Relationship Between Angiotensin-converting Enzyme Insertion/Deletion Gene Polymorphism and Systemic Lupus Erythematosus/Lupus Nephritis: A Systematic Review and Metaanalysis

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ABSTRACT. ***Objective.*** Results from studies of the association between angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism and systemic lupus erythematosus (SLE)/lupus nephritis (LN) are controversial. We performed this metaanalysis to evaluate the relationship between ACE I/D gene polymorphism and SLE/LN and to explore whether the *ACE* D allele or DD genotype could become a predictive marker for risk of SLE/LN.

Methods. Association studies were identified from the databases of PubMed, Embase, Cochrane Library and CBM-disc (China Biological Medicine Database) as of May 1, 2011, and eligible investigations were synthesized using a metaanalysis method. Results were expressed with OR for dichotomous data, and 95% CI were calculated.

Results. Sixteen investigations were identified for the analysis of association between ACE I/D gene polymorphism and SLE, consisting of 1959 patients with SLE and 2078 controls. In the overall populations, there was a marked association between D allele or DD genotype and SLE susceptibility (D: OR 1.29, 95% CI 1.04–1.58, p = 0.02; DD: OR 1.60, 95% CI 1.17–2.19, p = 0.003), and DD homozygous was associated with LN risk (OR 2.78, 95% CI 1.26–6.11, p = 0.01). In the subgroup analysis, DD genotype associated with SLE risk was observed in Asians; no other association was found in Asians, whites, Africans, and Brazilians.

Conclusion. D allele and DD homozygous are significant genetic molecular markers to predict SLE susceptibility, and DD genotype is a valuable marker to predict the LN risk. More investigations are required to clarify the association of the D allele or DD homozygous with SLE/LN susceptibility. (J Rheumatol First Release Feb 15 2012; doi:10.3899/jrheum.110863)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS LUPUS NEPHRITIS GENE POLYMORPHISM
ANGIOTENSIN-CONVERTING ENZYME INSERTION/DELETION METAANALYSIS

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease[1,2,3] mainly characterized clinically by involvement of joints, skin, and kidneys[4,5]. SLE is a severe disease that results from both genetic predisposition and environmental factors[6]. Lupus nephritis (LN) is one of the most common manifestations in SLE[7] and remains a predominant cause of morbidity and mortality in SLE[8]. SLE is characterized by increasing vascular lesion risk[9], and vascular lesions are encountered frequently in renal biopsy specimens of patients with SLE; the lesions can present in a variety of morphologic forms[10]. Some studies have found that gene polymorphism was associated with the risk of SLE[11,12] and LN susceptibility[13,14].

The activation of the renin-angiotensin-aldosterone system (RAAS) is part of the onset of SLE and LN[15,16]. Angiotensin-converting enzyme (ACE), a key zinc metallopeptidase, catalyzes the conversion of angiotensin I to angiotensin II, which is the main active product of the RAAS[17]. The ACE gene consists of either an insertion (I) allele or a deletion (D) allele and forms 3 possible genotypes: II, ID, and DD[18]. DD homozygous or D allele is associated with elevated circulating and tissue ACE activity compared to I allele. ACE is important in the development of SLE because its endproduct, angiotensin II,

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plays an integral role in the regulatory system responsible for endothelial control and vascular tone, systems that are commonly affected in patients with SLE[19]. Additionally, ACE inhibitors have been shown to alleviate the progression of SLE and LN[19].

The ACE I/D gene polymorphism, correlating with circulating and cellular ACE concentration[20], might be implicated in the etiology of SLE or LN and has been investigated in numerous epidemiologic studies. However, the available evidence is weak, due to sparseness of data or disagreements among the reported investigations. The evidence from meta-analysis may be powerful when compared with the individual investigations. Lee, *et al*[21] conducted an interesting meta-analysis to explore the association of ACE I/D gene polymorphism with the SLE or LN risk and found that there was a lack of association of the ACE I/D polymorphism with SLE and LN. However, that study included only 10 reports. We performed this metaanalysis to investigate whether the ACE I/D gene polymorphism was associated with the onset of SLE or LN by collecting the reported investigations, and to update the conclusions from Lee, *et al*.

MATERIALS AND METHODS

Search strategy for the association of ACE I/D gene polymorphism with SLE risk. The relevant studies were searched from the electronic databases of PubMed, Embase, Cochrane Library, and CBM-disc (China Biological Medicine Database) on May 1, 2011. The retrieval strategy of (Systemic lupus erythematosus OR SLE) AND (Angiotensin converting enzyme OR ACE) was entered into these databases. Additional articles were identified through references cited in retrieved articles.

Inclusion and exclusion criteria for SLE vs control/LN vs control. Inclusion criteria: (1) the outcome had to be SLE/LN; (2) there had to be at least 2 comparison groups (SLE group vs control group/LN group vs control group); and (3) investigation should provide detailed data of the ACE genotype distribution. Exclusion criteria: (1) review articles and editorials; (2) case reports; (3) preliminary result not on ACE I/D gene polymorphism or outcome; and (4) investigating the role of ACE inhibitor on disease. If multiple publications from the same study group were found, we included only the most complete report in our final analysis.

Data extraction and synthesis. Two investigators independently extracted the following information from each eligible study: first author's surname, year of publication, and number of cases and controls for ACE genotypes. Frequency of D allele was calculated for case group and control group, from the corresponding genotype distribution. The results were compared and disagreement was resolved by discussion.

