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The *ACE* insertion/deletion polymorphism and its association with metabolic syndrome

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ABSTRACT

The angiotensin-1–converting enzyme (*ACE*) gene has been suggested to be involved in the development of metabolic syndrome (MetS). However, results have been inconsistent. In this study, a meta-analysis was performed to investigate the association between *ACE* insertion/deletion (I/D) polymorphism and MetS. Published literature from PubMed, EMBASE, and ISI Web of Science databases was searched for eligible publications. All studies assessing the association between *ACE* I/D polymorphism and MetS were included. Pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated using a fixed- or random-effects model. Ten studies (1939 cases/2845 controls) for *ACE* I/D polymorphism were included in this meta-analysis. Most of the studies were performed in whites. The *ACE* I/D polymorphism was associated with an increased OR of MetS under a dominant model (DD + ID vs II: OR = 1.39; 95% CI, 1.22-1.60; $P < .001$). Using this model, similar results were found among studies using different ethnic populations, studies using different MetS definitions, and studies with more than 100 cases. This meta-analysis indicated that the D allele of the *ACE* gene, known to be related to higher levels of angiotensinogen, is associated with an increased OR of MetS. However, given the limited sample size, this association warrants further investigation.

1. Introduction

Metabolic syndrome (MetS) is characterized by a cluster of factors, such as central obesity, hypertension, hypertriglyceridemia, depressed plasma high-density lipoprotein cholesterol, elevated glucose, and microalbuminuria [1]. The prevalence of MetS is increasing worldwide; and as MetS is associated with an increased risk of cardiovascular disease, this is a burden for public health [2]. Besides the environmental risk factors, including higher caloric intake and less physical activity, genetic factors may also play an important role in predisposing individuals to MetS. It has been estimated that about 24% of the variability of MetS is determined by genetic factors [3].

The renin-angiotensin system (RAS) is a hormonal signaling mechanism implicated in the regulation of blood

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pressure and cardiovascular homeostasis. Through modulation of gene expression, growth, fibrosis, and inflammatory response, it also plays an important role in the pathological changes preceding kidney damage [4]. The angiotensin-1–converting enzyme (*ACE*) gene, located on chromosome 17q23, contains many polymorphisms. The 287–base pair Alu insertion/deletion (I/D) polymorphism in intron 16 is the most studied polymorphism and has been related to ACE levels [5]. Serum ACE concentrations were significantly higher in homozygotes with the "shorter" deletion allele (D/D) than in heterozygotes (I/D) or in homozygotes with the "longer" insertion allele (I/I) [6]. Many studies have indicated that this polymorphism is associated with susceptibility to hypertension [7], elevated glucose [8], central obesity [9], and hypertriglyceridemia [10], which are some of the components of MetS. Therefore, *ACE* I/D polymorphism might be involved in the pathogenesis of MetS; and this association has been studied as well frequently. However, results have been inconsistent [11-20].

Therefore, in this study, a meta-analysis was performed to clarify the association between *ACE* I/D polymorphism and MetS susceptibility.

2. Materials and methods

2.1. Literature and search strategy

PubMed, ISI Web of Science, and EMBASE were searched for eligible articles. The search strategy to identify all potential studies involved use of combinations of the following key words: (*the renin-angiotensin system gene* or *the angiotensin-1 converting enzyme gene* or *RAS* or *ACE*) and (*variant* or *polymorphism*) and (*metabolic syndrome* or *MetS* or *MS* or *metabolic syndrome X* or *syndrome X* or *cardiometabolic risk factor* or *insulin resistance syndrome*). The reference lists of retrieved reviews and articles were hand searched. The publication language was restricted to English. If more than one article was published using the same case series, only the study with largest sample size was selected. The literature search was updated on August 5, 2011.

2.2. Inclusion criteria and data extraction

Studies were included if they met the following 3 inclusion criteria: (1) using a case-control or cohort design, (2) evaluating the association of *ACE* I/D polymorphism with MetS, and (3) providing sufficient data for calculation of an odds ratio (OR) with 95% confidence interval (CI) (ie, the study should provide the genotype distributions of the *ACE* I/D polymorphism in patients with and without MetS, or the study should provide the OR with 95% CI).

