

Meta-Analysis

Association between glutathione S-transferase M1, P1, and *NFKB1* polymorphisms and systemic lupus erythematosus susceptibility: a meta-analysis

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Abstract: This study aimed to determine whether Glutathione S-transferase M1 (*GSTM1*), P1 (*GSTT1*), *NFKB1* polymorphisms confer susceptibility to systemic lupus erythematosus (SLE). We performed a meta-analysis on the associations between *GSTM1* and *GSTT1* null genotypes, and *NFKB1* -94 ins/delATTG polymorphisms and SLE. In total, seven studies were considered for this meta-analysis, which comprised 2,119 SLE patients and 3,014 healthy controls. Meta-analysis of the *GSTM1* null polymorphism in 869 SLE and 1,544 control subjects revealed an association between SLE and the *GSTM1* null genotype (OR = 1.321, 95% CI = 1.103–1.583, $p = 0.002$). Stratification by ethnicity indicated an association between the *GSTM1* null genotype and SLE in Asians (OR = 1.334, 95% CI = 1.096–1.623, $p = 0.004$). However, meta-analysis of the *GSTT1* null polymorphism, comprising 717 SLE and 1,008 control subjects, revealed no association between SLE and the *GSTT1* null genotype overall (OR = 0.850, 95% CI = 0.687–1.051, $p = 0.113$) or in an Asian population (OR = 0.794, 95% CI = 0.594–1.061, $p = 0.119$). Meta-analysis of the *NFKB1* -94 ins/delATTG polymorphism, comprising 1,250 SLE and 1,127 control subjects, revealed an association between SLE and the *NFKB1* D allele (OR = 1.127, 95% CI = 1.011–1.257, $p = 0.031$). Ethnicity-specific meta-analysis revealed an association between the *NFKB1* D allele and SLE in Asians (OR = 1.155, 95% CI = 1.026–1.300, $p = 0.017$). This meta-analysis demonstrates that the functional *GSTM1* and *NFKB1* polymorphisms are associated with the SLE risk in Asians.

Key words: Systemic lupus erythematosus, *GSTM1*, *GSTT1*, *NFKB1*, Polymorphism, Meta-analysis.

Introduction

Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease where immune regulation is disrupted, characterized by multisystem involvement that is mediated by autoantibodies and immune complex deposits. Although the etiology of SLE is not fully understood, it is evident that genetic components play a major role in its development (1).

Oxidative modifications of proteins and other biologic molecules may lead to the expression of neoantigens and increase the risk of autoimmune diseases (2). Furthermore, oxidation of nucleotides by reactive oxygen species (ROS) increases the DNA immunogenicity (3). Moreover, ROS are involved in the pathogenesis of SLE, because they cause immunogenicity of DNA, lipid oxidation, and immunoglobulin G, generating ligands for which autoantibodies show higher avidity that consequently lead to organ damage (4). The detoxification of products resulting from ROS activity is important and antioxidants might play a key protective role in SLE. In particular, glutathione S-transferases (GSTs) are involved in the detoxification that protects cells from ROS attack (5). Thus, polymorphisms associated with reduced GST activity are of interest in the context of SLE susceptibility. The *GSTM1* (*Mu*), *GSTT1* (*The-ta*), and *GSTP1* (*Pi*) genes have previously been reported to be polymorphic (6), and the *GSTM1* (chromosome 1p13.3) and *GSTT1* (chromosome 22q11.2) null genotypes are known to have no GST activity.

Nuclear factor- κ B (NFKB) is a transcription factor that binds to a 10-bp DNA element in kappa immunoglobulin light-chain enhancer in B cells, regulating the transcription of genes involved in immune and inflam-

matory responses (7). Thus, NFKB can function as a key regulator of inflammation and autoimmune disease development. The *NFKB1* gene, located on chromosome 4q24, contains an insertion (I)/deletion (D) polymorphism within the promoter region that may lack a 4-bp repeat sequence (*NFKB1* -94 ins/delATTG, rs28362491) (8). The D allele is associated with the loss of binding to nuclear proteins and reduced promoter activity of NFKB1 promoter-luciferase reporter constructs in transient transfection experiments (8). Thus, it seems plausible that the *NFKB1* D allele could play a key role in the pathogenesis of autoimmune diseases.

