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Original Article

Angiotensin-converting enzyme gene insertion/deletion polymorphism is associated with increased risk of arthritis: a meta-analysis

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Abstract: Angiotensin converting enzyme (ACE) insertion/deletion (I/D) polymorphism has been reported to be associated with the susceptibility to several kinds of arthritis by a number of association studies; however, the results from individual studies remain conflicting and inconclusive. To derive a more precise estimation of the association between the ACE gene I/D polymorphism and arthritis risk, a comprehensive meta-analysis was performed. The eligible studies retrieved from electronic databases were included after a systematical search. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of the association. A total of 16 case-control studies from 15 articles involving 1745 cases and 2311 controls were ultimately included in the meta-analysis. Overall, the ACE gene I/D polymorphism was found to be associated with a significantly elevated risk of arthritis (D vs. I: OR=1.38, 95% CI=1.05-1.79; DD vs. II: OR=1.75, 95% CI=1.10-2.80; DD vs. ID+II: OR=1.51, 95% CI=1.12-2.05). The subgroup analyses by ethnicity showed that this polymorphism was significantly associated with an increased risk of arthritis in Turkish population (DD+ID vs. II: OR=2.84, 95% CI=1.49-5.44; D vs. I: OR=1.83, 95% CI=1.08-3.08; DD vs. II: OR=3.31, 95% CI=1.40-7.85; ID vs. II: OR=2.78, 95% CI=2.03-3.82). Our study suggested that ACE gene I/D polymorphism might be associated with the susceptibility to arthritis, especially in Turkish population. More well-designed studies with larger sample sizes in populations with different ethnicities are warranted to verify these findings in the future.

Keywords: Angiotensin converting enzyme, arthritis, polymorphism, meta-analysis

Introduction

Arthritis referred commonly as a multifactorial disease generally occurring in joint and its surrounding tissue and comprising a variety of types such as osteoarthritis (OA), rheumatoid arthritis (RA), psoriatic arthritis (PA) and etc., has been considered as a major cause of impaired mobility or even disability and acts as an increasingly prominent social burden worldwide [1]. Effects of the diseases similarly characterized by inflammatory affection increase with the severity level and lead to muscle-skeleton morbity and function loss accordingly. Despite of a substantial amount of studies regarding the etiology and pathogenesis of the diseases, no uniform agreement was reached to date, however, it is widely accepted that genetic predetermination, age, gender, acute and chronic joint trauma, metabolic and particularly inflammatory and autoimmune mechanisms may be involved in the development of arthritis according to the specific form and additionally, interactions between gene and environmental factors may play an important role [2-4].

Angiotensin converting enzyme (ACE) encoded by ACE gene localized on chromosome 17q23.3 as an important regulator in inflammatory signal transduction pathways, has been found to be implicated in the pathogenesis and progression of several kinds of arthritis [5, 6]. ACE expression was found to be elevated in synovial

stroma in rheumatoid arthritis, and therefore contributed to inflammation-induced proliferation [7]. Moreover, synovial fluid (SF) ACE activity is also found higher in osteoarthritis patients [8], suggesting the potentially important role of ACE in the development of arthritis. Recently, several lines of evidence showed that a polymorphism of a 287 base pair ALU repeat sequence within intron 16 of ACE gene was identified, resulting in 3 different genotypes based on the presence (insertion, I) or absence (deletion, D): DD, II and ID. The concentrations of circulating ACE was found to vary with the polymorphism and the DD genotype was reported to contribute most to the expression and activity of ACE enzyme, which may be one of the possible underlying mechanisms involved in the arthritis development and progression [4, 9, 10]. Over decades, results of previous association studies have already indicated that ACE gene I/D polymorphism was associated with the susceptibility to arthritis, however, published results regarding this association remain conflicting and inconclusive, which may be due to the limited sample size, ethnicity variation and subtypes of arthritis. To address the concerns, a meta-analysis was employed to further characterize the association and the subgroup analysis based on ethnicity subtypes of arthritis was also performed.

