosus

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Abstract To investigate the associations of *IκBα* gene polymorphisms with the development and clinical manifestations of systemic lupus erythematosus (SLE), 110 patients with SLE and 120 unrelated healthy controls were enrolled in this study. The *IκBα* −881 A/G, −826 C/T, −550 A/T, −519 C/T, and −297 C/T polymorphisms were determined by the polymerase chain reaction/reaction fragment length polymorphism method. The genotype frequency of *IκBα* −826 C/T in the patients with SLE was significantly higher than that of the controls (p=0.003, OR=2.2, 95% CI=1.3–3.9). The SLE patients also have significantly higher carriage rate of *IκBα* −826 T than the controls (p=0.01, OR=2.0, 95% CI=1.2–3.4). We also found that the estimated haplotype frequency of *IκBα* −881A −826T −550A −519C −297C was significantly increased in the patients with SLE in comparison with that of the controls. This study also demonstrated that the association of *IκBα* −826 T with SLE was independent of *HLA-DR*15, which is associated with susceptibility to SLE in Taiwan. Moreover, a synergistic effect could also be found between *IκBα* −826 T and *HLA-DR*15. *IκBα* −826 T is associated with the development of SLE in Taiwan. The *IκBα* −881A −826T −550A −519C −297C haplotype is also associated with susceptibility to SLE. This study also demonstrated that *IκBα* -881G was associated with the occurrence of vasculitis in SLE patients. *IκBα* −550T might be a protective factor for the development of malar rash.

Keywords *IκBα* · NFκB inhibitor · polymorphism · systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease involving multiple organs and systems. Although the detailed etiology is still obscure, multiple genes and environmental factors are involved in the pathogenesis of this disease.

Many pro-inflammatory cytokines are involved in the inflammatory process of SLE. NFκB is related to the transcription of these pro-inflammatory cytokines, immune response, and anti-apoptotic genes [1–4]. Therefore, NFκB plays an important role in inflammatory disease and

Table I The Sequences of Primers and Restriction Enzymes for Determining *IκBα* Promoter Polymorphisms

IκBα promoter	Primers	Restriction enzyme
−881 and −826	5′-GGTCCTTAAGGTCCAATCG-3′ 5′-GTTGTGGATACCTTGCACTA-3′	−881: TspR I −826: Bfa I
−550	5′-TTGCTGCAAAGAGCCTGCT-3′ 5′-AGAGTGGAAATGATGGCTG-3′	Sfc I
−519	5′-GCTTTCACAACTTCTACCTG-3′ 5′-AGAGTGGAAATGATGGCTG-3′	Mnl I
−297	5′-GAAAGGACCGGCAGTTGG-3′ 5′-GTACTTCCCTGCAGCCTG-3′	Hpy8 I

underlined: mismatched nucleotide

in the development of autoimmunity [3, 5]. Abnormal NFκB activities with decreased p65-Rel A expression and increased expression of c-Rel could be found in T cells of SLE patients [6, 7]. The increased c-Rel cytosolic retention was caused by increased levels of IκBα and IκBβ. IκB is an inhibitor of NFκB, which binds with NFκB in the cytoplasm and influences the transcriptional activity of NFκB. Therefore, IκB may also play an important role in SLE.

In non-stimulated cells, NFκB complexes are sequestered in the cytoplasm in an inactive form via interaction with IκB. After cell activation by different stimuli such as

