Systematic Review and Meta-Analysis

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Genetic polymorphism of angiotensin-converting enzyme and hypertrophic cardiomyopathy risk

A systematic review and meta-analysis

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Abstract

Background: Genetic factors in the pathogenesis of cardiomyopathies have received a lot of attention during the past 2 decades. Some studies have reported that angiotensin-converting enzyme (*ACE*) gene has been associated with hypertrophic cardiomyopathy (HCM). However, there have been inconsonant results among different studies. To clarify the influence of *ACE* on HCM, a systemic review and meta-analysis of case–control studies were performed.

Methods: The following databases were searched to indentify related studies: PubMed database, the Embase database, the Cochrane Central Register of Controlled Trials database, China National Knowledge Information database, and Chinese Scientific and Technological Journal database. Search terms included "hypertrophic cardiomyopathy," "angiotensin converting enzyme" or "*ACE*," and "polymorphism or mutation."

Results: Fifteen separate studies were suitable for the inclusion criterion. The selected studies contained 2972 participants, including 1047 in HCM group and 1925 controls. Pooled odds ratios (ORs) were calculated to assess the association between *ACE* insertion/deletion (I/D) polymorphism and HCM. Our case–control data indicated that D allele carrier is a risk allele in all genetic models: allele contrast (D vs I: OR = 1.35, 95% confidence interval [CI]: 1.10–1.65, $P = .004$), homozygous comparison (DD vs II: OR = 1.69; 95% CI: 1.12–2.54; $P = .01$), dominant model (DD + ID vs II: OR = 1.52, 95% CI: 1.15–2.02, $P = .003$), and recessive model (DD vs ID + II: OR = 1.34, 95% CI: 0.99–1.81, $P = .03$).

Conclusion: In summary, the current meta-analysis provided solid evidence suggesting that *ACE* gene I/D polymorphism was probably a genetic risk factor for HCM.

Abbreviations: ACE = angiotensin-converting enzyme, CI = confidence interval, HCM = hypertrophic cardiomyopathy, HWE = Hardy–Weinberg equilibrium, I/D = insertion/deletion, LVH = left-ventricular hypertrophy, OR = odds ratio, RAS = renin–angiotensin system, SHCM = sporadic hypertrophic cardiomyopathy.

Keywords: *ACE*, hypertrophic cardiomyopathy, meta-analysis, polymorphism

1. Introduction

Left-ventricular hypertrophy (LVH) is a physiological adaptation of the heart to increased workload. LVH is frequently secondary to clinical conditions such as hypertension, valvular disease, and myocardial infarction.[1,2] However, some patients develop the cardiac hypertrophy in the absence of these conditions that impose overwork to the heart. This primary/essential form of LVH is frequently familial and caused by mutations in sarcomeric genes, and is designated as hypertrophic cardiomyopathy (HCM).[3] HCM, the most common hereditary cardiac disease, affects 1 in every 500 people in the general population and represents a major cause of sudden cardiac death in adolescent athletes.[4]

HCM is frequently caused by mutations in genes encoding sarcomeric proteins.[5–7] It is reported that several gene polymorphisms, including those encoding the components of the renin–angiotensin system (RAS), have been associated with the risk of developing LVH, and could also modify the clinical phenotype in HCM patients.[8,9] Previous studies suggested that RAS acted on cellular hypertrophy and cell proliferation,[10] and therefore played a regulatory role in cardiac function, blood pressure, and electrolyte homeostasis.[11] In the end, it can affect both left cardiac ventricle (LV) hypertrophy and remodeling.[12] It has been demonstrated that components of the RAS such as angiotensinogen, renin, angiotensin-converting enzyme (*ACE*), and angiotensin II receptors exist within the heart and may function independently from the circulating RAS.[13] ACE, through conversion of angiotensin I to angiotensin II, the latter as trophic as well as mitogenic hormone, acts as a growth factor for cardiac myocytes and induces cardiac hypertrophy independent of hemodynamic or neurohumoral effects.[14] *ACE* is 21 kb length, including 26 exons, located on long arm of chromosome 17 (17q23.3) locus of the human genome. It will be inherited independently of the diseased sarcomeric genes which are located on different chromosomes. The restriction fragment length polymorphism, a 287 base pair (bp) insertion/deletion (I/D), is

Editor: Weimin Guo.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:48(e8639)