Statistical analysis. Cochrane Review Manager Version 5 (Cochrane Library, UK) was used to calculate the available data from each investigation. The pooled statistic was counted using the fixed-effects model, but a random-effects model was conducted when the p value of the heterogeneity test was < 0.1[22]. Results were expressed with OR (95% CI) for dichotomous data. A value of $p < 0.05$ was required for the pooled OR to be statistically significant. I^2 was used to test the heterogeneity among the included studies. In order to avoid excessive comparisons, the OR was calculated by 3 methods: (1) allele comparison (D allele vs I allele); (2) comparing DD homozygous with the other 2 combinations (DD vs DI + II); and (3) comparing II genotype with the other 2 combinations (II vs DD + DI). A chi-square test using a Web-based program was applied to determine whether genotype distributions of the case group/control group reported conformed to Hardy-Weinberg equilibrium (HWE; $p < 0.05$ was considered significant). The gene distributions of the control group in the included studies were not in HWE, a situation that might result in heterogeneity[17,23], and the study indicating that the genotype distributions in the control group significantly deviated from HWE was excluded from our sensitivity analysis[24]. The Begg adjusted rank correlation test[25] and the Egger regression asymmetry test[26] were used for exploring publication bias ($p < 0.1$ was considered significant) when the number of included studies was > 5. All descriptive data were expressed as mean ± SD.

RESULTS

Study characteristics for SLE vs control. Sixteen studies[27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42] were used in our investigation. Three studies[27,30,36] were published in Chinese and the others were reported in English. These data were extracted: first author's surname, year of publication, and the number of cases and controls for ACE genotype (Table 1). Those 16 investigations contained 1959 case series and 2078 controls. The average distribution frequency of ACE D allele in patients with SLE was 55.85% and the average frequency in controls was 49.43%. The average distribution frequency of D allele in cases was slightly increased compared with that in the control group (SLE/control = 1.13).

Study characteristics for LN vs control. Seven studies[27,30,31,39,40,41,42] were included into our metaanalysis for LN versus control (Table 2). Those investigations involved 417 patients with LN and 981 controls. The average distribution frequency of the ACE D allele in patients with SLE was 60.37%, and the average frequency in controls was 47.98%. The average distribution frequency of the D allele in the LN group was markedly increased compared with that in the control group (LN/control = 1.26).

Association of the ACE I/D gene polymorphism with SLE risk (SLE vs control). In our metaanalysis, we found that the D allele and DD genotype were associated with SLE risk (Figure 1 for D allele and Figure 2 for DD genotype), but the association of II homozygous with SLE susceptibility was not observed (Table 3). The genotype distributions of the control population in 1 study[36] did not conform to HWE, and this investigation was excluded from our sensitivity analysis. In the analysis, the results were similar to those in the nonsensitivity analysis (Table 3).

We also performed a subgroup analysis according to different races. For Asians, we found that DD homozygous was associated with SLE risk, but the association for D allele or II genotype was not observed (Table 3). Sensitivity analysis according to HWE test was performed (1 report[36] was excluded), and no association between ACE I/D gene polymorphism and SLE risk was observed (Table 3).

Subgroup analyses for whites, Africans, and Brazilians were also performed. We found that the ACE I/D gene polymorphism was not associated with the onset of SLE in whites, Africans, and Brazilians (Table 3). The gene distributions of the control group in all the included reports were in HWE, so the results from the sensitivity analysis were the same as those of the nonsensitivity analysis.

Association of ACE I/D gene polymorphism with LN suscepti-

Table 1. Characteristics of the studies evaluating the effects of ACE genes on SLE risk.

Study	Ethnicity	SLE			Control			D Allele, %		HWE	
		DD	ID	II	DD	ID	II	Case	Control	Case	Control
Guan[27] 1997	Asian	42	44	58	9	59	82	44.44	25.67	0.000	0.706
Sato[28] 1998	Asian	12	36	45	15	50	35	32.26	40.00	0.270	0.677
Tassiulas[29] 1998	Overall*	81	110	25	88	90	22	62.96	66.50	0.177	0.888
	White	52	59	10	45	63	14	67.36	62.70	0.231	0.250
	African	24	44	10	43	27	8	58.97	72.44	0.143	0.240
Huang[30] 1999	Asian	4	13	11	3	18	19	37.50	30.00	0.960	0.651
Akai[31] 1999	Asian	9	33	42	15	50	35	30.36	40.00	0.516	0.677
Pullmann[32] 1999	White	39	49	13	43	68	37	62.87	52.03	0.694	0.333
Molad[33] 2000	White	33	20	3	26	15	7	76.79	69.80	0.989	0.073
Prkacin[34] 2001	White	9	5	4	5	11	5	63.89	50.00	0.091	0.827
Kaufman[41] 2001	Overall*	135	144	85	142	228	95	56.87	55.05	0.000	0.842
	White	61	91	54	85	144	62	51.70	53.95	0.097	0.944
	African	65	41	22	47	60	22	66.80	59.69	0.002	0.704
Uhm[35] 2002	Asian	42	87	82	18	57	39	40.52	40.79	0.036	0.708
Lv[36] 2002	Asian	15	23	12	24	40	52	53.00	37.93	0.588	0.004
Douglas[37] 2004	Overall*	77	110	38	89	127	55	58.67	56.27	0.904	0.432
	White	28	44	13	64	95	42	58.82	55.47	0.527	0.540
	African	49	66	25	25	32	13	58.57	58.57	0.735	0.627
Saeed[38] 2005	Asian	11	14	14	14	38	27	46.15	41.77	0.083	0.921
Sprovieri[40] 2005	Brazilian	61	69	17	18	39	8	64.97	57.69	0.706	0.065
Al-Awadhi[39] 2007	Asian	37	36	19	41	45	14	59.78	63.50	0.074	0.770
Hussain[42] 2010	Asian	54	3	4	23	32	6	90.98	63.93	0.000	0.283

