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ORIGINAL RESEARCH

The association of *ADAM12* polymorphism with osteoarthritis susceptibility: a meta-analysis

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Background: The pathology of osteoarthritis (OA) is partly attributed to genetic factors; however, the role of *ADAM12* polymorphism is still controversial. It is necessary to perform a meta-analysis to investigate this possible correlation.

Methods: Case–control studies on the association between OA susceptibility and *ADAM12* polymorphism were comprehensively collected by searching PubMed, Embase, and Web of Science. Odds ratios (ORs) and 95% confidence intervals (CIs) were pooled to evaluate OA risk that was possibly conferred by *ADAM12* variant. The analyses were performed not only among general population but also in male and female groups.

Results: A total of 8 studies with 10 populations were finally included in this meta-analysis. In the general population, 4 comparisons were carried out (C allele vs G allele, CC vs GG, GC + CC vs GG, and CC vs GC + GG) and found that *ADAM12 rs3740199* polymorphism was not associated with increased OA vulnerability. On the other hand, the analyses stratified by gender made 5 comparisons (C allele vs G allele, CC vs GG, GC vs GG, GC + CC vs GG, and CC vs GC + GG). It was shown that *rs3740199* polymorphism (GC + CC vs GG) was a risk factor for OA among male patients (OR =1.45, 95% CI =1.04–2.01). Sensitivity analysis indicated that it was an unstable outcome. No correlation was identified in women. Neither heterogeneity nor publication bias was detected in the analyses mentioned above.

Conclusion: *ADAM12 rs3740199* polymorphism is likely to be associated with OA susceptibility among male patients, other than the general population. More studies are needed to confirm this observation. The mechanism by which *ADAM12* variant plays a role in OA pathogenesis is also warranted and important for interpreting this possible correlation.

Keywords: osteoarthritis, meta-analysis, single nucleotide polymorphism, ADAM

Introduction

Osteoarthritis (OA) is a degenerative joint disease that results from breakdown of joint cartilages and bones. This disease is a major cause of disability worldwide, with poor functional outcomes and limited lifespan even after effective treatment. As a result, the focus is shifting to risk factor identification and disease prevention.[1] A number of risk factors for OA exist, including physical activity, obesity, gender, aging, and genetic predisposition.[2] In recent years, genetic risk factors associated with OA susceptibility have been extensively studied. At present, 21 independent OA susceptibility loci have been established from candidate gene studies, linkage studies, and genome-wide association studies (GWASs).[3] Apart from that, more specific genes which conferred vulnerability of OA are still being identified. Evidence has been published for the association of OA predisposition with single-nucleotide polymorphisms (SNPs) of a member from disintegrin and metalloprotease (ADAM) family – *ADAM12*.[4–6]

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The ADAM family comprises >30 zinc-dependent proteases that contribute to proteolysis, adhesion, fusion, and cell signaling.[7] ADAM12 is one of the splice forms of ADAMs and the gene for human *ADAM12* is located on chromosome 10q26.3.[8] Two SNPs of the *ADAM12* gene, *rs3740199* and *rs1871054*, have been studied most frequently with OA susceptibility. It has been demonstrated that *rs3740199* is associated with OA susceptibility among the general population,[9] or certain groups of the studied participants.[6,10] Apart from disease vulnerability, *ADAM12* mutation has also been linked to OA severity.[5] However, studies that did not observe any positive association of *ADAM12* SNP with OA also exist among various races.[11,12] As a result, until now, no consensus has been reached regarding the proposal that *ADAM12* polymorphisms are related to disease predisposition, severity, or phenotype. In addition, the power of genetic association study is of importance. Individual study, especially with limited sample size, provides insufficient power. Therefore, it is necessary to collect the up-to-date evidence, perform a meta-analysis, and present with the latest and robust overview of this subject. To better understand the association of OA susceptibility with *ADAM12* SNPs, a meta-analysis was conducted by a comprehensive literature search and synthesis of data from eligible case–control studies.

Materials and methods

Identification of eligible studies and data collection

The latest literature search was conducted in January 2017 on PubMed, Web of Science, and Embase. The following keywords were used: "osteoarthritis," "OA," "ADAM12," and "polymorphism." Case–control studies about the association of *ADAM12* polymorphisms with OA susceptibility were collected. Relative references were further reviewed to identify potential extra studies. No restrictions of race and publication year were imposed. Published articles with full text, other than reviews or records from conference proceedings, were included. To exclude overlapping data observed from the same cohort, only the newest study or the study with the largest sample size was selected. Records were dropped to remove flawed studies when the genotypic distribution deviated from Hardy–Weinberg equilibrium (HWE).

Two reviewers extracted data independently, and disagreements were solved by discussion. The following data were collected: first author, publication year, race, characteristics of cases and controls, diagnosis criteria, SNP position, methods of genotyping, genotypic distributions, and odds ratios (ORs). Additional information regarding the characteristics of the participants was required if stratification analyses were needed.

Statistical analysis

Chi-square test was applied to assess whether the genotypic distribution was in concordance with HWE and whether the original article did not mention the outcome of the HWE test. *Q*-statistic was performed to evaluate the heterogeneity across studies.[13] The magnitude of heterogeneity was measured by I^2-value, indicating the proportion of the total variance across studies due to heterogeneity, other than chance. $I^2 \geq 50\%$, $50\% > I^2 \geq 25\%$, and $25\% > I^2$ were defined as high, medium, and low heterogeneity, respectively.[14] If no inconsistency was detected, ORs were aggregated by Mantel–Haenszel's method in fixed-effect model. Otherwise, Dersimonian–Laird method in random-effect model was applied.[15] Publication bias was detected by Egger's linear regression test.[13] Sensitivity analysis was performed by omitting one study in each turn and then checking statistical significance. All statistical analyses were conducted by Stata 9.0 (Stata Crop LP, College Station, TX, USA). All *P*-values were two-sided, with <0.05 being statistically significant.

