

# 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. (First Release Feb 15 2012; J Rheumatol 2012;39:686–93; doi:10.3899/jrheum.110863)

## Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS  
ANGIOTENSIN-CONVERTING ENZYME

LUPUS NEPHRITIS  
INSERTION/DELETION

GENE POLYMORPHISM  
METAANALYSIS

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease<sup>1,2,3</sup> mainly characterized clinically by involvement of joints, skin, and kidneys<sup>4,5</sup>. SLE is a severe dis-

ease that results from both genetic predisposition and environmental factors<sup>6</sup>. Lupus nephritis (LN) is one of the most common manifestations in SLE<sup>7</sup> and remains a predominant cause of morbidity and mortality in SLE<sup>8</sup>. SLE is characterized by increasing vascular lesion risk<sup>9</sup>, and vascular lesions are encountered frequently in renal biopsy specimens of patients with SLE; the lesions can present in a variety of morphologic forms<sup>10</sup>. Some studies have found that gene polymorphism was associated with the risk of SLE<sup>11,12</sup> and LN susceptibility<sup>13,14</sup>.

The activation of the renin-angiotensin-aldosterone system (RAAS) is part of the onset of SLE and LN<sup>15,16</sup>. Angiotensin-converting enzyme (ACE), a key zinc metalloproteinase, catalyzes the conversion of angiotensin I to angiotensin II, which is the main active product of the RAAS<sup>17</sup>. The ACE gene consists of either an insertion (I) allele or a deletion (D) allele and forms 3 possible genotypes: II, ID, and DD<sup>18</sup>. DD homozygous or D allele is associated with elevated circulating

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and tissue ACE activity compared to I allele. ACE is important in the development of SLE because its endproduct, angiotensin II, plays an integral role in the regulatory system responsible for endothelial control and vascular tone, systems that are commonly affected in patients with SLE<sup>19</sup>. Additionally, ACE inhibitors have been shown to alleviate the progression of SLE and LN<sup>19</sup>.

The ACE I/D gene polymorphism, correlating with circulating and cellular ACE concentration<sup>20</sup>, 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*<sup>21</sup> 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  $< 0.1$ <sup>22</sup>. 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<sup>17,23</sup>, and the study indicating that the genotype distributions in the control group significantly deviated from HWE was excluded from our sensitivity analysis<sup>24</sup>. The Begg adjusted rank correlation test<sup>25</sup> and the Egger regression asymmetry test<sup>26</sup> 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  $\pm$  SD.

## RESULTS

**Study characteristics for SLE vs control.** Sixteen studies<sup>27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42</sup> were used in our investigation. Three studies<sup>27,30,36</sup> 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<sup>27,30,31,39,40,41,42</sup> 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<sup>36</sup> 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<sup>36</sup> 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.

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 <sup>27</sup> 1997	Asian	42	44	58	9	59	82	44.44	25.67	0.000	0.706
Sato <sup>28</sup> 1998	Asian	12	36	45	15	50	35	32.26	40.00	0.270	0.677
Tassiulas <sup>29</sup> 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 <sup>30</sup> 1999	Asian	4	13	11	3	18	19	37.50	30.00	0.960	0.651
Akai <sup>31</sup> 1999	Asian	9	33	42	15	50	35	30.36	40.00	0.516	0.677
Pullmann <sup>32</sup> 1999	White	39	49	13	43	68	37	62.87	52.03	0.694	0.333
Molad <sup>33</sup> 2000	White	33	20	3	26	15	7	76.79	69.80	0.989	0.073
Prkacin <sup>34</sup> 2001	White	9	5	4	5	11	5	63.89	50.00	0.091	0.827
Kaufman <sup>41</sup> 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 <sup>35</sup> 2002	Asian	42	87	82	18	57	39	40.52	40.79	0.036	0.708
Lv <sup>36</sup> 2002	Asian	15	23	12	24	40	52	53.00	37.93	0.588	0.004
Douglas <sup>37</sup> 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 <sup>38</sup> 2005	Asian	11	14	14	14	38	27	46.15	41.77	0.083	0.921
Sprovieri <sup>40</sup> 2005	Brazilian	61	69	17	18	39	8	64.97	57.69	0.706	0.065
Al-Awadhi <sup>39</sup> 2007	Asian	37	36	19	41	45	14	59.78	63.50	0.074	0.770
Hussain <sup>42</sup> 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 <sup>27</sup> 1997	Asian	42	44	58	9	59	82	44.44	25.67
Huang <sup>30</sup> 1999	Asian	10	16	4	3	18	19	60.00	30.00
Akai <sup>31</sup> 1999	Asian	9	33	42	15	50	35	30.36	40.00
Kaufman <sup>41</sup> 2001	Mix*	31	9	9	142	228	95	72.45	55.05
Sprovieri <sup>40</sup> 2005	Brazilian	32	34	9	18	39	8	65.33	57.69
Al-Awadhi <sup>39</sup> 2007	Asian	5	5	5	41	45	14	50.00	63.50
Hussain <sup>42</sup> 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.

