Associations Between Adipokines Gene Polymorphisms and Osteoarthritis: a Meta-analysis

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Title: Associations between adipokines gene polymorphisms and osteoarthritis: a meta-analysis

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Abstract

Background: Adipokines gene polymorphisms are speculated to have associations with the risk of osteoarthritis (OA), but evidences remain conflicting. This study therefore aimed to examine the potential associations between adipokines gene polymorphisms and OA.

Methods: A systematic search was performed on PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang up to March 31, 2020. Meta-analysis was carried out by focusing on associations between adipokines gene polymorphisms and OA with allele model, dominant model, recessive model, homozygote model, and heterozygote model.

Results: The present meta-analysis included 13 studies containing 3,661 OA patients and 4,864 controls for analysis. Significant associations were observed between ADIPOQ rs2241766 and OA in Asians (dominant: OR = 1.35, 95% CI 1.03-1.78; heterozygote: OR = 1.43, 95% CI 1.07-1.19), between LEPR rs1137101 and OA in the overall population (recessive: OR = 0.40, 95% CI 0.21-0.79; homozygote: OR = 0.38, 95% CI 0.18-0.79), between VISFATIN rs4730153 and OA in Asians (allele: OR = 0.58, 95% CI 0.41-0.83; dominant: OR = 0.57, 95% CI 0.39-0.83; heterozygote: OR = 0.59, 95% CI 0.40-0.86), and between VISFATIN rs16872158 and OA in Asians (allele: OR = 1.84, 95% CI 1.26-2.68; dominant: OR = 1.94, 95% CI 1.31-2.89; heterozygote: OR = 1.97, 95% CI 1.31-2.95).

Conclusions: Adipokines gene polymorphisms may be associated with OA. In particular, associations were observed in ADIPOQ rs2241766, LEPR rs1137101, VISCATIN rs4730153, and VISCATIN rs16872158 in the present study.
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Keywords: Meta-analysis, Adipokines, Osteoarthritis, Polymorphisms
Background

Osteoarthritis (OA), a highly prevalent disease, was estimated to affect 250 million people worldwide at present [1], and has therefore become a major contributor to global disability [2]. OA is characterized by degeneration of articular cartilage, synovial inflammation and bone remodeling, which can consequently lead to pain, physical activity limitations and markedly reduced quality of life [3]. At present, pharmacological treatment options for OA lack approved disease-modifying therapies and are largely limited to the relief of symptoms [4], while for end-stage OA patients, joint replacement is demanded [5]. Elucidation of the underlying etiology of OA would be helpful for confirming diagnosis in early stages and distinguishing individuals who are exposed to a higher risk of progression, therefore facilitating more effective clinical decision making. OA has a multifactorial pathophysiology, which may involve mechanical, metabolic and inflammatory contributors [6]. In addition, genetic factors may explain a large part of the susceptibility to OA [7]. In the past few years, several studies reporting OA risk loci have been published [8-12], among which genome-wide association studies were carried out to discover DNA variants, primarily the single nucleotide polymorphisms (SNPs) in large cohorts [12]. Insights from these relevant studies have firmly placed OA into the polygenic category of common diseases [13-16].

The recognized prominent risk factors of OA include increasing age, female sex and obesity [4]. In particular, obesity is a well-established risk factor [4] due to its
potential contribution in the mechanical aspect by increasing the joint load [17], as
well as in the metabolic aspect by playing the role of adipose tissue as an endocrine
organ secreting a variety of metabolically-active mediators. Among these secreted
mediators, adipokines are a main type [17]. Indeed, adipose tissue has been confirmed
to release an array of adipokines including adiponectin, leptin, resistin, and visfatin
[17, 18], among which leptin was first discovered by Friedman et al. in 1994 [19].
Then, in 2003, Dumond et al [20]. derived the earliest evidence supporting a pivotal
role of leptin in OA. This milestone study initiated the journey to examine adipokines
as a metabolic link between obesity and OA.

Several SNPs of the adipokines genes have been associated with OA [21-33],
however, the results are inconsistent. For instance, a study from Thailand rejected any
significant association between the ADIPOQ gene rs1501299 polymorphism and knee
OA [24], while Jin et al. reported that rs1501299 polymorphism intensified the risk of
knee OA in Chinese subjects [21]. In view of the limitations of individual studies and
the inconsistency among different studies, we intended to clarify whether there were
associations between the main types of adipokines gene SNPs and the susceptibility to
OA through meta-analysis.

Methods

Search methods

The PubMed, Embase, Web of Science, China National Knowledge Infrastructure
(CNKI), and Wanfang databases were searched through to retrieve observational studies that focused on the associations between adipokines gene polymorphisms and OA up to March 31, 2020 (Appendix A).