Results

Characteristics of the eligible studies

The process of study inclusion is illustrated in Figure 1. Overall, 8 studies with 10 populations, including 8,553 cases and 6,349 controls, were eligible for this meta-analysis.[4–6,9–12,16] The majority of the cases were individuals who were diagnosed with knee, hip, and hand OA from various races, according to the criteria of American College of Rheumatology (ACR).[4–6,9,11,12] Four candidate gene positions (*rs3740199*, *rs1871054*, *rs1278279*, and *rs1044122*) were investigated; among which *rs3740199* was the most frequently studied locus; therefore, the original data regarding the association of *rs3740199* polymorphism with OA susceptibility were primarily extracted. The genotypic distributions from all the included studies did not deviate from HWE according to the descriptions from the corresponding articles (Table 1).

The information obtained from the studies revealed that the most common comparison was between carriers of *rs3740199* C allele and carriers of *rs3740199* G allele.[4–6,10–12,16] Besides, the available genetic models that were introduced in the trials were CC versus GG, GC + CC versus GG, and CC versus GC + GG.[4–6,9–12,16] Thus, the ORs with 95% confidence intervals (95% CIs) regarding these comparisons were extracted and pooled into the meta-analysis. Stratification analyses dependent on gender were performed among 6 populations[6,10–12]; thus, these data were also obtained (Table 2).

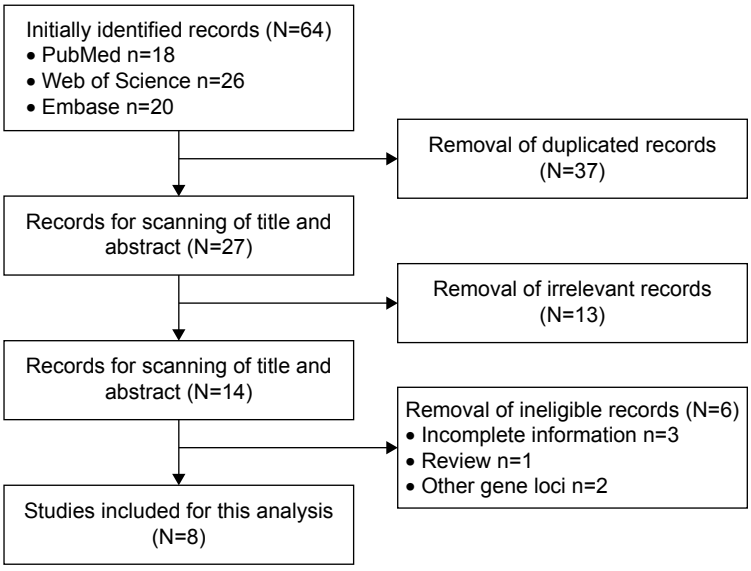


Figure 1 Flow diagram of the inclusion of the eligible studies.

ADAM12 rs3740199 polymorphism was not associated with OA susceptibility in the general population

The comparison of risk for OA susceptibility between *rs3740199* C allele carriers and G allele carriers was performed among 9 of 10 populations. As shown in Figure 2, no significant association was observed. Sensitivity analyses showed that all these insignificant results would not be influenced when any population was omitted. Neither heterogeneity across studies nor publication bias was detected.

Table 1 Main characteristics of the included studies

Study	Case population	Control population	Diagnosis criteria	SNPs	Genotyping method	Accordance with HWE
Poonpet et al[6]	Thai patients aged from 51 to 91 years with primary knee OA (N=200)	Comparable individuals with no symptoms or signs of OA, arthritis, or joint disease (N=200)	Criteria of the ACR	*rs3740199*	HRM analysis	Yes
Shin et al[12]	Individuals with K/L score ≥2 from Korean cohort aged 50 years or older (N=725)	Individuals without knee disease from Korean cohort aged 50 years or older (N=1,737)	Criteria of the ACR	*rs3740199*	TaqMan assay	Yes
Kerna et al[10]	Individuals with knee OA from South-Estonian town of Elva (N=118)	Individuals without radiological features of knee OA from South-Estonian town of Elva (N=71)	Grading system of Nagaosa et al[27]	*rs3740199*; *rs1871054*	PCR-RFLP	Yes
Rodriguez-Lopez et al[11]	Individuals with hand, knee, or hip OA from three recruitment sites of European Caucasians (N=4,870)	Individuals without any clinical manifestation of OA from three recruitment sites of European Caucasians (N=2,370)	Criteria of the ACR	*rs3740199*	PCR	Yes
Valdes et al[9]	Individuals from Chingford Study cohort[28] (N=280)	Individuals without knee disease from Chingford Study cohort (N=469)	Criteria of the ACR	*rs3740199*	PCR	Yes
Wang et al[5]	Chinese Han individuals with knee OA (N=164)	Age-matched unrelated healthy Chinese Han individuals (N=200)	Criteria of the ACR	*rs3740199*; *rs1871054*; *rs1278279*; *rs1044122*	iMLDR	Yes
Limer et al[16]	Knee and hip OA patients from GOAL study (N=2,044)	Asymptomatic individuals from GOAL study (N=1,123)	Criteria of Zhang et al[29]	*rs3740199*	TaqMan assay	Yes
Lou et al[4]	Chinese Han individuals with primary knee OA (N=152)	Age-matched healthy Chinese Han individuals with no signs or symptoms of OA (N=179)	Criteria of the ACR	*rs3740199*; *rs1871054*; *rs1278279*; *rs1044122*	TaqMan assay	Yes

Abbreviations: SNP, single-nucleotide polymorphism; ACR, American College of Rheumatology; HRM, high-resolution melting; HWE, Hardy–Weinberg equilibrium; K/L score, Kellgren/Lawrence score; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; iMLDR, improved multiplex ligase detection reaction; GOAL, genetics of OA and lifestyle; OA, osteoarthritis.