Received: 15 June 2017 / Received in final form: 17 October 2017 / Accepted: 24 October 2017

http://dx.doi.org/10.1097/MD.0000000000008639

located inside intron 16 of the *ACE* gene and corresponds to an Alu repetitive sequence. DD genotype subjects have a higher level of ACE and angiotensin II and, consequently, an increase in hypertrophy and fibrosis.[12,14–16] That is, the ACE levels in the human heart are in part determined by the so-called I/D polymorphism.[16] Therefore, the angiotensin II levels increase and then also affect the phenotypic expression in HCM.[15]

In spite of the above-mentioned reports associating RAS and HCM, the studies from different populations have been conflicting and the role of the RAS system in modifying the phenotype in HCM remains controversial. As meta-analysis is a reliable way to combine information from many studies and thus may provide more conclusive answers, we decide to evaluate the influence of *ACE* polymorphisms on the HCM phenotype.

2. Methods

This study was approved by the ethics committees of the First Hospital of Jilin University and conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant before entry into the study, and all of the procedures were in accordance with institutional guidelines.

2.1. Search strategy

The following database was searched to identify related studies: PubMed database, the Embase database, the Cochrane Central Register of Controlled Trials database, China National Knowledge Information data base, and the Wanfang databases. For the association of *ACE* I/D and HCM, the following search terms were used in searching the PubMed database: "hypertrophic cardiomyopathy", "angiotensin converting enzyme" or "*ACE*" and "polymorphism or mutation". The full texts of the retrieved articles were scrutinized to inspect whether data on the topic of interest were included. We systematically searched eligible studies reported before Nov 2016. The references of all retrieved articles were also screened.

2.2. Inclusion/exclusion criteria

The studies included in the meta-analysis must meet all the following three criteria: evaluating the association of *ACE* I/D polymorphism with HCM; using case–control design; containing genotype data of II, ID, and DD, and comprehensive statistical indicators directly or indirectly: odds ratio (OR) values and 95% confidence interval (CI); using similar themes and methods; and satisfying Hardy–Weinberg equilibrium (HWE) among the controls. However, all the patients were excluded for potential stimulus such as hypertension, ischemic heart disease, valvular heart disease, congenital malformations of the heart or vessels, and intrinsic pulmonary disease for HCM.

2.3. Data extraction

Two investigators independently reviewed all studies and extracted the data using a standard information extraction and reached consensus on all items. If there was discrepancy between them, it was settled by discussion until a consensus was reached. The data extracted from the studies included such details as the first author, publication year, country, ethnicity, age, genotype distribution in cases and controls, source of controls, diagnostic criteria, and HWE test. The excluded literatures were comprised of studies of poor research quality, providing little or insufficient data, violating the inclusion criteria, or repeated publications. If the same research result appeared in different articles, the result was only adopted once in the present meta-analysis.

2.4. Statistical methods

The pooled ORs and corresponding 95% CIs of different studies were calculated to compare dichotomous statistics between studies. The pooled ORs were calculated using 4 models: allele model (D vs I), homozygous comparison (DD vs II), dominant model (DD + ID vs II), and recessive model (DD vs II + ID). To assess heterogeneity across the studies, Cochrane Q test[17] and I^2 statistic[18,19] were calculated. If the studies were shown to be homogeneous with $P \geq .10$ and $I^2 < 50\%$, the fixed-effects model (the Mantel–Haenszel method) was selected. Otherwise, the random-effects model (the DerSimonian and Laird method) was applied.

If the outcomes were heterogeneous, prespecified subgroup comparisons were conducted to detect the influence of the following factors on the *ACE* gene I/D polymorphism-HCM correlation.

In addition, a sensitivity analysis was performed to assess the stability of the results. The significance of the pooled ORs was determined by the Z-test, and a $P < .05$ was considered significantly. Sensitivity analyses were conducted by deleting a single study each time involved in the meta-analysis to identify the potential influence of the individual data set on the pooled ORs. Egger test and the visual symmetry of funnel plot were assessed to examine publication bias of the related studies. This meta-analysis was performed using the software STATA version 13.0 (Stata Corporation, TX) and Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). All *P*-values were based on 2-sided tests.

