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Original Article

Association between *ADAM12* gene polymorphisms and osteoarthritis risk: a meta-analysis of 10,775 participants

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Abstract: It has been reported that a disintegrin and metalloproteinase domain (*ADAM)* 12 gene polymorphisms may be associated with the risk of osteoarthritis (OA). However, some studies have reported inconclusive results. Therefore, we conducted a meta-analysis to identify the association of *ADAM12* gene polymorphisms and the susceptibility to OA. We conducted a systematic search in PubMed, Embase, China National Knowledge Internet (CNKI) and Wanfang databases up to March 15, 2015. Odds ratio (OR) and 95% confidence interval (CI) were used to pool the effect size. Statistical analyses were performed with STATA 11.0 software. In total, seven studies with 10,755 subjects were included in this meta-analysis. The overall results suggested that a statistically significance was observed in the *ADAM12* rs1871054 polymorphism in allele model (C vs. T: OR=1.52, *P*=0.033), dominant model (CC+CT vs. TT: OR=1.36, *P*=0.037), recessive model (CC vs. CT+TT: OR=1.99, *P*=0.011) and co-dominant model (CC vs. TT: OR=2.03, *P*=0.027). In subgroup analysis, a significant relationship of *ADAM12* rs1871054 polymorphism and OA risk was also identified in the same four genetic comparisons in Asians (C vs. T: OR=1.85, *P*<0.001; CC vs. TT: OR=2.81, *P*<0.001; CC+CT vs. TT: OR=1.68, *P*=0.006; CC vs. CT+TT: OR=2.61, *P*<0.001). However, no evidence of association was found between *ADAM12* gene polymorphisms (rs3740199, rs1278279 and rs1044122) with OA susceptibility in any genetic model. In summary, this meta-analysis suggested that *ADAM12* gene rs1871054 polymorphism may increase risk of OA risk, especially in Asians.

Keywords: Osteoarthritis, *ADAM12*, polymorphism, meta-analysis

Introduction

Osteoarthritis (OA) is characterized by the progressive degenerative damage of cartilage, subchondral bone sclerosis, and synovial inflammation, which ultimately leads to loss of joint motion, physical disability, and pain [1, 2]. It has been reported that the prevalence of OA was 9.6% and 18% in man and woman who are 60 years or older, respectively [3]. To some extent, these figures are expected to rise with population aging [4]. There is no treatment available proven to be useful to control or arrest the disease progression, so OA trends to cause the great economic burden to the population who proceed to arthroplasty in end stage [5]. An increasing body of studies showed that a variety of risk factors-aging, traumatic injury, osteoporosis, genetics, obesity and metabolic diseases-accounted for the onset and progression of OA [5, 6]. Among these recognized risk factors, it is widely accepted that the genetic factors play a significant role in OA risk [6-8].

Several studies have been performed to disclose that the combination of single nucleotide polymorphisms (SNPs) in various possible predisposition genes were associated with osteoarthritis susceptibility, such as aspirin (ASPN), interleukin-6 (IL6), vitamin D receptor (VDR), and *ADAM12* [8-10]. The *ADAMs* are members of the zinc protease superfamily shown to have a variety of roles and there are currently 21 different *ADAM* gene members of the family appearing in human [11, 12]. Among them, *ADAM12* has been attracted much attention. *ADAM12*, an active proteinase, belongs to the family of *ADAMs*, which possess immune and

Table 1. Characteristics of included studies

Author	Year	Country	Ethnicity	Case/Control	Disease	Quality	HWE
Shin MH	2012	Korea	Asian	725/1737	KOA	7	0.88
Lou S	2014	China	Asian	152/179	KOA	9	0.6
Kerna I	2009	Estonia	Caucasian	163/215	KOA	7	0.83
Wang L	2015	China	Asian	164/200	KOA	8	0.77
Rodriguez-Lopez J	2009	America	Caucasian	1622/588	TKR, THR, HOA	8	NA
Rodriguez-Lopez J	2009	Greek	Caucasian	318/386	TKR	8	NA
Rodriguez-Lopez J	2009	UK	Caucasian	2930/1396	TKR, THR	8	NA

