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Review Acticle

The polymorphism of rs1799750 in *matrix metallopeptidase 1 (MMP-1)* gene contributes to osteoarthritis risk: a meta-analysis

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Abstract: Since 2010, many studies have investigated the association between common single nucleotide polymorphism (SNP) rs1799750 located on *matrix metallopeptidase 1* (*MMP-1*) and osteoarthritis (OA) risk; however, the results were inconclusive. To shed light on these contradictory results, we investigated the association between *MMP-1* rs1799750 and OA risk by meta-analytic techniques, combining all published data up to December 2015. A total number of 783 knee or temporomandibular joint (TMJ) OA cases and 748 controls in 5 case-control studies were included in this study and the odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Finally, individuals in homozygote comparison (1G1G vs. 2G2G: OR = 0.528, 95% CI: 0.285-0.979), heterozygote comparison (1G2G vs. 2G2G: OR = 0.599, 95% CI: 0.387-0.927) and dominant model (1G2G/1G1G vs. 2G2G: OR = 0.562, 95% CI: 0.346-0.913) were associated with a significantly decreased risk of OA. Sub-group analysis revealed that the homozygote comparison (1G1G vs. 2G2G: OR = 0.432, 95% CI: 0.251-0.746), heterozygote comparison (1G2G vs. 2G2G: OR = 0.411, 95% CI: 0.276-0.612) and dominant model (1G2G/1G1G vs. 2G2G: OR = 0.415, 95% CI: 0.285-0.603) still showed a decreased risk of OA in TMJ. As for ethnicity, in European, there was a statistically decreased OA risk in homozygote (1G1G vs. 2G2G: OR = 0.609, 95% CI: 0.378-0.980) and dominant model (1G2G/1G1G vs. 2G2G: OR = 0.591, 95% CI: 0.357-0.979). Together with the reported functional studies, the results suggested that *MMP-1* rs1799750 was associated with a significantly decreased risk of OA, especially the TMJ OA.

Keywords: Osteoarthritis, *MMP-1* rs1799750, SNP, meta-analysis

Introduction

Osteoarthritis (OA), the most common age-related degenerative disease of the synovial joint, is a health problem that predominantly affects 10% of men and 18% of women over 60 years of age [1, 2]. OA is characterized by cartilage degradation, formation of osteophytes, and subchondral sclerosis, which has a large economic impact [3]. Although the etiologies of OA are not fully understood, it is clear that genetic components play a role in the risk of developing OA in the knee, hip, or hand [4-6].

Previous studies have indicated an association of *COL11A1*, *VEGF*, *GDF5*, *DVWA* and *IL-8* gene with susceptibility to OA risk [1, 7-9]. These studies can provide new clues for specific disease manifestations, including joint damage, nociception and chronic pain [10]. It therefore remains a necessary to identify candidate genes or risk alleles that contribute to OA pathogenesis.

Recently, the role of *MMP-1* in the development and maintenance of bone and cartilage has been recognized for some time [11]. One genetic variant appears to be important to a single nucleotide polymorphism (SNP) at position -1607 in the *MMP1* promoter region (rs1799750) [12]. This SNP, which causes a guanine insertion/deletion, has been shown to increase *MMP1* expression and matrix degradation. A number of studies in recent years have reported that *MMP-1* rs1799750 was associated with OA risk. Interestingly, the res-