3. Results

3.1. Characteristics of eligible studies

Initially, 378 studies were identified as potentially eligible candidates from the electronic and manual searches. After screening the titles and abstracts, 322 studies were excluded because of not case–control trials or irrelevant studies or no desired polymorphism (including other review papers). Full texts of 56 papers were retrieved and most were excluded because they were duplicate publications or focused on *ACE* gene other polymorphisms or included no sufficient data. Additionally, studies no satisfying HWE were excluded. Finally, 15 articles met the selection criteria. Therefore, a total of 15 eligible original reports were included in the final meta-analysis. A flow diagram of the study selection is shown in Fig. 1.

Table 1 describes the characteristics of selected studies included in the meta-analysis. Briefly, the meta-analysis in the present study was performed with 15 articles.[15,20–33] A total of 8 studies included Asian populations,[24,26–31,33] and 6 studies included Caucasian populations.[19,23,25,32,34,35] All studies were case–control studies. The distributions of the genotypes in the control populations were consistent with HWE in all of the studies.

3.2. Association of ACE I/D polymorphisms and HCM susceptibility

For the genetic variant *ACE* I/D in the 15 studies, including 1047 cases and 1925 controls, D allele frequency was significantly

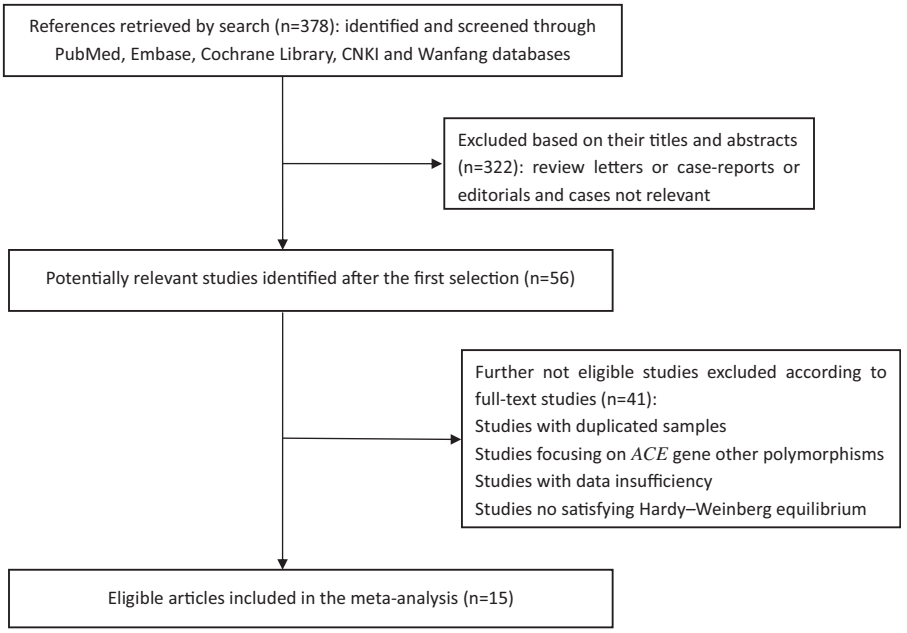

Figure 1. Flow chart of study selection.

higher in HCM group (75.5%) than in control group (71.0%), $P = .009$.

The potential heterogeneity was found in all comparisons (all $P < .10$), so random model was used in the meta-analysis (Table 2). For *ACE* I/D variant, the summary OR for allele D versus I is shown in Fig. 2 and Table 2, and the summary OR was 1.35 (allel model, D vs I: 95% CI: 1.10–1.65; $P = .004$). Overall comparison of DD genotype with II genotype showed significant association of this variant with HCM risk (homozygous model, DD vs II: OR = 1.69; 95% CI: 1.12–2.54; $P = .01$; Fig. 3). In the current meta-analysis, the association between *ACE* I/D polymorphism and the risk of HCM was also investigated under both the dominant genetic model and recessive genetic model. Under dominant genetic model, the association was also detected between the *ACE* I/D variant and HCM risk and the pooled OR was 1.52 (DD + ID vs II: 95% CI: 1.15–2.02; $P = .003$; Fig. 4). Under recessive genetic model, the *ACE* DD genotype was significantly associated with HCM risk compared with the wild-type I allele, and the pooled OR was 1.34 (DD vs ID + II: 95% CI: 0.99–1.81; $P = .03$; Table 2). In total, results in across different ethnic populations strongly indicated that D allele and DD genotype of the *ACE* gene I/D polymorphism were probably the genetic risk factor of HCM.