Numerous studies have examined associations between *GSTM1*, *GSTT1*, and *NFKB1* polymorphisms and SLE, but results reported are contradictory, owing possibly to the low statistical power of individual studies (9-15). Therefore, to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood of random errors that are responsible for false-positive or false-negative associations (16-18), we turned to meta-analysis. Here, we aimed to determine whether the *GSTM1* and *GSTT1* null genotypes and *NFKB1*-94 ins/delATTG polymorphisms confer susceptibility to SLE.

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Methods

Identification of eligible studies and data extraction

We performed a search for studies that examined associations between the *GSTMI*, *GSTTI*, and *NFKB1* polymorphisms and SLE using the MEDLINE, EMBASE databases and the grey literature to identify available reports where *GSTMI*, *GSTTI*, and *NFKB1* polymorphisms were analyzed in SLE patients (until December 2014). Combinations of keywords, such as, “GSTMI,” “GSTTI,” “NFKB1,” “polymorphism,” “systemic lupus erythematosus,” and “SLE” were entered as Medical Subject Heading (MeSH) components and as text words. References in the identified studies were also investigated to identify additional studies that not indexed by the electronic databases. Genetic association studies that determined the distributions of the *GSTMI*, *GSTTI* null, and *NFKB1* -94 ins/delATTG polymorphisms in SLE patients and normal controls were included. The inclusion criteria were as follows: (1) a case-control study design, (2) original data, and (3) sufficient genotype data to calculate odds ratios (ORs). No language restriction was applied in the meta-analysis. The exclusion criteria were as follows: (1) overlapping data, (2) inability to ascertain the number of null and wild genotypes, and (3) studies of family members based on linkage considerations. The following information was extracted from each study: author, year of publication, ethnicity of the study population, number of cases and controls, and the genotype and allele frequencies of the *GSTMI*, *GSTTI*, and *NFKB1* polymorphisms.

Evaluations of statistical associations

A chi-square test was used to determine whether observed genotype frequencies conformed to the Hardy-Weinberg equilibrium (HWE) (<http://ihg.gsf.de/cgi-bin/hw/hwa1.pl>). We performed meta-analyses using allelic contrast, homozygote contrast, and recessive and dominant models. Meta-analyses were performed on the association between *GSTMI* and *GSTTI* null genotypes, and *NFKB1* -94 ins/delATTG polymorphisms and SLE. Point estimates of risks, ORs, and 95% and 99% confidence intervals (CI) were estimated for each study. Moreover, Cochran’s Q-statistic was used to assess within- and between-study variations and heterogeneities. This heterogeneity test assesses the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity was quantified using I^2 , which ranges from 0 to 100%, and represents the proportion of between-study variability attributable to heterogeneity

rather than chance (19). I^2 values of 25%, 50%, and 75% were nominally considered low, moderate, and high estimates, respectively. The fixed effects model assumes that a genetic factor has a similar effect on SLE susceptibility across all studies investigated, and that observed variations among studies are caused by chance alone (20). However, the random effects model assumes that different studies show substantial diversity and assesses both within-study sampling errors and between-study variances (21). When study groups are homogeneous, the two models are similar, but if this is not the case the random effects model usually provides wider CIs than the fixed effects model. The random effects model is best used in the presence of significant between study heterogeneity (21). The threshold for statistical significance was 0.05. Statistical manipulations were performed using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA). The power of each study was computed as the probability of detecting an association between the polymorphisms and SLE at a level of significance of $p < 0.05$, assuming a small effect size (effect size convention $w = 0.1$). The power analysis was performed using the G*Power statistical program (<http://www.gpower.hhu.de>).

Evaluation of publication bias

Funnel plots are often used to detect publication bias. However, due to the limitations of funnel plotting, which requires a range of studies of varying sizes involving subjective judgments, we evaluated publication bias using Egger’s linear regression test (22), which measures funnel plot asymmetry using a natural logarithm scale of odds ratios (ORs).

Results

Studies included in the meta-analysis

Seven studies in total were considered in this meta-analysis, which in total involved 2,119 SLE patients and 3,014 controls, and five Asian and two European populations (9-15) (Table 1). Given the populations available, an ethnicity-specific meta-analysis was conducted on the European and Asian populations. Four studies examined the *GSTMI* polymorphism, three the *GSTTI* polymorphism, and three the *NFKB1* polymorphism. Details of the *GSTMI*, *GSTTI*, and *NFKB1* polymorphism studies included are summarized in Table 1. The statistical power of the studies ranged from 55.9% to 98.8%, and one of the studies had a statistical power exceeding 80%.