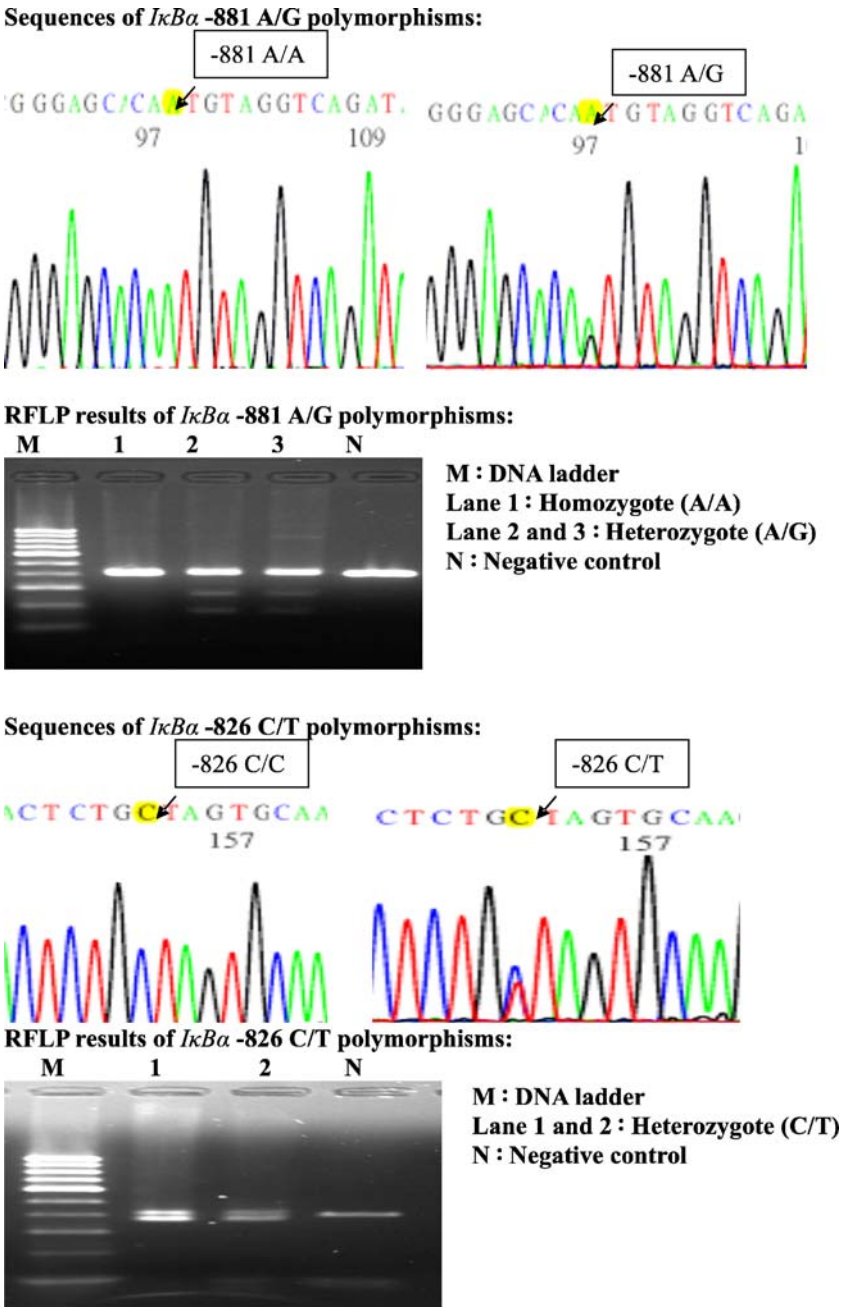

Fig. 1 The results of RFLP were confirmed by direct sequencing in *IκBα* −881 A/G and −826 C/T polymorphisms.

Table II Genotype Frequencies of *IκBα* Promoter Polymorphisms in the Patients with Systemic Lupus Erythematosus and the Controls

IκBα genotype	SLE; *n*=110 (%)	Controls; *n*=120 (%)	*p* Value (for overall genotype frequency)	*p* Value (for individual genotype frequency)	OR (95% CI)
−881					
A/A	91 (82.7)	91 (75.8)	NS		
A/G	18 (16.4)	27 (22.5)			
G/G	0 (0)	2 (1.7)			
−826					
C/C	52 (47.3)	77 (64.2)	0.006		1
C/T	56 (50.9)	37 (30.8)		0.003	2.2 (1.3–3.9)
T/T	2 (1.8)	6 (5.0)			
−550					
A/A	93 (84.5)	107 (89.2)	NS		
A/T	17 (15.5)	12 (10.0)			
T/T	0 (0)	1 (0.8)			
−519					
C/C	101 (91.8)	103 (85.8)	NS		
T/C	8 (7.3)	13 (10.8)			
T/T	1 (0.9)	4 (3.3)			
−297					
C/C	97 (88.2)	101 (84.2)	NS		
C/T	13 (11.8)	17 (14.2)			
T/T	0 (0)	2 (1.7)			

antigen recognition, cytokines, lipopolysaccharide, and viral infection, IκB is degraded by phosphorylation and ubiquitination. Then, NFκB dissociates from IκB and is translocated to the nucleus.

The IκB family includes IκBα, IκBβ, IκBγ, IκBδ, IκBε, IκBζ, IκB-R, Bcl-3, p100, and p105 [8, 9]. All of these proteins are characterized by the presence of multiple ankyrin repeats. IκBα is a classic form of the IκB family, which consists of six ankyrin repeats and can be found in cytoplasm and nucleus [9].