Table 2 Main results of the studies about the association of OA susceptibility with rs3740199

Study	Allelic frequencies*		Genotypic distribution*			Odds ratios with 95% confidence intervals				Stratification analysis
	C allele	G allele	CC	GC	GG	C allele versus G allele	CC versus GG	GC + CC versus GG	CC versus GG + GC	
Poonpet et al[6]	214/192	186/208	56/46	102/100	42/52	1.25 (0.94–1.66)	1.57 (0.86–2.85)	1.34 (0.84–2.13)	1.29 (0.82–2.02)	By gender
Shin et al[12]	658/1,563	792/1,911	147/350	364/863	214/524	0.99 (0.87–1.14)	1.01 (0.76–1.33)	1.03 (0.85–1.25)	1.01 (0.81–1.25)	By gender
Kerna et al[10] (TFOA part)	44/88	22/35	28/65	32/46	6/12	1.28 (0.52–4.35)	0.85 (0.29–2.49)	0.54 (0.17–1.75)	0.66 (0.36–1.20)	By gender
Kerna et al[10] (PFOA part)	70/62	27/30	53/41	34/43	10/8	1.16 (0.75–1.82)	1.01 (0.37–2.80)	0.83 (0.31–2.20)	1.50 (0.84–2.66)	By gender
Rodriguez-Lopez et al[11] (TKR part)	NG	NG	NG	NG	NG	0.92 (0.81–1.05)	NG	NG	NG	By gender
Rodriguez-Lopez et al[11] (THR part)	NG	NG	NG	NG	NG	1.08 (0.96–1.21)	NG	NG	NG	By gender
Valdes et al[9]	NG	NG	NG	NG	NG	NG	NG	1.84 (1.22–2.79)	NG	None
Wang et al[5]	47.6%/49.0%	52.4%/51.0%	36/47	84/102	44/51	0.93 (0.76–1.14)	0.87 (0.48–1.61)	0.92 (0.58–1.49)	0.90 (0.54–1.52)	None
Limer et al[16]	NG	NG	NG	NG	NG	1.01 (0.90–1.13)	NG	NG	NG	By hip and knee OA
Lou et al[4]	46.7%/49.4%	53.3%/50.6%	32/42	78/93	42/44	0.89 (0.65–1.22)	0.79 (0.41–1.50)	0.88 (0.53–1.46)	0.87 (0.52–1.47)	None

Note: *Data are presented as case number/control number or case percentage/control percentage.
Abbreviations: TKR, total knee replacement; THR, total hip replacement; TFOA, tibiofemoral knee OA; PFOA, patellofemoral knee OA; NG, not given; OA, osteoarthritis.

Similarly, the investigations on CC versus GG, GC + CC versus GG, and CC versus GG + GC genetic models did not yield any remarkable relationship, either. These results were also proven stable by sensitivity analyses. Heterogeneity and publication bias were not found, either (Table 3).

ADAM12 rs3740199 polymorphism was likely to be associated with OA susceptibility among males

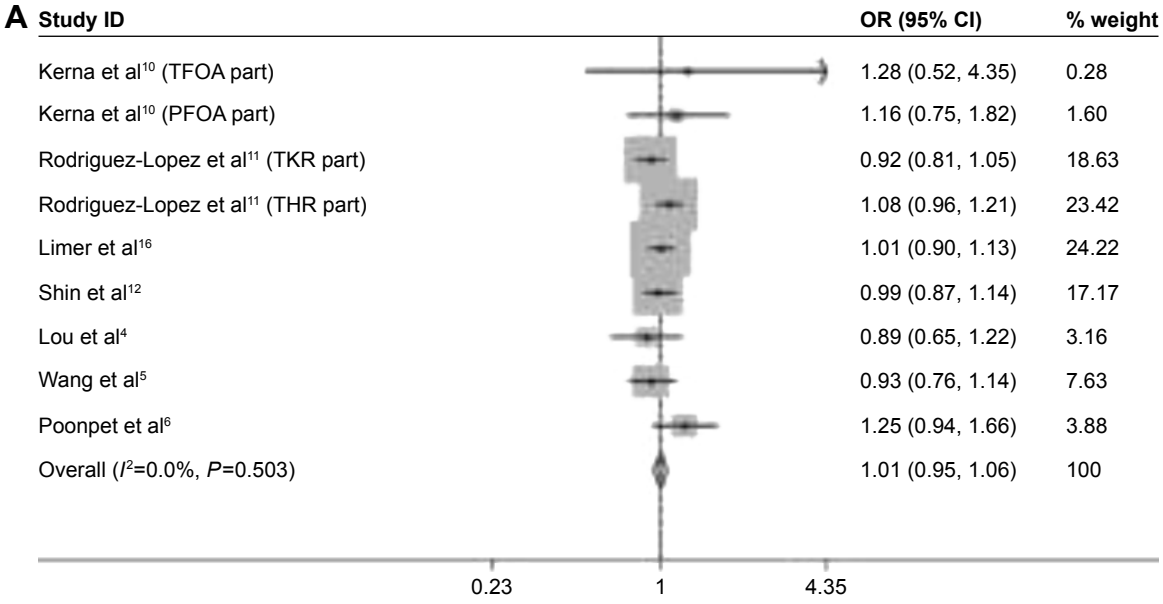
In some studies, the additional risk of OA conferred by *rs3740199* polymorphism was exclusively observed in a specific group of people[10,11,17]; thus, further investigation into this hypothesis was done by analyzing data that were stratified by gender. As illustrated in Figure 3, the only significant association was identified among males, indicating that the risk of OA was 45% higher (95% CI: 1.04–2.01, P=0.028) in carriers of CG and CC, compared with carriers of GG. In this comparison, neither inconsistency nor publication bias was detected. However, sensitivity analysis demonstrated that the exclusion of study from Poonpet et al[6] would reverse this relationship into insignificant.