* The data were used for the analysis in overall populations. ACE: angiotensin-converting enzyme; SLE: systemic lupus erythematosus; HWE: Hardy-Weinberg equilibrium; I: insertion allele; D: deletion allele.

Table 2. Characteristics of the studies evaluating the effects of ACE genes on LN risk.

Study	Ethnicity	LN			Control			D Allele (%)	
		DD	ID	II	DD	ID	II	Case	Control
Guan[27] 1997	Asian	42	44	58	9	59	82	44.44	25.67
Huang[30] 1999	Asian	10	16	4	3	18	19	60.00	30.00
Akai[31] 1999	Asian	9	33	42	15	50	35	30.36	40.00
Kaufman[41] 2001	Mix*	31	9	9	142	228	95	72.45	55.05
Sprovieri[40] 2005	Brazilian	32	34	9	18	39	8	65.33	57.69
Al-Awadhi[39] 2007	Asian	5	5	5	41	45	14	50.00	63.50
Hussain[42] 2010	Asian	20	0	0	23	32	6	1.00	63.93

* The data included whites, Africans, and others, and these data were used only for the analysis in overall populations. ACE: angiotensin-converting enzyme; LN: lupus nephritis; I: insertion allele; D: deletion allele.

bility (LN vs control). In our study of LN vs control, we found that DD genotype was associated with the risk of LN (OR 2.78, 95% CI 1.26–6.11, p = 0.01; Table 4) in overall populations. However, no associations for D allele and II genotype were found in this study for LN versus control (Table 4).

Subgroup analysis according to different races was also performed. We found no association between ACE I/D gene polymorphism and LN risk in Asians and Brazilians (Table 4).

The gene distributions of control groups in all the included reports were in HWE, so the results from sensitivity analysis were the same as those of nonsensitivity analysis.

Evaluation of publication bias. In the comparison of SLE versus control, no significant publication bias was found for overall populations, Asians, and whites (overall populations: Begg p = 0.964, Egger p = 0.680; Asians: Begg p = 0.466, Egger p = 0.975; whites: Begg p = 1.000, Egger p = 0.227). In the comparison of LN versus control, there was no significant publication bias for overall populations and Asians (overall populations: Begg p = 0.548, Egger p = 0.643; Asians: Begg p = 0.806, Egger p = 0.429).

DISCUSSION

The genetic origin of SLE and LN had been a focus of research in recent years, and some investigations found that the genetic alteration could become an early diagnosis indicator to predict the susceptibility of some diseases[43,44,45,46]. The level of plasma ACE, constitutively expressed in several types of somatic cells, is linked to an I/D polymorphism of 287 bp

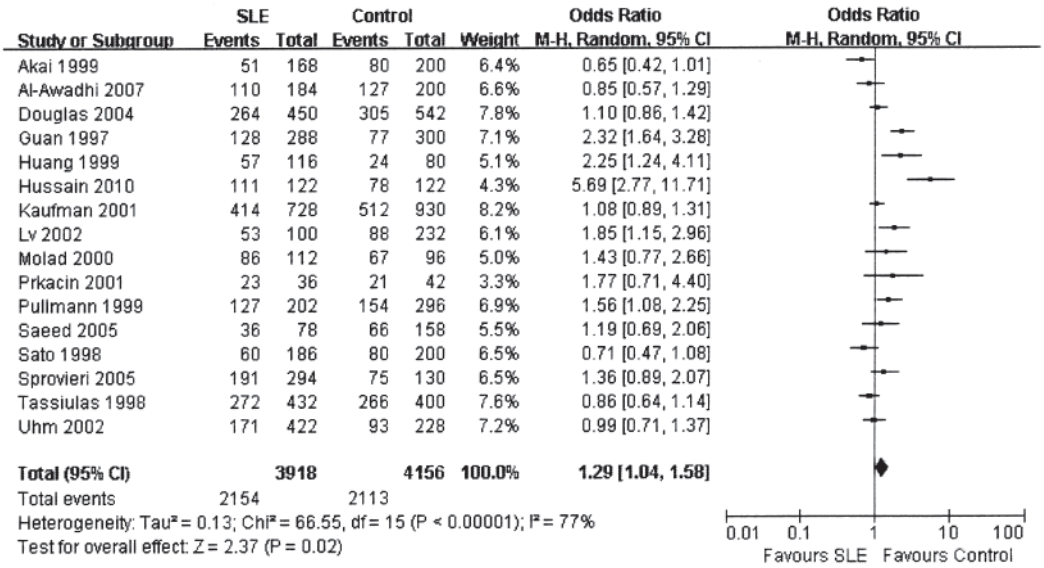

Figure 1. Association between D allele and risk for systemic lupus erythematosus (SLE). M-H: Mantel-Haenszel.

