Original Article

Association of two polymorphisms rs3740199 and rs1871054 at ADAM12 with susceptibility of knee osteoarthritis: a systematic review and meta-analysis

Wenxiang Chen[1], Yiying Wang[2], Xuesheng Jiang[1]

[1]Department of Orthopedics, Huzhou Central Hospital, Huzhou 313000, China; [2]Department of Biochemistry and Molecular Biology, School of Basic Medical Science, Nanjing Medical University, Nanjing 210029, China

Contributions: (I) Conception and design: W Chen; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: W Chen, Y Wang; (V) Data analysis and interpretation: W Chen, X Jiang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xuesheng Jiang. Department of Orthopedics, Huzhou Central Hospital, Huzhou 313000, China. Email: jiangxuesheng2000@163.com.

Background: Osteoarthritis (OA) is the most common joint disease that mainly influences the knees, hips, hands and spine. However, the pathogenesis of knee OA remains poorly understood. A number of studies have explored the association between ADAM12 polymorphisms and the risk of knee OA in different populations. We aimed to systematically review those observational studies, taking into account the variable quality of studies.

Methods: We carried out a systematic review and meta-analysis of these studies based on ADAM12 rs3740199 and rs1871054 genotypes. Four comparisons involving 2 Chinese, 1 Korean and 1 Thai population of 1,241 knee OA patients and 2,316 controls were included in our study.

Results: For the SNP rs1871054, the C allele was associated with an increased risk of knee OA in terms of the frequency of allele comparison. For a dominant model of the C allele, the CT + CC genotypes were associated with the risk for knee OA. The CC homozygote genotype was also associated with increased susceptibility to knee OA. However, the *ADAM12* rs3740199 polymorphism was suggested not to be related to knee OA susceptibility in all populations.

Conclusions: The present results suggested that there existed a positive relationship between the ADAM12 rs1871054 polymorphisms with the susceptibility of knee OA, while the ADAM12 rs3740199 was not observed to be associated with the risk of knee OA.

Keywords: Polymorphisms; ADAM12; susceptibility; knee osteoarthritis (knee OA); meta-analysis

Received: 04 December 2017; Accepted: 05 February 2018; Published: 03 April 2018.

doi: 10.21037/aoj.2018.02.03

View this article at: http://dx.doi.org/10.21037/aoj.2018.02.03

Introduction

Osteoarthritis (OA) is the commonest disease of the joints that mainly influences the knees, hips, hands, and spine (1-3). However, the multifactorial etiology of knee OA remains incompletely clarified, which includes environmental and genetic risk factors. Environmental factors may involve adiposity, history of knee injury, vocational factor, sex hormones, meniscectomy, gender, and age (1-7). Several studies have indicated genes of *ASPN* and *COL2A1* were associated with onset of knee OA (8,9). The progressive degeneration of articular cartilage is a prominent feature of Knee OA. Moreover, the subchondral sclerosis and bone remodeling causing pain and stiffness of affected joint (10).

A disintegrin and metalloprotease (ADAM), which belongs to the superfamily of Zn-dependent metzincin, has been demonstrated to have association with complex diseases like rheumatoid arthritis, heart disease, tumor, and Alzheimer's disease (11,12). ADAM12 is a member of