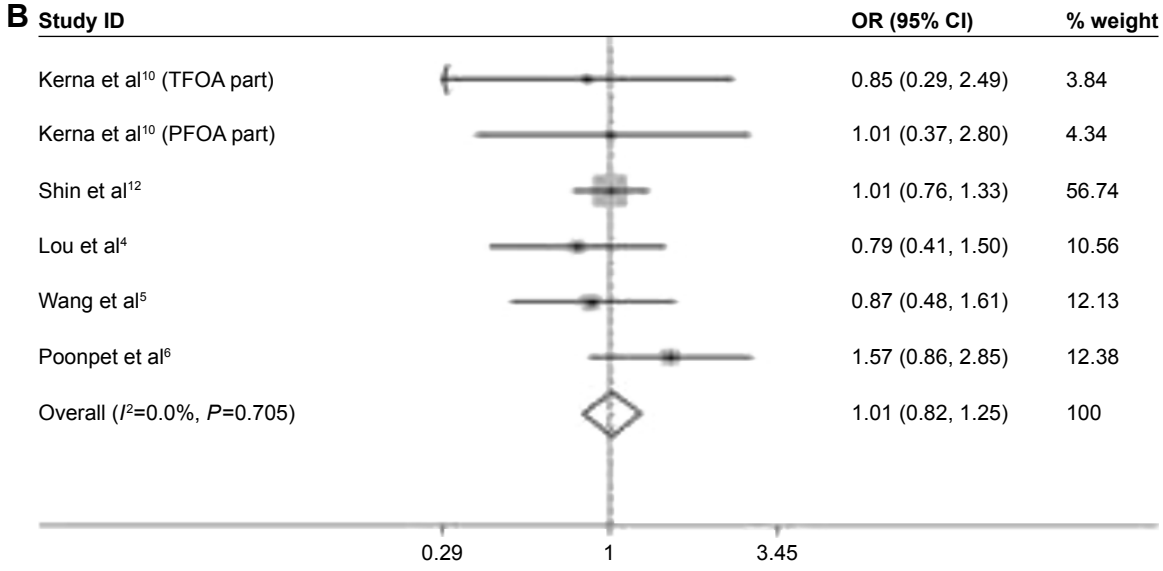
No remarkable and stable correlation was found for the remaining comparisons among men. Specifically, in the study of C allele versus G allele, the exclusion of one population[11] would result in a statistically significant association. The same scenario also happened when CC versus GG and CC versus GG + GC were studied, obtaining positive correlations between OA risk and *rs3740199* polymorphism.

In women patients, this meta-analysis demonstrated that *rs3740199* polymorphism was unlikely to confer extra risk for OA to this group of people, regardless of evaluating various genetic models. Sensitivity analyses confirm the stability of these outcomes. Neither heterogeneity nor publication bias was found (Table 4).

Discussion

OA is a complex disease, induced by a combination of three main risk factors: genetics, environmental factors, and aging.[17] Numerous candidate genes have been screened to identify susceptible loci of OA, and *ADAM12* is one of them. This is, to the authors' knowledge, the first meta-analysis to investigate the association between *ADAM12 (rs3740199)* polymorphism and OA predisposition. In this study, case–control studies on *ADAM12* polymorphism and OA susceptibility were comprehensively collected and 8 trials with 10 populations were obtained. The most frequently researched gene locus on *ADAM12* (*rs3740199*) was selected and analyzed. It was noteworthy that the unfavorable effect of *rs3740199* polymorphism (GC + CC vs GG) was





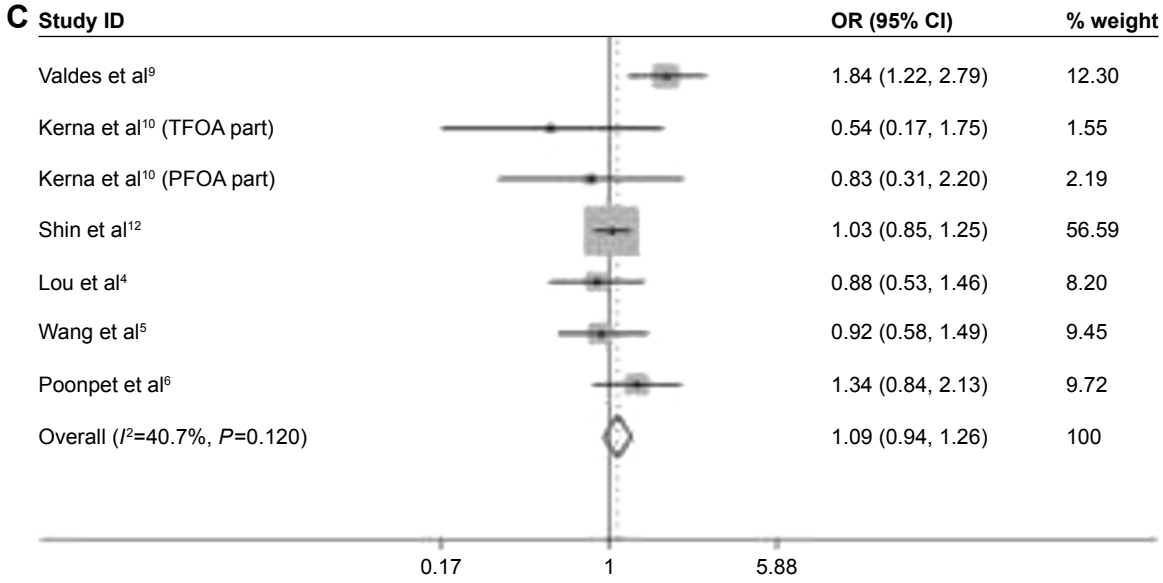


Figure 2 (*Continued*)