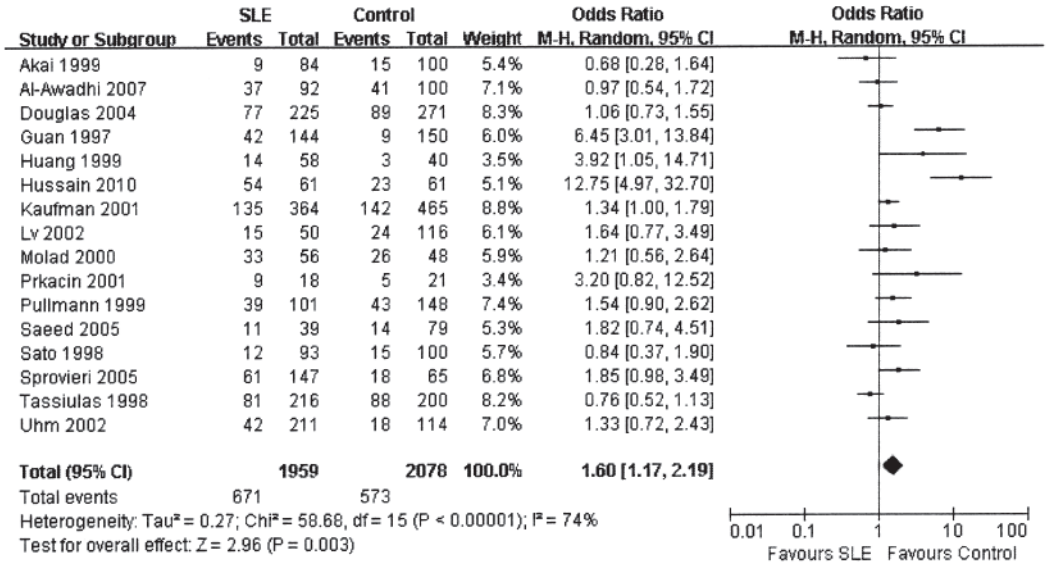

Figure 2. Association of DD genotype with risk for systemic lupus erythematosus (SLE). M-H: Mantel-Haenszel.

in intron 16 of the *ACE* gene[17,18]. D allele and DD homozygous have been reported to be associated with higher plasma ACE levels[23,47,48]. The increased protein expression of ACE is responsible for the elevation of plasma angiotensin II level[23,49]. There was some significant evidence showing that ACE was involved in the risk of SLE and LN[19,50,51]. So the D allele or DD homozygous might be important molecular markers for the risk of SLE or LN. Most of the studies investigating the association between ACE I/D gene polymorphism and the risk of SLE/LN explored whether the ACE I/D gene polymorphism could become a valuable indicator to predict the risk of SLE/LN. However, data were insufficient. Further, findings on the association of ACE I/D gene polymorphism with the susceptibility of SLE or LN have been controversial since the first investigation was reported. We investigated whether the ACE I/D gene polymorphism could become a valuable indicator to predict the risk of SLE or LN, and tried to draw a more robust conclusion by metaanalysis.

Our results indicated that the ACE D allele or DD genotype could predict the onset of SLE for overall populations. Our results were similar to those in nonsensitivity analyses, and there was no publication bias. The conclusions of our study might be robust. We performed subgroup analyses to explore this association in whites, Africans, and Brazilians. In Asians,

Table 3. Metaanalysis of the association of ACE I/D gene polymorphism with risk of SLE.

Genetic Contrasts	Groups and Subgroups	Studies, n	Q Test p	Model Selected	OR (95% CI)	p
D vs I	Overall	16	< 0.00001	Random	1.29 (1.04, 1.58)	0.02
	Asian	9	< 0.00001	Random	1.31 (0.89, 1.94)	0.17
	White	6	0.20	Fixed	1.16 (0.99, 1.35)	0.06
	African	3	0.01	Random	0.92 (0.56, 1.53)	0.76
	Brazilian	1	—	Fixed	1.36 (0.89, 2.07)	0.15
DD vs (DI + II)	Overall	16	< 0.00001	Random	1.60 (1.17, 2.19)	0.003
	Asian	9	< 0.00001	Random	1.89 (1.03, 3.47)	0.04
	White	6	0.58	Fixed	1.21 (0.97, 1.52)	0.10
	African	3	0.0007	Random	0.87 (0.35, 2.17)	0.77
	Brazilian	1	—	Fixed	1.85 (0.98, 3.49)	0.06
II vs (DI + DD)	Overall	16	0.001	Random	0.89 (0.69, 1.15)	0.37
	Asian	9	0.003	Random	1.00 (0.68, 1.46)	0.99
	White	6	0.08	Random	0.73 (0.46, 1.15)	0.17
	African	3	0.89	Fixed	1.04 (0.67, 1.61)	0.87
	Brazilian	1	—	Fixed	0.93 (0.38, 2.28)	0.88
Sensitivity analysis						
D vs I	Overall	15	< 0.00001	Random	1.26 (1.01, 1.56)	0.04
	Asian	8	< 0.00001	Random	1.26 (0.83, 1.93)	0.28
	White	6	0.20	Fixed	1.16 (0.99, 1.35)	0.06
	African	3	0.01	Random	0.92 (0.56, 1.53)	0.76
	Brazilian	1	—	Fixed	1.36 (0.89, 2.07)	0.15
DD vs (DI + II)	Overall	15	< 0.00001	Random	1.60 (1.16, 2.23)	0.005
	Asian	8	< 0.00001	Random	1.93 (0.96, 3.87)	0.06
	White	6	0.58	Fixed	1.21 (0.97, 1.52)	0.10
	African	3	0.0007	Random	0.87 (0.35, 2.17)	0.77
	Brazilian	1	—	Fixed	1.85 (0.98, 3.49)	0.06
II vs (DI + DD)	Overall	15	0.006	Random	0.94 (0.73, 1.21)	0.63
	Asian	8	0.02	Random	1.12 (0.78, 1.61)	0.53
	White	6	0.08	Random	0.73 (0.46, 1.15)	0.17
	African	3	0.89	Fixed	1.04 (0.67, 1.61)	0.87
	Brazilian	1	—	Fixed	0.93 (0.38, 2.28)	0.88