We performed a meta-analysis in 2 subgroups based on ethnicity: Asian population and Caucasian population. Results of the analysis in the Asian subgroup and the Caucasian subgroup are presented in Table 3. From our subgroup analyses, we found that Asian and Caucasian subgroups with the DD genotype of *ACE* showed a higher risk of HCM; however, between-study heterogeneity was not eliminated apart from Caucasian subgroup (DD + ID vs II: $P_{\text{heterogeneity}} = .28$, $I^2 = 20\%$; DD vs II: $P_{\text{heterogeneity}} = .16$, $I^2 = 37\%$).

3.3. Publication bias

Funnel plots of all the studies above were listed in Fig. 5. No publication bias was observed, as the shape of the funnel plots seemed to show no evident asymmetry in each meta-analysis. It is further validated by the Egger test ($P > .05$).

3.4. Sensitivity analysis

Deletion of 1 single study from the overall pooled analysis each time to check the influence of the removed dataset to the overall ORs to assess the sensitivity analysis did not alter or impact the overall ORs. This indicated that the results of the meta-analysis about *ACE* gene I/D polymorphism and risk of HCM were relatively stable and reliable (Fig. 6).

4. Discussion

In the present study, we systematically reviewed all available published studies and performed a meta-analysis to evaluate the association of *ACE* gene I/D polymorphisms with HCM. Fifteen studies were included in this meta-analysis. Pooled ORs showed a significant association between *ACE* I/D polymorphism and HCM susceptibility in the genetic models (allele, dominant, and recessive). Sensitivity analysis further showed that the association was stable, and Begg and Egger tests indicated a lack of publication bias. We conducted a comprehensive meta-analysis on 15 published studies with 1047 cases and 1925 controls relating the variant of the *ACE* I/D to the risk of HCM, which provided better ability to detect smaller effect sizes. Its strength was based on the accumulation of published data, giving greater information to detect significant differences.

The angiotensin I converting enzyme enhances the synthesis of angiotensin II (Ang II), which induces cell proliferation, migration, and hypertrophy, and enhances the proinflammatory cytokines and matrix metalloproteinases. Thus, overexpression of Ang II plays a powerful role in cardiomyopathy. Previous studies have found that *ACE* I/D polymorphisms are related with plasma Ang II levels. *ACE* I/D polymorphisms have been extensively examined for a variety of clinical endpoints, such as hypertension, coronary artery disease,[34] cough,[35] and

Table 1

Characteristic of eligible studies in the meta-analysis.