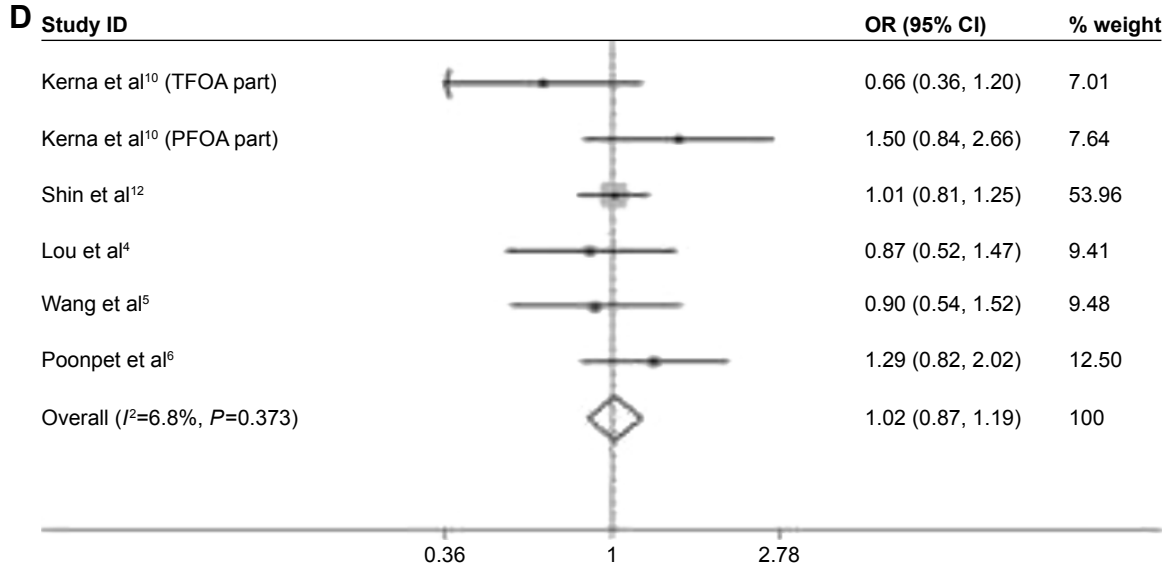


Figure 2 Forest plots of the analyses on the association of OA susceptibility with *rs3740199* polymorphism. (**A**) C allele versus G allele; (**B**) CC versus GG; (**C**) CC + GC versus GG; (**D**) CC versus GC + GG.
Abbreviations: OA, osteoarthritis; OR, odds ratio; CI, confidence interval; TFOA, tibiofemoral knee OA; PFOA, patellofemoral knee OA.

exclusively observed among male. Unfortunately, this result was unstable; therefore, the evidence was not strong. On the other hand, although comparisons concerning other genetic models did not yield significant correlations, these results were also unstable, heavily affected by the data from a single population. Therefore, until now, the available data indicated that *ADAM12 rs3740199* polymorphism was likely to be associated with OA vulnerability among male patients, other than the general population, but more studies are needed to draw a stable and safe conclusion.

In addition to the SNPs of *ADAM12*, its haplotypes have been related to OA predisposition, with much more remarkable effect. In the genetic study conducted among Chinese Han individuals, haplotype analysis revealed that 5 haplotypes (TATC, TATG, TACG, CATG, and CGTC) were associated with the increased risk of OA.[4] In line with that, haplotype CAAT has been found to elevate the risks for OA by as high as 6.10-fold among Caucasian women and 1.54-fold among Caucasian men.[18] The sexual difference is also found in the haplotype study. It has been reported that CCAA haplotype increased the risk for tibiofemoral joint OA among males, and GCGG haplotype increased the risk for joint space narrowing among females.[19] In contrast, some haplotypes may be protective against OA. *rs3740199/rs1871054* GC decreased the risk for patellofemoral joint OA among male patients (OR =0.10) and the risk for osteophytes among overall people (OR =0.24).[10] Besides, haplotype CGAT and CGGT were also related with smaller risk for knee OA predisposition.[18]

Apart from the genetic association studies about *ADAM12* SNPs and OA, some clinical trials investigating the role of ADAM12 protein and mRNA also provide valuable supporting evidence. In overall, it has been observed that overexpression of ADAM12 is related with OA. The level of ADAM12-L mRNA expression was remarkably higher in OA cartilage than in normal samples. In situ hybridization demonstrated that clustered chondrocytes in OA cartilage were the main source of ADAM12-L mRNA. The expression of this protein was visualized on clustered chondrocyte membranes by immunohistochemistry.[20] The expressions of

Table 3 Main results of the meta-analysis

Comparison	Number of studies	Estimated effects			Heterogeneity		Publication bias		Sensitivity analysis
		ORs (95% CI)	*Z*-value	*P*-value	I^2 (%)	*P*-value	*t*-value	*P*-value	
C allele versus G allele	9	1.01 (0.95–1.06)	0.20	0.843	0.0	0.503	0.55	0.602	Stable
CC versus GG	6	1.01 (0.82–1.25)	0.13	0.897	0.0	0.705	–0.19	0.862	Stable
GC + CC versus GG	7	1.09 (0.95–1.26)	1.19	0.233	40.7	0.120	–0.29	0.785	Stable
CC versus GG + GC	6	1.02 (0.87–1.19)	0.20	0.844	6.8	0.373	–0.13	0.906	Stable

Abbreviations: OR, odds ratio; CI, confidence interval.

