Association between the polymorphism of MMP-1 gene with knee osteoarthritis risk: a meta-analysis

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Abstract

Background: The existing studies on the association between polymorphisms of Matrix metalloproteinase-1 (MMP-1) (-1607 1G/2G) (rs1799750) polymorphism and the risk of knee osteoarthritis (OA, a complex multifactorial disease and a major degenerative form of arthritis) in different populations have yielded conflicting findings. Materials and Method: Literature search was performed in PubMed, Embase, Medline, Cochrane Library, Web of science, Google Scholar, CNKI, Wanfang database (last search update June 1st 2019), and assessing this association by calculating odds ratios with 95% confidence intervals. Subgroup analyses stratified by ethnicity were also conducted. Statistical heterogeneity was quantitatively evaluated by X2 test with the significance set $P<0.10$ or $I2>50\%$. Result: Five case-control based studies (924 cases and 928 controls) were included. The results show that in Allele model (1G1G vs. 2G2G: OR =1.22, 95% CI: 0.72-1.76), Recessive model (2G2G vs 1G2G+1G1G: OR = 1.12, 95% CI: 0.70-2.15) and Dominant model (2G2G+1G2G vs 1G1G: OR = 1.14, 95%CI: 0.64-2.04). Conclusions: There is no association between the polymorphism of MMP-1 (-1607 1G/2G) (rs1799750) polymorphism with the risk of knee osteoarthritis.

Background

Knee osteoarthritis (OA) is a common disease in people over 55 years of age. The incidence of KOA is more than 10%, and a quarter of the patients are severely disabled[1]. Knee OA is a common joint disease which is characterized by degeneration of the articular cartilage and subsequent subchondral bone changes. Knee OA is a combined result of environmental and genetic factors, while genetic factors account for nearly 50% of the risk of OA development[2].Although the underlying mechanisms remain unknown, many studies have shown that the occurrence of knee osteoarthritis is related to cytokines, including Matrix metalloproteinases (MMPs) family[3-7].

Matrix metalloproteinase-1 (MMP-1)is produced by synovial cells, chondrocytes, and osteoblasts, which can degrade extracellular matrix collagen and mediate cartilage destruction[7-8]. The expression of MMPs has been shown to be affected by single nucleotide polymorphisms (SNPs) occurring in MMP gene promoters[9].These promoter polymorphisms have allele-specific effects on the regulation of MMP gene transcription and are associated with the development and/or progression of some common diseases[3-5]. Matrix metalloproteinases secreted from chondrocytes are the main enzymes responsible for pathological cartilage destruction [6].Expression of MMP-1 is low in normal cells that leads to healthy cartilage remodeling. In pathological conditions, the level of MMP-1 expression increases significantly, resulting in aberrant connective tissue destruction[10]. MMP-1 is expressed at higher levels in OA chondrocytes than in normal chondrocytes, suggesting a predominant role of MMP-1 in OA pathogenesis[11].

MMP-1 (-1607 1G/2G) (rs1799750) has been shown to affect the transcriptional activity of its genes. The two alleles of MMP1 (-1607) gene polymorphism (1G and 2G) are formed by an insertion/deletion of guanine at position -1607. The presence of 2G creates the sequence 5'AAGGAT3', which is the consensus sequence of the E-

twenty six family of transcription factors[12]. Thus, the 2G allele leads to increased transcriptional activity and MMP-1 expression.

Several studies investigated the relationships of MMP-1 (-1607 1G/2G)(rs1799750) polymorphism with increased knee OA risk in different countries and draw different conclusions[11, 13-16]. Therefore, we conducted a meta-analysis to assess the effect of the MMP-1 (-1607 1G/2G)(rs1799750) polymorphism on the risk of knee OA. The purpose of this study was to evaluate the association studies on MMP-1 (-1607 1G/2G)(rs1799750) polymorphism and knee OA and to estimate the common genetic effect of the polymorphism.

Methods

2.1 Search strategy

PubMed, Embase, Medline, Cochrane Library, Web of science, Google Scholar, CNKI and Wanfang database were systematically searched to identify studies published through June 1st 2019 and to retrieve the genetic association studies on knee OA. The terms 'Matrix metalloproteinase', 'MMP-1', 'SNP', 'polymorphism', 'knee', 'osteoarthritis', and 'OA' were used to find all publications reporting MMP-1 (-1607 1G/2G) (rs1799750) gene polymorphisms and knee OA risk. No language or other restrictions were placed on the search. Full text was obtained if the abstract was insufficient to allow us to include or exclude a study. Furthermore, the reference lists of all the related citations were examined to identify any initially omitted studies.