					Genotypes								HWE in control
					HCM			Control					
First author	Year	Country	Ethnicity	Age, y (mean ± SD)	II	ID	DD	II	ID	DD	Source of controls	Diagnostic criteria	*P*
Marian et al[20]	1993	USA	NA	None	7	49	44	22	46	38	Familiar healthy subjects	Septal or ventricular thickness ≥13 mm without other potential causes	Yes
Pfeufer et al[21]	1996	Germany	Caucasian	HCM: 55.0 ± 15.0 control: 48.0 ± 17.0	26		24	36		14	Healthy subjects	Septal or ventricular thickness ≥13 mm without hypertension and valvular heart disease	Yes
Yamada et al[22]	1997	Japan	Japanese	HCM: 59.1 ± 10.3 control: 60.2 ± 11.0	31	32	8	50	55	17	Healthy subjects	LV hypertrophy without other potential causes	Yes
Moiseev et al[23]	1997	Russia	Russian	HCM: 31.5 ± 9.1 control: 54.0 ± 8.1	2	5	6	33	55	80	Normal subjects	LV hypertrophy without other potential causes	Yes
Lopez-Haldon et al[24]	1999	Spain	Caucasian	All: 44.3 ± 15.0 (range: 18–78)	2	13	25	33	125	111	Healthy subjects		Yes
Cai et al[25]	2000	China	Chinese	All: mean: 51.4 (range: 38–70)	16	16	13	26	23	7	Healthy subjects	Septal or ventricular thickness ≥13 mm without hypertension and valvular heart disease	Yes
Gao et al[26]	2000	China	Chinese	HCM: 53.4 ± 19.8 (range: 14–70) control: newborn	12	15	13	31	18	12	Healthy subjects	Septal or ventricular thickness ≥13 mm without hypertension and valvular heart disease	Yes
Li et al[27]	2001	China	Chinese	HCM: 43.8 ± 18.9 control: 43.5 ± 21.8	13	19	1	28	23	12	Healthy subjects	Septal or ventricular thickness ≥13 mm without hypertension and valvular heart disease	Yes
Ogimoto et al[28]	2002	Japan	Japanese	HCM: 63.0 ± 13.0 control: 70.0 ± 9.0	53	64	21	83	95	27	Healthy subjects	LV hypertrophy without other potential causes	Yes
Zou et al[29]	2003	China	Chinese	All: mean: 46.6 (range: 14–72)	5	7	1	28	20	5	Healthy subjects	Septal or ventricular thickness ≥13 mm without hypertension and valvular heart disease	Yes
Kawaguchi et al[30]	2003	Japan	Japanese	All: mean: 50.0	26	41	13	43	28	17	Familiar healthy subjects	LV hypertrophy without other potential causes	Yes
Doolan et al[31]	2004	Australia	Caucasian	None	10	14	12	48	94	58	Healthy subjects	LV hypertrophy ≥13 mm without other hypertrophic stimulus	Yes
Rai et al[32]	2008	India	Indian	HCM: 45.4 ± 14.4 control: 39.0 ± 12.8	11	63	44	47	87	30	Healthy subjects	Unexplained LV hypertrophy ≥13 mm or >2 standard deviations	Yes
Kaya et al[15]	2010	Turkey	Turkish	HCM: 55.9 ± 14.8 control: 53.9 ± 7.9	8	34	21	5	9	6	Healthy subjects	LV hypertrophy ≥13 mm without other hypertrophic stimulus	Yes
Coto et al[33]	2010	Spain	Caucasian	HCM: 46.0 ± 13.0 (range: 8–76) control: 51.0 ± 17.0 (range: 20–75)	35	100	72	46	135	119	Healthy subjects	LV hypertrophy ≥13 mm without other hypertrophic stimulus	Yes

All: the whole study population. HCM = hypertrophic cardiomyopathy, HWE = Hardy–Weinberg equilibrium, LV = left ventricular, NA = not available.

Table 2

Odds ratio and heterogeneity tests for ACE I/D polymorphism and HCM in different models.

	Heterogeneity				95% CI		
HCM vs control	I^2	P_Q	Model	Odds ratio	U limit	L limit	P_Z
D vs I	62%	.0008	Random	1.35	1.10	1.65	.004
DD vs II	59%	.002	Random	1.69	1.12	2.54	.01
DD+ID vs II	48%	.02	Random	1.52	1.15	2.02	.003
DD vs ID+II	52%	.006	Random	1.34	0.99	1.81	.03

ACE = angiotensin-converting enzyme, CI = confidence interval, HCM = hypertrophic cardiomyopathy, I/D = insertion/deletion.