Table 1. Characteristics of the individual studies included in the meta-analysis.

Study [Ref]	Country	Population	Numbers		Studied polymorphism	Association findings*	Power (%) ^a
			SLE	Control			
Kiyohara, 2012(9)	Japan	Asian	151	421	<i>GSTMI</i>	$p = 0.370$	66.7
Zhang, 2010(10)	China	Asian	298	284	<i>GSTMI</i> , <i>GSTTI</i>	<i>GSTMI</i> ($p = 0.003$), <i>GSTTI</i> ($p = 0.119$)	67.4
Kang, 2006(11)	Korea	Asian	330	270	<i>GSTMI</i> , <i>GSTTI</i>	<i>GSTMI</i> ($p = 0.311$), <i>GSTTI</i> ($p = 0.370$)	68.7
Ollier, 1996(12)	UK	European	90	569	<i>GSTMI</i> , <i>GSTTI</i>	<i>GSTMI</i> ($p = 0.322$), <i>GSTTI</i> ($p = 0.779$)	72.8
Cen, 2013(13)	China	Asian	845	950	<i>NFKB1</i>	$p = 0.047$	98.8
Gao, 2012(14)	China	Asian	224	256	<i>NFKB1</i>	$p = 0.176$	59.1
Orozco, 2005(15)	Spain	European	181	264	<i>NFKB1</i>	$p = 0.918$	55.9

Ref: reference; UK: United Kingdom; NS: not significant; *: *GSTMI*, *GSTTI* null vs. non-null, or *NFKB1* -94 delATTG vs. insATTG allele, ^aAssuming a small effect size (effect size convention $w = 0.1$) at a level of significance of 0.05.

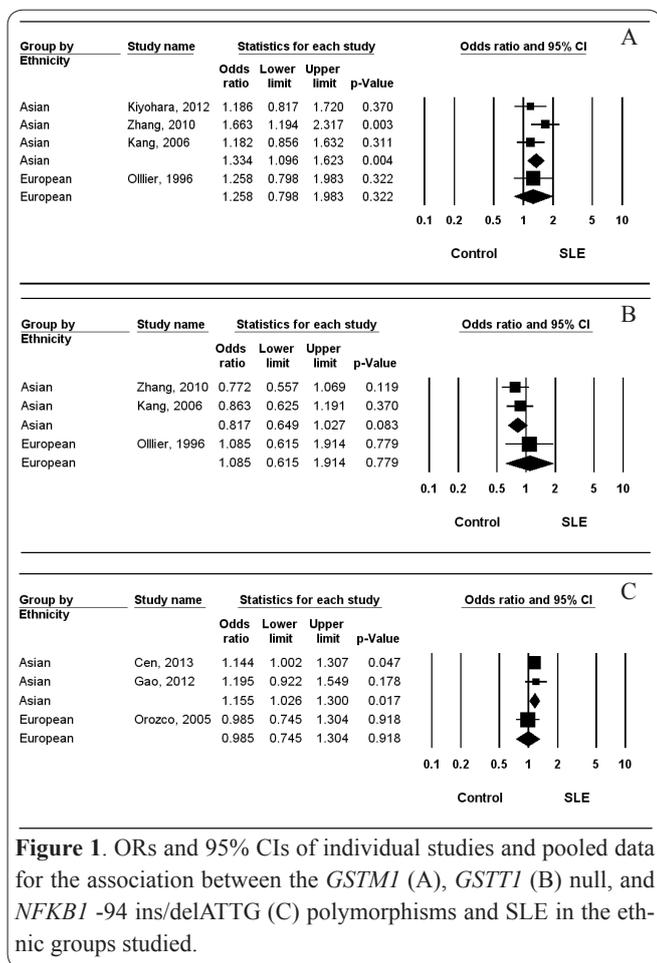


Figure 1. ORs and 95% CIs of individual studies and pooled data for the association between the *GSTM1* (A), *GSTT1* (B) null, and *NFKB1* -94 ins/delATTG (C) polymorphisms and SLE in the ethnic groups studied.

Meta-analysis of the association between the GSTM1 and GSTT1 null genotype and SLE susceptibility

We performed meta-analyses of the *GSTM1* and *GSTT1* null polymorphisms using allelic contrast due to limited data. Meta-analysis of *GSTM1* null poly-

morphism in 869 SLE and 1,544 controls revealed an association between SLE and the *GSTM1* null genotype (OR = 1.321, 95% CI = 1.103–1.583, p = 0.002) (Table 2). Stratification by ethnicity indicated an association between the *GSTM1* null genotype and SLE in Asians (OR = 1.334, 95% CI = 1.096–1.623, p = 0.004) (Fig. 1, Table 2, 3). The single European study showed no association between SLE and the *GSTM1* null genotype (OR = 1.258, 95% CI = 0.798–1.983, p = 0.322) (Fig. 1, Table 2,3).

