Effects of MMP-1 1G/2G polymorphism on osteoarthritis: A meta-analysis study

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A B S T R A C T

Objective: The aim of this meta-analysis was to clarify the role of Matrix metalloproteinase 1 (MMP-1) -1607 1G/2G (rs1799750) polymorphism on the osteoarthritis (OA) risk.

Methods: Articles were selected by retrieving the Web of Science, Embase and PubMed. The association between -1607 1G/2G polymorphism and OA risk was assessed by odds ratios (ORs) with the corresponding 95% confidence interval (CI) for each study.

Results: No significant association between -1607 1G/2G polymorphism and OA risk was found in all the models overall (2G2G vs 1G1G, OR (95%CI) = 0.69 (0.36–1.32), P = 0.54; 2G2G + 2G1G vs 1G1G, OR (95% CI) = 0.88 (0.47–1.63), P = 0.69; 2G2G vs 2G1G + 1G1G, OR (95%CI) = 1.30 (0.68–2.47), P = 0.41; 2G vs 1G, OR (95%CI) = 0.90 (0.86–1.54), P = 0.66). By subgroup analysis, significant association was found in the “<60 years” group (2G2G vs 1G1G, OR (95%CI) = 3.46 (2.13–5.62), P = 0.00; 2G2G + 2G1G vs 1G1G, OR (95%CI) = 0.49 (0.31–0.79), P = 0.00; 2G2G vs 2G1G + 1G1G, OR (95%CI) = 2.74 (1.80–4.16), P = 0.00; 2 G vs 1G, OR (95%CI) = 0.56 (0.35–0.89), P = 0.01).

Conclusions: This meta-analysis showed that -1607 1G/2G polymorphism may increase the susceptibility to OA among the younger populations (<60 years). More studies with detailed information are needed to validate our conclusion.

Level of Evidence: Level I Diagnostic Study.

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Introduction

Osteoarthritis (OA) is a multifactorial disease and often occurs among middle-aged and elderly people. The irreversible cartilage damage is the main characteristic of OA. Matrix metalloproteinase 1 (MMP-1), a member of the family of Matrix metalloproteinases (MMPs), synthesized by chondrocytes, osteoblasts, and synovial cells, can affect the regulation of cartilage damage by degrading extracellular matrix (ECM) collagen types I, II, and III. Low expression of MMP-1 in normal cells contributes to the remodeling of healthy cartilage. The expression of MMP-1 in the OA chondrocytes is higher than in normal chondrocytes, indicating that MMP-1 is involved in the pathogenesis of OA. Many kinds of cells can express the MMP-1 gene, which is located on the long arm of chromosome 11. Various single nucleotide polymorphisms (SNPs) in the promoter region can alter the expression level of MMP-1. It has been confirmed that an insertion/deletion of guanine at position -1607 in human MMP-1 promoter can lead to two different alleles: 1G (containing one guanine) and 2G (containing two guanines); additionally, there is a direct link between the 2G allele and the high expression of MMP-1. Although many recent studies have sought to clarify the relationship between 1G/2G polymorphism and the incidence of OA, the conclusions are inconsistent.

Therefore, in this study, we conducted a meta-analysis to examine whether there is a correlation between the 1G/2G polymorphism and OA risk.

Methods

Search strategy

Previous studies with relevant information for conducting the meta-analysis were retrieved from the Web of Science, Embase, and PubMed (up to April 16, 2018) using a combination of the following keywords: "MMP-1" and "OA."
keywords: matrix metalloproteinase 1 or MMP-1; osteoarthritis or OA; polymorphisms or polymorphism. Additionally, the references within the included articles and reviews were checked to avoid missing other qualifying studies. Xu and Xing independently selected the articles to minimize the deviation.

**Inclusion and exclusion criteria**

In this meta-analysis, the articles that provided information on MMP-1 were included. Simultaneously, the articles needed to meet the following criteria: (1) the number of cases and controls were provided; (2) genotype frequency and (or) allele frequency of the cases and controls were provided; (3) the research sample was independent of other research reports; and (4) other important information for the analysis was provided.

**Data extraction**

Two independent researchers collected the following information from all eligible articles: (1) the first author; (2) journal name; (3) publication year; (4) population information; (5) sample size; (6) phenotype information; (7) number of genotypes in cases and controls; (8) conclusions of studies.

**Statistical analysis**

The Hardy–Weinberg equilibrium (HWE) was used to assess the distribution of genotypes in the control populations. A meta-analysis was used to analyze the general data. First, a heterogeneity test was conducted by a chi-squared ($\chi^2$) test. If $P < 0.05$, the random effect model was adopted. If $P < 0.05$, the fixed effect model was adopted. Meta-regression analysis was used to look for possible sources of any heterogeneity. Funnel plots were used to evaluate the publication bias, and the results were further assessed using the Begg’s and Egger’s tests. The strength of the association between the 1G/2G polymorphism and OA risk was assessed by the odds ratios (ORs) and confidence interval (CI). STATA software was used for the meta-analysis (version 14; Stata Corporation, College Station, TX, USA). A $P$ value $< 0.05$ was considered as significant difference.