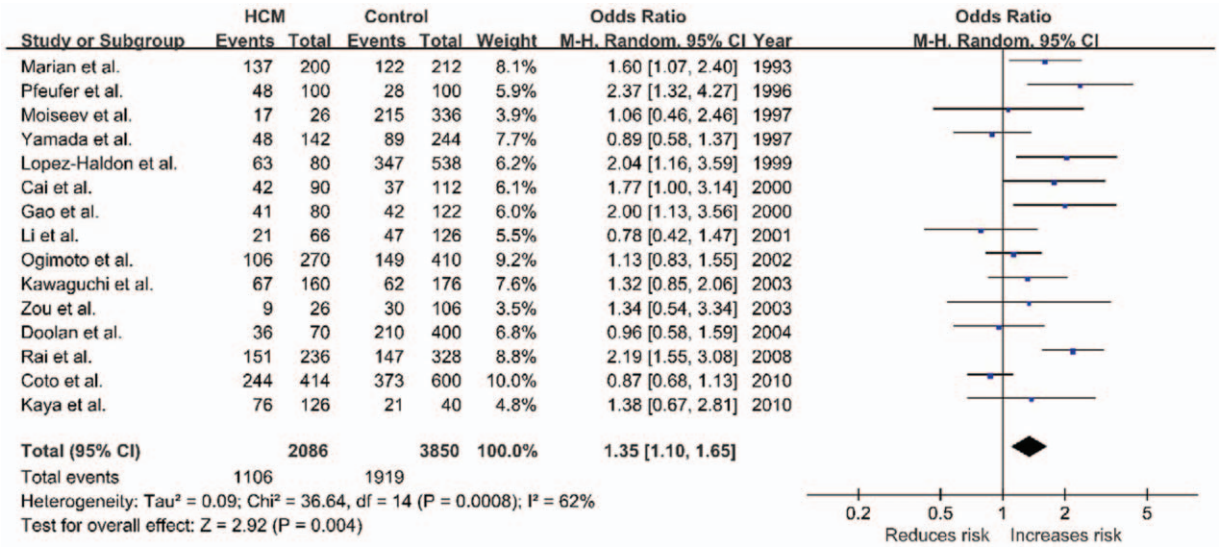

Figure 2. Forest plot of HCM and ACE I/D in an allel model (D vs I), the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI. ACE = angiotensin-converting enzyme, CI = confidence interval, HCM = hypertrophic cardiomyopathy, I/D = insertion/deletion, OR = odds ratio.

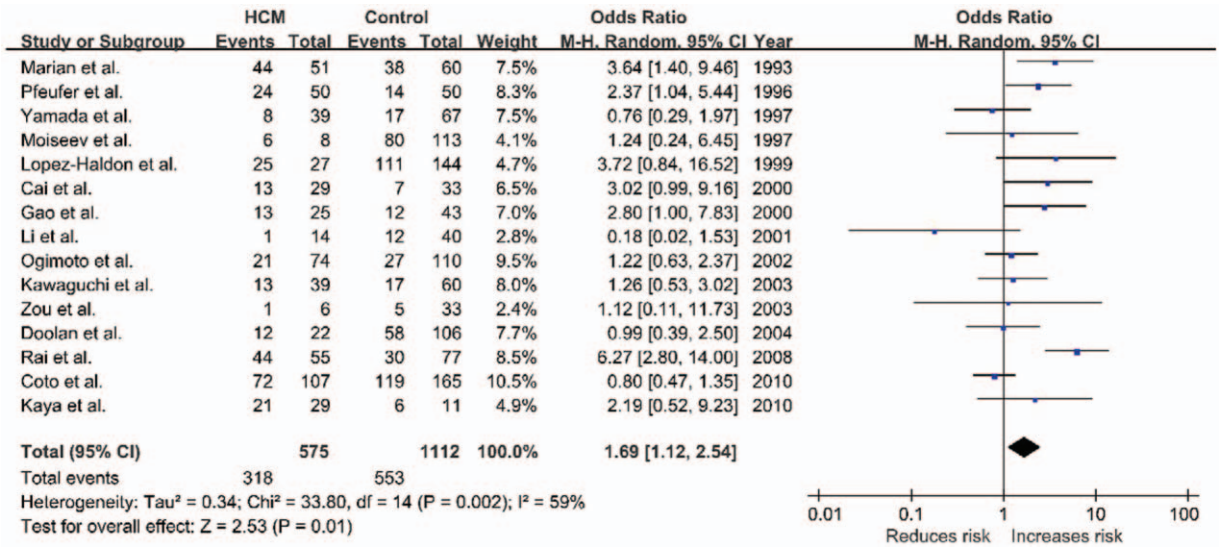

Figure 3. Forest plot of HCM and ACE I/D in a homozygous model (DD vs II), the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI. ACE = angiotensin-converting enzyme, CI = confidence interval, HCM = hypertrophic cardiomyopathy, I/D = insertion/deletion, OR = odds ratio.