Materials and methods

Search strategy

A systemic literature search in electronic databases of PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, and the Chinese Biomedicine Database was conducted to retrieve relevant publications regarding the association of ACE gene I/D polymorphism with the risk of arthritis up to September 2015. We developed a retrieval strategy by combining the following keywords variably: ["angiotensin-converting enzyme" or "ACE"] and ["SNP" or "polymorphism" or "genotype" or "variant"]. And "arthritis" was entered as medical subject heading (MeSH) components. Additional relevant studies were also identified through an individual and manual review of articles in the listed references of publications retrieved by the search strategy. In cases of duplication, we selected only the study with the largest sample size.

Inclusion and exclusion criteria

Studies were considered eligible for the meta-analysis if they met the following inclusion criteria: i) Studies were case-control design to evaluate the association between ACE polymorphism and arthritis risk. ii) Available information was provided for estimating the odds ratios (ORs) with their 95% confidence intervals (CIs) and extracting the frequencies of genotypes in case and control groups. Studies were excluded if: i) Reports contained overlapping data. ii) Reports only provided incomplete raw data. iii) Reports were duplicative studies with a less sample size. iv) Publications were abstracts, comments, letters, reviews, or editorial articles.

Data extraction

Two reviewers independently extracted the following information from the eligible studies included in the meta-analysis: first author, year of publication, region, ethnicity of study population, subtypes of arthritis, genotype distribution of ACE polymorphism in the case and control, sample size, genotyping methods, source of control and evidence of Hardy-Weinberg equilibrium (HWE). Any disagreement was resolved by discussion or consultation with a third reviewer.

Statistical analysis

The pooled ORs with their corresponding to 95% CIs were calculated for the strength of the association of ACE gene I/D polymorphism with the risk of arthritis using Review Manager version 5.2 software (Cochrane Collaboration, Oxford, England) under five genetic comparison models (dominant, recessive, homozygous, heterozygous, allele). Cochran's Q test was used to assess the heterogeneity across studies and the I^2 statistic was used to quantify the proportion of the total variation due to heterogeneity, $P<0.1$ and $I^2>50\%$ indicated significant heterogeneity [11]. The significance of pooled ORs was calculated by Z test ($P<0.05$ was considered significant) using a fixed- or random-effect model and if the heterogeneity across the included studies was significant, the random-effects model was selected; otherwise, the fixed-effects model was used [12, 13]. The subgroup analyses based on ethnicity and subtype of arthritis were also performed. Potential

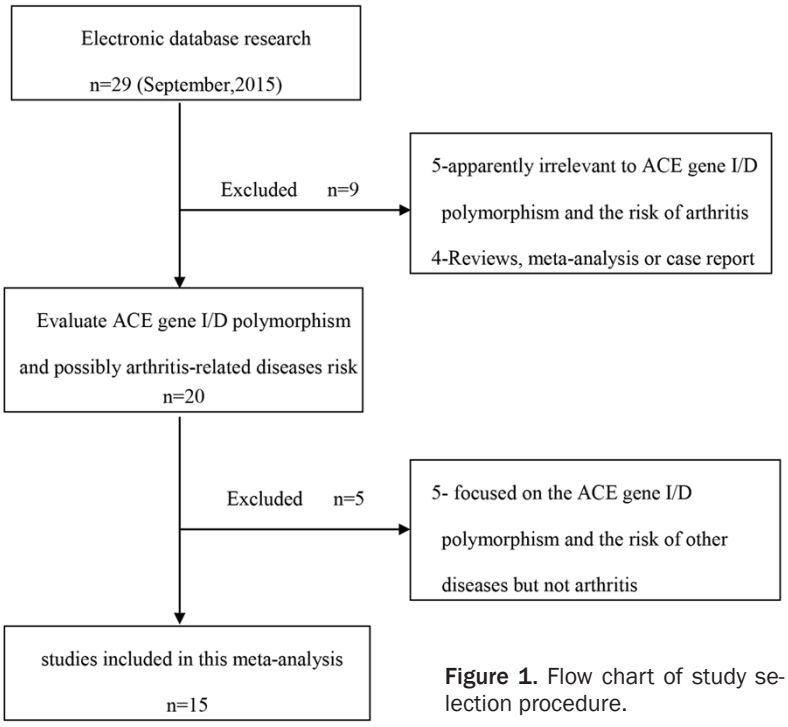

Figure 1. Flow chart of study selection procedure.

publication bias was accessed by Begg's funnel plot, and its asymmetry was further assessed by the Egger's regression test using Stata 12.0 software (Stata Corp., College Station, USA) and P<0.05 was considered significant [14, 15].