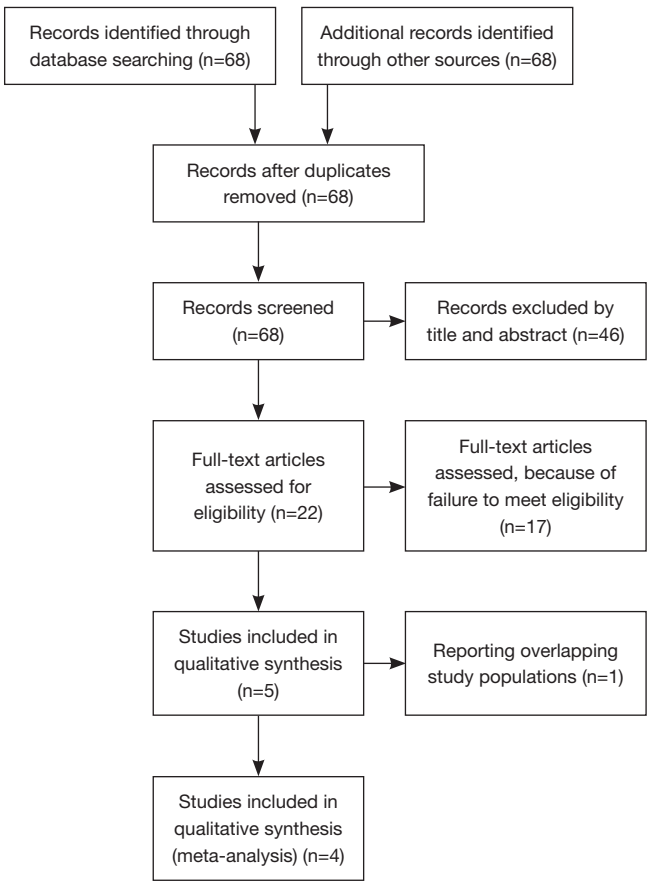

Figure 1 Flow diagram of the study selection process.

transmembrane proteins ADAMs family, which take part in several important processes through multiple functional domains, involving metalloproteinase, disintegrin and cysteine-rich domains (13,14). Twenty-three human *ADAMs* have been identified and *ADAM12* is one of the significant candidate genes for knee OA. The human *ADAM12* gene is located on chromosome 10q26 which encodes two different protein variants: a transmembrane form named ADAM12-L, and the other is a secreted type, ADAM12-S. ADAM12 was be considered as an active protease, which was overexpression in rapidly-growing and remodeling tissues like the malignant tumours and placenta. Some studies indicate that human ADAM12 plays a critical role in cartilage cell proliferation and maturation, as well as osteoclast differentiation, resulting in formation of bones (15,16). Furthermore, ADAM12 is up-regulated in knee OA chondrocyte and multinucleated giant cells which are surround incompact hip implants. One of the splice variants of ADAM12 was detected to be up-regulated in human knee OA cartilage (17) and Kerna *et al.* (18) described the elevation of ADAM12 protein in serum of knee OA patients.

Promising but conflicting data was demonstrated for the effect of ADAM12 on the pathogenesis of knee OA (19,20). Numerous studies have explored the relation between ADAM12 polymorphisms and the risk of knee OA in different populations (21-24). Otherwise, no systematic review and meta-analysis have evaluated the relationship of two polymorphisms rs3740199 and rs1871054 at ADAM12 with susceptibility of knee OA. We aimed to review literature systematically on the association between knee OA and *ADAM12* polymorphisms in primary knee OA patients, taking into consideration the researches variable quality.

Methods

Search strategy

We conducted a systematic review of observational studies evaluating the relationship between ADAM12 polymorphisms and knee OA susceptibility. We systematically searched Medline, PubMed, and Embase electronic databases for the relevant studies which have been published with the Combinations of keywords: ("ADAM12" or "rs3740199" or "rs1871054"), ("polymorphism" or "polymorphisms") and ("osteoarthritis" or "OA"). References of the retrieved manuscripts were also manually examined for further relevant publications and unpublished studies. Conference abstracts were not taken into consideration. Moreover, we searched unpublished studies by contacting clinical experts as well as the Arthritis Foundation National Office. *Figure 1* shows the flow diagram for the literature retrieval strategy.

Inclusion and exclusion criteria

To be eligible, the study had to fulfill the following criteria: (I) study design was a cohort or a case–control study; (II) knee OA was diagnosed on the basis of clinical criteria defined by the American College of Rheumatology; (III) a study investigated the association of *ADAM12* (rs3740199 or rs1871054) polymorphism (IV) the study showed sufficient alleles or genotypes frequency or adequate da ta for extraction. The following criteria should be excluded: (I) the study which was not performed on knee OA; (II) studies of *in vitro* cell culture models; (III) the data

which was unavailable after contacting with the authors. If overlapping data were detected between studies, we will select the most complete one.

Quality assessment of included studies

Using the Newcastle-Ottawa Scale (NOS), the quality of the studies was evaluated independently by two people. When the two people have diversity of opinion as to the quality scores, the third person takes part in resolving discrepancies through discussion. The quality of all the studies included was also evaluated by the Hardy-Weinberg equilibrium (HWE). Studies which are in keeping with HWE were regarded as high-quality, while those not in keeping with HWE were regarded as low-quality studies (25).