ACE: angiotensin-converting enzyme; I/D: insertion/deletion; SLE: systemic lupus erythematosus.

Table 4. Metaanalysis of the association of ACE I/D gene polymorphism with risk of lupus nephritis.

Genetic Contrasts	Groups and Subgroups	Studies	Q Test p	Model Selected	OR (95% CI)	p
D vs I	Overall	7	< 0.00001	Random	1.63 (0.93, 2.84)	0.09
	Asian	5	< 0.00001	Random	1.70 (0.71, 4.09)	0.23
	Brazilian	1	—	Fixed	1.38 (0.85, 2.24)	0.19
DD vs (DI + II)	Overall	7	< 0.0001	Random	2.78 (1.26, 6.11)	0.01
	Asian	5	< 0.0001	Random	3.14 (0.82, 12.03)	0.10
	Brazilian	1	—	Fixed	1.94 (0.96, 3.95)	0.07
II vs (DI + DD)	Overall	7	0.001	Random	0.84 (0.44, 1.60)	0.60
	Asian	5	0.0002	Random	0.78 (0.30, 2.04)	0.62
	Brazilian	1	—	Fixed	0.97 (0.35, 2.68)	0.96

ACE: angiotensin-converting enzyme; I/D: insertion/deletion.

the DD genotype was associated with the risk of SLE. Further, the pooled OR for D allele was favorable to the SLE group in Asians, although the difference was not statistically significant. So DD homozygous and D allele might be risk factors for SLE risk in Asians. We also found that the pooled OR for D allele or DD homozygous in whites was favorable to the SLE group, although no statistically significant difference was found. D allele/DD genotype might be a risk factor for SLE in whites. In Africans and in Brazilians, no association of ACE I/D gene polymorphism and the risk of SLE was found. The number of included studies of Asians or whites was much larger than that of Africans or Brazilians (Asians: 9; whites: 6; Africans: 3; Brazilians: 1). Results for Asians or whites might be more convincing than those for Africans or Brazilians.

LN is a common and potentially severe complication of SLE[52]. We performed a metaanalysis for LN versus control. An association of the DD genotype with the onset of LN was observed. Further, the pooled OR for the D allele was favorable to the LN group, although no statistically significant difference was found. DD genotype/D allele might be a factor in LN risk susceptibility. The results from the sensitivity analysis were the same as those of the nonsensitivity analysis, and no publication bias was found. The results for overall populations might be robust to some extent. However, the number of included studies for Asians or Brazilians was small, and it was difficult to draw a convincing conclusion for Asians or Brazilians.

The HWE test was performed and the result that the genotype distributions in the control group significantly deviated from HWE was excluded from our sensitivity analysis. In our study, the genotype distributions of the control group in 1 report[36] were not in HWE. This was a factor that could cause bias and was excluded from our sensitivity analysis. The disequilibrium of the genotype distributions of the control group might be caused by methodological weaknesses, such as biased selection of subjects, genotyping errors, or population stratification[53]. In our study, we also provided the results of HWE for the SLE group. We found that the case groups in Guan, *et al*[27] and Hussain, *et al*[42] were not in HWE, and the case group for overall populations/Africans in Kaufman, *et al*[41] also was not in HWE. In the case of genetic association, deviation from HWE can be expected in cases, while it should not be strong in controls[54]. So the deviation from HWE of those studies reflected the positive association between ACE I/D gene polymorphism and risk for SLE.

In Guan[27], Hussain[42], and Kaufman[41], the D allele and DD homozygous might be associated with the onset of SLE. Further, DD genotype was associated with the risk of LN, and the D allele was a risk factor for LN (although the difference was not statistically significant). We speculated that the mechanisms were as follows: the DD homozygous or D allele was associated with elevated circulating and tissue ACE activity, and the increased ACE could raise the risk of SLE and LN[19,50,51]. So the DD homozygous or D allele might be associated with susceptibility to SLE/LN.

There were also studies of the association of ACE I/D gene polymorphism and some diseases using the metaanalysis method. They found that ACE I/D gene polymorphism was associated with the susceptibility of some diseases correlating with the vascular system. Samani, *et al*[55] conducted a meta-analysis to investigate the association between ACE I/D gene polymorphism and risk of myocardial infarction, and found that D allele and DD genotype were associated with the onset of myocardial infarction. Qin, *et al*[46] performed a metaanalysis to explore the relationship between ACE I/D gene polymorphism and risk of IgA nephropathy, and found that the D allele and DD homozygous were associated with the onset of IgA nephropathy. Zintzaras, *et al*[56] performed a metaanalysis to investigate the relation between ACE I/D gene polymorphism and coronary artery disease, and found that the D allele and DD genotype were associated with the onset of coronary artery disease. Sayed-Tabatabaei, *et al*[57] conducted a meta-analysis and showed evidence of a positive association between the D allele of the ACE gene and common carotid intima-media thickness.