KOA, knee osteoarthritis; TKR, knee osteoarthritis requiring total knee arthroplasty; THA: hip osteoarthritis requiring total hip arthroplasty; HOA, hand osteoarthritis; NA, not available.

inflammatory reaction properties [12]. Therefore, the level of *ADAM12* in human serum is an important predictor for some pathologic states in tissues, such as cartilage, bone, synovium, and muscle [12-14]. A previous study demonstrated that *ADAM12* in serum has been shown to be up-regulated in OA [15]. Furthermore, the polymorphisms of *ADAM12* gene were found to be involved in pathogenesis of OA [16-18]. However, some others studies failed to replicate such association in different races [19, 20]. Nevertheless, no meta-analysis has been carried out to identify the susceptibility of *ADAM12* to OA.

The aim of the meta-analysis is to derive a more precise estimation about whether the *ADAM12* SNPs (rs1871054, rs3740199, rs1278279, and rs1044122) variants were associated with OA susceptibility. To our knowledge, this is the first meta-analysis to found the precise association between the *ADAM12* gene polymorphisms and OA risk.

Materials and methods

Literature search strategy

PubMed, Embase, CNKI and Wanfang databases were searched by two independent investigators, using the following key words: 'osteoarthritis' or 'OA', '*ADAM12*' or 'a disintegrin and metalloproteinase domain 12', 'polymorphism' or 'polymorphisms' or 'variant' or 'mutation'. There was no language or other limitation of search and the latest electronic search was performed on March 15, 2015. Furthermore, References of all the related articles were manually examined to identify as many relative articles as possible.

Inclusion/exclusion criteria

Studies in this meta-analysis were selected according to the following inclusion criteria: (1) case-control design or cohort study; (2) diagnosis based on clinical symptoms or/and radiographic signs of OA; (3) the association between *ADAM12* gene polymorphisms and OA risk; (4) providing detailed genotype or allele frequencies. Exclusion criteria: (1) duplicative or overlapping publications; (2) comment, review, and abstract; (3) study with no genotype or allele frequencies. Two investigators independently screened all abstracts and citations to extract potential eligible studies. Any disagreement was resolved through discussion.

Data extraction

The information of eligible studies was collected in duplicate by two investigators independently, the following items were extracted: first authors, publication year, countries, ethnicity, case and control sizes, allele/genotype distributions, and genotyping methods. Different ethnicity was stratified into Asians and Caucasians. If a dispute existed, two investigators would check the collected data and reach consensus on each item. The information is shown in **Tables 1** and **2**.

Methodological quality assessment

The qualities of included studies were estimated according to the Newcastle–Ottawa Scale (case-control study) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The scale use a '-' rating system to evaluate quality based on three points including selection, comparability, and exposure in the case-control study (data not shown). The total scores ranged

Table 2. Distributions of ADAM12 gene polymorphisms allele and genotypes in different groups