Meta-analysis of the *GSTT1* null polymorphism, involving 717 SLE and 1,008 control subjects, revealed no association between SLE and the *GSTT1* null genotype (OR = 0.850, 95% CI = 0.687–1.051, p = 0.113) (Table 2). Stratification by ethnicity showed no association between the *GSTT1* null genotype and SLE in Asians (OR = 0.794, 95% CI = 0.594–1.061, p = 0.119) (Fig 1, Table 2), and the single European study showed no association between SLE and the *GSTT1* null genotype (Fig 2, Table 2).

Meta-analysis of the NFKB1 -94 ins/delATTG polymorphism and SLE susceptibility

We performed meta-analyses of the *NFKB1* -94 ins/delATTG polymorphism using allelic contrast, homozygote contrast, and recessive and dominant models. Meta-analysis of the *NFKB1* polymorphism, involving 1,250 SLE and 1,127 control subjects, revealed an association between SLE and the *NFKB1* D allele (OR = 1.127, 95% CI = 1.011–1.257, p = 0.031) (Table 2). Stratification by ethnicity indicated an association between the *NFKB1* D allele and SLE in Asians (OR = 1.155, 95% CI = 1.026–1.300, p = 0.017) (Fig 1, Table 2), and the single European study showed no association between SLE and the *NFKB1* D allele (Table 2). Furthermore, analysis using homozygote contrast mo-

Table 2. Meta-analysis of associations between the *GSTM1*, *GSTT1* null, and *NFKB1* -94 ins/delATTG promoter polymorphisms and SLE.

Contrast	Population	No. of studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	p-val	Model	p-val	I ²
			A							
GSTM1 null vs. non-null	Overall	4	869	1,544	1.321	1.103-1.583	0.002	F	0.444	0
	Asian	3	779	975	1.334	1.096-1.623	0.004	F	0.269	23.7
	European	1	90	569	1.258	0.798-1.983	0.322	NA	NA	NA
GSTT1 null vs. non-null	Overall	3	717	1,008	0.850	0.687-1.051	0.113	F	0.591	0
	Asian	2	628	554	0.817	0.649-1.027	0.083	F	0.634	0
	European	1	89	454	1.085	0.615-1.914	0.773	NA	NA	NA
B										
D vs. I	Overall	3	1,250	1,470	1.127	1.011-1.257	0.031	F	0.569	0
	Asian	2	1,069	1,206	1.155	1.026-1.300	0.017	F	0.769	0
	European	1	181	264	0.985	0.745-1.304	0.918	NA	NA	NA
DD + DI vs. II	Overall	3	1,250	1,470	1.156	0.998-1.352	0.071	F	0.690	0
	Asian	2	1,069	1,206	1.162	0.979-1.380	0.187	F	0.397	0
	European	1	181	264	1.124	0.766-1.651	0.550	NA	NA	NA
DD vs. DI + II	Overall	3	1,250	1,470	1.167	0.784-1.736	0.446	R	0.066	63.1
	Asian	2	1,069	1,206	1.256	1.018-1.551	0.034	F	0.123	57.8
	European	1	181	264	0.720	0.399-1.216	0.273	NA	NA	NA
DD vs. II	Overall	3	1,250	1,470	1.250	1.004-1.558	0.046	F	0.51	27.7
	Asian	2	1,069	1,206	1.331	1.053-1.683	0.017	F	0.452	0
	European	1	181	264	0.802	0.429-1.500	0.490	NA	NA	NA

R: random effects model; F: fixed effects model; NA: not available.

