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

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ABSTRACT

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 strength of 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; 2 G 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.

Introduction

Osteoarthritis (OA) is a multifactorial disease and often occurs among middle-aged and elderly people.[1] 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.[2,3] Low expression of MMP-1 in normal cells contributes to the remodeling of healthy cartilage.[4] 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.[5,6] Many kinds of cells can express the MMP-1 gene, which is located on the long arm of chromosome 11.[7] 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[8,9]. 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

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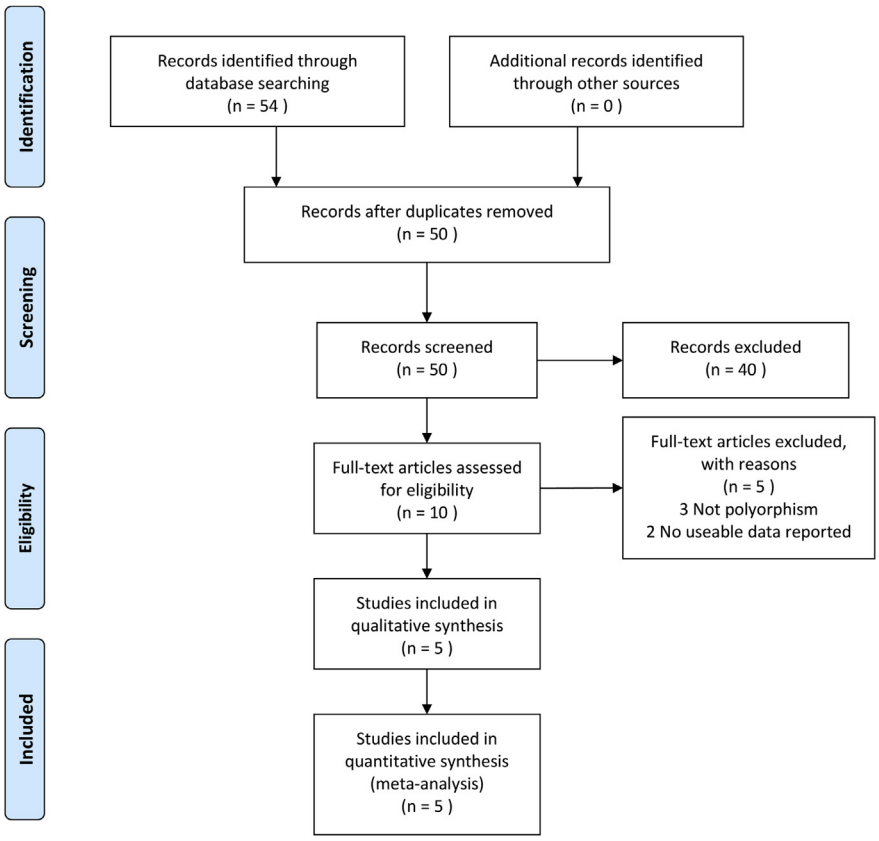

Fig. 1. Flowchart of the study selection.

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 (χ^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
	Case	Control							
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.

Table 2
Distributions of genotypes and alleles among cases and controls.

Study	Case				Control						P_{HWE}
	1G1G	1G2G	2G2G	1G	2G	1G1G	1G2G	2G2G	1G	2G	
Allah 2012	27	46	27	100	100	50	40	10	140	60	0.63
Barlas 2009	31	57	68	119	193	5	24	52	34	128	0.33
Lepetsos 2014	28	64	63	120	190	34	58	47	126	152	0.06
Luo 2015	49	91	66	140	157	63	93	29	156	122	0.10
Yang 2015	27	88	92	142	272	20	89	98	129	285	0.97

HWE, Hardy–Weinberg equilibrium.

Results

Characteristics of the studies

Based on the search terms, a total of 54 studies were selected. Among these, only 5 studies were eligible after applying the criteria, and 49 studies were excluded; the detailed process of study selection is shown in Fig. 1. The first author's name, genotyping method, diagnostic criteria, publication year, ethnicity, distributions of genotypes and alleles in OA cases and controls and HWE of controls for each study are listed in Table 1 and Table 2. The genotype distributions of the control groups were all consistent with the HWE.

Quantitative synthesis

The results of the meta-analysis for 1G/2G polymorphism and OA risk are listed in Table 3.