Author	Year	Case					Control				
rs3740199		CC	CG	GG	C (%)	G (%)	CC	CG	GG	C (%)	G (%)
Shin MH	2012	147	364	214	658 (45.38)	792 (54.62)	350	863	524	1563 (44.99)	1911 (55.01)
Lou S	2014	32	78	42	142 (46.71)	162 (53.29)	42	93	44	177 (49.44)	181 (50.56)
Kerna I	2009	81	66	16	228 (69.94)	98 (30.06)	106	89	20	301 (70.00)	129 (30.00)
Wang L	2015	36	84	44	156 (47.56)	172 (52.44)	47	102	51	196 (49.00)	204 (51.00)
Rodriguez-Lopez J	2009	NA	NA	NA	1857 (57.24)	1387 (42.76)	NA	NA	NA	654 (55.61)	522 (44.39)
Rodriguez-Lopez J	2009	NA	NA	NA	361 (56.76)	275 (43.24)	NA	NA	NA	479 (62.05)	293 (37.95)
Rodriguez-Lopez J	2009	NA	NA	NA	3158 (53.89)	2702 (46.11)	NA	NA	NA	1488 (53.30)	1304 (46.70)
rs1871054		CC	CT	TT	C (%)	T (%)	CC	CT	TT	C (%)	T (%)
Lou S	2014	69	57	26	195 (64.14)	109 (35.86)	44	88	47	176 (49.16)	182 (50.84)
Kerna I	2009	42	79	42	163 (50.00)	163 (50.00)	50	111	54	211 (49.07)	219 (50.93)
Wang L	2015	76	59	29	211 (64.33)	117 (35.67)	49	99	52	197 (49.25)	203 (50.75)
rs1044122		CC	CT	TT	C (%)	T (%)	CC	CT	TT	C (%)	T (%)
Lou S	2014	24	81	47	129 (42.43)	175 (57.57)	31	92	56	154 (43.02)	204 (56.98)
Wang L	2015	25	88	51	138 (42.07)	190 (57.93)	37	101	62	175 (43.75)	225 (56.25)
rs1278279		AA	AG	GG	A (%)	G (%)	AA	AG	GG	A (%)	G (%)
Lou S	2014	9	59	84	77 (25.33)	227 (74.67)	13	60	106	86 (24.02)	272 (75.98)
Wang L	2015	10	62	92	82 (25.00)	246 (75.00)	15	64	121	94 (23.50)	306 (76.50)

NA, not available.

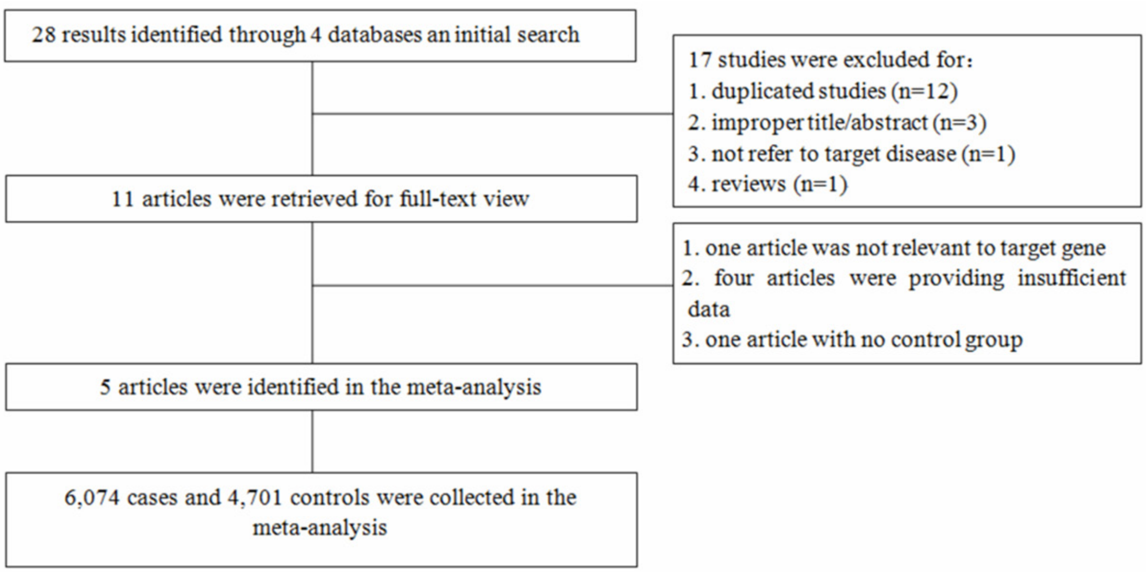

Figure 1. Flow diagram of included and excluded studies.