2.2 Inclusion and exclusion criteria

Two researchers screened the relevant investigations and further determined the eligible studies which met the following inclusion criteria: (1) case–control study on humans; (2) study evaluating the association between MMP-1 (-1607 1G/2G) (rs1799750) gene polymorphisms and susceptibility to knee OA; and (3) study with sufficient genetic frequency for extraction. The exclusion criteria were as follows: (1) incomplete data; (2) review or case report; and (3) duplicate or overlapping publication. All questionable publications were discussed and addressed by consensus. In cases of uncertainty regarding any of the above essential information, the full article was retrieved for further scrutiny, or the authors of the individual trials were contacted directly for further information when necessary.

2.3 Data extraction

Two researchers extracted all data independently according to the criteria described above. We developed a data extraction sheet including year of publication, the first author's name, OA region, ethnicity, source of control groups, genotype, and allele frequency. Any controversies of the data were discussed within our research team and the authors reached a consensus on all items.

2.4 Statistical analysis

Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association between MMP-1 (-1607 1G/2G) (rs1799750) gene polymorphisms and knee OA susceptibility. The observed

genotype frequencies in control groups of the MMP-1 (-1607 1G/2G) (rs1799750) gene polymorphisms were assessed for Hardy Weinberg equilibrium (HWE) by using the Chi-square test. Three genetic models were used: (1) allele model; (2) recessive model; (3) dominant model. $P < 0.05$ was considered significant. Heterogeneity assumption across studies was assessed by using the Q statistic with its P-value and I^2 statistic. If $I^2 < 50\%$ and $P > 0.10$, a fixed effects model was used in the calculations ; otherwise, a random effects model was applied[17-18]. Subgroup analysis were carried out on the basis of ethnicity. Potential publication bias was assessed with Begg's test[19].Sensitivity analysis by omitting each study in turn to determine the impact on the heterogeneity test and assessing the stability of the overall results. All statistical analyses were conducted in Stata15.1 (Stata Corporation, College Station, TX, U.S.A.).

Results

3.1 Characteristics of the included studies

The online search yielded 239 records, of which 64 duplicates were removed. Then 144 of the 175 remaining records were excluded after reviewing of titles and abstracts. The remaining 31articles were sent for full text review, which excluded 11 articles without relevant to association between MMP-1 gene with OA, 8 not relevant to knee OA, 5 not about -1607 1G/2G polymorphism and 2 not case-control study (Figure 1). Finally, we identified five case-control studies about the association between MMP-1 (-1607 1G/2G) (rs1799750) gene polymorphisms and OA. Our meta-analysis involved a total of 924 knee OA cases and 928 controls. The distribution of genotypes of all the studies was in agreement with HWE. More characteristics of the included articles are shown in Table 1.

3.2 Study quality assessment

The methodological quality of the studies was assessed using a modified version of the Jadad Scale (0 ["very poor"] to 7 ["rigorous"]). The modified version of Jadad Scale includes four domains: randomization, concealment of allocation, double blinding, withdrawals and dropouts (Figure 2). The assessment was independently performed by two authors.

3.3 Meta-analysis

Based on the test results of heterogeneity, we use random effect model to make this meta-analysis. The result of the association betweenMMP-1 (-1607 1G/2G) (rs1799750) gene polymorphisms and the risk of knee OA and the heterogeneity test are shown in Table 2. The results suggested that the MMP-1 (-1607 1G/2G) (rs1799750) gene polymorphisms were not associated with knee OA risk in all genetic models (Allele model OR =1.22, 95% CI: 0.72-1.76, p=0.615, Recessive model OR = 1.12, 95% CI: 0.70-2.15, p=0.486, and Dominant model OR = 1.14, 95%CI: 0.64-2.04, p=0.659, Figure 3-5).

We then performed sub-group analyses to investigate the effect of the ethnicity with the risk of the knee OA. The results showed that there was no significant difference between MMP-1 (-1607 1G/2G) (rs1799750) gene polymorphisms and the risk of knee OA in both Asian and Caucasian populations (Table 2).

Sensitivity analysis was used to determine the pooled ORs regarding the effects of this SNP on knee OA risk by omitting each study in turn to determine the effect on the heterogeneity test and evaluate the stability of the overall results, the results indicated that our data were stable and credible.

