Associations between the FAS -670 A/G, -1377 G/A, and FASL -844 T/C polymorphisms and susceptibility to systemic lupus erythematosus: a meta-analysis

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Abstract

Objective

The aim of this study was to determine whether the FAS, and FASL polymorphisms are associated with susceptibility to systemic lupus erythematosus (SLE).

Methods

A meta-analysis was conducted on the associations between the FAS -670 A/G, FAS -1377 G/A, and FASL -844 T/C polymorphisms and SLE.

Results

A total of eleven articles met the study inclusion criteria. Meta-analysis indicated an association between SLE and the FAS -670 A/G polymorphism in the dominant model (OR=0.629, 95% CI=0.409–0.967, p=0.035). Stratification by ethnicity indicated an association between the FAS -670 GG+GA genotype and SLE in Asian populations (OR=0.464, 95% CI=0.218–0.988, p=0.046). Meta-analysis indicated an association between SLE and the FAS -1377 AA+AG genotype (OR=0.712, 95% CI=0.528 - 0.961, p=0.027), and an association between SLE and the FASL +844 C allele was found (OR=1.377, 95% CI=1.162 - 1.633, p=2.3x10^{-4}). Meta-analyses using the recessive model or homozygote contrast showed the same pattern as the meta-analysis of the FASL +844 C allele, that is, a significant association with SLE.

Conclusion

This meta-analysis demonstrates that the FAS -670 A/G, FAS -1377 G/A, and FASL -844 T/C polymorphisms are associated with susceptibility to SLE.

Key words

systemic lupus erythematosus, FAS, polymorphism, meta-analysis

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Introduction

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease, in which immune regulation is disrupted, leading to intense inflammation and multiple organ damage. Although the multifactorial natures of SLE are well recognised, genetic factors are likely strong determinants of SLE (1), and this has encouraged researchers to search for the genes responsible.

Fas/Fas ligand interactions play a major role in undergoing the development of apoptosis. FAS (TNFSF6/CD95/APO-1) is a cell surface receptor required for transmission of the apoptotic signal in cells of the immune system (2). FAS binds the FAS ligand (FASL) to initiate the death signal cascade, leading to programmed cell death (3), and mediates apoptosis of many types of cells, including lymphocytes, epithelial, fibroblast, and endothelial cells. It is possible that dysfunction of FAS contributes to the pathogenesis of SLE (4). The FAS gene, which is located on chromosome 10q24.1, is highly polymorphic, and of these polymorphisms, FAS -670A/G (rs1800682) and FAS -1377 G/A (rs2234767) have been best studied in SLE (5). The FAS -670 A/G and FAS -1377 G/A polymorphisms are located within the consensus sequences of binding sites for signal transducers and activators of transcription 1 (STAT1) and transcriptional factors stimulatory protein 1 (SP1), respectively. These two polymorphisms reduce FAS gene expression, probably by disrupting the binding elements for the transcriptional factors (6). The FASL gene maps to chromosome 1q23. A T to C transition at position 844 in the promoter region, located within the transcription factor binding site for CAAT/enhancer-binding protein β (C/EBPβ), induces a significantly higher basal expression of FASL (7). The functional FASL +844 T/C polymorphism (rs763110) has been most frequently studied in SLE.

The FAS/FASL gene is one such gene in the context of SLE. Based on their functional significance, the FAS -670 A/G, FAS -1377 G/A, and FASL -844 T/C polymorphisms have been studied as candidate genes for SLE susceptibility, with mixed results (8-17). The reasons for these disparities may be small sample sizes, low statistical power, or clinical heterogeneity. To overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood that random errors are responsible for false-positive or false-negative associations, we turned to meta-analysis (18-20). The aim of the present study was to determine, using a meta-analysis, whether the FAS -670 A/G, FAS -1377 G/A, and FASL -844 T/C polymorphisms are associated with susceptibility to SLE.