ADAM12 mRNA and protein in synovium were significantly linked to the severity of histological synovitis.[21] ADAM12-S protein in serum could be increased in some OA patients, correlating with the grade of this disease and osteophyte occurrence.[22] However, the amount of ADAM12 protein may not be linked with gene polymorphism, and since it has been reported that the functional protein level is not determined by genetic variants (*rs3740199*, *rs1871054*, *rs1278279*, and *rs1044122*),[23] the involvement of ADAM12 gene and protein in OA pathogenesis needs further research.

Despite the fact that so many observational studies have been conducted, little is known about the molecular biological role of ADAM12 on OA pathogenesis. The possible mechanism by which ADAM12 participates in OA is illustrated in Figure 4. Human ADAM12 consists of two forms produced by alternative splicing gene, which are secreted, short form (ADAM12-S) and larger, membrane-bounding form (ADAM12-L).[8] Similar to the archetypical structure of ADAM proteins, the amino acid sequence of ADAM12 includes proprotease, metalloprotease, disintegrin, cysteine-rich domains, and in the case of L form, a transmembrane and cytoplasmic domains.[8] The metalloprotease domain converts from latent state into functional state after cleavage of the prodomain, resulting in an ADAM12 protein with catalytic activity.[24] Activated ADAM12 has the capacity to degrade extracellular matrix (ECM) components, including gelatin, fibronectin, and type IV collagen.[25] The molecular interaction between ADAM12 and β1 integrins may change cell–matrix contacts in the growth plate and modulate proliferation and differentiation of chondrocyte.[26] As it is known, articular cartilage is a narrow layer of specialized ECM that is elaborated and maintained by articular chondrocytes. In normal cartilage, chondrocytes maintain a balance between the production and the degeneration of ECM, resulting in stability of the tissue. This equilibrium is disturbed in degenerative joint diseases such as OA.[20] Therefore, it is plausible that

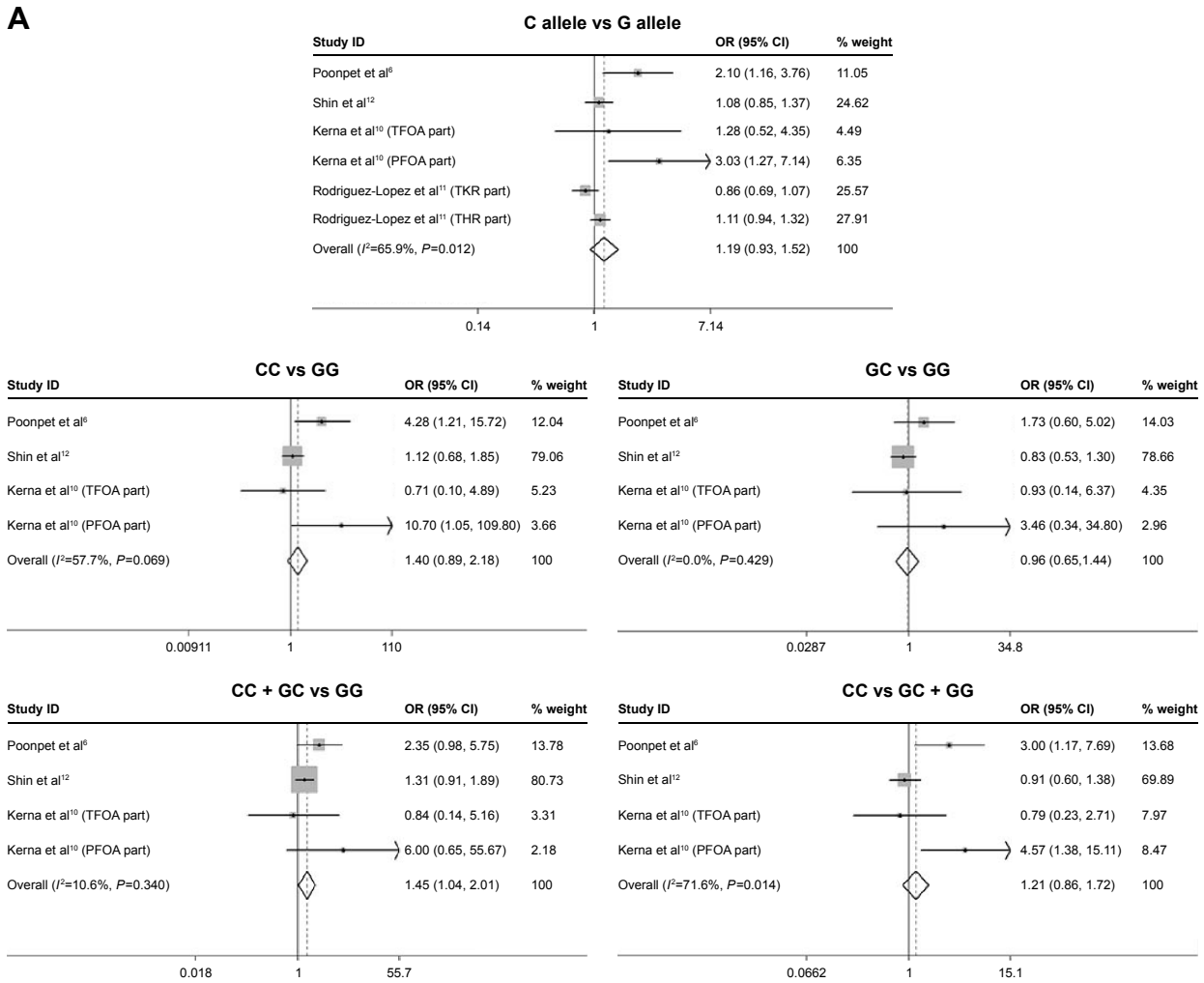


Figure 3 (*Continued*)