Several polymorphisms in the promoter region of *IκBα*, including −881 A/G, −826 C/T, −550 A/T, −519 C/T, and −297 C/T, have been identified. The *IκBα* promoter polymorphisms may affect IκBα expression and influence the regulation of inflammatory or immune response. Therefore, the *IκBα* promoter polymorphisms may be associated with SLE, a chronic inflammatory autoimmune disease.

Our previous study showed that the *IκBα* promoter polymorphisms were associated with the development of rheumatoid arthritis [10]. The *IκBα* promoter polymorphisms may also be associated with the development of SLE. A report with regard to the association between *IκBα* promoter polymorphisms and SLE is still unavailable. Therefore, the association of *IκBα* promoter polymorphisms with the development and clinical manifestations of SLE will be investigated in this study.

Materials and Methods

One hundred and ten patients with SLE (102 females and 8 males; mean age±SD=39.1±11.1 years) and 120 unrelated healthy controls (101 females and 19 males; mean age± SD=37.2±10.8 years) were enrolled in this study. All patients and controls are Taiwanese. The diagnosis of SLE was according to the American College of Rheumatology 1997 revised criteria for the classification of SLE. This study has been approved by the Institutional Review Board of Kaohsiung Medical University Hospital.

Table III Carriage Rates of *IκBα* Promoter Polymorphisms in the Patients with Systemic Lupus Erythematosus and the Controls

Carriage rate *of IκBα*	SLE; *n*=110 (%)	Controls; n=120 (%)	*p* Value	OR (95% CI)
−881 A	109 (99.1)	118 (98.3)	NS	
G	18 (16.4)	29 (24.2)	NS	
−826 C	108 (98.2)	114 (95.0)	NS	
T	58 (52.7)	43 (35.8)	0.01	2.0 (1.2–3.4)
−550 A	110 (100)	119 (99.2)	NS	
T	17 (15.5)	13 (10.8)	NS	
−519 C	109 (99.1)	116 (96.7)	NS	
T	9 (8.2)	17 (14.2)	NS	
−297 C	110 (100)	118 (98.3)	NS	
T	13 (11.8)	19 (15.8)	NS	

Table IV Estimated Haplotype Frequency of *IκBα* Polymorphisms in the Patients with SLE and the Controls

Haplotype of *IκBα*	SLE	Controls	OR(95% CI)	*p*	P_{corr}
−881A −826C −550A −519C −297C	0.66	0.75	NS		
−881A −826C −550A −519T −297C	0.02	0.01	–		
−881A −826C −550T −519T −297C	0	0.05	–		
−881A −826T −550A −519C −297C	0.16	0.05	3.2 (1.6–6.2)	<0.001	<0.002
−881A −826T −550A −519C −297T	0.024	0.004	–		
−881G −826T −550A −519C −297C	0.02	0.045	–		
−881G −826T −550A −519C −297T	0.015	0.044	–		
−881G −826T −550A −519T −297T	0.013	0.021	–		
−881G −826T −550T −519C −297C	0.021	0	–		

The *p* value was not calculated due to the fact that the number of cases is too small.
P_{corr}: Corrected *p* value

The *IκBα* −881 A/G, −826 C/T, −550 A/T, −519 C/T, and −297 C/T polymorphisms were detected by the polymerase chain reaction (PCR)/restriction fragment length polymorphism (RFLP) method. The sequences of primers and restriction enzymes are shown in Table I. A mismatched nucleotide (underlined) was used in the downstream primer to determine −881 A/G and −826 C/T polymorphisms. PCR was carried out under the following conditions: initial denaturation at 95°C for 3 min and 5 cycles of denaturation at 95°C for 1 min, annealing at 56°C for 1 min, and extension at 72°C for 1 min, and then 35 cycles of denaturation at 95°C for 1 min, annealing at 54°C for 1 min and extension at 72°C for 1 min. A final extension phase was also performed at 72°C for 7 min. The restriction enzymes TspR I and Bfa I were used to determine the −881 A/G and −826 C/T polymorphisms, respectively.