Methods

Identification of eligible studies and data extraction

We performed a search of studies that examined the associations between the FAS and FASL polymorphisms and SLE. The literature was searched using the PUBMED and EMBASE citation databases to identify articles in which FAS and FASL polymorphisms were analysed in patients with SLE. Combinations of keywords, such as, 'FAS,' 'FASL,' 'polymorphism,' 'systemic lupus erythematosus,' and 'SLE' were entered as Medical Subject Headings (MeSH) and as text words. All references were reviewed to identify additional studies not indexed by PUBMED and EMBASE. Studies were included in the analysis if they met all of the following criteria: (1) they were case-controlled studies; (2) they included patients with SLE which was defined as two or more unexplained pregnancy losses in the first two trimesters of pregnancy; and (3) they included genotype data for the FAS -670 A/G, FAS -1377 G/A, or FASL -844 T/C polymorphisms. No language restriction was applied. We excluded the following: (1) studies containing overlapping data; (2) studies in which the genotype data could not be ascertained; (3) studies that were review articles; and (4) studies in which family members had been included and the analysis was based on linkage considerations. Information on the methods and results of the analyses was extracted from the original studies by two independent researchers. Disagreements were resolved by consensus or by a third researcher. The following

information was extracted from each study: author, year of publication, ethnicity of the study population, numbers of cases and controls, and the genotype and allele frequencies of the FAS and FASL polymorphisms.

Evaluations of statistical associations

A chi-square test was used to determine whether observed frequencies of genotypes conformed to Hardy-Weinberg (H-W) expectations. Meta-analyses were performed using: 1) allelic contrast, 2) recessive model, 3) dominant model, and 4) homozygote contrast. Subgroup analyses were performed by ethnicity to evaluate the ethnic-specific effects. Point estimates of risks, odds ratios (OR), and 95% confidence intervals (CI) were estimated for each study. Cochran's Q-statistic was used to assess within- and between-study variations or heterogeneities. This heterogeneity test assesses the null hypothesis that all studies were evaluating the same effect. I^2 values were used to quantify the effect of heterogeneity values in the range between 0% and 100% and represent the proportion of between-study variability that can be attributed to heterogeneity rather than by chance (21). I^2 values of 25%, 50%, and 75% were nominally assigned as low, moderate, and high estimates. The fixed effects model assumes that a genetic factor has the same effect on disease susceptibility across all studies investigated, and that observed variations between studies are caused by chance alone. The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance. 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 used in the presence of significant between-study heterogeneity (22). Statistical manipulations were undertaken using the Comprehensive Meta-Analysis (CMA) software (Biostat, Englewood, NJ, USA).

Evaluation of heterogeneity and publication bias

To identify the potential source of heterogeneity observed in the meta-analysis, meta-regression was performed using the following variables: Hardy-Weinberg equilibrium (HWE), ethnicity, publication year, and sample size. Funnel plots are often used to detect publication bias. However, because funnel plotting requires a range of studies of varying sizes that involve subjective judgments, we evaluated publication bias using Egger's linear regression test (23), which measures funnel plot asymmetry using a natural logarithm scale of OR.

Results

Studies included in the meta-analysis

We identified 100 reports using electronic and manual searches, with 21 selected for full-text review based on their title and the details in the abstract. We excluded ten reports because six did not include the FAS/FASL polymorphisms (24-29), two were review articles (30, 31), one contained family data (32), and one did not involve SLE (33). Thus, eleven relevant studies met the study inclusion criteria (8-17) (Table I). One of the eligible studies contained data on two different ethnic groups (34). Each of these was treated independently. Eight studies on the FAS -670 A/G polymorphism involved 789 patients and 924 controls, three studies on the FAS -1377 G/A polymorphism involved 444 patients and 442 controls, and four studies on the FASL -844 T/C polymorphism involved 665 patients and 787 controls (Table I). Of the eight studies on the FAS -670 A/G polymorphism, three examined LN. Ethnicity-specific meta-analysis was conducted for the Caucasian, Asian, and Middle Eastern populations. Selected characteristics of these studies related to the association between the FAS/FASL polymorphisms and SLE are summarised in Table I.