Results

Study characteristics

With the established search strategy, a total of 29 potentially relevant citations were reviewed after an initial search. After reading the titles and abstracts, 5 articles apparently irrelevant to ACE gene I/D polymorphism and the risk of arthritis were excluded. 4 articles including 2 reviews, 1 meta-analysis and 1 case-report were also excluded according to the selection criteria. 5 studies were excluded for that they focused on the ACE gene I/D polymorphism and the risk of other diseases but not arthritis. Finally, 15 articles were established to be analyzed in the meta-analysis. Ghelani's study [16] sorted the data for Caucasians and Asians; therefore, each group in the study was considered separately in the pooled analyses. The study by Shehab et al. [17] was focused on the association between ACE gene I/D polymorphism and the risk of spondylarthropathies including ankylosing spondylitis (AS), psoriatic arthritis (PA), reactive arthritis enteropathic and undifferentiated arthropathies, but only the cases with AS and PA were included in the meta-analysis. Therefore, 16 case-control studies from 15 articles involving 1745 cases and 2311 controls were ultimately included in the meta-analysis [4, 7, 10, 16-27]. The flow chart of study selection procedure is shown in **Figure 1**. All the included studies were reported in English. Of which, 7 studies were conducted in Asian population, 3 conducted in Caucasian population, 5 conducted in Turkish population and 1 conducted in African population. Moreover, 5 case-control studies were concerned with the association of ACE gene I/D polymorphism with OA risk, 7 case-control studies were concerned with the association of ACE gene I/D polymorphism with RA risk, and 4 case-control studies were concerned with the association between ACE gene I/D polymorphism and other kinds of arthritis risk. The distributions of genotypes in the controls of all the included studies were in agreement with the HWE test except for five studies [4, 17-19, 22]. Detailed characteristics of the included studies are listed in **Table 1**.

Meta-analysis results

As shown in **Table 2** and **Figure 2**, significant heterogeneity between individual studies was presented (all P_h<0.1) under all genetic comparison models, the random- effects model was thereby selected for the pooled analyses. Overall, the ACE gene I/D polymorphism was found to be associated with a significantly elevated risk of arthritis (D vs. I: OR=1.38, 95% CI=1.05-1.79; DD vs. II: OR=1.75, 95% CI= 1.10-2.80; DD vs. ID+II: OR=1.51, 95% CI=1.12-2.05). The subgroup analyses by ethnicity showed that this polymorphism was significantly associated with an increased risk of arthritis in Turkish population (DD+ID vs. II: OR=2.84, 95% CI=1.49-5.44; D vs. I: OR=1.83,