Inclusion and exclusion criteria

Two investigators assessed the retrieved studies independently according to the pre-specified inclusion criteria as follows: (1) OA was diagnosed based on the American College of Rheumatology criteria or radiographic findings, or the patient received total joint replacement because of primary OA; (2) observational studies that investigated the associations between adipokines gene polymorphisms and OA; (3) observational studies that compared OA patients with healthy controls; (4) the allele and genotype distributions of healthy controls were compliant with the Hardy-Weinberg equilibrium (HWE) model; (5) the frequency distributions of alleles and genotype were available to extract. The exclusion rules were: (1) repeated publications; (2) conference abstract or commentary; (3) animal or in vitro studies; (4) review articles.

Data extraction and evaluation of study quality

Two investigators extracted the desired data (i.e., authors, publication year, study design, country, OA site, genotype method, sample size of the case group and control group, and the allele and genotype frequency of adipokines SNPs) from eligible studies independently.
Another two investigators analyzed the methodological quality of the studies independently by applying the Newcastle-Ottawa Scale (NOS) [34], in terms of the selection of study participants, comparability of outcome groups and outcome measures. A NOS score > 6 indicated a high-quality study [35, 36].

**Statistical analysis**

The conformity of the distributions of observed allele or genotype frequencies to HWE in the control group was verified by chi-square test. The statistical heterogeneity was tested by $I^2$ statistics. The odd ratios (ORs) and 95% confidence intervals (CIs) were estimated by the random effects model in case of high heterogeneity ($I^2 > 50\%$), and by the fixed effects model in case of low heterogeneity [37]. Publication bias was examined by the Begg’s test [38] and the Egger’s test [39], where $P < 0.05$ implied statistical significance. All data analyses were performed in Stata 15.0 (Stata Corp, College Station, TX, USA).

The meta-analysis was carried out on (1) the allele model, (2) the dominant model, (3) the recessive model, (4) the homozygote model, and (5) the heterozygote model. In order to examine the effects specific to demographic regions, subgroup analyses were categorized by different populations. Then, sensitivity analyses were carried out to evaluate the impact of any single study on the overall effects by examining the ORs alongside their matching 95% CIs before and after eliminating
each study from the meta-analysis.

Results

Eligible studies

Fig. 1 shows a flow chart that illustrates the selection process. A total of 13 publications (7 on ADIPOQ polymorphism, 4 on LEPR polymorphism, 2 on LEP polymorphism, 2 on RESISTIN polymorphism, and 1 on VISFATIN polymorphism) containing 3,661 OA patients and 4,864 controls were included [21-33]. Table 1 details the characteristics of the included studies. The allele and genotype distributions of the control group showed consistency with the HWE. All the included studies were judged as high quality (NOS score > 6).

Meta-analysis results

Altogether, 22 SNPs from 5 genes were reported, among which 5 SNPs from 3 genes were reported in ≥ 2 studies and were subsequently included into the meta-analysis. Table 2 presents the main results derived from the present meta-analysis. The pooled ORs and 95% CIs were calculated for the allele model, dominant model, recessive model, homozygotes model, and heterozygote model, respectively.

Association between ADIPOQ rs1501299 polymorphism and OA

The included studies focusing on rs1501299 showed no significant heterogeneity in both the overall analysis and subgroup analyses leveled by population groups in all
the models. Therefore, all the models were analyzed by the fixed effects model. None of the models showed any significant association in the overall analysis (allele model: OR = 1.08, 95% CI 0.95-1.22, \( P = 0.227 \); recessive model: OR = 1.27, 95% CI 0.92-1.75, \( P = 0.142 \); dominant model: OR = 1.08, 95% CI 0.91-1.29, \( P = 0.376 \); homozygote model: OR = 1.30, 95% CI 0.93-1.81, \( P = 0.120 \); heterozygote model: OR = 1.04, 95% CI 0.87-1.25, \( P = 0.641 \)). Meanwhile, none of the models showed any significant association in subgroup analyses leveled by population groups either.