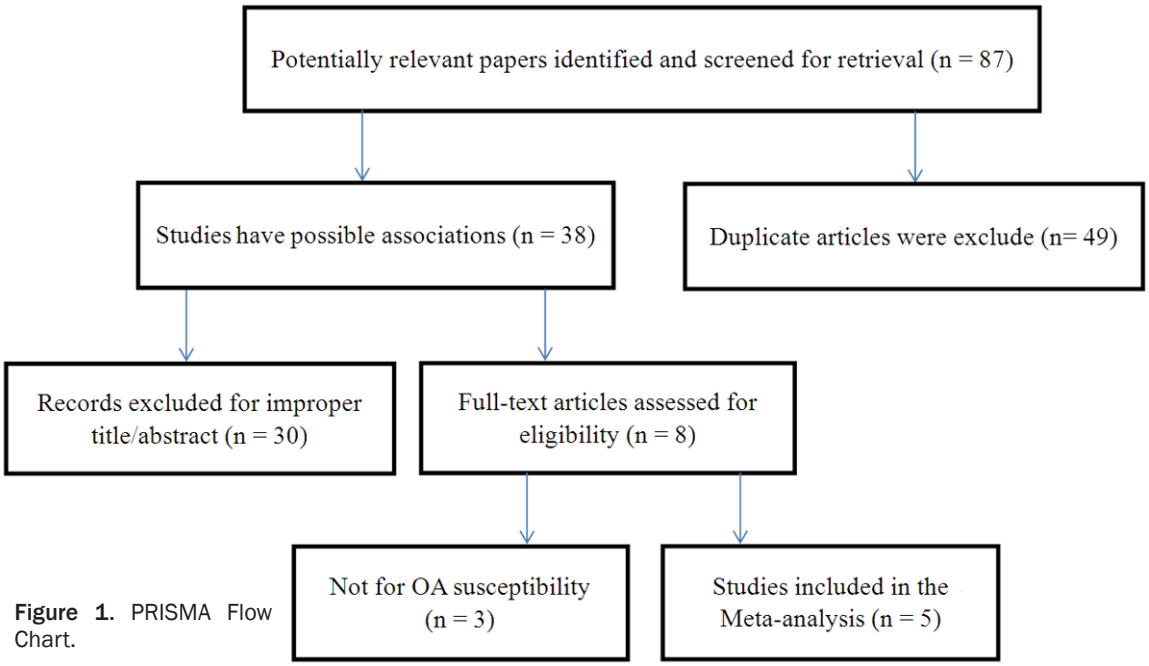


Figure 1. PRISMA Flow Chart.

ults were inconclusive. Planello AC found that SNP rs1799750 was associated with OA risk [13]. Meanwhile, this association was supported by results on a Chinese sample [14]. However, other studies failed to confirm this result in Greek and African populations [15, 16]. Possible reasons proposed for the noted inconsistencies in results include ethnic differences between cohorts, the heterogeneity of OA and perhaps the inadequate statistical power of some of the studies. To deal with the ambiguities raised by inconsistent results among the previous studies, the technology of meta-analysis, which could be performed to provide an effective way to assess size effects in different independent studies while maximizing the overall power.

To confirm the association between *MMP-1* rs1799750 polymorphism and OA risk, we performed the meta-analysis by pooling all eligible studies to calculate the estimate of overall cancer risk and evaluated influence of the types of OA and ethnicity.

Materials and methods

Literature search

A systematic search on the association of SNPs with susceptibility to OA was performed in PubMed and Google scholar. The following keywords used for search were "*MMP-1* OR Matrix metalloproteinase-1", "polymorphism or variation", "*MMP-1* rs1799750 or *MMP-1-1607*", and "Osteoarthritis or joint degeneration". We browsed the abstracts retrieved to identify studies that examined an association between a polymorphism within the *MMP-1* locus and OA risk. All references cited in these studies were also investigated to identify additional studies not indexed by MEDLINE and EMBASE.

Study selection

Studies were selected according to the following inclusion criteria: (1) to be human studies about independent case-control study; (2) to investigate the association between the *MMP-1* rs1799750 polymorphism and OA risk; (3) to present original data on genotype or allele distribution to calculate odds ratios (ORs); (4) the genotype distribution of the control population met the Hardy-Weinberg equilibrium (HWE) model. These studies were assessed by two reviewers using the inclusion criteria and disagreement was subjected to discussion with a third reviewer for a consensus agreement. Moreover, no language or country restrictions were applied.