Table 1. Characteristics of studies included in meta-analysis

First author	Year	Country	Ethnicity	Diseases	Genotype-case DD/ID/II	Genotype-control DD/ID/II	Source of control	Genotype method	HWE test
Hong	2003	Korea	Asian	OA	23/68/51	33/58/44	Population	PCR-RFLP	0.12
Bayram	2011	Turkey	Turkish	OA	81/51/8	24/20/16	Hospital	Taqman	0.01
Inanir	2013	Turkey	Turkish	OA	77/107/37	45/77/78	Hospital	Taqman	0.003
Shehab	2008	Kuwait	Asian	OA	70/22/23	74/18/19	Hospital	Taqman	<0.001
Poornima	2014	India	Asian	OA	44/38/18	22/46/32	Hospital	PCR-RFLP	0.48
Ahmed	2012	Egypt	African	RA	40/21/5	17/37/12	Hospital	Taqman	0.29
Ghelani	2011	UK	Asian	RA	30/48/50	31/64/52	Population	PCR-RFLP	0.18
	2011	UK	Caucasian	RA	54/43/38	42/71/27	Population	PCR-RFLP	0.76
Yigit	2012	Turkey	Turkish	RA	52/49/9	39/80/27	Population	PCR-RFLP	0.21
Uppal	2007	Kuwait	Asian	RA	39/11/10	12/13/10	Population	PCR-RFLP	0.13
Zapico	2000	Spain	Caucasian	RA	73/65/22	200/220/80	Hospital	PCR-RFLP	0.14
Alsaeid	2003	Kuwait	Asian	RA	34/31/17	25/22/1	Hospital	Taqman	0.12
Shehab	2008	Turkey	Turkish	arthritis	27/18/13	74/18/19	Hospital	PCR-RFLP	<0.001
Coto-Segura	2009	Spain	Caucasian	arthritis	23/27/5	93/145/34	Population	PCR-RFLP	0.051
Inanir	2012	Turkey	Turkish	AS	61/42/19	29/43/68	Population	PCR-RFLP	<0.001
Al-Awadhi	2007	Kuwait	Asian	PA	25/19/7	41/45/14	Hospital	PCR-RFLP	0.77

OA, osteoarthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; PA, psoriatic arthritis; PCR-RFLP, polymerase chain reaction-restriction fragment length Polymorphism; HWE, Hardy-Weinberg equilibrium.

Table 2. Summary results for the association of ACE polymorphism and arthritis risk in the meta-analysis

Contrasts	Study groups	Subgroups	No. of studies	OR [95% CI]	P	Effect model	Heterogeneity P_h	Heterogeneity I^2
DD+ID vs. II	Overall		16	1.47 [0.99, 2.17]	0.06	R	<0.001	80%
	Ethnicity	Asian	7	1.02 [0.66, 1.56]	0.93	R	0.03	57%
		Caucasian	3	0.95 [0.67, 1.33]	0.75	F	0.15	48%
		Turkish	5	2.84 [1.49, 5.44]	0.002	R	0.001	78%
		African	1	2.71 [0.90, 8.19]	0.08	-	-	-
	Arthritis types	OA	5	1.90 [0.94, 3.82]	0.07	R	<0.001	85%
		RA	7	1.13 [0.67, 1.91]	0.64	R	0.003	70%
		Other	4	1.57 [0.57, 4.32]	0.38	R	<0.001	84%
D vs. I	Overall		16	1.38 [1.05, 1.79]	0.02	R	<0.001	86%
	Ethnicity	Asian	7	1.09 [0.75, 1.58]	0.65	R	<0.001	80%
		Caucasian	3	1.15 [0.95, 1.38]	0.15	F	0.7	0%
		Turkish	5	1.83 [1.08, 3.08]	0.02	R	<0.001	90%
		African	1	2.80 [1.65, 4.75]	<0.001	-	-	-
	Arthritis types	OA	5	1.45 [0.90, 2.33]	0.13	R	<0.001	88%
		RA	7	1.33 [0.93, 1.89]	0.11	R	<0.001	82%
		Other	4	1.34 [0.59, 3.00]	0.48	R	<0.001	93%
DD vs. II	Overall		16	1.75 [1.10, 2.80]	0.02	R	<0.001	82%
	Ethnicity	Asian	7	1.10 [0.58, 2.08]	0.78	R	<0.001	74%
		Caucasian	3	1.20 [0.82, 1.76]	0.34	F	0.54	0%
		Turkish	5	3.31 [1.40, 7.85]	0.006	R	<0.001	85%
		African	1	5.65 [1.72, 18.5]	0.004	-	-	-
	Arthritis types	OA	5	2.05 [0.84, 5.02]	0.12	R	<0.001	88%
		RA	7	1.57 [0.83, 2.96]	0.17	R	<0.001	74%
		Other	4	1.73 [0.48, 6.20]	0.4	R	<0.001	88%
ID vs. II	Overall		16	1.26 [0.88, 1.82]	0.21	R	<0.001	71%