Association between ADIPOQ rs2241766 polymorphism and OA

The included studies focusing on rs2241766 showed no significant heterogeneity in the overall analysis in the allele, dominant, recessive, and homozygote model, and no significant heterogeneity in subgroup analyses leveled by population groups in the allele, dominant, recessive, homozygote, and heterozygote model. Therefore, all the models mentioned above were analyzed by the fixed effects model in the overall analysis and subgroup analyses. Meanwhile, the heterozygote model in the overall analysis was analyzed by the random effects model due to the existence of significant heterogeneity observed in this model. None of the models showed any significant association in the overall analysis (allele model: OR = 1.08, 95% CI 0.90-1.29, \( P = 0.411 \); recessive model: OR = 0.97, 95% CI 0.65-1.44, \( P = 0.861 \); dominant model: OR = 1.21, 95% CI 0.95-1.55, \( P = 0.125 \); homozygote model: OR = 1.13, 95% CI 0.74-1.71, \( P = 0.579 \); heterozygote model: OR = 1.19, 95% CI 0.87-1.77, \( P = 0.384 \)). In subgroup analyses, the rs2241766 polymorphism showed no significant association
with OA in Europeans and Latin Americans, while statistically significant associations were observed in Asians in the dominant model (OR = 1.35, 95% CI 1.03-1.78, \( P = 0.028 \)) and heterozygote model (OR = 1.43, 95% CI 1.07-1.19, \( P = 0.016 \)).

**Association between LEPR rs1137101 polymorphism and OA**

The included studies focusing on rs1137101 showed no significant heterogeneity in the overall analysis and subgroup analyses leveled by population groups in the heterozygote model. Therefore, the heterozygote model was analyzed by the fixed effects model. On the other hand, the other models were analyzed by the random effects model in both the overall analysis and subgroup analyses leveled by population groups, due to the existence of significant heterogeneity.

In the overall analysis, significant associations were observed in the recessive model (OR = 0.40, 95% CI 0.21-0.79, \( P = 0.008 \)) and homozygote model (OR = 0.38, 95% CI 0.18-0.79, \( P = 0.009 \)). In subgroup analyses, the rs1137101 polymorphism showed no significant association with OA in Europeans and Africans, while statistically significant associations were observed in Asians in the recessive model (OR = 0.43, 95% CI 0.19-0.96, \( P = 0.040 \)) and homozygote model (OR = 0.38, 95% CI 0.15-0.99, \( P = 0.049 \)).

**Association between VISFATIN rs4730153 polymorphism and OA**

There is one study containing 2 stages that illustrated the relationship between
rs4730153 polymorphism and OA risk. The included studies focusing on rs4730153 showed no significant heterogeneity in all the analyses. Therefore, all the models were analyzed by the fixed effects model.

Significant associations were observed in the allele model (OR = 0.58, 95% CI 0.41-0.83, \( P = 0.003 \)), dominant model (OR = 0.57, 95% CI 0.39-0.83, \( P = 0.004 \)) and heterozygote model (OR = 0.59, 95% CI 0.40-0.86, \( P = 0.007 \)), but not in other models.

**Association between VASFATIN rs16872158 polymorphism and OA**

There is one study containing 2 stages that illustrated the relationship between rs16872158 polymorphism and OA risk. The included studies focusing on rs16872158 showed no significant heterogeneity in all the analyses. Therefore, all the models were analyzed by the fixed effects model.

Significant associations were observed in the allele model (OR = 1.84, 95% CI 1.26-2.68, \( P = 0.001 \)), dominant model (OR = 1.94, 95% CI 1.31-2.89, \( P = 0.001 \)) and heterozygote model (OR = 1.97, 95% CI 1.31-2.95, \( P = 0.001 \)), but not in other models.

**Publication bias**

No publication bias was evidenced in the included studies by the Egger’s test and
Begg’s test. Table 2 presents the test results of publication bias on each gene polymorphism.

Sensitivity analyses

In view of that significant heterogeneity was detected among the studies of the rs2241766 heterozygote model, rs1137101 allele model, recessive model, dominant model and homozygote model, sensitivity analyses were performed to examine the impact of any single study on the aggregate findings above based on the ORs with the matching 95% CIs before and after eliminating each study from the meta-analysis. The results indicated that the significance of results was changed in none of the models for the gene polymorphisms above.

Discussion

The present meta-analysis included 13 published studies containing 3,661 OA patients and 4,846 controls. Significant associations were observed between ADIPOQ rs2241766 and OA in Asians, between LEPR rs1137101 and OA in the overall population, between VISFATIN rs7430153 and OA in Asians, and between VISFATIN rs16872158 and OA in Asians.

