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

Wenxiang Chen¹, Yiying Wang², Xuesheng Jiang¹

¹Department of Orthopedics, Huzhou Central Hospital, Huzhou 313000, China; ²Department 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
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 data 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 I² statistic. I²>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

<table>
<thead>
<tr>
<th>Study (Ref.)</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Genotyping</th>
<th>Numbers</th>
<th>Gender</th>
<th>Age</th>
<th>Polymorphism(s)</th>
<th>quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin Wang et al. (21)</td>
<td>2015</td>
<td>China</td>
<td>Case-control</td>
<td>PCR</td>
<td>164</td>
<td>200</td>
<td>58/106</td>
<td>65.9±5.3</td>
<td>rs3740199, rs1871054</td>
</tr>
<tr>
<td>Thitiya Poonpet et al. (22)</td>
<td>2016</td>
<td>Thailand</td>
<td>Case-control</td>
<td>PCR</td>
<td>200</td>
<td>200</td>
<td>53/147</td>
<td>57.3±5.8</td>
<td>rs3740199</td>
</tr>
<tr>
<td>Suliang Lou et al. (26)</td>
<td>2014</td>
<td>China</td>
<td>Case-control</td>
<td>PCR</td>
<td>152</td>
<td>179</td>
<td>58/94</td>
<td>62.2±4.2</td>
<td>rs3740199, rs1871054</td>
</tr>
<tr>
<td>Min-Ho Shin et al. (23)</td>
<td>2012</td>
<td>Korea</td>
<td>Case-control</td>
<td>PCR</td>
<td>725</td>
<td>1737</td>
<td>171/554</td>
<td>67.4±7.9</td>
<td>rs3740199</td>
</tr>
</tbody>
</table>

PCR, polymerase chain reaction; OA, osteoarthritis.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>OA site</th>
<th>P (G) (%)</th>
<th>p (C) (%)</th>
<th>PP (GG)</th>
<th>Pp (GC)</th>
<th>pp (CC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OA</td>
<td>Control</td>
<td>OA</td>
<td>Control</td>
<td>OA</td>
</tr>
<tr>
<td>Lin Wang et al.</td>
<td>China</td>
<td>Knee</td>
<td>52.4</td>
<td>51</td>
<td>47.6</td>
<td>49</td>
<td>44</td>
</tr>
<tr>
<td>Thitiya Poonpet et al.</td>
<td>Thailand</td>
<td>Knee</td>
<td>46</td>
<td>52</td>
<td>54</td>
<td>48</td>
<td>42</td>
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<tr>
<td>Suliang Lou et al.</td>
<td>China</td>
<td>Knee</td>
<td>53.3</td>
<td>50.6</td>
<td>46.7</td>
<td>49.4</td>
<td>42</td>
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<tr>
<td>Min-Ho Shin et al.</td>
<td>Korea</td>
<td>Knee</td>
<td>54.6</td>
<td>55</td>
<td>45.4</td>
<td>45</td>
<td>214</td>
</tr>
</tbody>
</table>

OA, osteoarthritis.
+ 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 (I²=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 and knee OA. 

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>OA site</th>
<th>P (G) (%)</th>
<th>p (C) (%)</th>
<th>PP (GG)</th>
<th>Pp (GC)</th>
<th>pp (CC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin Wang et al.</td>
<td>China</td>
<td>Knee</td>
<td>35.7</td>
<td>50.8</td>
<td>64.3</td>
<td>49.2</td>
<td>29</td>
</tr>
<tr>
<td>Suliang Lou et al.</td>
<td>China</td>
<td>Knee</td>
<td>35.9</td>
<td>60</td>
<td>64.1</td>
<td>40</td>
<td>26</td>
</tr>
</tbody>
</table>

OA, osteoarthritis.

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

**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).
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
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.

### Acknowledgements

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.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