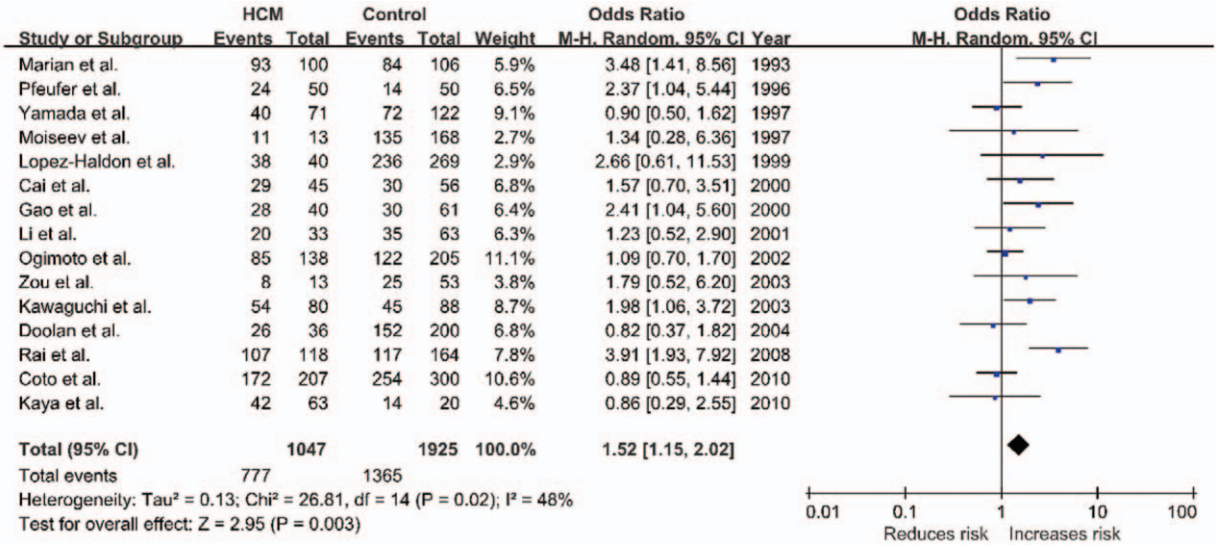

Figure 4. Forest plot of HCM and ACE I/D in a dominant model (DD + ID vs II), the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI. ACE = angiotensin-converting enzyme, CI = confidence interval, HCM = hypertrophic cardiomyopathy, I/D = insertion/deletion, OR = odds ratio.

Table 3

Subgroup analysis of different genetic models by ethnicity.

Subgroup	Analysis model	Analysis method	Heterogeneity		OR			
			I^2, %	*P*	Overall	Lower	Upper	*P*
Asian	D vs I	Random	61	.01	1.36	1.04	1.78	.03
	DD + ID vs II	Random	51	.05	1.61	1.13	2.31	.009
	DD vs ID + II	Random	52	.04	1.41	0.88	2.25	.15
	DD vs II	Random	66	.005	1.64	0.87	3.11	.13
Caucasian	D vs I	Random	67	.01	1.31	0.90	1.91	.16
	DD + ID vs II	Fixed	20	.28	1.26	1.06	1.44	.006
	DD vs ID + II	Random	62	.02	1.23	0.75	2.04	.40
	DD vs II	Fixed	37	.16	1.26	0.88	1.80	.20

OR = odds ratio.

pulmonary complications following esophagectomy.[36] The *ACE* I/D polymorphisms also modulate the phenotype in patients with HCM. However, studies from different populations have demonstrated conflicting data. Rai et al[32] found that D allele of *ACE* I/D polymorphism significantly influences the HCM phenotypes. In contrast, Yamada et al[22] reported that the *ACE* I/D polymorphisms are not related to HCM in a Japanese population. Analyses assuming additive, dominant, or recessive effects of the D allele failed to show any association with HCM. Moreover, our current meta-analysis found that compared with *ACE* II genotype, patients with D allele showed a significantly increased risk of HCM, suggesting that *ACE* I/D polymorphisms might attribute to HCM risk.

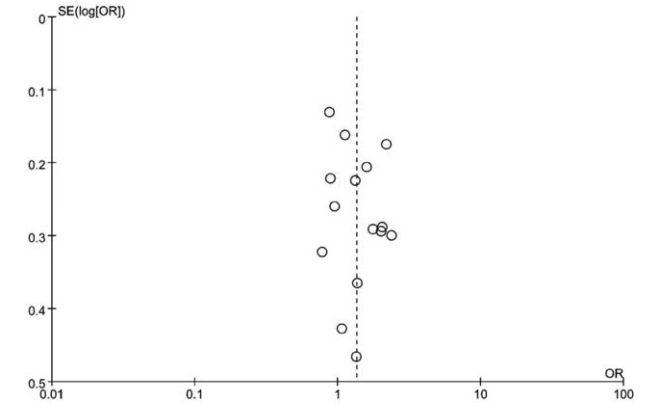

Figure 5. Begg funnel plot for publication bias tests. Each point represents a separate study for the indicated association. Log[OR] represents natural logarithm of odds ratio (OR). Vertical line represents the mean effects size.