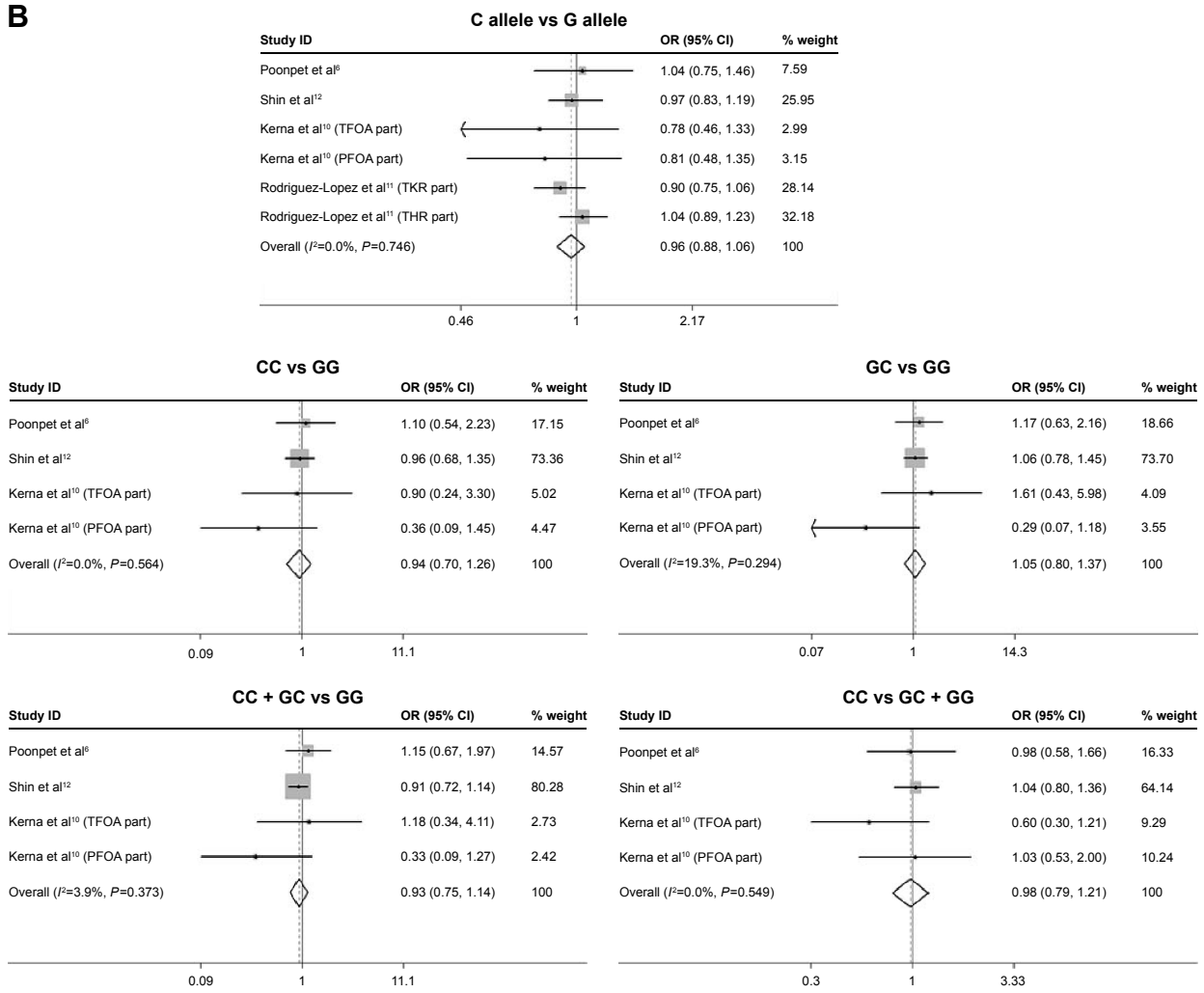


Figure 3 Forest plots of the analyses on the gender-dependent associations of OA susceptibility with *rs3740199* polymorphism. (**A**) Different comparisons among males; (**B**) different comparisons among females.
Note: Weights are from random-effects analysis.
Abbreviations: TFOA, tibiofemoral knee OA; PFOA, patellofemoral knee OA; OA, osteoarthritis; CI, confidence interval.