It was difficult to interpret the funnel plot, which is used to detect publication bias, because the number of studies included in the analysis was relatively small. Begg's test were performed to quantitatively evaluate the publication bias of literatures on knee OA. The results of the Begg's test suggested that there was no evidence of publication bias in the meta-analyses of association between the MMP-1 (-1607 1G/2G)(rs1799750) gene polymorphisms and risk of OA(p>0.05 Table 2).

Discussion

The most important finding was that there is no association between the polymorphism of MMP-1rs1799750 polymorphism with the risk of knee osteoarthritis. This contradicts our traditional view that MMP-1 is involved in the occurrence of knee osteoarthritis and is a risk factor for the knee OA.

The definite mechanisms of the knee OA remain unknown, but many studies have shown that genetic factors are considered to be strong determinants with them and the occurrence of knee osteoarthritis is related to inflammatory and cytokines[20-22]. A kind of conventional viewpoints is that inflammatory mechanism plays a crucial role in the pathogenesis and evolution of cartilage degeneration and expression of inflammatory reaction[23-25]. MMP-1 is produced by synovial cells, chondrocytes, and osteoblasts, which can degrade extracellular matrix collagen and mediate cartilage destruction[7-8]. Expression of MMP-1 is low in normal cells that leads to healthy cartilage remodeling. In pathological conditions, the level of MMP-1 expression increases considerably, resulting in aberrant connective tissue destruction[10]. MMP-1 is expressed at higher levels in OA chondrocytes than in normal chondrocytes, suggesting a predominant role of MMP-1 in OA pathogenesis[26].In this way, MMP-1 gene is considered to be associated with OA.

Recent studies have shown that some functional polymorphisms of MMPs, including MMP-1 (-1607 1G/2G)(rs1799750) polymorphism, have been associated with the risk of knee OA[11-16].However, due to the limited sample size of these studies, previous single studies may not be effective, so conflicting research results have been obtained, especially considering the heterogeneity of the study and different races, clinical heterogeneity and genetic diversity of other causes. Therefore, we conducted this meta-analysis to provide more confident evidence. Our data showed that MMP1 gene polymorphism do not increase the risk of OA. Furthermore, stratification analyses by ethnicity also indicated that this polymorphism do not increases the risk of knee OA in different ethnics.

In our study, 5 eligible studies, including 924 cases and 928 controls, were identified and analyzed. We demonstrated the association between MMP-1 (-1607 1G/2G) (rs1799750) and the knee OA risk by a meta-analysis to obtain a powerful conclusion. Our research suggests that MMP-1 (-1607 1G/2G) (rs1799750) polymorphism is not a risk or protective factor for knee osteoarthritis(p>0.05). It is believed that 2G genotype can promote the high expression of MMP-1, which may be a risk factor for the occurrence of osteoarthritis. In our study, the 2G allele in case groups was indeed higher than that in the control groups, but the difference was not

statistically significant (57% vs. 51%, p=0.615). The possible reason for this conclusion may be that the occurrence of knee osteoarthritis is the ultimate result of a variety of factors and genes, and a single gene may have little influence on this result. Secondly, there may be unknown alleles affecting the expression of 1G/2G gene, and - 1607 1G/2G is not the only factor affecting the expression of MMP-1 in the population. Third, although MMP-1 can mediate cartilage degeneration, it is not a direct determinant of osteoarthritis. Many cytokines of MMP family are involved in cartilage metabolism. The destruction of articular cartilage is the common result of many cytokines. MMP-1 cannot directly reflect the effect of cartilage metabolic changes on osteoarthritis. Subgroup analysis also confirmed that MMP-1 did not increase the risk of osteoarthritis among different ethnic groups.

Before our study, there was a meta-analysis providing comprehensive insights into the effects of the MMP-1 (-1607 1G/2G) (rs1799750)and risk of OA in European and African, with very highly significant association for the OA as measured by homozygote, heterozygote, dominant model comparison[27].The reasons why our research has come to different conclusions may be the following. First of all, our research has more stringent criteria for retrieval and exclusion, including a recently published literature. Secondly, the study we included was limited to knee osteoarthritis, not other types of osteoarthritis, making the results more representative. Thirdly, we used race subgroup analysis to analyze the effects of different races on gene expression in knee OA and we found that there was no significant difference between MMP-1 and the risk of knee osteoarthritis in different ethnics.