Studies have been published on the associations of 2 SNPs (rs2241766 and rs1501299) in the ADIPOQ gene with OA, but the results are inconsistent. According to a cross-sectional study from Finland, no association was observed between four
ADIPOQ gene polymorphisms (including rs2241766 and rs1501299) and the risk of hand OA [27]. Two studies conducted by Honsawek et al. from Thailand also found no association between ADIPOQ rs2241766 or rs1501299 polymorphism and the risk of knee OA [24, 25]. However, another two studies focusing on the Chinese population reported significant associations between ADIPOQ rs2241766 and rs1501299 polymorphisms and an increased risk of knee OA [21, 26]. The conflicting findings from the studies above might be attributed to three reasons. The first one might be the genetic heterogeneity among different ethnicities, and the second one might be the heterogeneity in clinical data (i.e., different populations, occupations and lesion sites). For example, the patients enrolled in the study from Finland were occupationallly-active female dentists and teachers with hand OA, while other studies generally focused on knee OA. The third reason might be the varying sample sizes across different studies, which might introduce differences in data accuracy; moreover, a small sample size might even lead to false-positive results. In the present meta-analysis, by investigating the associations of 2 SNPs (rs2241766 and rs1501299) with the risk of OA, we produced convincing evidence that rs2241766 within the ADIPOQ gene was a predisposing factor for the risk of OA in Asians.

Adiponectin, an adipocyte-derived hormone with multiple biological functions [40, 41], was also found to play a catabolic and pro-inflammatory role in OA. Adiponectin can stimulate the expression of interleukin-6 (IL6) and matrix metalloproteinase-1/-3/-13, and the production of inducible nitric oxide synthase in
both chondrocytes and OA synovium fluids through the mitogen-activated protein
kinases, AdipoR1/5′-AMP-activated protein kinase, and the nuclear factor-kappa B
pathway, which may eventually lead to inflammation and matrix degradation in
patients with OA [42-44]. An earlier meta-analysis revealed that the OA patients
exhibited higher adiponectin levels than their healthy counterparts [45]. There were
also evidences supporting the existence of an association between rs2241766 and
alterations of plasma adiponectin, especially in the Asian population [46-49].
Rs2241766, the exonic SNP, is a silent polymorphism which would not lead to
changes in the sequence of amino acids [50]. However, evidence has been reported
that many genes related to human diseases harbor exonic mutations could influence
the pre-mRNA splicing [51]. In particular, the translationally silent mutations might
inactivate genes by inducing the splicing machinery to skip mutant exons [51].
Consequently, SNP rs2241766 might affect the plasma level of adiponectin by
affecting the splicing efficiency and/or accuracy of adiponectin mRNA [51]. Although
the exact mechanism of rs2241766 modulation underlying OA susceptibility is still
unclear, the data from the present study could provide a better understanding of its
functional relevance to the pathogenesis of OA.

There are two studies targeting at the Chinese population indicating that LEPR
SNP was associated with the susceptibility to knee OA; hence, it was speculated that
there might be a genetic marker predicting the risk of this disease [28, 29]. On the
contrary, Doudar et al. reported neither direct genetic association between rs1137101
SNP and the susceptibility of primary knee OA nor any gender difference in the frequency distribution of alleles or genotypes in Egyptians [31]. In the present study, rs1137101 within the LEPR gene was found to be associated with a reduced risk of OA in the overall population and the Asian subgroup. Recently, due to the pro-inflammatory and pro-catabolic activities on the cartilage, the impaired leptin signal transduction was recognized as a new factor in the pathophysiology of OA [52]. Furthermore, due to the regulatory role of LEPR SNPs in the leptin signal pathway and the expression of LEPR in the cartilage [53, 54], LEPR was speculated to be a genetic risk factor for OA. By using arginine at codon 223 to replace the amino acid glutamine, the SNP rs1137101 in the LEPR gene represented a change in the extracellular domain of the LEPR protein, which would consequently result in structural changes in LEPR and potential alterations of the signaling capacity of leptin [55].

Visfatin is a multi-faceted, ubiquitous protein that acts on a number of diseases including OA [56, 57]. In accordance with a two-stage case-control study by Jiang et al. that examined the associations between 3 tagging polymorphisms in the VISFATIN gene and the risk for OA based on a sample containing 339 OA patients and 680 healthy subjects [33], the rs4730153 in VISFATIN appeared to be significantly associated with a reduced risk of OA, while the rs16872158 in VISFATIN was associated with an increased risk of OA in Chinese subjects. In view of that the genetic factors may be affected by different disease patterns, severities, genders and
populations, more large-scale replication studies are needed to further verify the results related to SNPs on different population groups. It has been established that visfatin played a role in the pro-inflammation process of OA. Meanwhile, 2 important mediators of cartilage destruction (i.e., IL-1β and lipopolysaccharide) in OA could enhance visfatin expression [58], which implied the existence of associations between inflammatory cytokines and visfatin [59]. Consistently, visfatin has been demonstrated to induce the expressions of IL-6 and monocyte chemoattractant protein 1 in chondrocytes and osteoblasts, implying a deleterious effect of this cytokine on OA [60]. Although evidence has been reported about the mechanism of visfatin underlying OA, there is a lack of evidence illustrating the mechanisms of rs4730153 and rs16872158 in affecting the expression of visfatin. Our study might provide a hint for detecting the pathogenesis of OA from a novel aspect.