Table I. Characteristics of the studies included in the meta-analysis.

Study	Ethnicity	Polymorphism	Number		SLE			Control			*p*-value for association*	HWE
			Case	Control	AA	AG	GG	AA	AG	GG		
Bollain, 2014 (8)	LA	FAS -670 A/G	43	54	14	13	16	28	12	14	0.034	No
Moudi, 2013 (9)	ME	FAS -670 A/G	106	149	34	55	17	37	73	39	0.053	Yes
Pradhan, 2012 (10)	Asian	FAS -670 A/G	70	70	22	37	11	7	42	21	0.003	No
Molin, 2012 (11)	Caucasian	FAS -670 A/G	46	96	17	21	8	11	51	34	0.001	Yes
Araste, 2010 (12)	ME	FAS -670 A/G	249	212	82	93	74	56	98	58	0.529	Yes
Kanemitsu, 2002 (13)	Asian	FAS -670 A/G	109	170	35	49	25	26	94	50	0.007	Yes
Lee, 2001 (14)	Asian	FAS -670 A/G	87	87	27	47	13	26	48	13	0.914	Yes
Huang, 1999 (15)	Caucasian	FAS -670 A/G	79	86	20	21	38	20	22	44	0.631	No
					GG	GA	AA	GG	GA	AA		
Araste, 2010 (12)	ME	FAS -1377 G/A	249	212	203	43	3	152	54	6	0.009	Yes
Kanemitsu, 2002 (12)	Asian	FAS -1377 G/A	109	140	42	42	25	45	62	33	0.434	Yes
Huang, 2000 (16)	Caucasian	FAS -1377 G/A	86	90	62	21	3	66	22	2	0.742	Yes
					TT	TC	CC	TT	TC	CC		
Moudi, 2013 (9)	ME	FASL +844 T/C	106	159	10	46	50	28	80	51	0.007	Yes
Chen, 2005 (17)	Asian	FASL +844 T/C	260	280	12	88	160	17	120	143	0.023	Yes
Wu-1, 2003 (34)	AA	FASL +844 T/C	211	150	135	57	19	102	43	5	0.113	Yes
Wu-2, 2003 (34)	Caucasian	FASL +844 T/C	88	198	9	40	39	22	99	77	0.466	Yes

LA: Latin American; ME: Middle Eastern; HWE: Hardy-Weinberg equilibrium; AA: African American; *: Allele contrast; NA: not available.

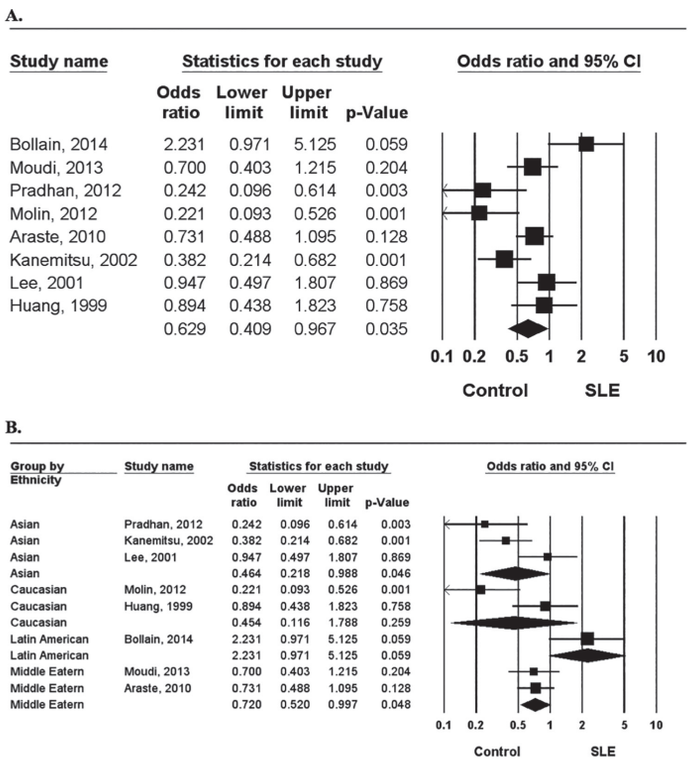

Fig. 1. Odds ratios (ORs) and 95% confidence intervals (CIs) from individual studies and from pooled data for the association between the FAS -670 GG+GA genotype and SLE in overall group (**A**) and each ethnic group (**B**).