To determine the −519 C/T polymorphisms, the amplification conditions consisted of initial denaturation at 96°C for 3 min, followed by 5 cycles of denaturation at 95°C for 1 min, annealing at 56°C for 1 min, and extension at 72°C for 1 min, and 30 cycles of denaturation at 95°C for 1 min, annealing at 54°C for 1 min, and extension at 72°C for 1 min, and then a final extension phase at 72°C for 7 min. Then, the PCR product was digested with Mnl I.

To determine the *IκBα* -550 A/T polymorphisms, a nested PCR was performed with the PCR product to determine −519 C/T polymorphisms and a set of new primers (Table I). A mismatched nucleotide (underlined) was also used in the upstream primer. The PCR was performed under the following conditions: initial denaturation at 96°C for 3 min and 5 cycles of denaturation at 95°C for 1 min, annealing at 57°C for 1 min, and extension at 72°C for 1 min, followed by 30 cycles of denaturation at 95°C for 1 min, annealing at 54°C for 1 min and extension at 72°C for 1 min, and then a final extension phase at 72°C for 7 min. The PCR product was subjected to digestion with Sfc I.

The polymorphisms of *IκBα* −297 C/T were also determined by the PCR/RFLP method. The amplification conditions were as follows: initial denaturation at 96°C for 3 min, followed by 5 cycles of denaturation at 95°C for 1 min, annealing at 57°C for 1 min, and extension at 72°C for 1 min, and 30 cycles of denaturation at 95°C for 1 min, annealing at 52°C for 1 min, and extension at 72°C for 1 min, and then a final extension at 72°C for 7 min.

Direct sequencing was performed to verify the genotypes measured by the method of PCR/RFLP (Fig. 1). *HLA-DRB1* genotypes were determined by using a Dynal Allset SSP kit (Dynal Biotech).

The chi-square test with Yates' correction or Fisher's exact test was used for statistical analysis. The odds ratio (OR) and its 95% confidence interval (CI) were calculated by the SPSS statistical program. The *p* values were corrected by multiplying the number of comparisons (P_{corr}). The EH program was used for calculating estimated haplotype frequencies (Web Resources of Genetic Linkage Analysis). The Mantel–Haenszel test was used in a statistic with stratification.

Results

The genotype distributions of *IκBα* promoter polymorphisms were compatible with that of Hardy–Weinberg equilibrium in controls. This study showed that the

Table V Frequencies of *IκBα* -826T in the Patients with SLE and the Controls Stratified by *HLA-DR*

IkBα	DR15 (+)		DR15 (−)		*P* Value	Adjusted OR (95% CI)
	SLE (*n*=34)	Controls (*n*=22)	SLE (*n*=76)	Controls (*n*=98)		
−826T (+)	16	5	42	37	0.03	2.04 (1.11–3.75)
(−)	18	17	34	61		

The Mantel-Haenszel test was used for statistical analysis.

Table VI Interactions Between *IκBα* -826T and *HLA- DR*15 in the Patients with SLE and the Controls

IκBα	*HLA-DR*	SLE (n=110)	Controls (n=120)	OR (95% CI)	*P* Value
−826T (−)	*DR*15 (−)	34	61	1	
−826T (+)	*DR*15 (−)	42	37	2.0 (1.1–3.7)	0.02
−826T (−)	*DR*15 (+)	18	17	1.9 (0.9–4.2)	0.15
−826T (+)	*DR*15(+)	16	5	5.5 (1.8–16.2)	0.001

genotype distributions of *IκBα* −826 C/T polymorphisms were significantly different between the patients with SLE and the controls (Table II, p=0.006). In comparison with *IκBα* −826 C/C, the SLE patients had a significantly higher genotype frequency of *IκBα* −826 C/T than the controls (Table II, p=0.003, OR=2.2, 95% CI=1.3–3.9).

The carriage rate of *IκBα* −826T was significantly higher in the patients with SLE than in the controls (Table III, p=0.01, OR=2.0, 95% CI=1.2–3.4).

The estimated haplotype frequency of *IκBα* −881A −826T −550A −519C −297C was significantly higher in the patients with SLE than in the controls (Table IV, P_{corr}< 0.002, OR=3.2, 95% CI=1.6–6.2).

Our previous study revealed that *HLA-DR*15 was associated with the susceptibility to SLE in Taiwan. This study demonstrated that the frequency of *IκB* −826T in the patients with SLE was significantly higher than that of the controls independently of *HLA-DR15* (Table V).