*Association of ACE I/D gene polymorphism with LN susceptibility (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<sup>43,44,45,46</sup>. The level of plasma ACE, constitutively expressed in several types

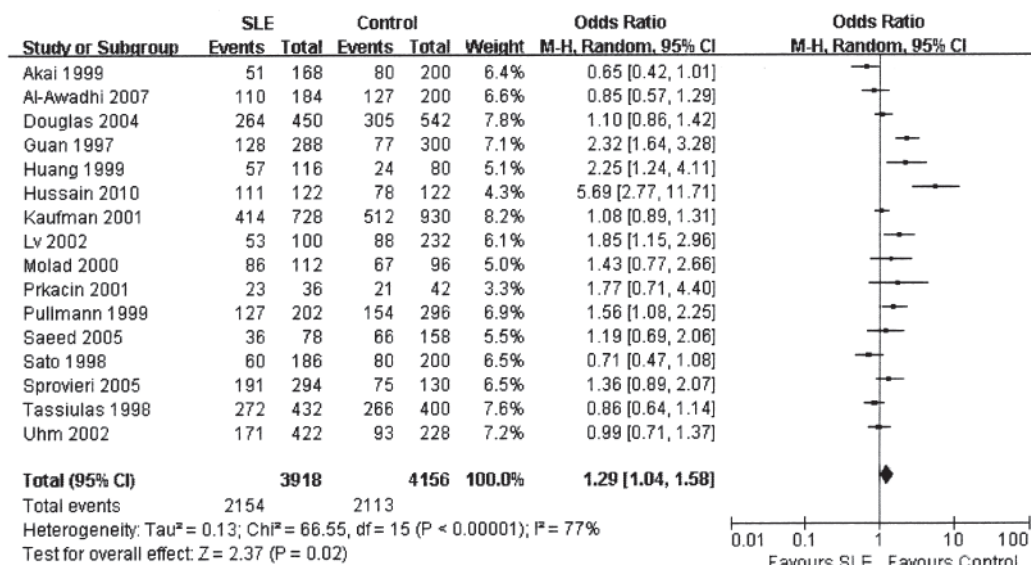


Figure 1. Association between D allele and risk for systemic lupus erythematosus (SLE). M-H: Mantel-Haenszel.

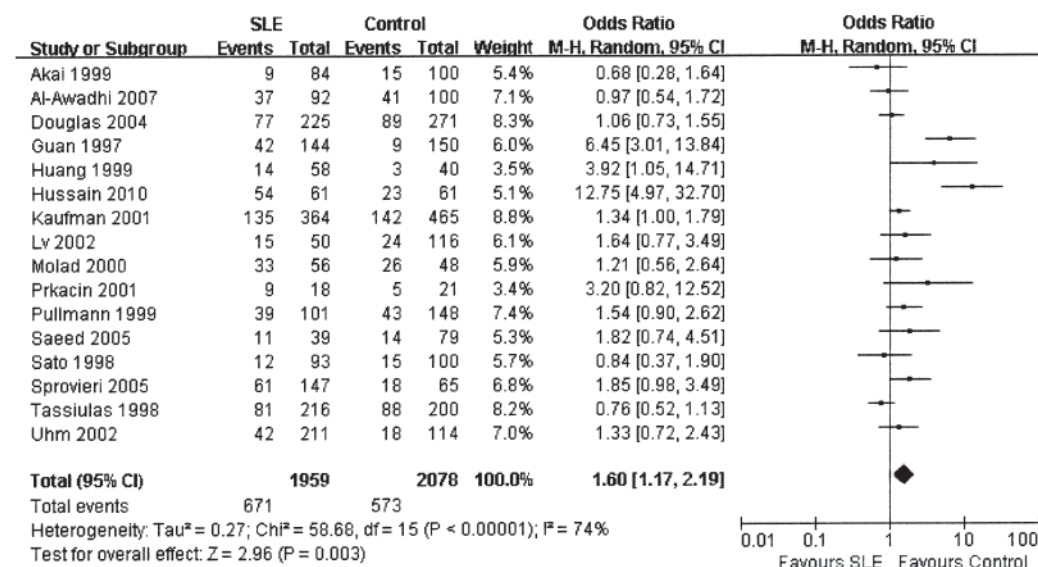


Figure 2. Association of DD genotype with risk for systemic lupus erythematosus (SLE). M-H: Mantel-Haenszel.

of somatic cells, is linked to an I/D polymorphism of 287 bp in intron 16 of the *ACE* gene<sup>17,18</sup>. D allele and DD homozygous have been reported to be associated with higher plasma ACE levels<sup>23,47,48</sup>. The increased protein expression of ACE is responsible for the elevation of plasma angiotensin II level<sup>23,49</sup>. There was some significant evidence showing that ACE was involved in the risk of SLE and LN<sup>19,50,51</sup>. 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



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.

this association in whites, Africans, and Brazilians. In Asians, 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<sup>52</sup>. 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<sup>36</sup> 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<sup>53</sup>. In our study, we also provided the results of HWE for the SLE group. We found that the case groups in Guan, *et al*<sup>27</sup> and Hussain, *et al*<sup>42</sup> were not in HWE, and the case group for overall populations/Africans in Kaufman, *et al*<sup>41</sup> 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<sup>54</sup>. So the deviation from HWE of those studies reflected the positive association between ACE I/D gene polymorphism and risk for SLE.

In Guan<sup>27</sup>, Hussain<sup>42</sup>, and Kaufman<sup>41</sup>, 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<sup>19,50,51</sup>. 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*<sup>55</sup> conducted a metaanalysis 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*<sup>46</sup> performed a metaanalysis to explore the relationship between ACE I/D gene poly-

morphism 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*<sup>56</sup> 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*<sup>57</sup> conducted a metaanalysis 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*<sup>56</sup> and Sayed-Tabatabaei, *et al*<sup>57</sup>, 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<sup>27,28,29,31,32,35,37,39,41</sup> for SLE and 2<sup>27,31</sup> 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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