0-9. We assessed the qualities of each study with all authors. A study with Scores of 7 or more was considered to be a high quality study (**Table 1**).

Data analysis

All of the data in included studies were dichotomous data expressed as odds ratio (OR) with 95% confidence interval (95% CI) to evaluate the association strength between *ADAM12* gene polymorphisms and OA susceptibility. Heterogeneity was evaluated by χ^2-based Q-test and I^2 statistics. When I^2 was more than 50% and P<0.10 for Q test, the heterogeneity was considered statistically significant, and the random-effects model was applied to estimate pooled OR. Otherwise, the fixed-effects model

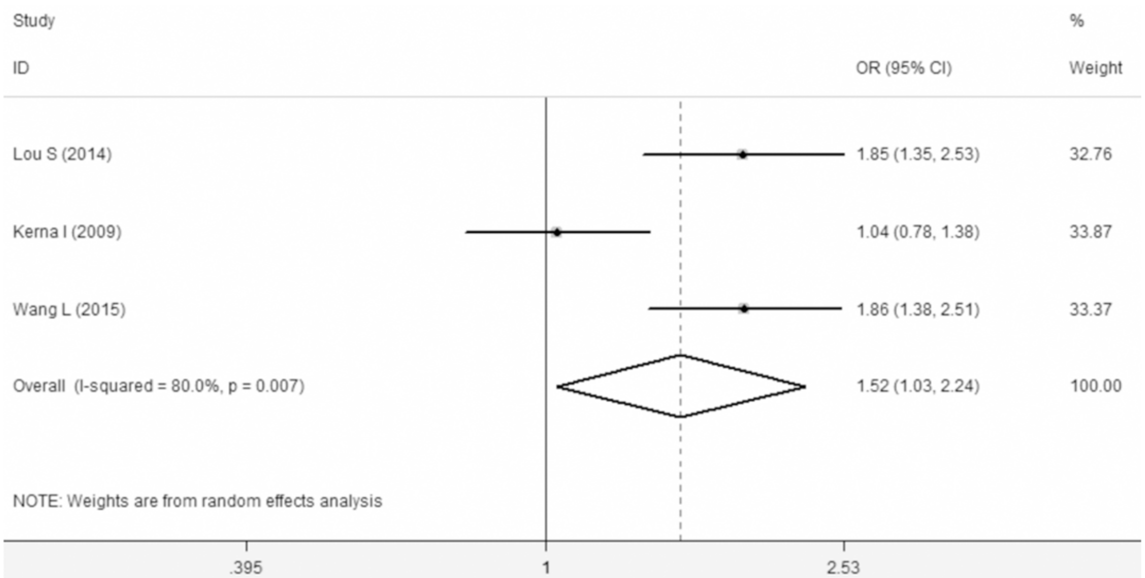

Figure 2. Meta-analysis of ORs and 95% CIs of individual studies and pooled data for the association of *ADAM12* rs1871054 polymorphism and OA susceptibility (C vs. G).

was used. Potential publication bias was tested by several methods. Visual inspection of asymmetry in funnel plots was carried out. Furthermore, publication bias was also detected with Egger' regression and Begg's test, and a $P<0.05$ was considered statistically significant. In addition, Hardy-Weinberg equilibrium (HWE) was evaluated in control groups by Pearson's χ^2 test before this meta-analysis was performed (**Table 1**). Besides, to evaluate the ethnicity and gender specificity, subgroup analyses were stratified by ethnicity and gender for *ADAM12* polymorphisms. All data analysis was performed with STATA 11.0 software (StataCorp, College Station, TX, USA).