The following information was extracted from each study: (1) name of the first author, (2) year of publication, (3) country of origin, (4) ethnicity of the studied population, (5) mean age and sex frequency of subjects with and without MetS, (6) genotype distributions of subject with and without MetS, (7) *P* value for the test of Hardy-Weinberg equilibrium (HWE) in those without MetS, and (8) definition of MetS used to assess cases. Two authors independently assessed the articles for compliance with the inclusion criteria; disagreement was followed by discussion until consensus was reached.

2.3. Statistical analysis

The association between *ACE* I/D polymorphism and MetS was estimated by calculating a pooled OR and 95% CI under a codominant model, a dominant model, a recessive model, and a multiplicative model. The significance of the pooled OR was determined by a *Z* test ($P < .05$ was considered statistically significant). A *Q* test was performed to evaluate whether the variation was due to heterogeneity or due to chance. A random- (DerSimonian-Laird method) or fixed- (Mantel-Haenszel method) effects model [21] was used to calculate the pooled OR in the presence ($P <= .10$) or absence ($P > .10$) of heterogeneity, respectively. Begg funnel plot, a scatter plot of effect against a measure of study size, was generated as a visual aid to detect bias or systematic heterogeneity [22]. Publication bias was assessed by Egger test [23] ($P < .05$ was considered statistically significant). Subgroup analyses based on ethnicity (white, Asian vs Mexican), definition of MetS used to assess cases (the National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III] [24], the World Health Organization [WHO] [25] vs others), and sample size of the study (number of cases <100 vs ≥100) were performed. Sensitivity analyses were performed by removing one study at a time to evaluate the stability of the results. Data analyses were performed using STATA version 11 (StataCorp, College Station, TX).

3. Results

3.1. Characteristics of the studies

The literature search identified a total of 151 potentially relevant articles. Of these, 135 articles were excluded after reading the title or abstract because of obvious irrelevance to our study aim. For example, articles that investigated the association of *ACE* I/D with a single metabolic parameter were excluded after initial screening. In addition, 4 studies [26-29] were excluded because they did not provide sufficient data for the calculation of an OR and 95% CI. For 2 studies [26,27], only a *P* value (<.05) was provided indicating that the D/D genotype of *ACE* I/D polymorphism was more frequent in patients with MetS than subjects without MetS. Other studies performed an analysis of risk factors associated with MetS [28] or mentioned the association between *ACE* I/D polymorphism and MetS in the title but did not study it. [29] Two letters to the editor concerning this topic [30,31] and one study in which genotypes deviated from HWE in controls [20] were excluded as well. Therefore, 9 articles met the inclusion criteria [11-19]. Because the article by Danková et al [15] included analyses in 2 ethnic groups, these groups were considered as 2 separate studies. At last, 10 studies were included for *ACE* I/D polymorphism. [11-19] A flowchart summarizing the process of study inclusion is depicted in Fig. 1. Of all, 8 studies were performed in whites, one was performed in Asians, and one was performed in Mexicans; 4 studies used the NCEP ATP III criteria for the definition of MetS, 3 used the WHO criteria, and