The interactions of *IκBα* −826T with *HLA-DR15* are shown in Table VI. In comparison with *IκBα* −826T (−) *HLA-DR15* (−), the odds ratio of *IκBα* −826T (+) *HLA-DR15* (+) was higher than that of *IκBα* −826T (−) *HLA-DR15* (+) and that of *IκBα* −826T (+) *HLA-DR15* (−), which meant that a synergistic effect was present between *IκBα* −826T and *HLA-DR15* on susceptibility to SLE.

This study revealed that patients with *IκBα* −881G had significantly higher prevalence of vasculitis than those without *IκBα* −881G. The prevalence of malar rash was significantly decreased in patients with *IκBα* −550T in comparison with those without *IκBα* −550T (Table VII).

Discussion

This study demonstrates that the *IκBα* −881A −826T −550A −519C −297C haplotype is associated with susceptibility to SLE in Taiwan. It also reveals that *IκBα* −826T is associated with the development of SLE independently of *HLA-DR15*, the susceptible genes of SLE. A synergistic effect is present between *IκBα* −826T and *HLA-DR15* on the susceptibility to SLE.

IκB inhibits the transcription function of NFκB. Different IκB molecules preferentially inhibit distinct NFκB/Rel protein dimmers [8]. The central portion of the IκB molecules contains several ankyrin repeats. Ankyrin repeats bind to the Rel homology domain of NFκB/Rel, which

Table VII Associations Between *IκBα* Promoter Polymorphisms and Clinical Manifestations in Patients with Systemic Lupus Erythematosus

IκBα	−881		−826		−550		−519		−297	
Clinical manifestations	A n=109 (%)	*G* n=18(%)	C n=108 (%)	T n=58 (%)	A n=110 (%)	T n=17 (%)	C n=109 (%)	T n=9 (%)	C n=110 (%)	T n=13 (%)
Malar rash	60 (55)	9 (50)	61 (56.5)	27 (46.6)	61 (55.5)	5 (29.4)*	60 (55)	6 (66.7)	61 (55.5)	5 (38.5)
Discoid lupus	8 (7.3)	2 (11.1)	8 (7.4)	4 (6.9)	8 (7.3)	1 (5.9)	8 (7.3)	2 (22.2)	8 (7.3)	1 (7.7)
Photosensitivity	32 (29.4)	6 (33.3)	31 (28.7)	17 (29.3)	32 (29.1)	0 (0)	31 (28.4)	2 (22.2)	32 (29.1)	3 (23.1)
ONP ulcer	34 (31.2)	9 (50)	34 (31.5)	19 (32.8)	34 (30.9)	7 (41.2)	33 (30.3)	3 (33.3)	34 (30.9)	4 (30.8)
Raynaud's phenomenon	18 (16.5)	3 (16.7)	18 (16.7)	11 (19)	18 (16.4)	2 (11.8)	18 (16.5)	2 (22.2)	18 (16.4)	2 (15.4)
Arthritis	62 (56.9)	13 (72.2)	62 (57.4)	31 (53.4)	62 (56.4)	8 (47.1)	61 (56)	6 (66.7)	62 (56.4)	9 (69.2)
Serositis	14 (12.8)	3 (16.7)	14 (13)	6 (10.3)	14 (12.7)	3 (17.6)	14 (12.8)	3 (33.3)	14 (12.7)	1 (7.7)
Neurological disorder	3 (2.8)	1 (5.6)	3 (2.8)	2 (3.4)	3 (2.7)	0 (0)	3 (2.8)[3]	0 (0)	3 (2.7)	0 (0)
Renal disorder	39 (35.8)	9 (50)	40 (37)	20 (34.5)	40 (36.4)	6 (35.3)	40 (36.7)	4 (44.4)	40 (36.4)	7 (53.8)
Hematologic disorder	62 (56.9)	8 (44.4)	63 (58.3)	28 (48.3)	63 (57.3)	8 (47.1)	62 (56.9)	5 (55.6)	63 (57.3)	5 (38.5)
Anti-Ro	50 (45.9)	12 (66.7)	50 (46.3)	25 (43.1)	50 (45.5)	9 (52.9)	49 (45)	5 (55.6)	50 (45.5)	6 (46.2)
Anti-La	20 (18.3)	4 (22.2)	20 (18.5)	9 (15.5)	20 (18.2)	4 (23.5)	19 (17.4)	3 (33.3)	20 (18.2)	2 (15.4)
Anti-Sm	28 (25.7)	3 (16.7)	28 (25.9)	10 (17.2)	28 (25.5)	4 (23.5)	27 (24.8)	1 (11.1)	28 (25.5)	1(7.7)
Anti-RNP	43 (39.4)	7 (38.9)	43 (39.8)	18 (31)	43 (39.1)	6 (35.3)	42 (38.5)	5 (55.6)	43 (39.1)	4 (30.8)
Vasculitis	20 (18.3)	7 (38.9)**	19 (17.6)	12 (20.7)	20 (18.2)	4 (23.5)	20 (18.3)	3 (33.3)	20 (18.2)	2 (15.4)
Sjögren	30 (27.5)	8 (44.4)	29 (26.9)	13 (22.4)	30 (27.3)	5 (29.4)	29 (26.6)	3 (33.3)	30 (27.3)	4 (30.8)