Results

Study inclusion and characteristics

In total, 28 articles were identified based on the criteria after we systemically searched PubMed, Embase, CNKI, and Wan-fang databases. After reading titles and abstracts, 11 articles were screened in full-text review (**Figure 1**). One article [21] was excluded because it did not evaluate the relationship of *ADAM12* SNPs and OA risk, but other gene polymorphisms. Four articles [9, 10, 19, 22] were excluded owe to insufficient data. One article [7] was excluded because of no control group. In the case-control study performed by Rodriguez-Lopez J [23], the participants were recruited from US, UK, and Greek, and the allele frequencies were presented separately, so each of them was considered as an independent study. Therefore, in total, seven studies from five articles [17, 18, 20, 23, 24] were identified, which involved 10,755 subjects (6,074 cases and 4,701 controls) to investigate the association between *ADAM12* polymorphisms and OA risk. The characteristics of included studies are shown in **Table 1**.

Association of rs1871054 and OA meta-analysis

All three studies [17, 18, 24] involving 1,073 subjects (479 cases and 594 controls) were pooled to investigate association between *ADAM12* rs1871054 polymorphism and OA risk. For presence of a moderate heterogeneity, random-effects model was used in allele model, recessive model, and homozygote model, fixed-effects model in other genetic models. The overall results suggested that a significant association of *ADAM12* rs1871054 polymorphism and OA susceptibility was observed in four models (C vs. T: OR=1.52, 95% CI=1.03-2.24, *P*=0.033; CC+CT vs. TT: OR=1.36, 95% CI 1.02-1.81, *P*=0.037; CC vs. CT+TT: OR=1.99, 95% CI=1.17-3.38, *P*=0.011; CC vs. TT: OR=2.03, 95% CI=1.08-3.82, *P*=0.027) (**Figure 2**; **Table 3**), but not in co-dominant model (CT vs. TT: OR=1.03, 95% CI (0.76-1.41), *P*=0.844). No publication bias was found in funnel plot or Egger's test.

Table 3. Summary of overall results and subgroup analysis from different genetic models

	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
rs1871054	C vs. T		CT vs. TT		CC vs. TT		CC vs. CT+TT		CC+CT vs. TT	
Ethnicity										
Overall	1.52	1.03-2.24	1.03	0.76-1.41	2.03	1.08-3.82	1.99	1.17-3.38	1.36	1.02-1.81
Asian	1.85	1.49-2.30	1.12	0.75-1.67	2.81	1.84-4.27	2.61	1.89-3.60	1.68	1.16-2.43
Caucasian	1.04	0.78-1.38	0.92	0.56-1.50	1.08	0.61-1.92	1.15	0.71-1.84	0.97	0.61-1.54
rs3740199	C vs. G		CG vs. GG		CC vs. GG		CC vs. CG+GG		CC+CG vs. GG	
Ethnicity										
Overall	1.00	0.95-1.06	1.00	0.84-1.19	0.98	0.79-1.20	0.98	0.83-1.16	0.99	0.85-1.17
Caucasian	1.01	0.94-1.08	0.93	0.45-1.92	0.96	0.47-1.96	1.02	0.68-1.53	0.94	0.47-1.88
Asian	0.99	0.89-1.10	1.00	0.84-1.20	0.98	0.79-1.21	0.98	0.81-1.17	1.00	0.85-1.18
Gender										
Overall	0.97	0.88-1.08	1.00	0.82-1.22	1.00	0.78-1.28	1.00	0.82-1.22	1.00	0.83-1.21
Man	1.03	0.83-1.28	1.40	0.97-2.04	1.25	0.79-1.98	1.07	0.74-1.54	1.36	0.95-1.94
Woman	0.94	0.83-1.05	0.87	0.68-1.10	0.91	0.68-1.22	0.98	0.78-1.23	0.88	0.70-1.11
rs1044122	C vs. T		CT vs. TT		CC vs. TT		CC vs. CT+TT		CC+CT vs. TT	
Overall	0.95	0.77-1.81	1.05	0.75-1.48	0.87	0.55-1.37	0.84	0.56-1.26	1.01	0.73-1.39
rs1278279	A vs. G		AG vs. GG		AA vs. GG		AA vs. AG+GG		AA+AG vs. GG	
Overall	1.08	0.84-1.38	1.26	0.92-1.71	0.88	0.47-1.62	0.80	0.44-1.47	1.19	0.88-1.61