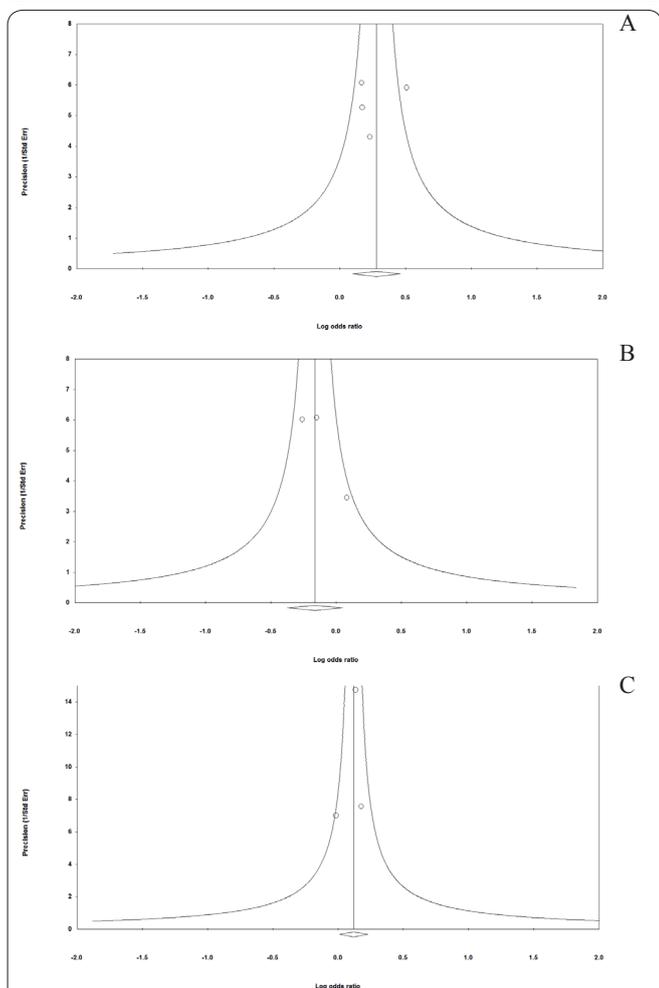


Figure 2. Funnel plot of studies that examined the association between the *GSTM1* (A), *GSTT1* (B) null, and *NFKB1* -94 ins/delATTG (C) polymorphisms and SLE.

dels showed the same pattern for the *NFKB1* D allele, indicating an association between the *NFKB1* -94 ins/

delATTG polymorphism and SLE in Asians (Table 2).

Heterogeneity and publication bias

The distribution of genotypes in normal control group was not consistent with HWE in one study (13), and the distribution of genotypes in SLE group was not consistent with HWE in another study (14). There were no between-study heterogeneities during meta-analyses, except for the meta-analysis of the *NFKB1* DD vs. DI + II genotype (Table 2). In subgroup analysis, there was some heterogeneity with no statistical significance (Table 2). This may be explained that ORs of studies in the subgroup showed the same direction, and the difference of ORs of each study were not big different. The same reason may be the case in the meta-analysis in overall group. ORs of studies in the overall group showed the same direction, and the difference among ORs of each study were not different in overall group. Funnel plots, which are usually used to detect publication bias, were difficult to correlate, presumably because of the small number of studies included (Fig. 2). Egger’s regression test showed no evidence of publication bias in this meta-analysis of the *GSTM1*, *GSTT1*, and *NFKB1* polymorphisms in any of the studies included (Egger’s regression test p-values > 0.1).

Discussion

The increases in ROS levels result in oxidation of DNA and lipids and the production of a variety of cytotoxic products (3). The widely expressed, GST supergene family seems to provide critical cellular protection against ROS. GSTs catalyze the conjugation of glutathione to a variety of substrates, including ROS and other toxins, and thus, facilitate their elimination (5). Previous studies on the *GSTM1* and *GSTT1* polymorphisms in SLE

Table 3. Meta-analysis of associations between the *GSTM1*, *GSTT1* null, and *NFKB1* -94 ins/delATTG promoter polymorphisms and SLE.

Contrast	Population	No. of studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	99% CI	p-val	Model	p-val	I ²
GSTM1 null vs. non-null	Overall	4	869	1,544	1.321	1.043-1.675	0.002	F	0.444	0
	Asian	3	779	975	1.334	1.030-1.727	0.004	F	0.269	23.7
	European	1	90	569	1.258	0.692-2.288	0.322	NA	NA	NA
GSTT1 null vs. non-null	Overall	3	717	1,008	0.850	0.643-1.124	0.113	F	0.591	0
	Asian	2	628	554	0.817	0.604-1.104	0.083	F	0.634	0
	European	1	89	454	1.085	0.514-2.289	0.773	NA	NA	NA

R: random effects model; F: fixed effects model; NA: not available.