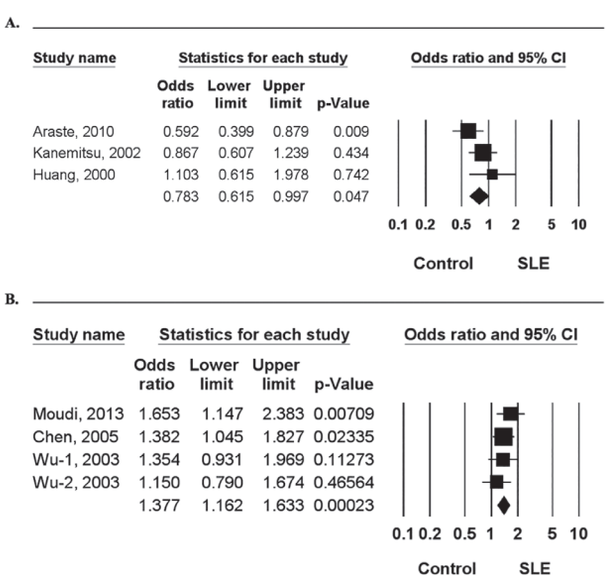

Fig. 2. Odds ratios (ORs) and 95% confidence intervals (CIs) from individual studies and from pooled data for the allelic association between the FAS -1377 A/G (A) or the FASL -844 T/C (**B**) polymorphisms and SLE.

Meta-analysis of the FAS -670 A/G polymorphism and SLE

Meta-analysis indicated a negative association between SLE and the FAS -670 A/G polymorphism in the dominant model (OR=0.629, 95% CI=0.409–0.967, p=0.035) (Fig. 1, Table II). Stratification by ethnicity indicated an association between the FAS -670 GG+GA genotype and SLE in Asian populations (OR=0.464, 95% CI=0.218–0.988, p=0.046), Middle Eastern populations (OR=0.720, 95% CI=0.520–0.997, p=0.048), but no association in Caucasian populations (Fig. 1, Table II). Meta-analyses using contrast of alleles, or the homozygote contrast showed a similar pattern as the meta-analysis of the FAS -670 GG+GA genotype, that is, a significant association in overall and Asian populations (Table II). Three studies were included in the meta-analysis of the association between the FAS -670 A/G polymorphism and lupus nephritis (LN) (8, 10, 14). Meta-analysis showed no association between LN and the FAS -670 A/G polymorphism (Table II).

Meta-analysis of the FAS -1377 G/A and FASL -844 T/C polymorphism and SLE

Meta-analysis indicated a negative association between SLE and the FAS -1377 A allele (OR=0.783, 95% CI=0.613–0.997, p=0.047) (Fig. 2, Table III). A single Middle Eastern study showed an association between SLE and the FAS -1377 A allele (OR=0. 592, 95% CI=0.399–0.879, p=0.009). Meta-analyses using the dominant model showed the same pattern as the meta-analysis of the FAS -1377 A allele, that is, a significant association with SLE (OR=0.712, 95% CI=0.528–0.961, p=0.027) (Table III). Meta-analysis revealed an association between SLE and the FASL +844 C allele (OR=1.377, 95% CI=1.162–1.633, p=2.3x10^{-4}) (Fig. 2, Table III). A single Asian study showed an association between SLE and the FASL +844 C allele (OR=1.653, 95% CI=1.147–2.383, p=0.007). Meta-analyses using the recessive model or homozygote contrast showed the same pattern as the meta-analysis of the FAS -1377 A allele, that is, a significant association with SLE (Table III).