Data extraction

We extracted the following data from each full-text study, including: first author name, publication year, country where the study was conducted, study design, number of the two groups, sex, age, genotyping, polymorphism, and numbers of the two groups for each of the rs3740199 and rs1871054 genotypes. Any disagreements in the results of data extraction were resolved through discussion with the third person until consensus was reached.

Statistical analysis

All statistical progress was conducted using Review Manager 5.3 software. We calculated ORs and 95% CI to evaluate the relation between *ADAM12* polymorphisms and knee OA susceptibility. The Chi-square test was performed to confirm if the identified study was in keeping with HWE for the control genotype distribution. The heterogeneity of the studies was assessed using the Q statistic and was quantified by the I^2 statistic. I^2>30% or when P<0.1 for Q statistics indicated significant heterogeneity between the studies (25). Sensitivity analyses were conducted for the effect size omitting the trial for which data were imputed, and were used to assess the stability of the results.

Results

Search results

Sixty-eight correlative studies were found in the database search, of which 4 finally met the inclusion criteria. The included studies were explored the association between *ADAM12* polymorphisms and knee OA risk. Four studies involving a total of 3,557 participants (1,241 knee OA patients and 2,316 controls), which included two Chinese, one Thai and one Korean populations, assessed the relation between the *ADAM12* polymorphism and knee OA risk. General characteristics of the study are listed in *Table 1*.

Quality assessment

All 4 studies had a good NOS quality score (*Table 1*). The distribution of genotypes in the control group was in keeping with HWE (P>0.05) in the studies, therefore all were classified as high-quality.

Allele and genotype counts and quality assessment

Allelic counts of the *ADAM12* rs3740199 polymorphism were assessed for G and C alleles. The frequency of the G allele was higher in knee OA cases than in controls. Genotype counts of the *ADAM12* rs3740199 polymorphism were assessed for GG, GC, and CC genotypes, and in three studies it was found with no statistical difference when compared with the genotype frequencies between the two groups no matter for which model of comparison. In another study, the rs3740199 at *ADAM12* was related to knee OA susceptibility in Thai male patients. Allele and genotype counts for the *ADAM12* rs3740199 polymorphism in the two groups are shown in *Table 2*. Allelic counts of the *ADAM12* rs1871054 polymorphism were assessed for C and T alleles. In one study the C allele frequency was higher in knee OA cases than in the controls. Genotype counts of the *ADAM12* rs1871054 polymorphisms were assessed for TT, CT, and CC genotypes, and the CC genotype frequency was generally higher in knee OA cases than in controls. The CC+TC genotype frequency was generally higher in knee OA cases than controls. In the remained study, the rs1871054 polymorphism was not related to knee OA susceptibility. Allele and genotype counts for the *ADAM12* rs1871054 polymorphism in cases and controls are shown in *Table 3*. All four studies had a good NOS quality score (*Table 1*).

Meta-analysis findings

The *ADAM12* rs3740199 polymorphism was suggested not to be related to knee OA susceptibility in all populations (G *vs.* C: OR 1.02, 95% CI: 0.89–1.18, P=0.75; CC *vs.* GC

Table 1 Characteristics of individual studies included in meta-analysis

Study (Ref.)	Year	Country	Study design	Genotyping	Numbers		Gender		Age		Polylmorphism(s)	quality score
					OA	Control	OA	Control	OA	Control		
Lin Wang *et al.* (21)	2015	China	Case-control	PCR	164	200	58/106	62/138	67.4±4.2	65.9±5.3	rs3740199, rs1871054	6 (2/1/3)
Thitiya Poonpet *et al.* (22)	2016	Thailand	Case-control	PCR	200	200	53/147	51/149	69.0±8.2	57.3±5.8	rs3740199	8 (3/2/3)
Suliang Lou *et al.* (26)	2014	China	Case-control	PCR	152	179	58/94	77/102	63.1±5.2	62.2±4.2	rs3740199, rs1871054	7 (2/2/3)
Min-Ho Shin *et al.* (23)	2012	Korea	Case-control	PCR	725	1737	171/554	882/855	62.7±7.9	67.4±7.9	rs3740199	8 (3/2/3)

PCR, polymerase chain reaction; OA, osteoarthritis.