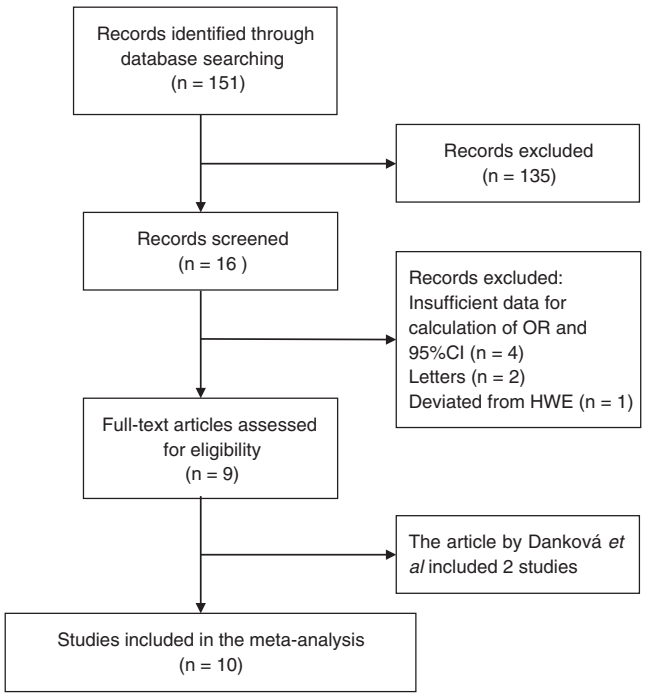

Fig. 1 – Flowchart of the studies included in this meta-analysis investigating the association between *ACE* I/D polymorphism and MetS.

3 used other definitions. The characteristics of the included studies are listed in Table 1.

3.2. *Meta-analysis results*

A total of 1939 cases and 2845 controls were identified for the analysis of the association between *ACE* I/D polymorphism and MetS. All results reported subsequently for *ACE* I/D are for the dominant model (DD + ID vs II); all other models are reported in Table 2. The overall result showed that there was a statistically significant association between this polymorphism and MetS susceptibility (OR = 1.39; 95% CI, 1.22-1.60; $P < .001$; Table 2 and Fig. 2). Subgroup analyses based on ethnicity showed that the effect sizes were statistically significant in whites (OR = 1.24; 95% CI, 1.02-1.51; $P = .028$), Asians (OR = 1.38; 95% CI, 1.12-1.71; $P = .002$), as well as Mexicans (OR = 2.55; 95% CI, 1.64-3.95; $P < .001$). In the stratified analysis based on the different definitions of MetS used to assess cases, the statistically significant associations were observed among studies using the NCEP ATP III criteria and WHO criteria for the assessment of MetS, respectively (OR = 1.91; 95% CI, 1.41-2.57; $P < .001$ and OR = 1.35; 95% CI, 1.10-1.65; $P = .004$), but not in studies using other criteria for the definition of MetS. The effect size was statistically significant in studies with more than 100 cases (OR = 1.47; 95% CI, 1.14-1.89; $P < .001$), but not in small studies with less than 100 cases (OR = 1.19; 95% CI, 0.75-1.89; $P = .452$; Table 2).

3.3. *Sensitivity analysis*

Sensitivity analyses were performed by excluding one study at a time (data not shown). Results for the association

Table 1 – Characteristics of the studies included in the meta-analysis of the association between *ACE* I/D polymorphism and MetS

Study	Country	Ethnicity	Sex (female, %)		Age, y, mean ± SD		Sample size		Genotype distribution in cases and controls			P_{HWE} [a]	Definition of MetS
			Cases	Controls	Cases	Controls	Cases	Controls	II	ID	DD		
Lee and Tsai, 2002	China	Asian	56.4 [b]		59.7 ± 10.7 [b]		616	845	256/419	280/349	80/77	.724	WHO
Milionis et al, 2007	Greece	White	60.0	57.0	56.3 ± 11.1	52.1 ± 12.0	60	72	11/11	27/35	22/26	.890	AHA/NHLBI
Alvarez-Aguilar et al, 2007	Mexico	Mexicans	52.3	52.8	57 ± 7	58 ± 9	245	269	36/82	111/144	98/43	.125	NCEP ATP III
Nikzamiret al, 2008	Iran	White	50.4	43.1	58.6 ± 7.5	59.5 ± 8.1	119	51	20/8	67/32	32/11	.064	WHO
Danková et al (Romany), 2009	Slovak	White	54.7 [b]		40.6 ± 10.5 [b]		51	86	12/30	28/40	11/16	.680	NCEP ATP III
Danková et al (Slovak), 2009	Slovak	White	73.1 [b]		49.4 ± 5.4 [b]		33	134	7/31	19/63	7/40	.521	NCEP ATP III
Siváková et al, 2009	Slovak	White	68.5	46.3	72.1 ± 6.8	72.8 ± 7.5	116	209	21/52	52/95	43/62	.199	NCEP ATP III
Sesal et al, 2009	Turkey	White	NA	NA	NA	NA	34	26	4/3	18/16	12/7	.184	WHO
Procopciuc et al, 2010	Romania	White	100.0	100.0	48.0 ± 4.2	47.0 ± 4.7	24	32	2/3	10/15	12/14	.721	European guidelines
Fiatal et al, 2011	Hungary	White	49.3	55.1	51.7 ± 11.7	42.4 ± 13.5	641	1121	125/259	315/577	201/285	.315	IDF