There are still some limitations in our paper. Firstly, our several genetic models have great heterogeneity when combining OR values, which may affect the accuracy of the article. For this reason, we used random effect model to combine OR values and conduct sensitivity analysis to reduce the impact of heterogeneity. Secondly, although five papers have been included in the study, the data scale is still small, and further experiments are needed to verify this conclusion. Thirdly, the study is limited to the study of MMP-1 (-1607 1G/2G) (rs1799750), and If we included more factors, the result might be more comprehensive.

Conclusion

Our results do not support a genetic association between MMP-1 (-1607 1G/2G) (rs1799750) polymorphisms and the risk of knee OA. Although itis possible that these individual SNPs could be associated with knee OA, a large number of studies may be necessary to verify this association between the susceptibility of knee OA in different populations and environmental factors.

Abbreviations

MMP: Matrix metalloproteinase OR: odds ratio OA: osteoarthritis

SNPs: single nucleotide polymorphisms HWE: Hardy Weinberg equilibrium

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

FF-L and QD-Z contributed to the conception and design. WS-G and QD-Z did interpretation. P-L and FFL did the data collection and analysis. FF-L wrote the article. QD-Z and WG-W did the final approval of the version to be submitted.

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Not applicable.

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Figures
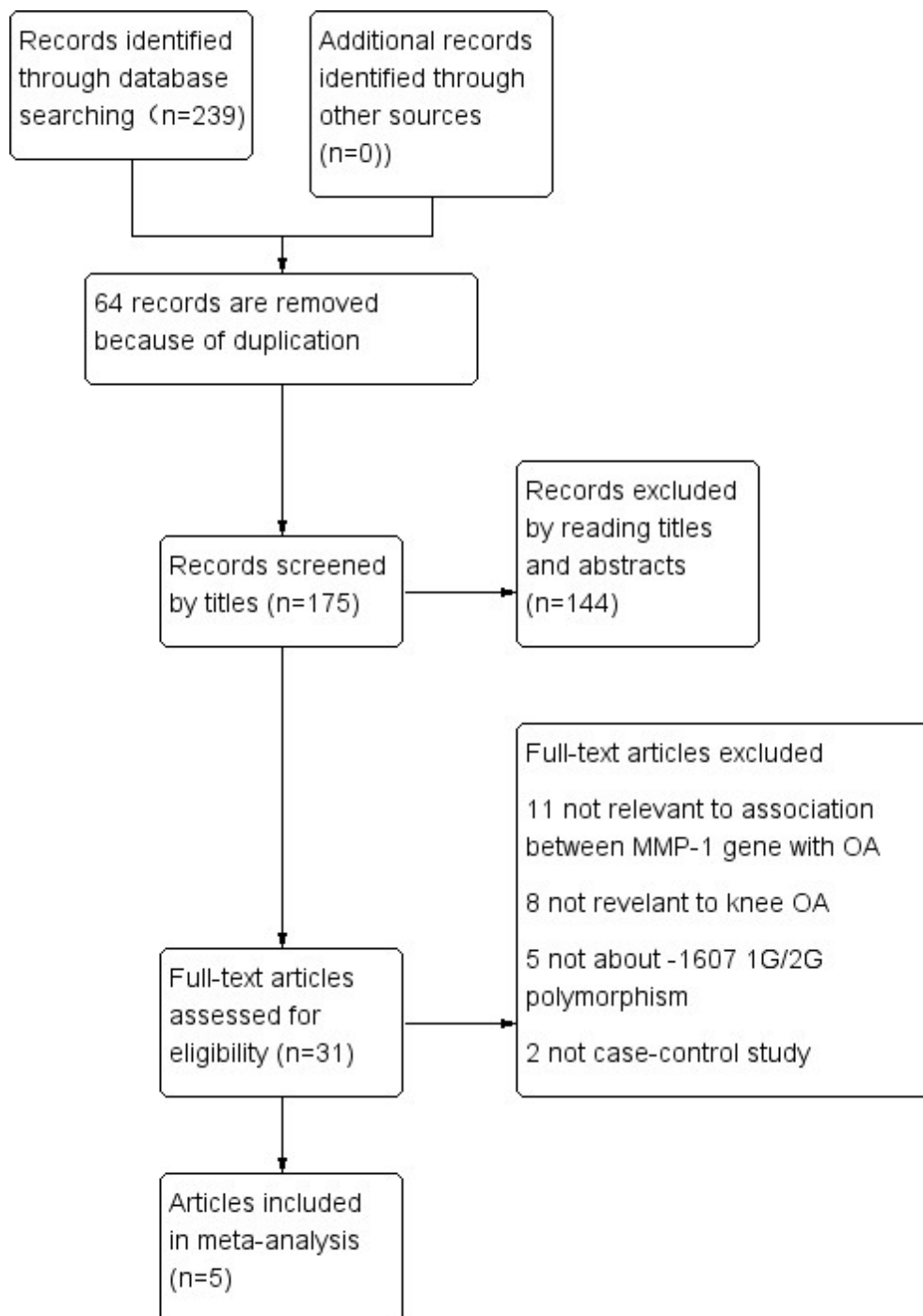
Figure 1