Table 2 Genotype and allele counts for the *ADAM12* rs3740199 polymorphism in the included studies

Study	Country	OA site	P (G) (%)		p (C) (%)		PP (GG)		Pp (GC)		pp (CC)	
			OA	Control	OA	Control	OA	Control	OA	Control	OA	Control
Lin Wang *et al.*	China	Knee	52.4	51	47.6	49	44	51	84	102	36	47
Thitiya Poonpet *et al.*	Thailand	Knee	46	52	54	48	42	54	102	100	56	46
Suliang Lou *et al.*	China	Knee	53.3	50.6	46.7	49.4	42	44	78	93	32	42
Min-Ho Shin *et al.*	Korea	Knee	54.6	55	45.4	45	214	524	364	863	147	350

OA, osteoarthritis.

Table 3 Genotype and allele counts for the *ADAM12* rs1871054 polymorphism in the included studies

Study	Country	OA site	P (G) (%)		p (C) (%)		PP (GG)		Pp (GC)		pp (CC)	
			OA	Control	OA	Control	OA	Control	OA	Control	OA	Control
Lin Wang *et al.*	China	Knee	35.7	50.8	64.3	49.2	29	52	59	99	76	49
Suliang Lou *et al.*	China	Knee	35.9	60	64.1	40	26	47	57	88	69	44

OA, osteoarthritis.

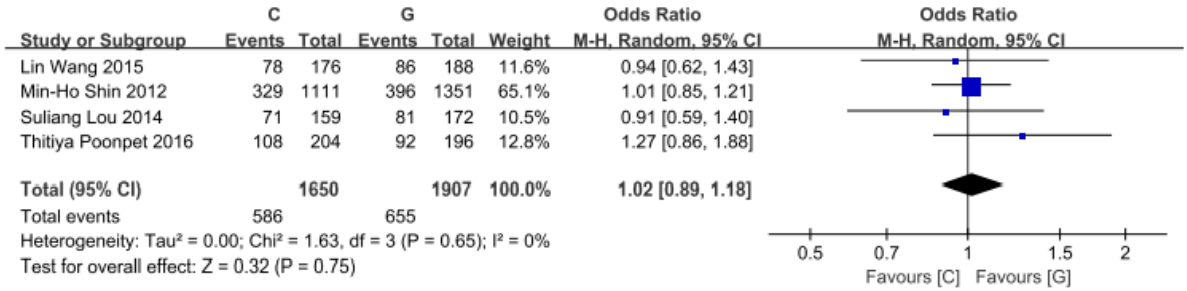

Figure 2 Forest plots of meta-analysis of the association between the *ADAM12* rs3740199 polymorphism (C *vs.* G).

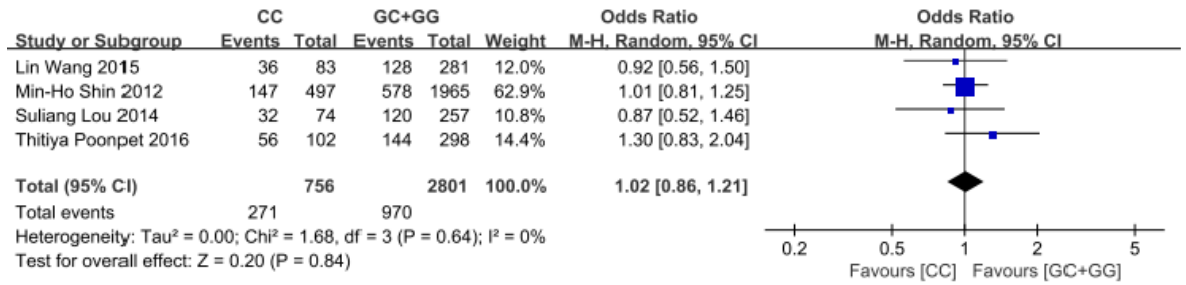

Figure 3 Forest plots of meta-analysis of the association between the *ADAM12* rs3740199 polymorphism (CC *vs.* GC + GG).