NA indicates not available.
[a] *P* value for the test of HWE in controls.
[b] For cases and controls.

Table 2 – Pooled ORs and 95% CIs of the association between I/D polymorphism in *ACE* gene and MetS

Contrasts	No. of studies	DD vs II				ID vs II				DD + ID vs II				DD vs ID + II				D vs I			
		OR	95% CI	P_Z	P_H	OR	95% CI	P_Z	P_H	OR	95% CI	P_Z	P_H	OR	95% CI	P_Z	P_H	OR	95% CI	P_Z	P_H
All	10	1.67	1.17-2.38	.004	.008	1.27	1.10-1.46	.001	.791	1.39	1.22-1.60	.000	.263	1.45	1.10-1.91	.008	.008	1.30	1.10-1.54	.003	.005
Ethnicity																					
White	8	1.41	1.12-1.76	.003	.908	1.15	0.94-1.41	.176	.916	1.24	1.02-1.51	.028	.921	1.29	1.08-1.53	.004	.879	1.19	1.07-1.33	.002	.889
Asian	1	1.70	1.20-2.41	.003	–	1.31	1.05-1.64	.016	–	1.38	1.12-1.71	.002	–	1.49	1.07-2.07	.019	–	1.31	1.12-1.53	.001	–
Mexican	1	5.19	3.05-8.83	.000	–	1.76	1.10-2.79	.017	–	2.55	1.64-3.95	.000	–	3.50	2.32-5.30	.000	–	2.25	1.75-2.89	.000	–
Definition of cases																					
NCEP ATP III	4	2.03	0.90-4.58	.089	.005	1.59	1.16-2.18	.004	.893	1.91	1.41-2.57	.000	.297	1.49	0.72-3.07	.278	.001	1.42	0.95-2.13	.084	.004
WHO	3	1.62	1.17-2.25	.004	.776	1.27	1.03-1.57	.027	.574	1.35	1.10-1.65	.004	.634	1.47	1.09-1.97	.011	.970	1.28	1.11-1.48	.001	.741
Others	3	1.40	1.07-1.83	.013	.591	1.10	0.86-1.41	.432	.754	1.21	0.96-1.52	.111	.666	1.31	1.07-1.60	.009	.778	1.19	1.04-1.36	.009	.648
Sample size in cases																					
<100	5	1.10	0.63-1.91	.736	.843	1.21	0.75-1.96	.435	.764	1.19	0.75-1.89	.452	.793	1.05	0.70-1.56	.822	.775	1.08	0.83-1.39	.582	.795
≥ 100	5	1.98	1.25-3.13	.004	.001	1.27	1.10-1.48	.002	.464	1.47	1.14-1.89	.000	.061	1.69	1.18-2.42	.005	.002	1.41	1.13-1.76	.003	.001

P_Z indicates *P* value for Z test; P_H, *P* value based on Q test for heterogeneity (If $P_H \leq .10$, the random-effects model was used, otherwise, the fixed-effects model was applied).

between *ACE* I/D polymorphism and MetS remained statistically significant.

3.4. *Potential publication bias*

Using the Egger test, no publication bias could be detected for the studies published on *ACE* I/D polymorphism (DD vs II, *P* = .704; ID vs II, *P* = .673; DD + ID vs II, *P* = .777; DD vs ID + II, *P* = .688; D vs I, *P* = .710).