Flowchart of the literature search and selection for the present study

Figure 2

Results of the methodological quality evaluations. Green indicates that the criterion is satisfied. Yellow indicates that it is unclear whether the criterion is satisfied or not. Red indicates that the study did not meet the criterion.
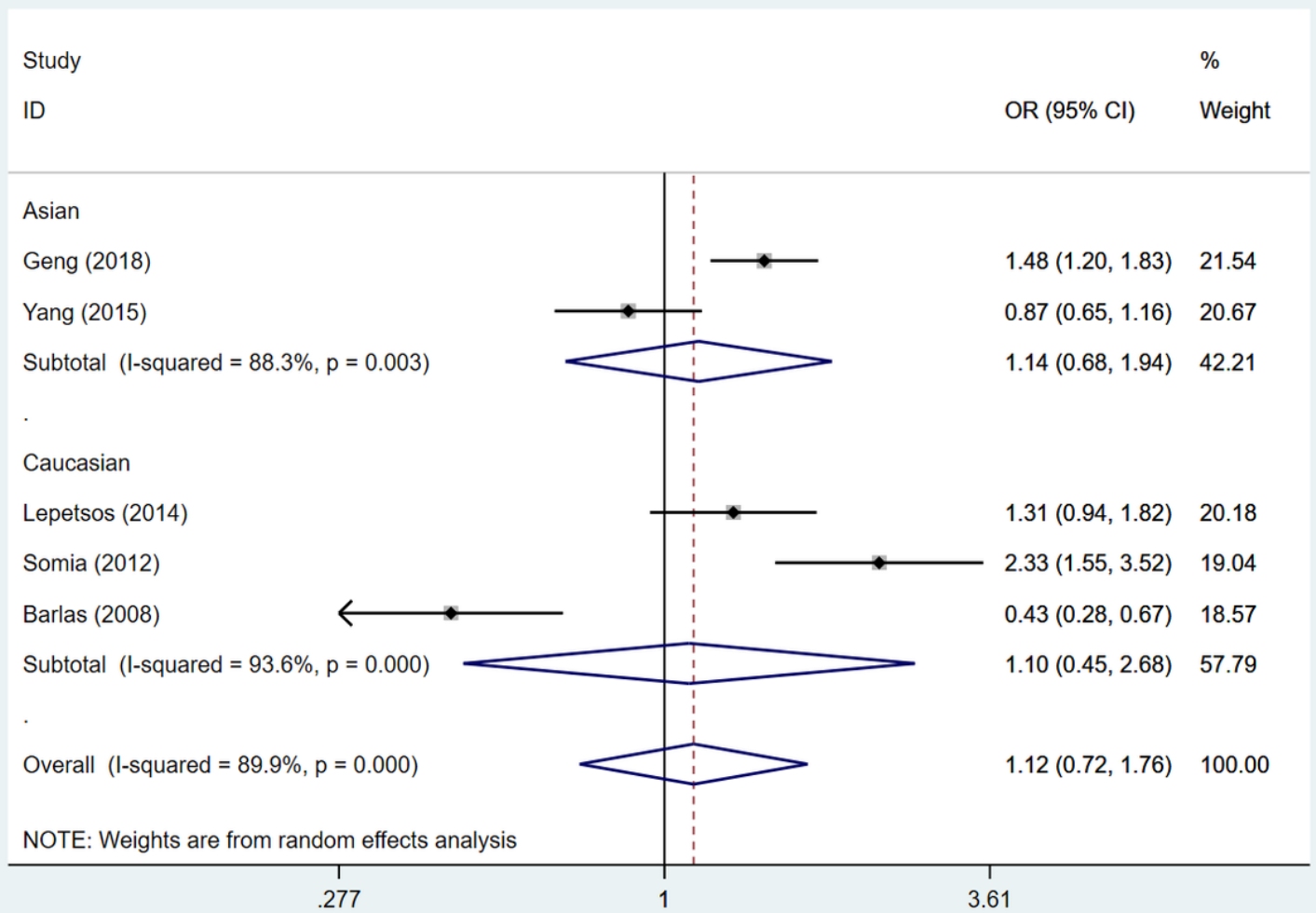
Figure 3