+ GG: OR 1.02, 95% CI: 0.86–1.21, P=0.84; GG *vs.* GC + CC: OR 0.97, 95% CI: 0.83–1.13, P=0.66) (*Figures 2,3,4*). However, for the SNP rs1871054, the C allele was related to an increased risk of knee OA of the frequency of allele comparison (C *vs.* T: OR 2.04, 95% CI: 1.20–2.77, P<0.001). For a dominant model of the C allele, the CT + CC genotypes were related to the risk for knee OA (CT + CC *vs.* TT: OR 1.68, 95% CI: 1.16–2.43, P=0.006). The CC homozygote genotype was also related to increased risk to knee OA (CC *vs.* CT + TT: OR 2.61, 95% CI 1.89–3.60, P<0.001) (*Figures 5,6,7*) (*Table 4*).

Sensitivity analysis

Although meta-analysis showed heterogeneity of all the studies was not significant (I^2=0). The study of Min-Ho Sin involved the most participants. After excluding that study, the corresponding OR and CI did not alter under all models in essence, which suggested that the results of our meta-analysis are stable.

Discussion

This is the first meta-analysis that summarizes available data on the association between knee OA and *ADAM12* polymorphisms. Using strict criteria for inclusion, totals of four studies involving 3,557 participants (1,241 knee OA patients and 2,316 controls) were included that evaluated the *ADAM12* rs3740199 and rs1871054 polymorphisms in associated with knee OA. On the basis of these researches, we conclude that there is moderate evidence for a positive relationship between the *ADAM12* rs1871054

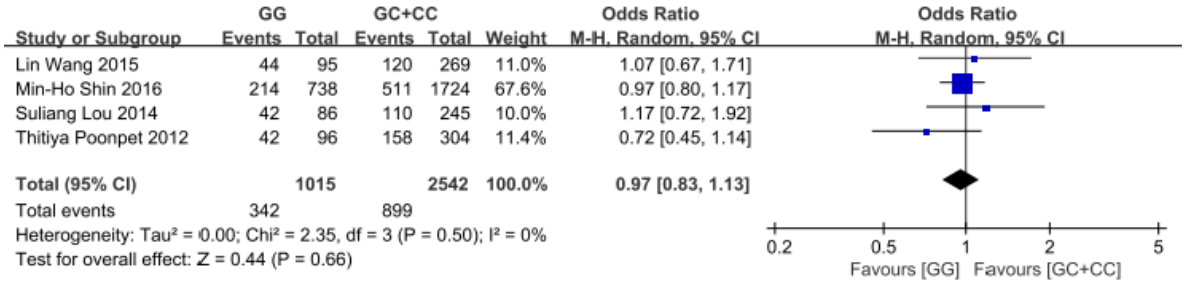

Figure 4 Forest plots of meta-analysis of the association between the *ADAM12* rs3740199 polymorphism (GG *vs.* GC + CC).

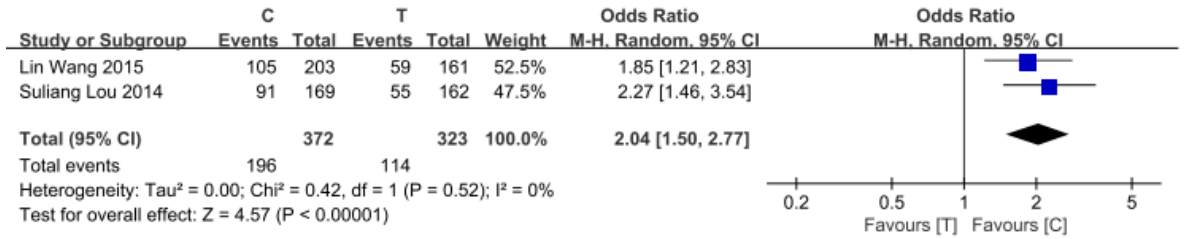

Figure 5 Forest plots of meta-analysis of the association between the *ADAM12* rs1871054 polymorphism (C *vs.* T).