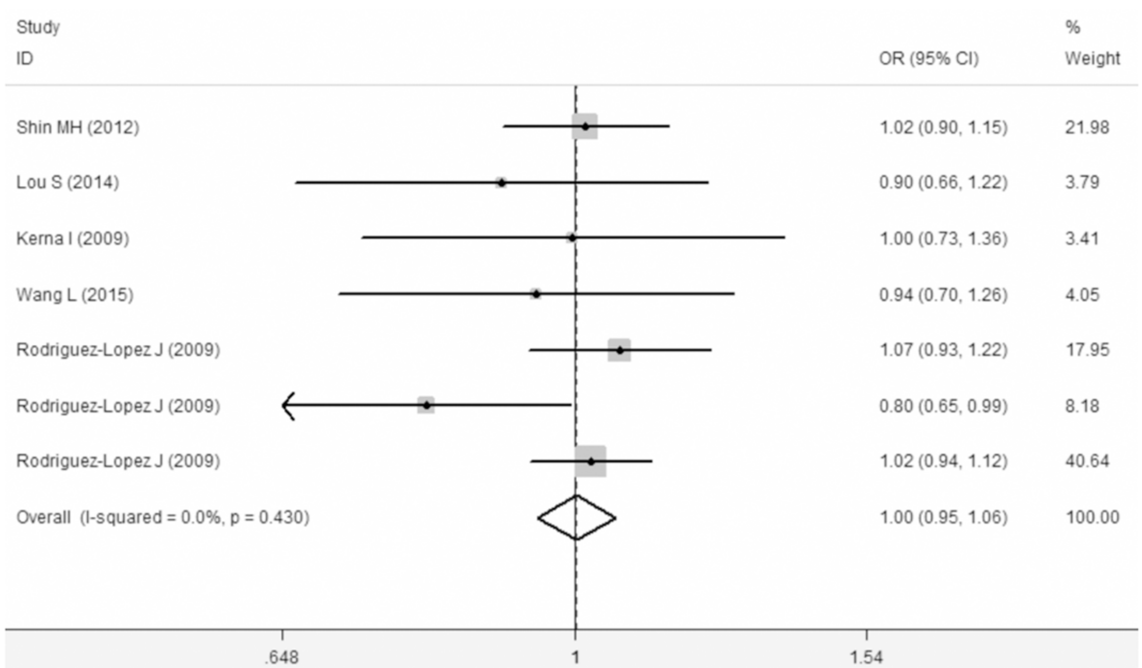

Figure 3. Meta-analysis for the association of *ADAM12* rs3740199 polymorphism and OA risk (C vs. G).

Then, we performed the subgroup analysis stratified by ethnicity, and also found a statistically significant relationship between *ADAM12* rs1871054 polymorphism and OA risk in four models(C vs. T: OR=1.85, 95% CI=1.49-2.30, *P*<0.001; CC vs. TT: OR=2.81, 95% CI=1.84-4.27, P<0.001; CC+CT vs. TT: OR=1.68, 95% CI=1.16-2.43, *P*=0.006; CC vs. CT+TT: OR=2.61, 95% CI=1.89-3.60, *P*<0.001) in Asians (**Table 3**). Other genetic models were also summarized in **Table 3**.

Association of rs3740199 and OA meta-analysis

All seven studies [17, 18, 20, 23, 24] containing 10,755 subjects (6,074 cases and 4,701 controls) reported the association between

ADAM12 rs3740199 polymorphism and OA risk. As no significant heterogeneity was detected in each genetic model, fixed-effects model was utilized, and no statistically significant association was identified in any genetic model (**Figure 3**; **Table 3**).