**Table 1**

Characteristics of the included studies.

| Study   | Mean age (years) | Ethnicity | OA type           | Design   | Surgery | Genotyping | Cases | Controls |
|---------|------------------|-----------|--------------------|----------|---------|------------|-------|----------|
| Allah 2012 | 54.2 51.4        | Caucasian | Knee               | PCC      | NO      | PCR-RFLP   | 100   | 100      |
| Barlas 2009 | 61.7 62.3        | Caucasian | Knee               | HCC      | NO      | PCR-RFLP   | 156   | 81       |
| Lepetsos 2014 | 73.1 73.8       | Caucasian | Knee               | HCC      | YES     | PCR-RFLP   | 155   | 139      |
| Luo 2015       | 37.2 33.5        | Asian     | Temporomandibular  | PCC      | YES     | PCR        | 206   | 185      |
| Yang 2015       | 70.1 71.0        | Asian     | Knee               | PCC      | YES     | PCR-RFLP   | 207   | 207      |

PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; HCC, Hospital based case-control study; PCC, Population based case-control study.
In our study, we found that a relationship between the 1G/2G polymorphism and OA risk only existed among the "< 60 years" age group (2G2G vs. 1G1G, OR (95% CI) = 3.46 (2.13–5.62), P = 0.00; 2G2G + 2G1G vs. 1G1G, OR (95% CI) = 0.49 (0.31–0.79), P = 0.00; 2G2G vs. 2G1G + 1G1G, OR (95% CI) = 2.74 (1.80–4.16), P = 0.00; 2G vs. 1G, OR (95% CI) = 0.56 (0.35–0.89), P = 0.01). No significant association was found in other groups (Table 3, Fig. 3).

Test of heterogeneity

Heterogeneity was observed in all the subjects. Thus, a random effects model was adopted except for the "< 60 years" group. In order to find the possible sources of heterogeneity, we carried out a meta-regression analysis. However, no source of heterogeneity was found except for age. Next, based on the types of OA, ethnicity, and age, we carried out subgroup analyses.

Publication bias

The potential publication bias was assessed qualitatively using funnel plots. Taking the allele contrast model (2G vs. 1G) as an example, we analyzed the results of the funnel plots and found no apparent asymmetry (Fig. 4). Moreover, the potential publication bias was tested by the Begg's and Egger's tests, for which the P values were all greater than 0.05 (Egger's: P = 0.89; Begg's: P = 0.80), indicating no publication bias.

Discussion

Lately, there have been an increasing number of studies examining the association between genetic polymorphisms and the occurrence of OA. Genetic factors have been reported to play a key role in the occurrence of OA. Notably, family and twin studies have shown that genetic factors have a significant influence on more than half of the patients with OA. Many genes have been studied.
reported to promote the occurrence and development of OA, although the effects were relatively minor.\textsuperscript{13} MMP-1 is one such important gene that has been most closely associated with OA.\textsuperscript{5,18,19} Recently, multiple studies were conducted to find the association between 1G/2G polymorphism and OA risk\textsuperscript{2,14–17}; however, the results were inconsistent.

The current study aimed to conduct a meta-analysis to find an association between 1G/2G polymorphism and OA risk among different studies. In this meta-analysis, no significant association was demonstrated in any of the models, which is inconsistent with the conclusions of other studies on MMP-1 polymorphism. Many factors can lead to the occurrence of OA, such as different genetic backgrounds and lifestyles. Type II error could also lead to inaccuracy of the result of 1G/2G polymorphism. Recently, some genes, such as GDF5, FILIP1, and COG5, have been confirmed to have a close relationship with occurrence of OA by genome-wide association studies (GWAS); however, MMP-1 1G/2G polymorphism was not confirmed.\textsuperscript{20} Moreover, other factors, including age, sex, and environmental factors, are considered to be related to the occurrence of OA. Thus, we carried out subgroup-analysis and found that the relationship between 1G/2G polymorphism and OA risk only existed among the “< 60 years” group, but not among other groups. This result is consistent with some studies, where a significant association was found between 1G/2G SNP polymorphism and knee OA, when the average age of the population was about 50 years old.\textsuperscript{15,16} It is not yet completely clear why this
link exists only in young populations. However, we propose that at a young age, the pathogenic factors and pathogenesis may be relatively simple, and genes may play a leading role in the development of the disease. With aging, the internal and external environment of the body changes, likely allowing multiple other pathogenic factors to influence the pathogenesis, which becomes complex. Thus, the role of genes may become relatively weak at an older age. In addition, the differences in lifestyle and environmental factors among different groups of people are related to occurrence of OA and may also interact with genes.

This meta-analysis study has some inevitable limitations. First, there was considerable heterogeneity between studies on 1G/2G polymorphism, which may lead to misinterpretation of the meta-analysis results. Second, the total sample size from all eligible studies may not be enough to draw a robust conclusion. In addition, information on factors proven to be closely related to the occurrence of OA, such as smoking, trauma, overweight and drug therapy, were not available or considered in this study. Future studies including such detailed information may lead to more accurate conclusions.

Conclusions

In conclusion, the meta-analysis shows that 1G/2G polymorphism may increase the susceptibility to OA among the younger population. However, because of the existence of inevitable limitations, the conclusion should be carefully interpreted and more studies with detailed information are needed to validate our conclusion.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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