*p=0.03, OR=0.28, (CI=0.09–0.85)
**p=0.03, OR=3.87 (1.27–11.79)

causes NFκB to remain in the cytoplasm by masking the nuclear localization sequence of NFκB. Nuclear import of IκBα is also found [11, 12]. When IκBα is expressed in the nucleus, it can inhibit the interaction of NFκB with DNA and promote the export of NFκB from the nucleus to the cytoplasm [12, 13]. The C-terminal domain of IκB may block DNA binding by NFκB, dissociate DNA-bound NFκB dimmers, and insure a nuclear export of NFκB [13, 14].

In patients with lupus nephritis, apoptosis of renal cells, which plays an important role in mediating chronic renal injury, is associated with transcriptional activation of the inducible nitric oxide synthase gene by NFκB [15]. Li showed that dihydroarteannuin ameliorated the lupus symptom of BXSB mice by inhibiting TNFα production via blocking IκB degradation [16]. Moreover, *IκBα*-deficient mice died of a wasting disease that was attributed to over-expression of TNFα [17]. *IκBα* deficiency also resulted in a sustained NFκB response and severe widespread dermatitis in mice [18].

The polymorphisms in the promoter of *IκBα* may influence the expression of IκBα, and then influence the NFκB function. Therefore, the polymorphisms in the promoter of *IκBα* may be associated with the development of autoimmune disease. An 8-bp insertion in the promoter region of *IκBα* (*IκBα* −708 ins 8) protected individuals from the development of primary progressive multiple sclerosis [19]. Our previous study also showed that the *IκBα* −826T −550A −519C haplotype was associated with susceptibility to RA in Taiwan. This study demonstrated that the *IκBα* −826 T and a haplotype were related to the development of SLE in Taiwan. Moreover, the associations of *IκBα* promoter polymorphisms with clinical manifestations of SLE could be demonstrated in this study. *IκBα* −881G was related to the development of vasculitis. *IκBα* −550T prevented SLE patients from the development of malar rash.

The *IκBα* −826 C/T polymorphisms are near a putative binding site of transcription factor GATA-2. A functional study is being conducted to investigate the influence of *IκBα* −826 C/T polymorphisms on the promoter activity of *IκBα*.

The correlations between *IκBα* promoter polymorphisms and other diseases have also been reported. Mozzato-Chamay showed that the *IκBα* −881 G/−826 T haplotype prevented the development of scarring tracoma in Gamdian [20]. Abdallah et al. demonstrated that the *IκBα* −297T allele carriage was more prevalent in patients with sarcoidosis than in controls in Caucasians [21]. They also found that the *IκBα* −881G −826T −297T haplotype was associated with the development of sarcoidosis, and the *IκBα* −826T allele carriage was related to disease stages.

A polymorphism in the 3′-UTR of *IκBα* was related to the risk for type 2 diabetes and Crohn's disease, while a similar finding could not be demonstrated in patients with SLE [22, 23]. In this study, the 3′-UTR polymorphisms of *IκBα* were not determined.

Mutations of *IκBα* may also be associated with the development of malignancies. A mutation in the coding region of *IκBα* might result in the over-expression of IκBα, which was implicated in the development of lymphoma [24]. Mutations of *IκBα* in Hodgkin's disease suggested a tumor suppressor role for IκBα [25].

In conclusion, *IκBα* −826 T may be a risk factor for the development of SLE. The *IκBα* −881A −826T −550A −519C −297C haplotype is associated with susceptibility to SLE in Taiwan. The *IκBα* promoter polymorphisms are also related to the clinical manifestations of SLE. However, further study is needed to investigate the effect of *IκBα* −826C/T polymorphisms on the promoter activity of *IκBα*.

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