Forest plot showing OR for the associations between the MMP-1 polymorphism and knee OA risk (Allele model)
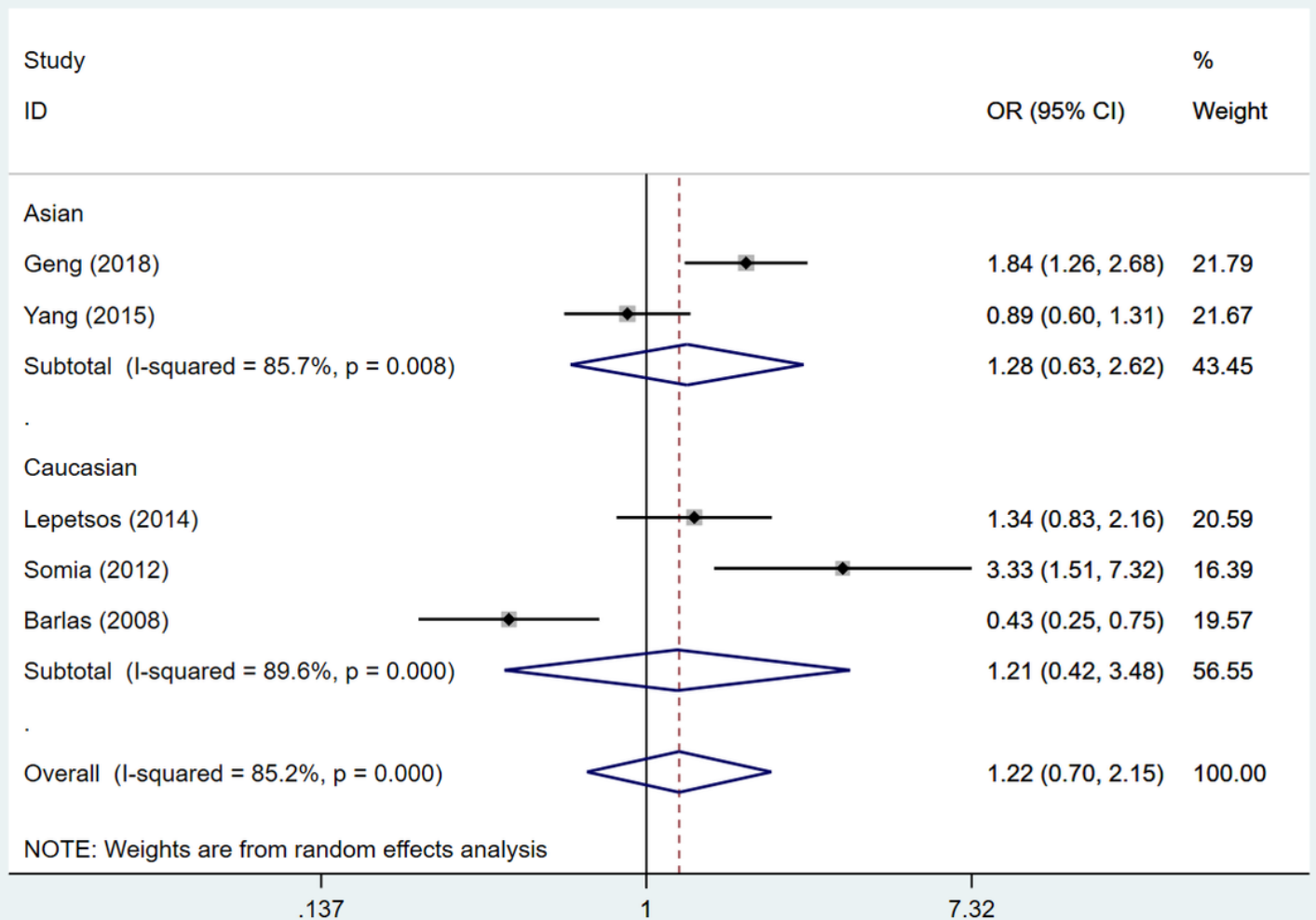
Figure 4