Contrast	Population	No. of studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	99% CI	p-val	Model	p-val	I ²
D vs. I	Overall	3	1,250	1,470	1.127	0.977-1.301	0.031	F	0.569	0
	Asian	2	1,069	1,206	1.155	0.988-1.349	0.017	F	0.769	0
	European	1	181	264	0.985	0.684-1.424	0.918	NA	NA	NA
DD + DI vs. II	Overall	3	1,250	1,470	1.156	0.940-1.420	0.071	F	0.690	0
	Asian	2	1,069	1,206	1.162	0.927-1.456	0.187	F	0.397	0
	European	1	181	264	1.124	0.679-1.863	0.550	NA	NA	NA
DD vs. DI + II	Overall	3	1,250	1,470	1.167	0.908-1.531	0.446	R	0.066	63.1
	Asian	2	1,069	1,206	1.256	0.952-1.658	0.034	F	0.123	57.8
	European	1	181	264	0.720	0.332-1.560	0.273	NA	NA	NA
DD vs. II	Overall	3	1,250	1,470	1.250	0.937-1.669	0.046	F	0.51	27.7
	Asian	2	1,069	1,206	1.331	0.978-1.811	0.017	F	0.452	0
	European	1	181	264	0.802	0.352-1.827	0.490	NA	NA	NA

R: random effects model; F: fixed effects model; NA: not available.

have produced disparate results (9-15), which is not surprising because discordant results are common among genetic studies on complex diseases due to low statistical power, and small sample size. The statistical power of all of the studies except for one study had a statistical power lower than 80%. GSTM1 plays an essential role in the xenobiotics detoxification (5). Because the *GSTM1* null genotype lead to a complete lack of enzyme activity, the *GSTM1* null genotype is associated with higher ROS levels (23). However, each of the individual studies failed to show an association between the *GSTM1* polymorphism and SLE. In this meta-analysis of the *GSTM1* null polymorphism in 869 SLE and 1,544 healthy controls, we found an association between SLE and the *GSTM1* null genotype (OR = 1.334, 95% CI = 1.096–1.623, $p = 0.004$). In addition, stratification by ethnicity indicated an association between the *GSTM1* null genotype and SLE in Asians. In contrast, with respect to the *GSTTI* null polymorphism, we found no association between SLE and the *GSTTI* null genotype in all study subjects or in Asians. Our results of no association between the *GSTTI* polymorphism and SLE risk are not consistent with previous functional studies on the polymorphism (24). However, epidemiologic results often do not coincide with functional studies because SLE is a complex disease with contributions from multiple genes, different genetic backgrounds, and environmental factors. The negative results for the *GSTTI* polymorphisms might also be due to a Type II error. We could not perform a meta-analysis for *GSTPI*, because only one study on *GSTPI* was identified. NFKB plays an important role in the innate and adaptive immune responses, and dysregulated NFKB-signaling may be involved in the pathogenesis of autoimmune diseases, including SLE (25). Moreover, the *NFKBI* -94 ins/delATTG promoter polymorphism has functional effects on the transcription of the *NFKBI* (8). Our analysis of the *NFKBI* -94 ins/delATTG polymorphism, involving 1,250 SLE and 1,127 healthy controls, revealed an association between SLE and the *NFKBI* D allele (OR = 1.127, 95% CI = 1.011–1.257, $p = 0.031$), and in Asians, indicating the functional *NFKBI* -94 ins/delATTG polymorphism contributes to SLE susceptibility.

Genetic association studies on relations between genetic variants and complex outcomes must be considered with caution because many factors can influence the results. Thus, our results should be interpreted with caution because of the limited number of studies included, which restricted further subgroup analyses.

The present study has some limitations that require consideration. First, publication bias or confounding factors may have distorted the meta-analysis, because studies that produced negative results may not have been published or identified in this study. Although we performed the Egger's regression test, we could not eliminate the possibility of bias. Second, this ethnicity-specific meta-analysis included data from Asian patients, and thus, our results are applicable to only one ethnic group. Third, the small number of studies included in this analysis, especially in the subgroup analysis by environmental factors, prevented our results from reaching a definitive conclusion.

In summary, this meta-analysis suggests that the functional *GSTM1* and *NFKBI* polymorphisms are asso-

ciated with the susceptibility to SLE in Asians, but the *GSTTI* polymorphisms is probably not associated with SLE risk. Further studies of a larger scale in populations with different ethnicities are required to explore the roles played by the *GSTM1*, *GSTTI*, and *NFKBI* polymorphisms in the pathogenesis of SLE.

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