Heterogeneity and publication bias

No between-study heterogeneity was found during analyses of the FAS -1377 G/A and FASL -844 T/C polymorphisms, but between-study heterogeneity was found during meta-analyses of the FAS -670 A/G polymorphism. Meta-regression showed that ethnicity (p=0.004), but not HWE (p=0.414), publication year (p=0.786), or sample size (p=0.396) had a significant impact on the heterogeneity in the FAS -670 A/G polymorphism. The distributions of genotypes of the FAS polymorphisms in normal control groups were not consistent with the HWE in three studies on FAS -670 A/G polymorphism (8, 10, 15). Deviation from the HWE among controls implies potenti≤al bias during control selection, or genotyping errors. However, excluding these studies did not affect our results for the FAS

Table II. Meta-analysis of the association between the FAS -670 A/G polymorphism and SLE, LN.

A. SLE

Polymorphism	Population	No. of studies	Subject no.		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	*p*-value	Model	*p*-value	I^2
FAS -670 A/G G *vs*. A allele	Overall	8	789	924	0.770	0.593-1.000	0.050	R	0.001	70.2
	Caucasian	2	125	182	0.614	0.287-1.313	0.209	R	0.025	80.1
	Asian	3	266	327	0.671	0.462-0.975	0.036	R	0.085	59.3
	Middle Eastern	2	355	361	0.839	0.680-1.034	0.099	F	0.233	29.6
GG *vs.* GA+AA (Recessive)	Overall	8	789	924	0.780	0.571-1.066	0.119	R	0.088	43.4
	Caucasian	2	125	182	0.671	0.407-1.107	0.118	F	0.124	57.8
	Asian	3	266	327	0.686	0.459-1.026	0.067	F	0.371	0
	Middle Eastern	2	355	361	0.811	0.397-1.658	0.566	R	0.056	72.5
GG+GA *vs*. AA (Dominant)	Overall	8	789	924	0.629	0.409-0.967	0.035	R	0.001	71.3
	Caucasian	2	125	182	0.454	0.116-1.788	0.259	R	0.015	83.2
	Asian	3	266	327	0.464	0.218-0.988	0.046	R	0.032	71.0
	Middle Eastern	2	355	361	0.720	0.520-0.997	0.048	F	0.900	0
GG *vs*. AA	Overall	8	789	924	0.568	0.333-0.968	0.038	R	0.001	71.8
	Caucasian	2	125	182	0.379	0.069-2.073	0.263	R	0.010	84.9
	Asian	3	266	327	0.404	0.166-0.982	0.045	R	0.057	65.1
	Middle Eastern	2	355	361	0.725	0.484-1.086	0.119	F	0.176	45.4

B. LN

Polymorphism	Population	No. of studies	Subject no.		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	*p*-value	Model	*p*-value	I^2
FAS -670 A/G G *vs*. A allele	LN	3	85	211	0.904	0.433-1.887	0.788	R	0.018	75.2
GG *vs*. GA+AA (Recessive)	LN	3	85	211	0.921	0.498-1.702	0.792	F	0.458	0
GG+GA *vs*. AA (Dominant)	LN	3	85	211	0.726	0.186-2.834	0.644	R	0.004	82.2
GG *vs*. AA	LN	3	85	211	0.715	0.170-3.000	0.647	R	0.021	73.9

F: Fixed effect model; R: Random effect model, LN: lupus nephritis.

polymorphism. Egger's regression test showed no evidence of publication bias in this meta-analysis (Egger's regression test *p*-values >0.1).

Discussion

SLE is the prototype autoimmune disease that is characterised by multi-systemic organ involvement, polyclonal B cell activation, and production of autoantibodies (35, 36). One possible explanation for the pathogenesis of SLE is the failure of apoptosis of self-reactive T cells (37, 38). Apoptosis is likely to contribute to the pathogenesis of autoimmune diseases by the impaired elimination of autoreactive T and B cells (4). FAS/FASL plays an important role in the regulation of the immune system by deleting autoreactive peripheral lymphocytes through the induction of apoptosis (4). Either enhanced or defective FAS-mediated apoptosis might result in an impaired clearance of apoptotic cells or failure in the elimination of autoreactive cells, and might be one of the susceptibility factors for SLE. The FAS promoter region encompasses a 2000 bp sequence that consists of the basal promoter, the enhancer and silencer regions, and contains two polymorphisms: a -670 A/G polymorphism in the enhancer region and a -1377 G/A polymorphism in the silencer region (5). The two polymorphisms are of functional significance (6). It is possible that the FAS -670 A/G and -1377 G/A polymorphisms alter of FAS gene expression in immune cells, thereby contributing to SLE.