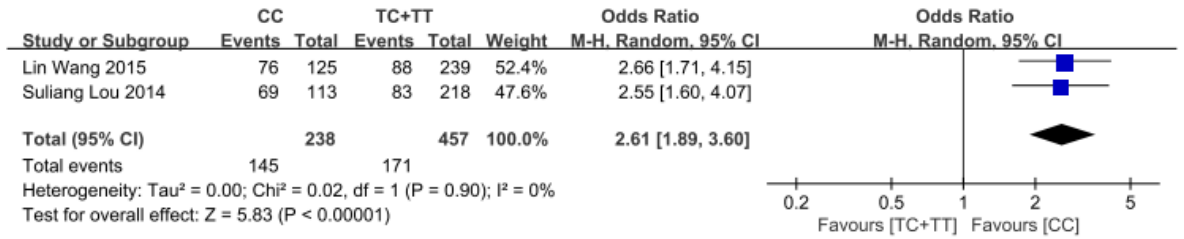

Figure 6 Forest plots of meta-analysis of the association between the *ADAM12* rs1871054 polymorphism (CC *vs.* TC + TT).

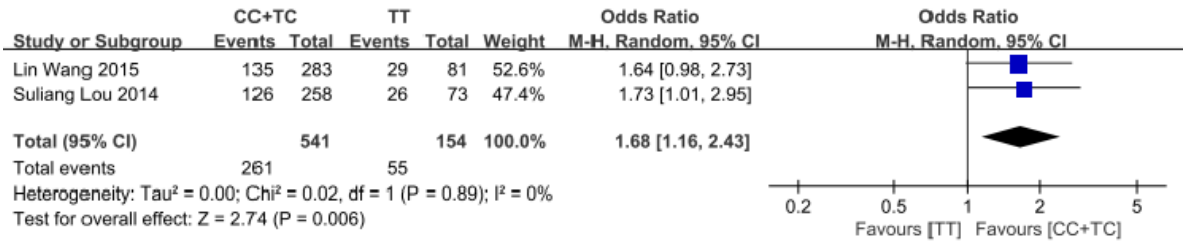

Figure 7 Forest plots of meta-analysis of the association between the *ADAM12* rs1871054 polymorphism (TT *vs.* CC + TC).

polymorphisms and the knee OA susceptibility, but there is no effect on the *ADAM12* rs3740199 and risk of knee OA.

Four studies including 3,557 participants investigated the relation between the *ADAM12* rs3740199 polymorphism and knee OA susceptibility. The alleles and genotypes frequency of the *ADAM12* rs3740199 were compared between the two groups. Our meta-analysis indicated that the *ADAM12* rs3740199 polymorphism had no effect on the risk of knee OA in any population. Two studies with a total of 695 participants assessed the correlation between the *ADAM12* rs1871054 polymorphism and knee OA susceptibility. C allele, the CT + CC genotype and CC

Table 4 Meta-analysis of *ADAM12* rs3740199 and rs1871054 polymorphisms and OA susceptibility

Polymorphism comparison	Comparison	Test of association			Test of heterogeneity			
		OR	95% CI	P value	Model	Q test	P value	I^2
rs3740199	C *vs.* G	1.02	0.89–1.18	0.75	Ramdom	1.63	0.65	0
	CC *vs.* GC + GG	1.02	0.89–1.18	0.84	Ramdom	1.68	0.64	0
	GG *vs.* GC + CC	0.97	0.83–1.13	0.66	Ramdom	2.35	0.66	0
rs1871054	C *vs.* T	2.04	1.50–2.77	0.00001	Ramdom	0.42	1.00	0
	CC *vs.* TC + TT	2.61	1.89–3.60	0.00001	Ramdom	0.02	0.90	0
	TT *vs.* CC + TC	1.68	1.16–2.43	0.006	Ramdom	0.02	0.89	0

genotype were found to have correlation with the risk for knee OA.

ADAM12 is a multifunctional protein, which includes two different splice protein variants: a long membrane anchored one (ADAM12-L) and a secreted short form (ADAM12-S) without transmembrane and cytoplasmatic domains (27). Vitro studies suggest ADAM12 play an important role in formation of bones and differentiation of osteoclast (16). Several researchers have focused on the association between *ADAM12* rs1871054, rs3740199 polymorphisms and the risk of knee OA and the results were not conformity, while meta-analysis on this field is shortage at present. Expanded sample size and different ethnic groups will be essential further to investigate the relationship between *ADAM12* polymorphisms and knee OA susceptibility. Despite the number of the studies was not that adequate, the amount of the subjects has increased to 3557. Moreover, heterogeneity between studies was assessed using the I^2 test and the Q statistic. Our meta-analysis showed heterogeneity of all studies might not be important.