	Ethnicity	Asian	7	0.88 [0.67, 1.17]	0.38	F	0.29	19%
		Caucasian	3	0.80 [0.40, 1.58]	0.52	R	0.06	65%
		Turkish	5	2.78 [2.03, 3.82]	<0.001	F	0.33	13%
		African	1	1.36 [0.42, 4.40]	0.61	-	-	-
	Arthritis types	OA	5	1.81 [1.01, 3.23]	0.05	R	0.006	72%
		RA	7	0.82 [0.51, 1.32]	0.41	R	0.03	57%
		Other	4	1.67 [0.86, 3.24]	0.13	R	0.09	53%
DD vs. ID+II	Overall		16	1.51 [1.12, 2.05]	0.008	R	<0.001	78%
	Ethnicity	Asian	7	1.21 [0.75, 1.97]	0.43	R	<0.001	75%
		Caucasian	3	1.36 [1.05, 1.76]	0.02	F	0.79	0%
		Turkish	5	1.76 [0.93, 3.32]	0.08	R	<0.001	85%
		African	1	4.43 [2.11, 9.30]	<0.001	-	-	-
	Arthritis types	OA	5	1.37 [0.79, 2.40]	0.26	R	<0.001	80%
		RA	7	1.71 [1.13, 2.60]	0.01	R	0.001	73%
		Other	4	1.35 [0.55, 3.30]	0.51	R	<0.001	88%

ACE, angiotensin-converting enzyme; RA, rheumatoid arthritis; OA, osteoarthritis; OR, odds ratio; CI, confidence interval; F, fixed effects model; R, random effects model; P_h, *p*-value for heterogeneity; I^2, quantitative estimate for heterogeneity.

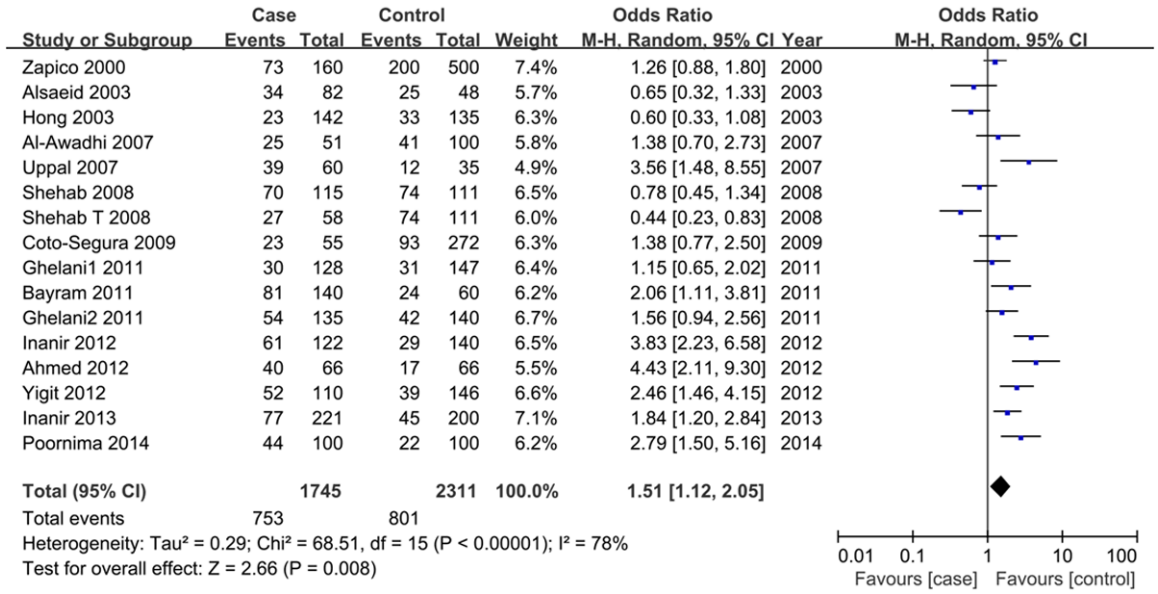

Figure 2. Forest plot for the association of ACE gene I/D polymorphism with the risk of arthritis under the recessive model.