Our results indicated that there was an association between the D allele or DD genotype and SLE risk, and DD homozygous was associated with the risk of LN. The outcome might be robust. We speculated that the increased ACE level was associated with the risk of SLE/LN. However, those findings should be regarded cautiously because many other factors, such as language bias, small sample size of the included report, limited statistical power, heterogeneity of enrolled cases, variable study designs, and different interventions could have affected the results.

Language bias might affect our conclusion. We analyzed the gene distribution of ACE I/D polymorphism in English reports and Chinese reports separately (detailed data not shown). In the metaanalysis for English reports, we found that the DD genotype was associated with the risk of SLE but not with risk for LN, and that the D allele was not associated with risk for SLE/LN. In the analysis for Chinese reports, the D allele and DD genotype were associated with susceptibility to SLE/LN. As in Zintzaras, *et al*[56] and Sayed-Tabatabaei, *et al*[57], the D allele and DD genotype might be genetic markers to predict the risk of SLE/LN in Chinese people.

The sample size in some studies was small and might have affected the strength of our outcome. We excluded those reports with a sample size < 80. Finally, 9 reports[27,28,29,31,32,35,37,39,41] for SLE and 2[27,31] for LN were included in the metaanalysis. We found that ACE I/D polymorphism was not associated with risk for SLE/LN in the analysis for overall populations and subgroup analysis according to different races (detailed data not shown). However, the number of included reports was small and the conclusion was not robust.

Our study supports the notion that the D allele or DD genotype is associated with risk for SLE, and there is an association between DD homozygous and risk for LN. However, more association investigations with larger sample sizes are required to clarify the role of the ACE I/D gene polymorphism in predicting the risk of SLE/LN.

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REFERENCES

1. Mak A, Liu Y, Ho RC. Endothelium-dependent but not endothelium-independent flow-mediated dilation is significantly reduced in patients with systemic lupus erythematosus without vascular events: A metaanalysis and metaregression. J Rheumatol 2011;38:1296-303.