Although the meta-analysis of the effect on the *ADAM12* rs3740199 polymorphism and the risk of knee OA showed negative, some studies conducted by stratification according to gender suggested there existed association with male patients. Poonpet *et al.* (22) detected that the rs3740199 at *ADAM12* had relationship on the risk of knee OA in Thai male patients, and individuals carrying the CC genotype had the highest susceptibility, comparing it to the GG and GC genotypes, while no significant association was observed in female patients. Kerna *et al.* (24) found that rs3740199 polymorphism has a statistically significant association with patellofemoral knee OA in male patients and the most significant relation between the tibiofemoral joint space narrowing and SNP rs3740199 in knee OA progression in women. However, in view of a small amount of this type of study and the limited primary outcome based on age and six differences in allele frequencies and genotype distributions, it was unlikely for us to conduct a subgroup analysis according to age and sex.

Several potential study limitations are present in the current meta-analysis. It is unlikely to conduct subgroup analysis for individuals on knee OA in different sites including hip, knee and hand with the same population due to the limited raw data. Moreover, the size of the study population is relatively small and the number of studies is also insufficient. Our results need to be confirmed in larger samples. Otherwise, knee OA is a multifactorial disease which is dominantly associated with genetic factors and environmental factors. Therefore, the environmental factors should be taken into consideration to achieve a true effect of *ADAM12* (28). Finally, we cannot evacuate publication bias, which may be explained by a choice of positive studies for publication.

Conclusions

The present results suggested that *ADAM12* rs1871054 polymorphisms had a positive association on the risk of knee OA, while the *ADAM12* rs3740199 was not observed to effect the knee OA susceptibility. Given it is unable to rule out that methodology, publication bias and small sample size of the eligible researched have affected the results, we suggest that large well-designed researches are essential to identify the role of ADAM12 on knee OA with more populations.

Acknowledgments

The authors thank their colleagues at the Department of

Orthopedics, Huzhou Central Hospital, Huzhou, China. We would like to thank Editage [www.editage.cn] for English language editing.
Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aoj.2018.02.03). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Jiang L, Tian W, Wang Y, et al. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2012;79:291-7.
2. McWilliams DF, Leeb BF, Muthuri SG, et al. Occupational risk factors for osteoarthritis of the knee: a meta-analysis. Osteoarthritis Cartilage 2011;19:829-39.
3. Tanamas SK, Wijethilake P, Wluka AE, et al. Sex hormones and structural changes in osteoarthritis: a systematic review. Maturitas 2011;69:141-56.
4. Papalia R, Del BA, Osti L, et al. Meniscectomy as a risk factor for knee osteoarthritis: a systematic review. Br Med Bull 2011;99:89-106.
5. Hu H, Yang B, Li Y, et al. Blocking of the P2X7 receptor inhibits the activation of the MMP-13 and NF-κB pathways in the cartilage tissue of rats with osteoarthritis. Int J Mol Med 2016;38:1922-32.
6. Ni J, Yuan XM, Yao Q, et al. OSM is overexpressed in knee osteoarthritis and Notch signaling is involved in the effects of OSM on MC3T3-E1 cell proliferation and differentiation. Int J Mol Med 2015;35:1755-60.
7. Liu C, Cao Y, Yang X, et al. Tauroursodeoxycholic acid suppresses endoplasmic reticulum stress in the chondrocytes of patients with osteoarthritis. Int J Mol Med 2015;36:1081-7.
8. Nakamura T, Shi D, Tzetis M, et al. Meta-analysis of association between the ASPN D-repeat and osteoarthritis. Hum Mol Genet 2007;16:1676-81.
9. Gálvez-Rosas A, González-Huerta C, Borgonio-Cuadra VM, et al. A COL2A1 gene polymorphism is related to advanced stages of osteoarthritis of the knee in Mexican Mestizo population. Rheumatol Int 2010;30:1035-9.
10. Felson DT. Developments in the clinical understanding of osteoarthritis. Arthritis Res Ther 2009;11:203.
11. Maheswaran E, Pedersen CB, Ditzel HJ, et al. Lack of ADAM2, CALR3 and SAGE1 Cancer/Testis Antigen Expression in Lung and Breast Cancer. PLoS One 2015;10:e0134967.
12. Ruff M, Leyme A, Le CF, et al. The Disintegrin and Metalloprotease ADAM12 Is Associated with TGF-β-Induced Epithelial to Mesenchymal Transition. PLoS One 2015;10:e0139179.
13. Kwon J, Jeong SM, Choi I, et al. ADAM10 Is Involved in Cell Junction Assembly in Early Porcine Embryo Development. PLoS One 2016;11:e0152921.
14. Lorenzatti Hiles G, Bucheit A, Rubin JR, et al. ADAM15 Is Functionally Associated with the Metastatic Progression of Human Bladder Cancer. PLoS One 2016;11:e0150138.
15. Kveiborg M, Albrechtsen R, Rudkjaer L, et al. ADAM12-S stimulates bone growth in transgenic mice by modulating chondrocyte proliferation and maturation. J Bone Miner Res 2006;21:1288-96.
16. Verrier S, Hogan A, McKie N, et al. ADAM gene expression and regulation during human osteoclast formation. Bone 2004;35:34-46.
17. Okada A, Mochizuki S, Yatabe T, Kimura T, Shiomi T, Fujita Y, et al. ADAM-12 (meltrin alpha) is involved in chondrocyte proliferation via cleavage of insulin-like growth factor binding protein 5 in osteoarthritic cartilage. Arthritis Rheum 2008;58:778-89.
18. Kerna I, Kisand K, Laitinen P, et al. Association of ADAM12-S protein with radiographic features of knee osteoarthritis and bone and cartilage markers. Rheumatol Int 2012;32:519-23.
19. Valdes AM, Hart DJ, Jones KA, et al. Association study of candidate genes for the prevalence and progression of knee osteoarthritis. Arthritis Rheum 2004;50:2497-507.
20. Limer KL, Tosh K, Bujac SR, et al. Attempt to replicate