95% CI=1.08-3.08; DD vs. II: OR=3.31, 95% CI=1.40-7.85; ID vs. II: OR=2.78, 95% CI=2.03-3.82) and African population (D vs. I: OR=2.80, 95% CI=1.65-4.75; DD vs. II: OR=5.65, 95% CI=1.72-18.52; DD vs. ID+II: OR=4.43, 95% CI=2.11-9.30). Similar association was also found in Caucasian population but only in recessive model (DD vs. ID+II: OR=1.36, 95% CI=1.05-1.76). Moreover, a significantly increased risk of OA associated with the polymorphism was revealed in the stratification analysis based on subtypes of arthritis but only in heterozygous model (ID vs. II: OR=1.81, 95% CI=1.01-3.23), and similar association for RA was also found only in recessive model (DD vs. ID+II: OR=1.71, 95% CI=1.13-2.60).

Sensitivity analysis and publication bias

Sensitivity analysis was performed by sequential omission of every single study to explore the influence of individual study on the overall

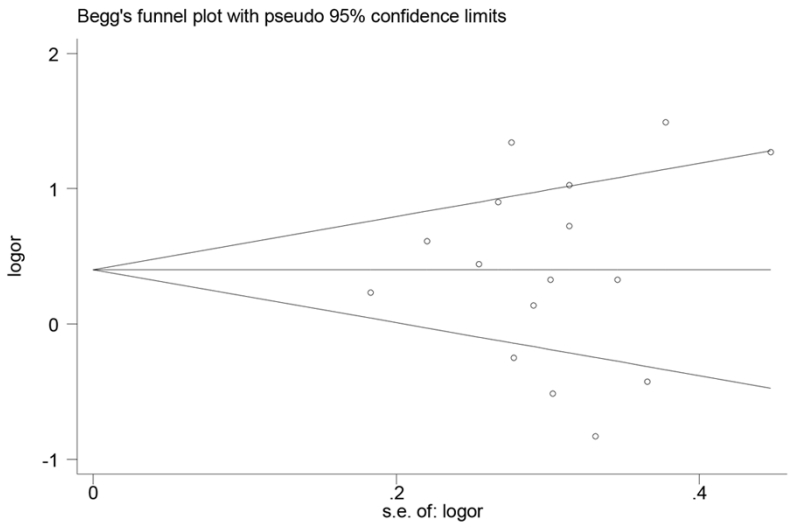

Figure 3. Begg's funnel plot for the association of ACE gene I/D polymorphism with the risk of arthritis under the recessive model.

ORs. The significance of pooled ORs was not materially altered in all genetic models except for the dominant model by omitting the study by Hong et al. [7], Alsaeid et al. [27], Shehab et al. [19] and Shehab et al. [17], suggesting a possible association between ACE gene I/D polymorphism and the risk of arthritis, which, however, may remain to be further verified. Evaluation of publication bias was performed using Begg's funnel plot and Egger's test. As shown in **Figure 3**, no obvious asymmetry for all genetic models was exhibited by the Begg's funnel plot, which was also supported by the results of Egger's test (all P>0.05, data not shown), suggesting no evident publication bias.

Discussion

The present study is the first to provide comprehensive and objective evidence by the method of meta-analysis showing that ACE gene I/D polymorphism was associated with a significantly elevated risk of arthritis, particularly in Turkish population.

Accumulative evidence has indicated that inflammation and immune response is a common manifestation of arthritis [28]. ACE presented as an important regulator of the renin-angiotensin system (RAS) by catalyzing the conversion of angiotensin I to angiotensin II has been found to have a significant role in the physiology of inflammatory and autoimmune processes [29, 30]. Recent reports suggested that the conversion of angiotensin I to angiotensin II by ACE may simultaneously lead the increase of the generation of reactive oxygen species (ROS) and the synthesis of cytokines such as interleukin-6 (IL-6), IL-8, IL-12 and tumor necrosis factor-α (TNF-α) in monocytes and macrophages [31, 32], thus exerting pro-inflammatory effects, which may be due to the direct link between Ang II and pro-inflammatory molecule NF-kappaB (NF-κB) regulated genes activation [33]. The potential mechanisms mentioned above were also supported by the observation that the higher expression and activity of ACE in patients with several kinds of arthritis than that in controls in many clinical studies [34]. As ACE gene I/D polymorphism was found to be associated with the regulation of expression and activity of ACE [9], the association between ACE gene I/D polymorphism and susceptibility to arthritis has been extensively studied, however, the results remain conflicting and inconclusive. This may be due to the limited sample size, ethnicity variation and subtypes of arthritis, which prompted us to reassess this association using a scientific approach with more efficacy and power. To our knowledge, this is the first comprehensive meta-analysis investigating the influence of the ACE I/D polymorphism on arthritis susceptibility.