Several limitations in this meta-analysis need to be highlighted. Firstly, the included studies were retrieved from sources in English and Chinese language only. Secondly, as the targeted populations were restricted to Europeans, Latin Americans and Asians, it is unclear whether the results could be generalized to other ethnic groups. Thirdly, there are only a small number of studies focusing on VISFATIN gene polymorphisms, and therefore, the statistical power was not sufficient to examine the associations between VISFATIN polymorphisms and OA with more accurate results. Despite aforementioned limitations, our study is the first meta-analysis focusing on the associations between adipokines gene polymorphisms and the risk for OA, and
might provide new insights into the etiology of OA.

Conclusion

The present meta-analysis demonstrates potential associations between adipokines gene polymorphisms and OA. In particular, associations were observed in ADIPOQ rs2241766, LEPR 1137101, VISMATIN rs4730153 and VISMATIN rs16872158.

Further research with better quality and larger sample sizes is needed by focusing on different population groups.

Abbreviations

OA: Osteoarthritis; SNPs: single nucleotide polymorphisms; NOS: Newcastle-Ottawa Scale; ORs: odd ratios; CIs: confidence intervals; NA: not available; PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction and restriction fragment length polymorphism; R: random effects model; F: fixed effects model.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials
The data analysed during this study are included in the published articles and its supplementary information files.

**Competing interests**

None declared.

**Author contributions**

W. Yuqing: Conceptualized and designed the study, Acquired and interpreted the data, Drafted the manuscript.

M. Fanqiang: Searched the literature, Processed the data.

W. Jing: Performed the statistical analyses.

L. Huizhong: Searched the literature, Processed the data.

L. Jiatian: Evaluated the methodological quality of the included studies.

W. Ziying: Evaluated the methodological quality of the included studies.

H. Hongyi: Acquired and interpreted the data.

W. Haochen: Acquired and interpreted the data.

W. Ning: Acquired and interpreted the data.

X. Dongxing: Conceptualized, designed, and supervised the study, Interpreted the data, Critically reviewed the manuscript.

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Table 1. Main Characteristics of Studies Included in This Meta-analysis.

| Study          | Design      | Country     | OA site | Sample size | Mean Age (years) | Gender (M/F) | Genotyping method        | NOS | Gene (SNPs)                                                                 |
|----------------|-------------|-------------|---------|-------------|------------------|--------------|--------------------------|-----|-----------------------------------------------------------------------------|
| Jin 2019       | Case-control| China       | Knee    | 372/453     | 50.23/51.12      | 158/214/199/254 | PCR-RFLP 7          |     | ADIPOQ (rs1501299)                                                        |
| Espinoza-Morales 2019 | Case-control| Mexico      | Knee    | 92/147      | 47.2/40.9        | 12/80/42/105   | TaqMan 7           |     | ADIPOQ (rs1501299, rs2241766)                                              |
| Liu 2018       | Case-control| China       | Knee    | 196/442     | 62.19/57.17      | 48/148/139/303  | PCR 8             |     | ADIPOQ (rs182052, rs2082940, rs6773957)                                     |
| Hamalainen 2018 | Case-control| Finland     | Hand    | 320/764     | NA/NA            | NA/NA/NA/NA     | TaqMan 6           |     | ADIPOQ (rs1730539, rs182052, rs2241766, rs1501299); LEP (rs7799039, rs2167270); LEPR (rs1137100, rs1137101, rs1805094); RESISTIN (rs3745367, rs4804765, rs1423096, rs10401670) |
| Honsawek 2017  | Case-control| Thailand    | Knee    | 202/196     | 68.8/65.2        | 66/136/68/128   | PCR-RFLP 7         |     | ADIPOQ (rs2241766, 1501299)                                               |
| Honsawek 2014  | Case-control| Thailand    | Knee    | 100/100     | 68.2/67.0        | 25/75/20/80     | PCR-RFLP 8         |     | ADIPOQ (rs1501299)                                                        |
| Zhan 2016      | Case-control| China       | Knee    | 255/201     | 64.2/65.2        | 39/216/68/133   | PCR-RFLP 8         |     | ADIPOQ (rs2241766, 1501299)                                               |
| Yang 2016      | Case-control| China       | Knee    | 587/628     | 61.37/60.46      | 134/453/143/485 | PCR-RFLP 8         |     | LEPR (rs1137101)                                                          |
| Jin 2013       | Case-control| China       | Knee    | 148/155     | 53.18/54.27      | 46/102/54/101   | PCR 7             |     | LEPR (rs1137101)                                                          |
| Doudar 2020    | Case-control| Egypt       | Knee    | 73/73       | 56.6/53.2        | 15/58/12/61     | PCR-RFLP 7         |     | LEPR (rs1137101)                                                          |
| Jiang 2010     | Case-control| China       | Knee    | 697/699     | 59.6/58.5        | 168/928/411/288 | TaqMan 7          |     | LEP (rs11761556, rs12706832, rs2071045)                                     |
| Murtaza 2019   | Case-control| Pakistani   | Knee    | 280/308     | 54.6/53.5        | 120/160/152/156 | PCR-RFLP 8         |     | RESISTIN (rs3745367, rs1862513)                                            |
| Jiang 2016     | Case-control| China       | Knee    | 196/442     | 62.19/57.17      | 48/148/139/303  | PCR-RFLP 8         |     | VISFATIN (rs4730153, rs16872158, rs3801267)                                 |
| Jiang 2016     | Case-control| China       | Knee    | 143/238     | 62.10/56.95      | 31/112/65/173   | PCR-RFLP 8         |     | VISFATIN (rs4730153, rs16872158)                                            |