As *ACE* gene may modify the phenotypic expression of the HCM, the administration of angiotensin-converting enzyme inhibitor (ACEI) or the angiotensin II type 1 receptor (AT1-R) antagonist remains interesting in HCM. It is now known that in presence of HCM, patients expressing D/D genotype for ACE gene show an increased level of serum ACE, have an increased risk of sudden death, and present an increased severity of hypertrophy.[20,37–39] Angiotensin II has trophic effects on the heart and plays an important role in the development of myocardial hypertrophy.[40] This knowledge has generated interest in ACEI or AT1-R antagonist as a potential therapeutic tool to prevent or reduce myocardial fibrosis, perhaps reduce the risk of arrhythmias and sudden death, and reduce the progression of diastolic dysfunction in HCM.[41–43] A double-blind, placebo-controlled,

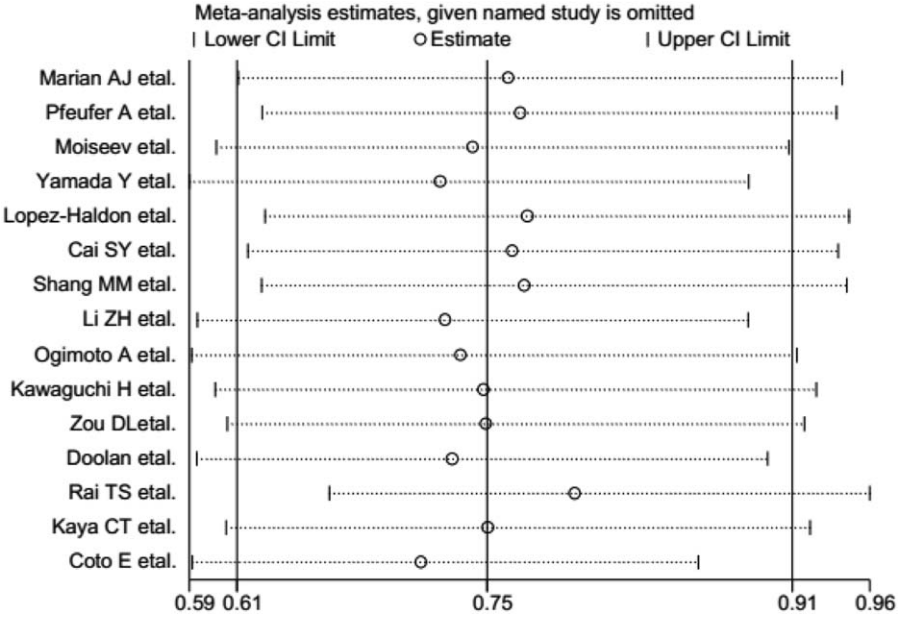

Figure 6. Potential outliers (ie, data points that are far outside the norm) were identified by a sensitivity analysis.

randomized study showed that the long-term administration of the AT1-R antagonist candesartan in patients with HCM was associated with the significant regression of LVH, improvement of left ventricular function, and exercise tolerance.[43] Thus, AT1-R antagonist has the potential to attenuate myocardial hypertrophy and may, therefore, provide a new treatment option to prevent sudden cardiac death in patients with HCM.

The results of this meta-analysis should be interpreted with some degree of caution, because there were several limitations in our analysis. First, we failed to subgroup the familial HCM and sporadic HCM in HCM patients due to the relatively insufficient studies. Second, heterogeneity among the included studies may affect the interpretation of the results of the meta-analysis. Third, most of the sample sizes of the referenced studies are relatively small, which might weaken the meta-analysis results. Furthermore, we could not investigate various ethnic distributions because most of the studies included only the Caucasian or Asian populations. It may be a result of various factors such as differences in study designs, environmental backgrounds, genetic constitution, or sample selection between studies. Taken together, all of these limitations may have affected the results of the present study.

5. Conclusions

The present meta-analysis finds an association between HCM and *ACE* I/D polymorphism. The findings of the current study may add benefit to risk stratification strategies in patients with HCM and may encourage further study focusing on the effect of *ACE* I/D polymorphisms on HCM risk. These results also suggest a potential treatment approach by regulating RAS in HCM patients. Prospective and more genome-wide association studies are needed to clarify the real role of the ACE gene in determining susceptibility to HCM.

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