In the present meta-analysis, 16 case-control studies from 15 articles involving 1745 cases and 2311 controls were pooled to assess the association of ACE gene I/D polymorphism with susceptibility to arthritis. Overall, a significant association was revealed, suggesting a contribution of the ACE gene I/D variant genotype to an increased risk of arthritis. Additionally, the subgroup analysis by ethnicity showed that this association was also significant in Turkish population in four genetic models. Similarly, such association was found in the Caucasian population as well, however, the concerned relationship was only revealed in the recessive model, which would limit our confidence in drawing a

conclusion. Moreover, we also found an association between ACE gene I/D polymorphism and increased risk of arthritis in African population in three genetic models, while only a single study was included, the result should be interpreted with caution. The inconsistency and limitation of the findings in the subgroup analysis by ethnicity indicated that ethnicity variation or sample size may have an influence on the association of ACE gene I/D polymorphism with susceptibility to arthritis, suggesting the necessity to confirm this association with a large sample size in different ethnicities. Furthermore, a significant association between ACE gene I/D polymorphism and increased risk of rheumatoid arthritis was presented in the stratification analysis based on subtypes of arthritis, which was in line with the finding of a previous meta-analysis [35]. Although this association was suggested by the previous pooled analysis, the current meta-analysis further confirmed this association with a lager sample size (242 cases and 548 controls added), suggesting the significant role of ACE gene I/D polymorphism in the susceptibility to RA. Additionally, a borderline association was also found for OA but only in heterozygous genetic model. However, we failed to show any significant associations of this variant with other arthritis risk. The discrepancy may be due to different mechanisms involved in the pathogenesis of different kinds of arthritis.

Heterogeneity is a common concern for the meta-analysis, which may affect the interpretation of the results. Obvious between-study heterogeneity was found in the overall comparisons of this meta-analysis. Although the heterogeneity was partially reduced in the subgroup analysis by ethnicity, the existence of significant heterogeneity was still observed. Moreover, the significance of pooled ORs regarding this association was materially altered in the dominant model by omitting four studies separately in the sensitivity analysis, suggesting that caution should be under consideration when interpreting the results. Nevertheless, in light of the diversity in subtypes and complicated pathogenesis of arthritis, we have less capability to perform more comprehensive subgroup analyses to clarify the concerns due to the lack of original data. Despite of these limitations, the present meta-analysis provided more convincing evidence focusing on the association of ACE gene I/D polymorphism and arthritis risk than individual association studies.

Despite the considerable efforts have been made, several limitations are still needed to be aware. First, arthritis is a multifactorial disease, involving interactions between genes and environment. The results of included studies were based on unadjusted estimates, a more precise analysis should be conducted by adjusting for other significantly compounding factors. Second, the sample size is relatively small in the meta-analysis due to the lack of available studies, especially for the subgroup analyses according to the subtype of arthritis. In addition, because of a lack of available studies, less case-control studies conducted in Caucasian and African population were included in the meta-analysis, particularly, only one case-control study in African population was enrolled, which would limit the comprehensiveness and veracity of the results.

Conclusions

In summary, the present study suggests that ACE gene I/D polymorphism may contribute to the susceptibility to arthritis, especially in Turkish population. However, considering the heterogeneity and limitations in the meta-analysis, more well-designed studies with larger sample sizes in populations with different ethnicities are warranted to verify these findings in the future.

Disclosure of conflict of interest

None.

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