Abbreviations: OA, osteoarthritis; NA, not available; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism; SNP, single nucleotide polymorphism.
Table 2. Meta-analysis of associations between adipokines polymorphisms and OA.

| Polymorphism | Population | No. of studies | Tests of association | Tests of heterogeneity | Begg’s test | Egger’s test |
|--------------|------------|----------------|----------------------|------------------------|-------------|-------------|
|              |            |                | OR | 95% CI | P-value | Model | P-value | P (%) | P-value | P-value |
| ADIPOQ       |            |                |    |        |         |       |        |       |         |         |
| rs1501299    |            |                | 6  | 1.08   | 0.95, 1.22 | 0.227 | F | 0.525 | 0.452 | 0.085 |
| allele       | Latin American | 1  | 0.78 | 0.48, 1.27 | 0.326 | / | / | / | / | / |
|              | European   | 1  | 1.00 | 0.76, 1.32 | 0.972 | / | / | / | / | / |
|              | Asian      | 4  | 1.13 | 0.98, 1.30 | 0.093 | F | 0.604 | 0 | / | / |
|              | Overall    | 5  | 1.27 | 0.92, 1.75 | 0.142 | F | 0.744 | 0.462 | 0.209 |
|              | Latin American | 1  | 0.60 | 0.15, 2.48 | 0.481 | / | / | / | / | / |
|              | Asian      | 4  | 1.33 | 0.95, 1.84 | 0.093 | F | 0.846 | 0 | / | / |
|             |            |                | 5  | 1.08   | 0.91, 1.29 | 0.376 | F | 0.535 | 0.221 | 0.077 |
| recessive    | Latin American | 1  | 0.77 | 0.43, 1.38 | 0.381 | / | / | / | / | / |
|              | Asian      | 4  | 1.12 | 0.93, 1.34 | 0.228 | F | 0.635 | 0 | / | / |
|              | Overall    | 5  | 1.30 | 0.93, 1.81 | 0.120 | F | 0.600 | 0.462 | 0.187 |
|              | Latin American | 1  | 0.55 | 0.13, 2.32 | 0.420 | / | / | / | / | / |
|              | Asian      | 4  | 1.37 | 0.97, 1.92 | 0.071 | F | 0.728 | 0 | / | / |
|              | Overall    | 5  | 1.04 | 0.87, 1.25 | 0.641 | F | 0.724 | 0.221 | 0.062 |
|              | Latin American | 1  | 0.80 | 0.44, 1.47 | 0.477 | / | / | / | / | / |
|              | Asian      | 4  | 1.07 | 0.89, 1.30 | 0.473 | F | 0.738 | 0 | / | / |
|             |            |                | 3  | 0.97   | 0.65, 1.44 | 0.861 | F | 0.961 | 0.296 | 0.124 |
| recessive    | Latin American | 1  | 1.20 | 0.24, 6.11 | 0.824 | / | / | / | / | / |
|              | Asian      | 2  | 0.95 | 0.63, 1.43 | 0.813 | F | 0.945 | 0 | / | / |
|              | Overall    | 3  | 1.21 | 0.95, 1.55 | 0.125 | F | 0.166 | 44.3 | 0.296 | 0.078 |
|              | Latin American | 1  | 0.73 | 0.40, 1.30 | 0.283 | / | / | / | / | / |
|              | Asian      | 2  | 1.35 | 1.03, 1.78 | 0.028 | F | 0.977 | 0 | / | / |
|              | Overall    | 3  | 1.13 | 0.74, 1.71 | 0.579 | F | 0.996 | 0 | 1.000 | 0.360 |
|              | Latin American | 1  | 1.05 | 0.20, 5.44 | 0.950 | / | / | / | / | / |