Overall population

After screening, 5 studies were finally selected for conducting the meta-analysis. Upon completion of whole analysis, no significant association was observed in all the models (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), $P = 0.41$; 2 G vs. 1G, OR (95%CI) = 0.90 (0.86–1.54), $P = 0.66$) (Table 3, Fig. 2).

Subgroup analysis

In our study, we found that a relationship between the 1G/2G polymorphism and OA risk only existed among 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, $P = 0.00$; 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.[10] Notably, family and twin studies have shown that genetic factors have a significant influence on more than half of the patients with OA.[11,12] Many genes have been

Table 3
Meta-analysis for 1G/2G polymorphism with OA risk.

Category	n[a]	2G2G vs. 1G1G				2G2G + 2G1G vs. 1G1G				2G2G vs. 2G1G + 1G1G				2G vs. 1G			
		I^2 (%)	$P^{b,c}$	OR (95% CI)	P^d	I^2 (%)	$P^{b,c}$	OR (95% CI)	P^d	I^2 (%)	$P^{b,c}$	OR (95% CI)	P^d	I^2 (%)	$P^{b,c}$	OR (95% CI)	P^d
Total	5	87.8	0.00	0.69 (0.36–1.32)	0.54	80.9	0.00	0.88 (0.47–1.63)	0.69	87.1	0.00	1.30 (0.68–2.47)	0.41	89.0	0.00	0.90 (0.86–1.54)	0.66
OA type																	
Knee	4	88.3	0.00	1.06 (0.35–3.25)	0.90	84.7	0.00	1.00 (0.43–2.34)	0.98	84.7	0.00	1.09 (0.55–2.14)	0.79	91.1	0.00	0.96 (0.52–1.76)	0.90
Other	1	/	/	2.92 (1.64–5.19)	0.00	/	/	0.60 (0.38–0.9)	0.02	/	/	2.53 (1.54–4.15)	0.00	/	/	0.69 (0.50–0.96)	0.03
Ethnicity																	
Asian	2	90.6	0.00	1.22 (0.25–5.99)	0.61	79.0	0.02	0.89 (0.39–2.03)	0.79	90.7	0.00	1.48 (0.53–4.14)	0.45	80.2	0.02	0.90 (0.55–1.47)	0.68
Caucasian	3	91.0	0.00	1.22 (0.25–5.99)	0.80	87.4	0.00	0.91 (0.30–2.79)	0.87	89.6	0.00	1.20 (0.42–3.48)	0.72	93.6	0.00	0.90 (0.37–2.20)	0.83
Age																	
<60	2	2.5	0.31	3.46 (2.13–5.62)	0.00	41.3	0.19	0.49 (0.31–0.79)	0.00	0.0	0.56	2.74 (1.80–4.16)	0.00	69.7	0.06	0.56 (0.35–0.89)	0.01
≥60	3	83.2	0.00	0.66 (0.23–1.88)	0.43	78.7	0.00	1.42 (0.59–3.39)	0.43	78.6	0.00	0.82 (0.45–1.46)	0.49	87.3	0.00	1.25 (0.71–2.19)	0.44

I^2, 0–25: no heterogeneity; 25–50: modest heterogeneity; 50: high heterogeneity.
[a] Number of studies.
[b] P value for heterogeneity test.
[c] Random effect model was used when P value < 0.05 for heterogeneity test; otherwise, fixed effect model was used.
[d] P value for each test.