The present study addressed the association between the FAS -670 A/G, FAS -1377 G/A, and FASL -844 T/C polymorphisms and susceptibility to SLE. We found an association between SLE and the FAS and FASL polymorphisms. Meta-analysis indicated a negative association between SLE and the FAS -670 GG+GA genotype (OR=0.629, 95% CI=0.409–0.967, *p*=0.035). When stratified separately according to ethnicity, subgroup meta-analysis indicated an association between the FAS -670 GG+GA genotype and SLE in Asian populations (OR=0.464, 95% CI=0.218–0.988, *p*=0.046), but not in Caucasian populations. In addition, the FAS -1377 A allele was associated with a decreased SLE risk (OR=0.783, 95% CI=0.613 - 0.997, *p*=0.047), and the FASL +844 C allele is associated with an increased SLE risk (OR=1.377, 95% CI=1.162–1.633, $p=2.3\times10^{-4}$).

In this meta-analysis, we found an under-representation of the FAS -670 G and FAS -1377 A alleles in SLE patients *versus* control patients. The negative association between the FAS -670 G allele and SLE susceptibility might be due to a lower level of soluble FAS (sFAS) associated with the FAS -670 G and FAS -1377 A alleles compared to

Table III. Meta-analysis of the association between the FAS -1377 G/A, FASL -844 T/C polymorphisms and SLE.

Polymorphism	Population	No. of studies	Subject no.		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	*p*-value	Model	*p*-value	I^2
FAS -1377 G/A	Overall	3	444	442	0.783	0.615-0.997	0.047	F	0.169	43.8
A *vs*. G allele	Caucasian	1	86	90	1.103	0.615-1.978	0.742	NA	NA	NA
	Asian	1	109	140	0.867	0.607-1.239	0.434	NA	NA	NA
	Middle Eastern	1	249	212	0.592	0.399-0.879	0.009	NA	NA	NA
AA *vs*. AG+GG	Overall	3	444	442	0.895	0.531-1.510	0.678	F	0.453	0
(Recessive)	Caucasian	1	86	90	1.590	0.259-9.758	0.616	NA	NA	NA
	Asian	1	109	140	0.965	0.533-1.746	0.906	NA	NA	NA
	Middle Eastern	1	249	212	0.419	0.103-1.695	0.222	NA	NA	NA
AA+AG *vs*. GG	Overall	3	444	442	0.712	0.528-0.961	0.027	F	0.303	16.3
(Dominant)	Caucasian	1	86	90	1.065	0.548-2.067	0.853	NA	NA	NA
	Asian	1	109	140	0.756	0.447-1.276	0.295	NA	NA	NA
	Middle Eastern	1	249	212	0.574	0.371-0.889	0.013	NA	NA	NA
AA *vs*. GG	Overall	3	444	442	0.763	0.430-1.352	0.354	F	0.437	0
	Caucasian	1	86	90	1.597	0.258-9.879	0.615	NA	NA	NA
	Asian	1	109	140	0.812	0.416-1.584	0.541	NA	NA	NA
	Middle Eastern	1	249	212	0.374	0.092-1.521	0.170	NA	NA	NA
FASL +844 T/C	Overall	4	665	787	1.377	1.162-1.633	$2.3x10^{-4}$	F	0.604	0
C *vs*. T allele	Caucasian	1	88	198	1.150	0.790-1.674	0.466	NA	NA	NA
	Asian	1	260	280	1.382	1.045-1.827	0.023	NA	NA	NA
	Middle Eastern	1	106	159	1.653	1.147-2.383	0.007	NA	NA	NA
CC *vs*. CT+TT	Overall	4	665	787	1.592	1.251-2.014	$1.5x10^{-4}$	F	0.446	0
(Recessive)	Caucasian	1	88	198	1.251	0.752-2.080	0.388	NA	NA	NA
	Asian	1	260	280	1.533	1.088-2.159	0.015	NA	NA	NA
	Middle Eastern	1	106	159	1.891	1.140-3.137	0.014	NA	NA	NA
CC+CT *vs*. TT	Overall	4	665	787	1.319.	0.961-1.810	0.086	F	0.648	0
(Dominant)	Caucasian	1	88	198	1.097	0.483-2.490	0.824	NA	NA	NA
	Asian	1	260	280	1.336	0.625-2.854	0.455	NA	NA	NA
	Middle Eastern	1	106	159	2.052	0.951-4.425	0.067	NA	NA	NA
CC *vs*. TT	Overall	4	665	787	1.924	1.254-2.953	0.003	F	0.466	0
	Caucasian	1	88	198	1.238	0.521-2.943	0.629	NA	NA	NA
	Asian	1	260	280	1.586	0.732-3.432	0.243	NA	NA	NA
	Middle Eastern	1	106	159	2.745	1.208-6.237	0.016	NA	NA	NA