2. Zhang G, Li H, Huang W, Li X, Li X. Clinical features of lupus cystitis complicated with hydroureteronephrosis in a Chinese population. J Rheumatol 2011;38:667-71.
3. Lee YH, Nath SK. Systemic lupus erythematosus susceptibility loci defined by genome scan meta-analysis. Hum Genet 2005;118:434-43.
4. Touma Z, Gladman DD, Urowitz MB, Beyene J, Uleryk EM, Shah PS. Mycophenolate mofetil for induction treatment of lupus nephritis: A systematic review and metaanalysis. J Rheumatol 2011;38:69-78.
5. Lin LH, Ling P, Liu MF. The potential role of interferon-regulatory factor 7 among Taiwanese patients with systemic lupus erythematosus. J Rheumatol 2011;38:1914-9.
6. Salloum R, Niewold TB. Interferon regulatory factors in human lupus pathogenesis. Transl Res 2011;157:326-31.
7. Chen HA, Wang JJ, Chou CT, Chien CC, Chu CC, Sheu MJ, et al. Predictors of longterm mortality in patients with and without systemic lupus erythematosus on maintenance dialysis: A comparative study. J Rheumatol 2011;38:2390-4.
8. Lee YH, Bae SC, Choi SJ, Ji JD, Song GG. Associations between vitamin D receptor polymorphisms and susceptibility to rheumatoid arthritis and systemic lupus erythematosus: A meta-analysis. Mol Biol Rep 2011;38:3643-51.
9. Thacker SG, Berthier CC, Mattinzoli D, Rastaldi MP, Kretzler M, Kaplan MJ. The detrimental effects of IFN-alpha on vasculogenesis in lupus are mediated by repression of IL-1 pathways: Potential role in atherogenesis and renal vascular rarefaction. J Immunol 2010;185:4457-69.
10. Abdellatif AA, Waris S, Lakhani A, Kadikoy H, Haque W, Truong LD. True vasculitis in lupus nephritis. Clin Nephrol 2010;74:106-12.
11. Koga M, Kawasaki A, Ito I, Furuya T, Ohashi J, Kyogoku C, et al. Cumulative association of eight susceptibility genes with systemic lupus erythematosus in a Japanese female population. J Hum Genet 2011;56:503-7.
12. Bronson PG, Goldstein BA, Ramsay PP, Beckman KB, Noble JA, Lane JA, et al. The rs4774 CIITA missense variant is associated with risk of systemic lupus erythematosus. Genes Immun 2011;12:667-71.
13. Dasgupta S, Demirci FY, Dressen AS, Kao AH, Rhew EY, Ramsey-Goldman R, et al. Association analysis of PON2 genetic variants with serum paraoxonase activity and systemic lupus erythematosus. BMC Med Genet 2011;12:7.
14. Santos MJ, Carmona-Fernandes D, Caetano-Lopes J, Perpétuo IP, Vidal B, Capela S, et al. TNF promoter -308 G>A and LTA 252 A>G polymorphisms in Portuguese patients with systemic lupus erythematosus. Rheumatol Int 2011 May 5 [E-pub ahead of print].
15. Shilkina NP, Stoliarova SA, Iunonin IE, Driazhenkova IV. Neurohumoral regulation of blood pressure in rheumatic patients. Ter Arkh 2009;81:37-41.
16. Ryan MJ. The pathophysiology of hypertension in systemic lupus erythematosus. Am J Physiol Regul Integr Comp Physiol 2009;296:R1258-67.
17. Zhou TB, Qin YH, Su LN, Lei FY, Huang WF, Zhao YJ, et al. The association between angiotensin-converting enzyme insertion/deletion gene variant and risk of focal segmental glomerulosclerosis: A systematic review and meta-analysis. J Renin Angiotensin Aldosterone Syst 2011;12:624-33.
18. Zhou TB, Qin YH, Su LN, Lei FY, Huang WF, Zhao YJ. ACE I/D gene polymorphism can't predict the steroid responsiveness in Asian children with idiopathic nephrotic syndrome: A meta-analysis. PLoS One 2011;6:e19599.
19. Rabbani MA, Mahmood MS, Mekan SF, Frossard PM. Association of angiotensin-converting enzyme gene dimorphisms with severity of lupus disease. Saudi J Kidney Dis Transpl 2008;19:761-6.
20. Settin A, Elbaz R, Abbas A, Abd-Al-Samad A, Noaman A. Angiotensin-converting enzyme gene insertion/deletion polymorphism in Egyptian patients with myocardial infarction. J Renin Angiotensin Aldosterone Syst 2009;10:96-100.
21. Lee YH, Rho YH, Choi SJ, Ji JD, Song GG. Angiotensin-converting enzyme insertion/deletion polymorphism and systemic lupus erythematosus: A metaanalysis. J Rheumatol 2006;33:698-702.
22. Qin YH, Zhou TB, Su LN, Lei FY, Zhao YJ, Huang WF. The efficacy of different dose intravenous immunoglobulin in treating acute idiopathic thrombocytopenic purpura: A meta-analysis of 13 randomized controlled trials. Blood Coagul Fibrinolysis 2010;21:713-21.
23. Zhou TB, Qin YH, Su LN, Lei FY, Huang WF, Zhao YJ, et al. Insertion/deletion (I/D) polymorphism of angiotensin-converting enzyme gene in steroid-resistant nephrotic syndrome for children: A genetic association study and meta-analysis. Ren Fail 2011;33:741-8.
24. Economopoulos KP, Sergentanis TN. Three polymorphisms in cytochrome P450 1B1 (CYP1B1) gene and breast cancer risk: A meta-analysis. Breast Cancer Res Treat 2010;122:545-51.
25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.
26. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
27. Guan T, Liu Z, Chen Z. Angiotensin-converting enzyme gene polymorphism and the clinical pathological features and progression in lupus nephritis [Chinese]. Zhonghua Nei Ke Za Zhi 1997;36:461-4.
28. Sato H, Akai Y, Iwano M, Kurumatani N, Kurioka H, Kubo A, et al. Association of an insertion polymorphism of angiotensin-converting enzyme gene with the activity of systemic lupus erythematosus. Lupus 1998;7:530-4.
29. Tassiulas IO, Aksentijevich I, Salmon JE, Kim Y, Yarboro CH, Vaughan EM, et al. Angiotensin I converting enzyme gene polymorphisms in systemic lupus erythematosus: Decreased prevalence of DD genotype in African American patients. Clin Nephrol 1998;50:8-13.
30. Huang J, Yang YX, Li LY. Study of relationship between ACE gene I/D polymorphism and renal predisposition in SLE. J Clin Int Med 1999;4:205-6.
31. Akai Y, Sato H, Iwano M, Kurumatani N, Kurioka H, Kubo A, et al. Association of an insertion polymorphism of angiotensin-converting enzyme gene with the activity of lupus nephritis. Clin Nephrol 1999;51:141-6.
32. Pullmann RJ, Lukac J, Skerenova M, Rovensky J, Hybenova J, Melus V, et al. Association between systemic lupus erythematosus and insertion/deletion polymorphism of the angiotensin converting enzyme (ACE) gene. Clin Exp Rheumatol 1999;17:593-6.
33. Molad Y, Gal E, Magal N, Sulkes J, Mukamel M, Weinberger A, et al. Renal outcome and vascular morbidity in systemic lupus erythematosus (SLE): Lack of association with the angiotensin-converting enzyme gene polymorphism. Semin Arthritis Rheum 2000;30:132-7.
34. Prkacin I, Novak B, Sertic J, Mrzljak A. Angiotensin-converting enzyme gene polymorphism in patients with systemic lupus. Acta Med Croatica 2001;55:73-6.
35. Uhm WS, Lee HS, Chung YH, Kim TH, Bae SC, Joo KB, et al. Angiotensin-converting enzyme gene polymorphism and vascular manifestations in Korean patients with SLE. Lupus 2002;11:227-33.
36. Lv QQ, Shao RR, Xu FF. Association of angiotensin-converting enzyme gene polymorphism with the risk of systemic lupus erythematosus. Chin J Integ Trad West Nephrol 2002;1:41-2.