Subgroup analyses were performed to investigate the potential effect of ethnicity and gender. We found no statistically significant relationship of *ADAM12* rs3740199 polymorphism and OA risk in either Asians or Caucasians. Additionally, in the subgroup analysis of gender, *ADAM12* rs3740199 was also found with no significant association with OA risk in all genetic models (**Table 3**).

Association of rs1044122 or rs1278279 and OA meta-analysis

We analyzed two studies [17, 18] including 695 subjects (316 cases and 379 controls) to assess the association between *ADAM12* rs1044122 and rs1278279 with OA susceptibility, respectively. No significant heterogeneity was detected by Q-test and I^2 statistic, so fixed-effects model was utilized in any genetic comparison. Overall, the pooled results indicated that there was no significant relationship of *ADAM12* rs1044122 and rs1278279 and OA risk in any genetic comparison, respectively (**Table 3**).

Discussion

OA is the most common cause of musculoskeletal disability and impairing life quality [2, 4]. The disease affected estimated 10% of the world population over the age of 60 years [2, 5]. Joint replacement is often the only treatment for late-stage OA, which creates a terrible burden in the health care system [1-3]. Many risk factors take part in the pathogenesis and progression of OA, such as bone density, obesity, gender, age, and hormonal level. Several studies investigated that genetic factors were also significant determinant of OA [6, 16]. Recently, the *ADAM12* SNPs (rs1871054, rs3740199, rs1278279, and rs1044122) variants was found to be associated with OA susceptibility [8, 10, 24, 25]. Previous studies found the overexpression of *ADAM12* was associated with synovial membrane inflammation and cartilage injury in OA [14, 25, 26]. Several studies have reported the association between *ADAM12* polymorphism and OA risk [10, 25], but some other studies failed to replicate the association in other races [19, 20]. Until now, no meta-analysis has been performed to comprehensively evaluate the association of *ADAM12* polymorphism and OA risk. Therefore, we carried out this first meta-analysis to investigate the relationship.

In this current meta-analysis, the overall results demonstrated that *ADAM12* rs1871054 polymorphism may increase the risk of OA. However, no evidence was found with the association between *ADAM12* rs3740199, rs1044122, and rs1278279 polymorphisms and OA susceptibility. Since a moderate heterogeneity was detected in this meta-analysis, we performed a subgroup analysis by ethnicity and gender to identify the origin of heterogeneity. In subgroup analysis, for rs1871054, the pooled results suggested that the C allele may strongly increase the risk of OAin Asians (CC vs. TT: OR=2.81, 95% CI (1.84-4.27), P<0.001). But *ADAM12* rs3740199 polymorphism was found with no relation with OA risk no matter for which model of comparison in Asians and Caucasians, either was in male and female.

Although the mechanism pertaining to the association of *ADAM12* gene polymorphisms and OA risk remains unclear, by combining the present and previous data, we can propose a hypothesis that the T>C substitution within *ADAM12* rs1871054 may induce the overexpression of *ADAM12* in cartilage, synovium, and bone, and cause inflammatory and immune reaction, thereby result in synovial fibrosis, progression of cartilage degradation, and bone remolding. Therefore, individuals with the variant C allele are at higher risk of developing OA, especially in Asians. However, there are several limitations in current meta-analysis. First, there are only two studies focusing on rs1871054 polymorphism in Asians, the two studies including a relatively small samples may result in an unreliable result. Second, for the lacking of sufficient original data, we was unable to perform further subgroup analysis to investigate other risk factors of OA susceptibility, such as environment-gene/gene-gene interaction and different types of OA.

In conclusion, the meta-analysis results suggested that *ADAM12* rs1871054 polymorphism may increase the risk of OA susceptibility, especially in Asians. While the *ADAM12* rs3740199, rs1044122, and rs1278279 polymorphisms may not be associated with the OA risk. In the future, well-designed studies with larger sample size and more ethnic groups are needed to validate the results in the current meta-analysis.

Disclosure of conflict of interest

None.

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