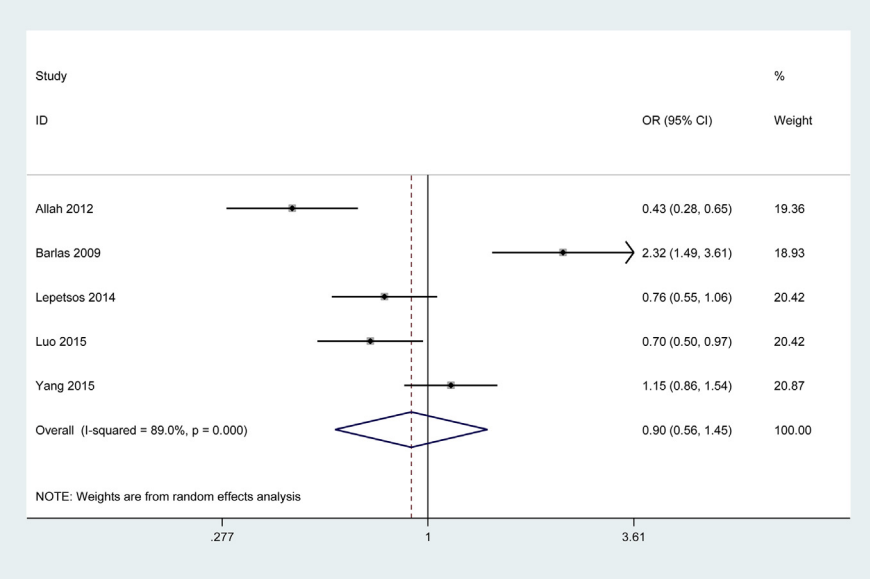

Fig. 2. Forest plot of the association between 1G/2G polymorphism and OA risk (2G vs. 1G).

reported to promote the occurrence and development of OA, although the effects were relatively minor.[13] MMP-1 is one such important gene that has been most closely associated with OA.[5,18,19] Recently, multiple studies were conducted to find the association between 1G/2G polymorphism and OA risk[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.[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.[15,16] It is not yet completely clear why this

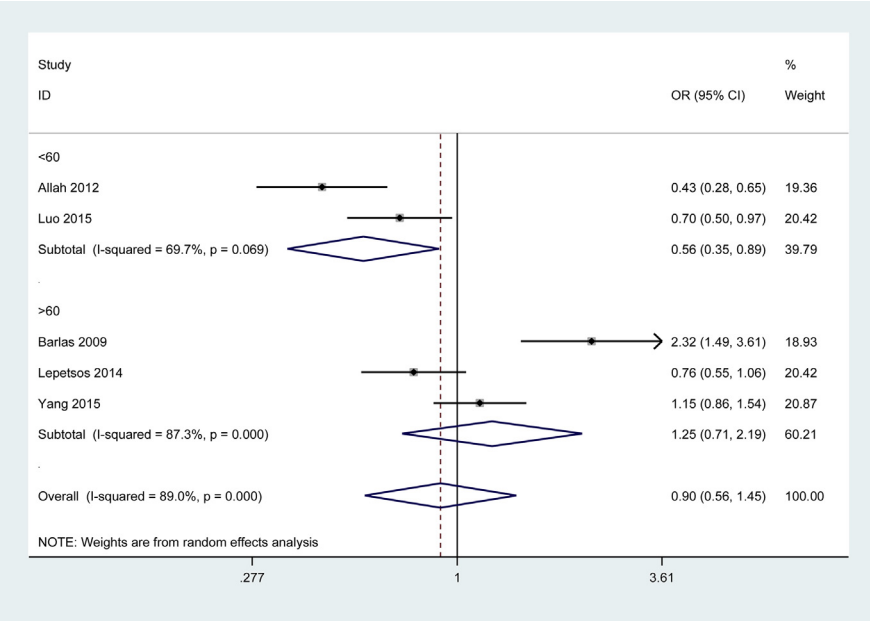

Fig. 3. Forest plot of the association between 1G/2G polymorphism and OA risk in the "< 60 years" group (2G vs. 1G).

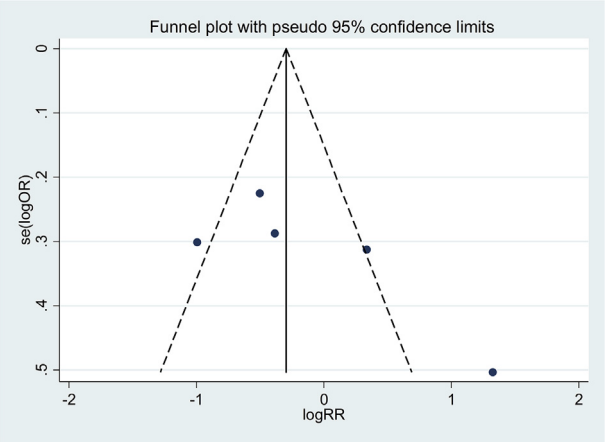

Fig. 4. Funnel plot for publication bias test (2G vs. 1G).

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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