37. Douglas G, Reilly C, Dooley MA, Page G, Cooper G, Gilkeson G. Angiotensin-converting enzyme (insertion/deletion) and endothelial nitric oxide synthase polymorphisms in patients with systemic lupus erythematosus. J Rheumatol 2004;31:1756-62.
38. Saeed M, Mekan SF, Rabbani MA, Arain FM, Arif M, Shaharyar S. Angiotensin converting enzyme (ACE) gene polymorphisms and lupus disease severity: A promising link. Ann Rheum Dis 2005;64:164-5.
39. Al-Awadhi AM, Haider MZ, Sharma PN, Hasan EA, Botaiban F, Al-Herz A, et al. Angiotensin-converting enzyme gene polymorphism in Kuwaiti patients with systemic lupus erythematosus. Clin Exp Rheumatol 2007;25:437-42.
40. Sprovieri SR, Sens YA. Polymorphisms of the renin-angiotensin system genes in Brazilian patients with lupus nephropathy. Lupus 2005;14:356-62.
41. Kaufman KM, Kelly J, Gray-McGuire C, Asundi N, Yu H, Reid J, et al. Linkage analysis of angiotensin-converting enzyme (ACE) insertion/deletion polymorphism and systemic lupus erythematosus. Mol Cell Endocrinol 2001;177:81-5.
42. Hussain N, Jaffery G, Hasnain S, Sabri AN. Angiotensin-converting enzyme gene I/D polymorphism in Pakistani systemic lupus erythematosus patients. Afr J Biotechnol 2010;9:8134-8.
43. Sun QP, Li LY, Chen Z, Pang J, Yang WJ, Zhou XF, et al. Detection of TMPRSS2-ETS fusions by a multiprobe fluorescence in situ hybridization assay for the early diagnosis of prostate cancer: A pilot study. J Mol Diagn 2010;12:718-24.
44. Jung S, Jeong D, Kim J, Yi L, Koo K, Lee J, et al. The role of hLHX6-HMR as a methylation biomarker for early diagnosis of cervical cancer. Oncol Rep 2010;23:1675-82.
45. Moribe T, Iizuka N, Miura T, Stark M, Tamatsukuri S, Ishitsuka H, et al. Identification of novel aberrant methylation of BASP1 and SRD5A2 for early diagnosis of hepatocellular carcinoma by genome-wide search. Int J Oncol 2008;33:949-58.
46. Qin YH, Zhou TB, Su LN, Lei FY, Huang WF, Zhao YJ. Association between ACE polymorphism and risk of IgA nephropathy: A meta-analysis. J Renin Angiotensin Aldosterone Syst 2011;12:215-23.
47. Zhou TB, Qin YH, Su LN, Lei FY, Huang WF, Zhao YJ. Relationship between angiotensin-converting enzyme insertion/deletion gene polymorphism and susceptibility of minimal change nephrotic syndrome: A meta-analysis. Int J Nephrol 2011;2011:360357.
48. Zhou TB, Ou C, Qin YH, Su LN, Lei FY, Huang WF, et al. Association of angiotensin converting enzyme insertion/deletion gene polymorphism with idiopathic nephrotic syndrome susceptibility in children: A meta-analysis. J Renin Angiotensin Aldosterone Syst 2011;12:601-10.
49. Zhou TB, Qin YH, Ou C, Su LN, Lei FY, Huang WF, et al. A meta-analysis of the association between angiotensin-converting enzyme insertion/deletion gene polymorphism and steroid-sensitive nephrotic syndrome in children. J Renin Angiotensin Aldosterone Syst 2011 Sep 23 [E-pub ahead of print].
50. Xu J, Wang Y, Pan F, Stankovich J, Ye D, Lian L, et al. Association of ACE gene polymorphism with genetic susceptibility to systemic lupus erythematosus in a Chinese population: A family-based association study. J Rheumatol 2007;34:2408-11.
51. Li X, An J, Guo R, Jin Z, Li Y, Zhao Y, et al. Association of the genetic polymorphisms of the ACE gene and the eNOS gene with lupus nephropathy in northern Chinese population. BMC Med Genet 2010;11:94.
52. Croca SC, Rodrigues T, Isenberg DA. Assessment of a lupus nephritis cohort over a 30-year period. Rheumatology 2011;50:1424-30.
53. Sergentanis TN, Economopoulos KP. Cyclin D1 G870A polymorphism and breast cancer risk: A meta-analysis comprising 9,911 cases and 11,171 controls. Mol Biol Rep 2010;38:4955-63.
54. Ziegler A, Van Steen K, Wellek S. Investigating Hardy-Weinberg equilibrium in case-control or cohort studies or meta-analysis. Breast Cancer Res Treat 2011;128:197-201.
55. Samani NJ, Thompson JR, O'Toole L, Channer K, Woods KL. A meta-analysis of the association of the deletion allele of the angiotensin-converting enzyme gene with myocardial infarction. Circulation 1996;94:708-12.
56. Zintzaras E, Raman G, Kitsios G, Lau J. Angiotensin-converting enzyme insertion/deletion gene polymorphic variant as a marker of coronary artery disease: A meta-analysis. Arch Intern Med 2008;168:1077-89.
57. Sayed-Tabatabaei FA, Houwing-Duistermaat JJ, van Duijn CM, Witteman JC. Angiotensin-converting enzyme gene polymorphism and carotid artery wall thickness: A meta-analysis. Stroke 2003;34:1634-9.