4. Discussion

To our knowledge, this study represents the first meta-analysis investigating the association of *ACE* I/D polymorphism with MetS susceptibility across different ethnic populations. Our results suggested that a statistically significant association exists between *ACE* I/D and MetS. Results remained statistically significant following various sensitivity analyses; when applying different genetic models, results varied somewhat but were fairly consistent as well. The conflicting results published in the literature for the association between *ACE* I/D polymorphisms and MetS might be due to differences in MetS definition, in ethnic population, in methodology, and in sample size/statistical power between the studies.

Currently, different definitions for the assessment of MetS are in use. Many criteria, such as those from the NCEP ATP III [24], the WHO [25], the International Diabetes Federation criteria (IDF) [32], the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) [33], the updated Harmonized Definition of MetS [34], the American Association of Clinical Endocrinologists [35], the European Group for the Study of Insulin Resistance [36], and so on, have been suggested to assess the presence of MetS. These definitions share several characteristics; but on some features, they are different. For example, the current definition of NCEP ATP III as reported by Grundy states that subjects need to meet 3 of 5 criteria, but do not specify which ones. The WHO criteria specify that subject must have glucose intolerance, impaired glucose tolerance, or diabetes and/or insulin resistance together with 2 or more components. The European Group for the Study of Insulin Resistance also requires insulin resistance. In addition, there are different requirements for the severity of central obesity, hypertension, hypertriglyceridemia, hyperglycemia, microalbuminuria, and depressed plasma high-density lipoprotein cholesterol included in the various MetS definitions [37]. Because it is important to pool studies with uniform criteria of disease when performing a meta-analysis, we performed a subgroup analysis based on the definitions used to assess the presence of MetS. The significant association was observed among studies using the NCEP ATP III and WHO criteria as MetS definitions but not for those studies using other criteria.

It is possible that the effect sizes of genetic factors predisposing to human diseases are different across various ethnic populations. As with many polymorphisms, the distribution of this polymorphism is not constant in the human population [38]. In whites as well as Mexicans, the I allele frequency of the *ACE* I/D polymorphism is around 0.4