F: Fixed effect model; R: Random effect model; NA: Not available.

the FAS -670 A and FAS -1377 G alleles. Serum sFAS levels are higher in SLE patients compared to levels in healthy controls (39) and mice injected with sFAS showed autoimmune features (40). sFAS downregulates the FAS receptors on the cell membrane and binds to FAS ligand, thereby antagonising the FAS/FASL pathway (41). The FAS -670 A/G and FAS -1377 G/A polymorphisms correlate with serum sFAS levels in normal individuals, and subjects carrying the FAS -670 GG or FAS -1377 AA genotype have significantly lower sFAS levels than those carrying the FAS-670 AA or FAS -1377 GG genotype (42, 43). The FASL -844 T/C polymorphism is also of functional significance. A higher basal expression of the FASL gene is observed in association with the C allele compared to the T allele of the C- 844 T polymorphism of FASL. Our data suggest that increased expression of FASL in individuals carrying the FASL -844 C allele leads to an elevated apoptosis rate, coupled with a possible clearance deficiency, may enhance SLE risk.

This meta-analysis differs from the previous meta-analyses on the relation between the FAS -670 A/G and FAS -1377 G/A polymorphisms and SLE risk performed by Xiang *et al*. (31) and by Lee *et al*. (30), because the present study included six more studies (8-11, 17, 34) and 824 more SLE patients and 997 more controls, and because we performed additional meta-analyses to examine the potential association of the FASL -844 T/C polymorphism with SLE. The results of our meta-analysis, which indicate an association between the FAS -670 A/G, and -1377 G/A polymorphisms and SLE risk, are in agreement with the findings of the previously reported meta-analysis study; however our results also provide the new finding that the FASL -844 C allele increases the risk for SLE.

The present study has some limitations that require consideration. First, heterogeneity and confounding factors may have distorted the analysis. Second, our ethnic-specific meta-analysis included data from Caucasian, Asian, and Middle Eastern patients and, thus, our results are applicable to only these ethnic groups. Third, the study numbers and numbers of subjects included in subgroup analysis stratified by ethnicity and LN were small. They may have been underpowered to detect a small association. Our meta-analysis showed no association between LN and the FAS -670 A/G polymorphism, but the sample size was too small to reach definite conclusion.

In conclusion, this meta-analysis demonstrates that the FAS -670 A/G, FAS

-1377 G/A, and FASL -844 T/C polymorphisms are associated with susceptibility to SLE. Given the important roles of FAS and FASL in apoptosis, it is possible that FAS and FASL polymorphisms may modulate development of SLE. Further studies are warranted to clarify the role of the FAS and FASL genes in the pathogenesis of SLE.

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