Table 4 Results of the meta-analysis dependent on gender

Comparison	Number of studies	Estimated effects			Heterogeneity		Publication bias		Sensitivity analysis
		ORs (95% CI)	*Z*-value	*P*-value	I^2 (%)	*P*-value	*t*-value	*P*-value	
Male									
C allele versus G allele	6	1.19 (0.93–1.52)	1.40	0.162	65.9	0.012	1.81	0.145	Unstable
CC versus GG	4	1.40 (0.90–2.18)	1.47	0.142	57.7	0.069	1.15	0.368	Unstable
GC versus GG	4	0.97 (0.65–1.44)	0.18	0.859	0.0	0.429	1.72	0.228	Stable
GC + CC versus GG	4	**1.45 (1.04–2.01)**	**2.20**	**0.028**	10.6	0.340	0.93	0.451	Unstable
CC versus GG + GC	4	1.21 (0.86–1.72)	1.09	0.274	71.6	0.014	1.30	0.322	Unstable
Female									
C allele versus G allele	6	0.96 (0.88–1.06)	0.77	0.442	0.0	0.746	−1.14	0.319	Stable
CC versus GG	4	0.94 (0.70–1.29)	0.43	0.667	0.0	0.564	−0.95	0.441	Stable
GC versus GG	4	1.05 (0.80–1.37)	0.35	0.725	19.3	0.294	−0.53	0.649	Stable
GC + CC versus GG	4	0.93 (0.75–1.14)	0.74	0.460	3.9	0.373	−0.34	0.766	Stable
CC versus GG + GC	4	0.98 (0.79–1.21)	0.21	0.835	0.0	0.549	−1.18	0.358	Stable

Notes: Bold values indicate the results were statistically significant.
Abbreviations: OR, odds ratio; CI, confidence interval.

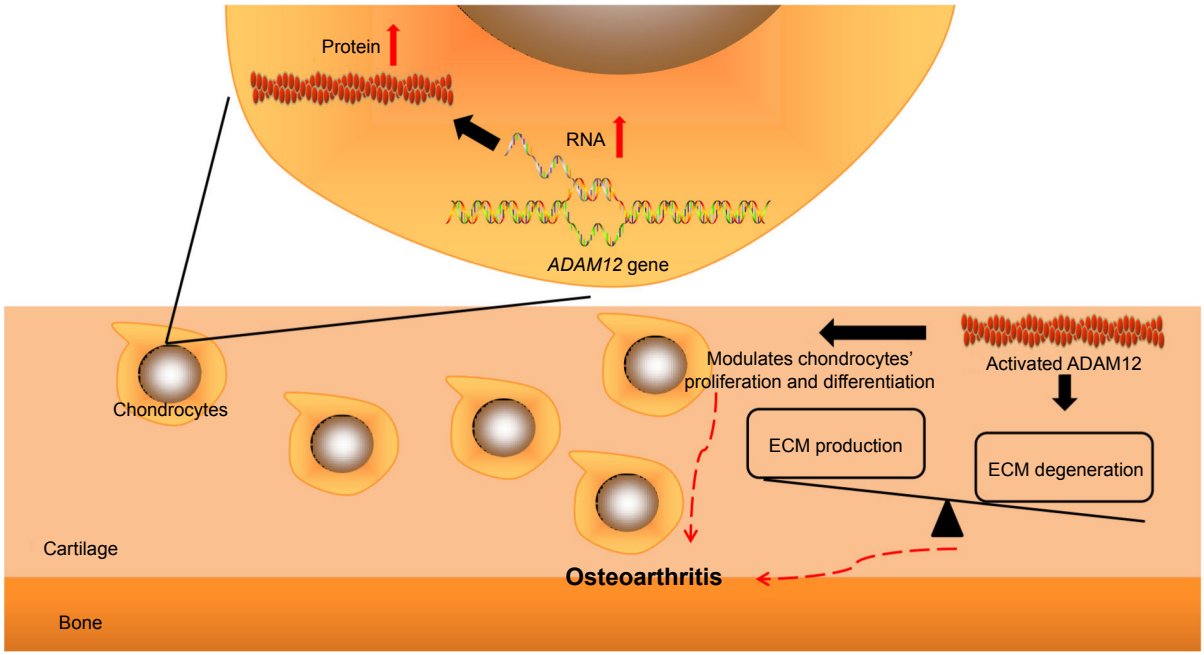


Figure 4 Possible mechanism by which ADAM12 participates in OA pathogenesis.
Abbreviations: ADAM, disintegrin and metalloprotease; OA, osteoarthritis; ECM, extracellular matrix.

ADAM12 may contribute to the pathogenesis of OA by the influence on ECM and chondrocytes. Existing evidence has demonstrated that OA chondrocytes produce more ADAM12-L mRNA and protein after administration with TGF-β in a dose-dependent fashion.[20] The overexpression of ADAM12-L could result in chondrocyte proliferation via insulin-like growth factor signaling.[20]

There are some limitations in this study, so the results should be treated with caution. The adverse impact of *rs3740199* polymorphism was demonstrated by insufficient studies. Only 3 trials with 4 groups of individuals, involving 1,043 cases and 2,008 controls, were pooled together to address this issue. Furthermore, this positive correlation was proven to be unstable since it was remarkably influenced by the exclusion of study from Poonpet et al.[6] In Poonpet's study,[6] limited male cases and controls were recruited. It was reported that CC male carriers had 328% higher risk than GG male carriers. Male patients with C allele had 110% higher risk than male patients with G allele. The extremely high OR values among males might be partly attributed to the insufficient sample size or selection bias. In addition, some of the extracted ORs with their 95% CIs originated from multivariate analyses and were adjusted for potential confounders.[4,5,12,16] On the other hand, some ORs were given from the univariate model.[6,10,18] Therefore, the aggregation of these heterogeneous ORs might distort the truth. Finally, the controversial association of OA with *ADAM12* haplotype frequency was not investigated. It was mainly attributed to lack of evidence, different haplotypes, and different outcomes of interest.

In conclusion, *ADAM12 rs3740199* polymorphism was likely to be associated with OA vulnerability among male patients, other than the general population, based on limited evidence. More studies are needed to further investigate this proposal. In addition, the biological mechanism by which *ADAM12* gene and protein link with OA occurrence and progression needs to be elucidated.

Disclosure

The authors report no conflicts of interest in this work.

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