|              | Asian      | 2  | 1.13 | 0.73, 1.74 | 0.578 | F | 0.964 | 0 | / | / |
|             |            |                | 3  | 1.19   | 0.80, 1.77 | 0.384 | R | 0.115 | 53.8 | 0.296 | 0.084 |
| recessive    | Latin American | 1  | 0.70 | 0.38, 1.28 | 0.250 | / | / | / | / | / |
|              | Asian      | 2  | 1.43 | 1.07, 1.19 | 0.016 | F | 0.965 | 0 | / | / |
|             |            |                | 3  | 0.76   | 0.53, 1.11 | 0.153 | R | 0 | 84.8 | 0.734 | 0.746 |
| LEPR         |            |                |    |        |         |       |        |       |         |         |
| rs1137101    | Asian      | 2  | 0.61 | 0.32, 1.14 | 0.120 | R | 0.001 | 91.4 | / | / |
| allele       | European   | 1  | 1.13 | 0.86, 1.47 | 0.374 | / | / | / | / | / |
|              | African    | 1  | 0.82 | 0.50, 1.36 | 0.441 | / | / | / | / | / |
|              | Overall    | 3  | 0.40 | 0.21, 0.79 | 0.008 | R | 0.029 | 71.7 | 1.000 | 0.661 |
| recessive    | Asian      | 2  | 0.43 | 0.19, 0.96 | 0.040 | R | 0.010 | 85.1 | / | / |
|              | African    | 1  | 0.30 | 0.08, 1.18 | 0.084 | / | / | / | / | / |
|              | Overall    | 3  | 0.74 | 0.50, 1.10 | 0.137 | R | 0.126 | 51.7 | 1.000 | 0.724 |
| Allele       | Overall | Asian | African | P-value | Odds Ratio | 95% CI     | Random Effects | Fixed Effects |
|-------------|---------|-------|---------|---------|------------|------------|----------------|---------------|
| **VISFATIN**|         |       |         |         |            |            |                |               |
| rs7430153   |         |       |         |         |            |            |                |               |
| recessive   | Overall | 2     | 0.38    | 0.07    | 2.26       | 0.289      | F              | 0.667          |
| dominant    | Overall | 2     | 0.57    | 0.39    | 0.83       | 0.004      | F              | 0.946          |
| homozygote  | Overall | 2     | 0.35    | 0.06    | 2.08       | 0.250      | F              | 0.668          |
| heterozygote| Overall | 2     | 0.59    | 0.40    | 0.86       | 0.007      | F              | 0.870          |
| VISFATIN    | Overall | 2     | 1.84    | 1.26    | 2.68       | 0.001      | F              | 0.724          |
| rs16872158  |         |       |         |         |            |            |                |               |
| recessive   | Overall | 2     | 1.34    | 0.22    | 8.14       | 0.752      | F              | 0.833          |
| dominant    | Overall | 2     | 1.94    | 1.31    | 2.89       | 0.001      | F              | 0.747          |
| homozygote  | Overall | 2     | 1.45    | 0.24    | 8.81       | 0.688      | F              | 0.830          |
| heterozygote| Overall | 2     | 1.97    | 1.31    | 2.95       | 0.001      | F              | 0.769          |