published genetic associations in a large, well-defined osteoarthritis case-control population (the GOAL study). Osteoarthritis Cartilage 2009;17:782-9.
21. Wang L, Guo L, Tian F, et al. Analysis of single nucleotide polymorphisms within ADAM12 and risk of knee osteoarthritis in a Chinese Han population. Biomed Res Int 2015;2015:518643.
22. Poonpet T, Tammachote R, Tammachote N, et al. Association between ADAM12 polymorphism and knee osteoarthritis in Thai population. Knee 2016;23:357-61.
23. Shin MH, Lee SJ, Kee SJ, et al. Genetic association analysis of GDF5 and ADAM12 for knee osteoarthritis. Joint Bone Spine 2012;79:488-91.
24. Kerna I, Kisand K, Tamm AE, et al. Missense single nucleotide polymorphism of the ADAM12 gene is associated with radiographic knee osteoarthritis in middle-aged Estonian cohort. Osteoarthritis Cartilage 2009;17:1093-8.
25. Ren Y, Tan B, Yan P, et al. Association between polymorphisms in the estrogen receptor alpha gene and osteoarthritis susceptibility: a meta-analysis. BMC Musculoskelet Disord 2015;16:44.
26. Lou S, Zhao Z, Qian J, et al. Association of single nucleotide polymorphisms in ADAM12 gene with susceptibility to knee osteoarthritis: a case-control study in a Chinese Han population. Int J Clin Exp Pathol 2014;7:5154-9.
27. Gilpin BJ, Loechel F, Mattei MG, et al. A novel, secreted form of human ADAM 12 (meltrin alpha) provokes myogenesis in vivo. J Biol Chem 1998;273:157-66.
28. Reynard LN, Loughlin J. Insights from human genetic studies into the pathways involved in osteoarthritis. Nat Rev Rheumatol 2013;9:573-83.

doi: 10.21037/aoj.2018.02.03
Cite this article as: Chen W, Wang Y, Jiang X. Association of two polymorphisms rs3740199 and rs1871054 at ADAM12 with susceptibility of knee osteoarthritis: a systematic review and meta-analysis. Ann Joint 2018;3:29.