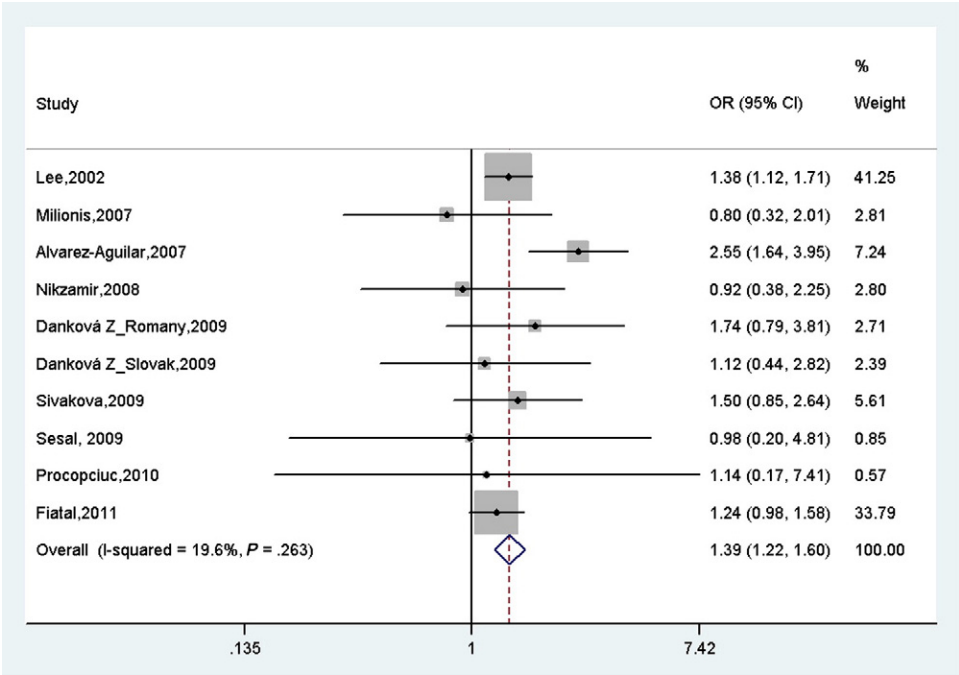

Fig. 2 – Meta-analysis of the association between *ACE* I/D polymorphism and an increased OR of MetS under the dominant genetic model (DD + ID vs II). Note: D is the risk allele, and I is the nonrisk allele. Studies were ordered by year of publication. Square sizes are proportional to the weight of each study in the meta-analysis.

[39]. However, in Chinese, the frequency of the I allele is estimated at 0.7 [40]. Therefore, an analysis stratified by ethnicity was performed. The OR was somewhat higher in Mexicans than in Asians and whites. However, it remains possible that the ORs varied because of different allele frequencies in the various study populations. In addition, the studies performed in Mexicans and Asians were of limited sample size; and therefore, these differences should be interpreted with caution.

Studies with a small sample size may overestimate the true association compared with those with a large sample size [41]; a large study with either finding might reflect a true association, as it has sufficient statistical power. Therefore, we performed another subanalysis stratified by study sample size (number of cases). The results suggested that the effect size was larger in studies with more than 100 cases than in those studies with less than 100 cases. In addition, in the stratum of studies with more than 100 cases, the association between *ACE* I/D polymorphism and MetS remained statistically significant, but not for studies with less than 100 cases.

The biological mechanism through which *ACE* I/D polymorphism may be related with an increased OR of MetS is unclear. Although serum ACE concentrations are significantly higher in those carrying the D/D genotype than in those carrying the I/D or the I/I genotype, other potential mechanisms have been suggested as well. It has been hypothesized that RAS influences adipokine secretion and insulin secretion from pancreatic β-cells; furthermore, the RAS has been hypothesized as well to inhibit adipogenesis, which limits the storage capacity of adipose tissues and allows ectopic lipid storage that results in lipotoxicity [42]. As adipose tissue also hosts a local RAS, it has been speculated to be possibly involved in the development of obesity-associated hypertension [43]. Angiotensin-1–converting enzyme is known to play an important role in sodium/-water balance and blood pressure regulation [44]. In addition, several studies have suggested that the RAS is involved in the regulation of insulin resistance, glucose, and lipid metabolism [7,9]. In addition, significant reductions in cardiovascular and renal risk, as well as a reduction of new-onset diabetes risk, have been demonstrated in the clinical trials of ACE inhibitors and AT1-receptor blockers [45]. However, as further elucidation of the applicable biological mechanisms is warranted, the present clinical relevance of this association needs to be determined.

Our study has several limitations: first, the present meta-analysis was based primarily on unadjusted effect estimates; and potential confounding factors, including age, sex, and environmental factors (eg use of ACE inhibitors), were not controlled for. However, most of the studies included in our analyses only provided the genotype distributions in cases and controls (or a crude OR and 95% CI); and consequently, we were not able to adjust our analysis for basic covariates like age and sex. Second, as none of the studies included in this meta-analysis considered the effect of gene-environment interactions, this issue could not be addressed in this meta-analysis. Third, the results of the subgroup analyses for *ACE* I/D polymorphism should be interpreted with caution because of limited statistical power. Fourth, because none of the studies included in our study used the updated Harmonized Definition of MetS, which was recently proposed by IDF and AHA/NHLBI [34], we were not able to take this into account in our analyses.

In conclusion, the results of our study indicate the presence of a significant association between the D allele of the *ACE* I/D polymorphism and MetS susceptibility. Given the limited sample size, large-scale studies with the consideration of gene-gene and gene-environment interactions should be conducted to further investigate this association. Furthermore, more in-depth research is required as well to clarify the mechanisms by which the *ACE* gene may increase predisposition to MetS.

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Conflicts of Interest

None.

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