Abreviations: R, random effects model; F, fixed effects model.
Fig. 1 Selection process of eligible studies

Records identified through Database searching (n=119):
- Pubmed (n=21)
- Web of science (n=58)
- Embase (n=37)
- CNKI and Wanfang (n=3)

Records after duplicates removed (n=65)

Records excluded based on title or abstract (n=51):
- Review article (n=7)
- Not osteoarthritis (n=13)
- Animal or in vitro study (n=19)
- Conference abstract or commentary (n=5)
- Not observational design (n=6)

Full-text articles reviewed (n=15)

Full-text articles excluded (n=2):
- Relevant to other gene (n=1)
- Not observational design (n=1)

Articles included in quantitative synthesis (n=13)
Appendix A: Supplementary Material

Search strategies

**Pubmed:**
1. osteoarthriti*[tiab] or osteoarthriti*[mh] or osteoarthro*[tiab] or gonarthriti*[tiab] or gonarthro*[tiab] or coxarthriti*[tiab] or coxarthro*[tiab] or osteoarthritis*[tiab]
2. polymorphism*[tiab] or SNP*[tiab] or variant*[tiab] or mutation*[tiab] or genotype*[tiab] or allele*[tiab] or haplogroup*[tiab] or haplotype*[tiab] or “genetic predisposition”*[tiab] or “genetic susceptibility”*[tiab] or “Polyorphism, Single Nucleotide”*[MeSH]
3. ADIPOQ*[tiab] or adiponectin*[tiab] or “C1Q and collagen domain containing”*[tiab] or ACDC*[tiab] or ACRP30*[tiab] or ADIPQTL1*[tiab] or ADPN*[tiab] or APM-1*[tiab] or APM1*[tiab] or GBP28*[tiab]
4. LEP*[tiab] or leptin*[tiab] or OB*[tiab] or OBS*[tiab] or LEPD*[tiab]
5. LEPR*[tiab] or “leptin receptor”*[tiab] or OBR*[tiab] or OB-R*[tiab] or CD295*[tiab] or LEP-R*[tiab] or LEPRD*[tiab]
6. RETN*[tiab] or resistin*[tiab] or ADSF*[tiab] or RSTN*[tiab] or XCP1*[tiab] or FIZZ3*[tiab] or RETN1*[tiab]
7. NAMPT*[tiab] or “nicotinamide phosphoribosyltransferase”*[tiab] or VF*[tiab] or PBEF*[tiab] or PBEF1*[tiab] or VIFATIN*[tiab] or 1110035014Rik*[tiab]
8. APLN*[tiab] or apelin*[tiab] or APEL*[tiab] or XNPEP2*[tiab]
9. CMKLR1*[tiab] or “chemerin chemokine-like receptor 1”*[tiab] or DEZ*[tiab] or RVER1*[tiab] or ChemR23*[tiab] or CHEMERINR*[tiab]
10. lipocalin-2*[tiab] or LCN2*[tiab] or p25*[tiab] or 24p3*[tiab] or MSFI*[tiab] or NGAL*[tiab]
11. or: 3-10
12. 1 and 2 and 11

**Embase:**
1. (osteoarthriti* or osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or arthros* or arthrot*):ti,ab
2. (polymorphism or SNP* or variant* or mutation or genotype or allele or haplogroup or haplotype or “genetic predisposition” or “genetic susceptibility”):ti,ab or (“Polyorphism, Single Nucleotide”*[MeSH])
3. (ADIPOQ or adiponectin or C1Q and collagen domain containing” or ACDC or ACRP30 or ADIPQTL1 or ADPN or APM-1 or APM1 or GBP28):ti,ab
4. (LEP or leptin or OB or OBS or LEPD):ti,ab
5. (LEPR or “leptin receptor” or OBR or OB-R or CD295 or LEP-R or LEPRD):ti,ab
6. (RETN or resistin or ADSF or RSTN or XCP1 or FIZZ3 or RETN1):ti,ab
7. (NAMPT or “nicotinamide phosphoribosyltransferase” or VF or PBEF or PBEF1 or VIFATIN or 1110035014Rik):ti,ab
8. (APLN or apelin or APEL or XNPEP2):ti,ab
9. (CMKLR1 or “chemerin chemokine-like receptor 1” or DEZ or RVER1 or ChemR23 or CHEMERINR):ti,ab
10. (lipocalin-2 or LCN2 or p25 or 24p3 or MSFI or NGAL):ti,ab
11. or: 3-10
12. 1 and 2 and 11

**Web of Science:**

1. TOPIC:(osteoarthriti* or osteoarthro* or gonarthriti* or gonarthro* or gonarthro* or coxarthriti* or coxarthro* or arthros* or arthrot*)
2. TOPIC:(polymorphism or SNP* or variant* or mutation or genotype or allele or haplogroup or haplotype or “genetic predisposition” or “genetic susceptibility”) or (“Polymorphism, Single Nucleotide”[MeSH])
3. TOPIC:(ADIPOQ or adiponectin or “C1Q and collagen domain containing” or ACDC or ACRP30 or ADIPQTL1 or ADPN or APM-1 or APM1 or GBP28)
4. TOPIC:(LEP or leptin or OB or OBS or LEPD)
5. TOPIC:(LEPR or “leptin receptor” or OBR or OB-R or CD295 or LEP-R or LEPRD)
6. TOPIC:(RETN or resistin or ADSF or RSTN or XCP1 or FIZZ3 or RETN1)
7. TOPIC:(NAMPT or “nicotinamide phosphoribosyltransferase” or VF or PBEF or PBEF1 or VISFATIN or 1110035014Rik)
8. TOPIC:(APLN or apelin or APEL or XNPEP2)
9. TOPIC:(CMKLR1 or “chemerin chemokine-like receptor 1” or DEZ or RVER1 or ChemR23 or CHEMERINR)
10. TOPIC:(lipocalin-2 or LCN2 or p25 or 24p3 or MSFI or NGAL)
11. or: 3-10
12. 1 and 2 and 11