Forest plot showing OR for the associations between the MMP-1 polymorphism and knee OA risk (Recessive model)
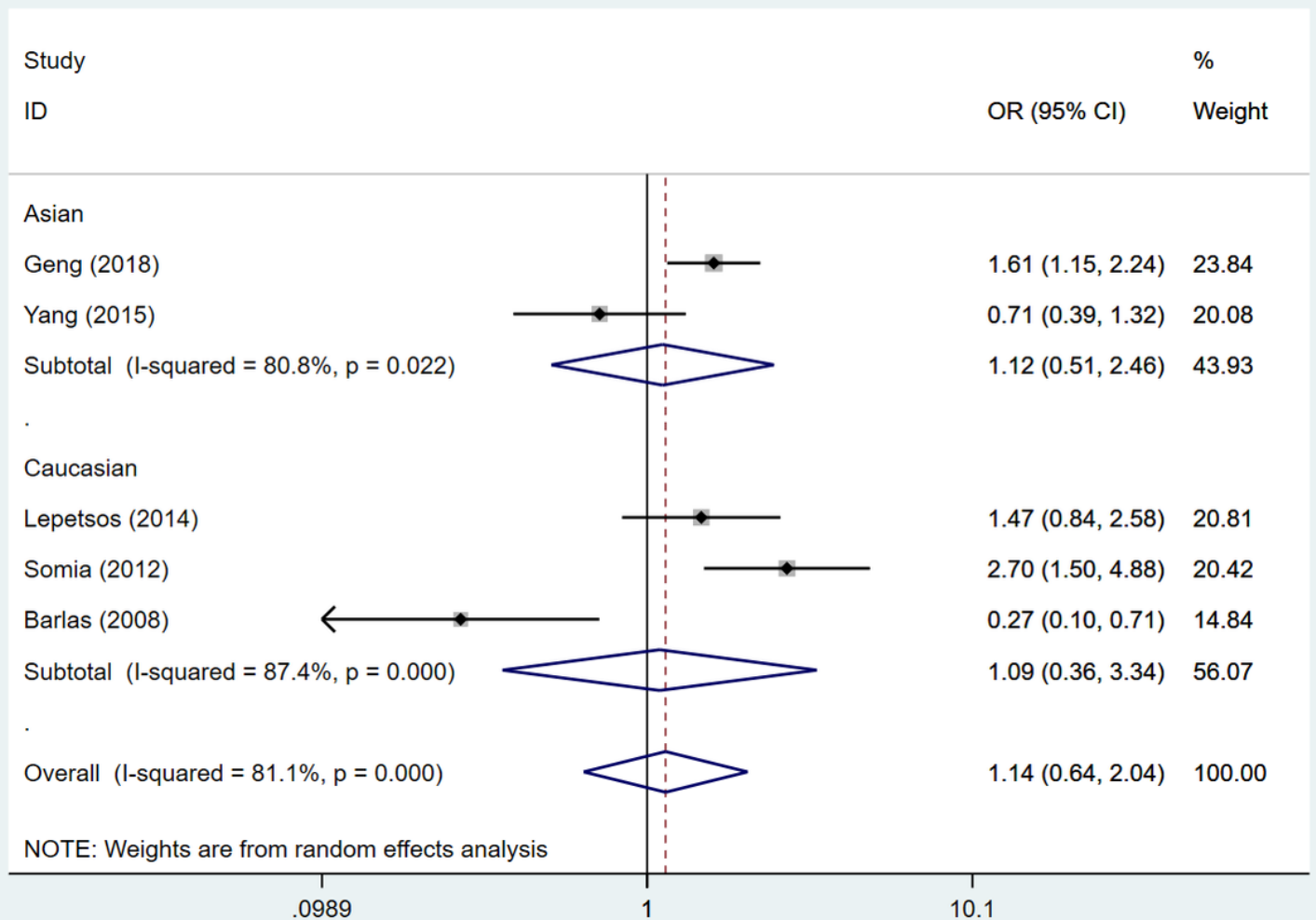
Figure 5

Forest plot showing OR for the associations between the MMP-1 polymorphism and knee OA risk (Dominant model)