We excluded the following: (1) studies that non-original data; (2) insufficient information about

Table 1. Characteristics of individual studies included in the meta-analyses

Authors (Ref)	Diseased region	Year	Ethnic group	Sample Size	Case Alleles			Control Alleles		
				case/control	2G2G	1G2G	1G1G	2G2G	1G2G	1G1G
Shufang Luo	TMJ OA	2015	Asian	206/185	66	91	49	29	93	63
Planello AC	TMJ OA	2011	European	115/117	45	44	26	26	66	25
Panagiotis Lepetsos	keen OA	2014	European	155/139	63	64	28	47	58	34
H.Y. Yang	keen OA	2015	Asian	207/207	92	88	27	98	89	20
Somia H	keen OA	2012	Africa	100/100	27	46	27	10	40	50

OA = osteoarthritis; TMJ = temporomandibular joint.

Table 2. Meta-analysis results

	N	1G1G vs. 2G2G			1G2G vs. 2G2G			1G1G/1G2G vs. 2G2G			1G1G vs. 2G1G/ 2G2G		
		OR	95% CI	p_h	OR	95% CI	p_h	OR	95% CI	p_h	OR	95% CI	p_h
Total	5	0.528*	0.285-0.979	0.002	0.599*	0.387-0.927	0.016	0.562*	0.346-0.913	0.002	0.734	0.479-1.126	0.020
OA Types													
TMJ OA	2	0.432*	0.251-0.746	0.234	0.411*	0.276-0.612	0.79	0.415*	0.285-0.603	0.757	0.772	0.442-1.349	0.139
Keen OA	3	0.581	0.206-1.637	0.002	0.807	0.523-1.246	0.161	0.685	0.361-1.301	0.011	0.704	0.337-1.472	0.009
Ethnicities													
Asian	2	0.696	0.170-2.844	0.001	0.683	0.284-1.644	0.008	0.673	0.241-1.880	0.001	0.895	0.393-2.039	0.029
European	2	0.609	0.378-0.980*	0.964	0.574	0.273-1.207	0.064	0.591*	0.357-0.979	0.174	0.839	0.537-1.31	0.286
African	1	0.200*	0.084-0.474	NA	0.426*	0.184-0.978	NA	0.300*	0.346-0.913	NA	0.370*	0.205-0.667	NA

N = number of studies included; OA = osteoarthritis; TMJ = temporomandibular; OR = odds ratio; p_h = *p* value for heterogeneity. NA = not available. *OR with statistical significance.

genotype frequency; (3) studies in which rheumatoid, inflammatory, or other forms of arthritis were not incorporated in the OA datasets; and (4) studies using non-human subjects or specimens.

Data extraction

We collected data including: (1) author's first name; (2) years of publication; (3) country origin; (4) ethnicity of study population; (5) the number of cases and controls; (6) and genotype frequency information for the *MMP-1* rs1799750 polymorphism from each available study. When HWE in the controls was not reported, an online program (https://ihg.gsf.de/cgi-bin/hw/hwa1.pl) was used to test the HWE by x^2 test for goodness of fit.

Statistical analysis

ORs and 95% confident intervals (CIs) were performed to evaluate the strength of the correlation between *MMP-1* rs1799750 polymorphism and the risk of OA by means of pooled. We calculated the pooled ORs for homozygote model (1G1G versus 2G2G), heterozygote model (2G1G versus 2G2G), dominant model (1G1G/1G2G versus 2G2G), recessive model (1G1G versus 1G2G/2G2G), respectively. Heterogeneity among the trials was analyzed in this study using the Q statistic (significance level of p value < 0.05) and the I^2 test (greater than 50% as evidence of significant inconsistency). If significant heterogeneity ($p < 0.05$ or $I^2 > 50\%$) was achieved, the random effect model was used to combine the effect sizes of the included studies. The fixed-effects model was selected to pool the data when heterogeneity was not indicated [17]. The random-effects model assumes that studies show substantial diversity, and assesses both within-study sampling errors and between-study variances [18]. The fixed-effect model assumes that genetic factors have similar effects on disease susceptibility across all of studies, and that observed variations between studies are caused by chance alone [19, 20]. In addition, subgroup analyses were stratified by ethnicity and types of OA. Potential publication bias was estimated by the Begg test. Funnel plot asymmetry was used to analyze and display Egger's results. All calculations were measured and analyzed by the software program STATA (version 11.0).

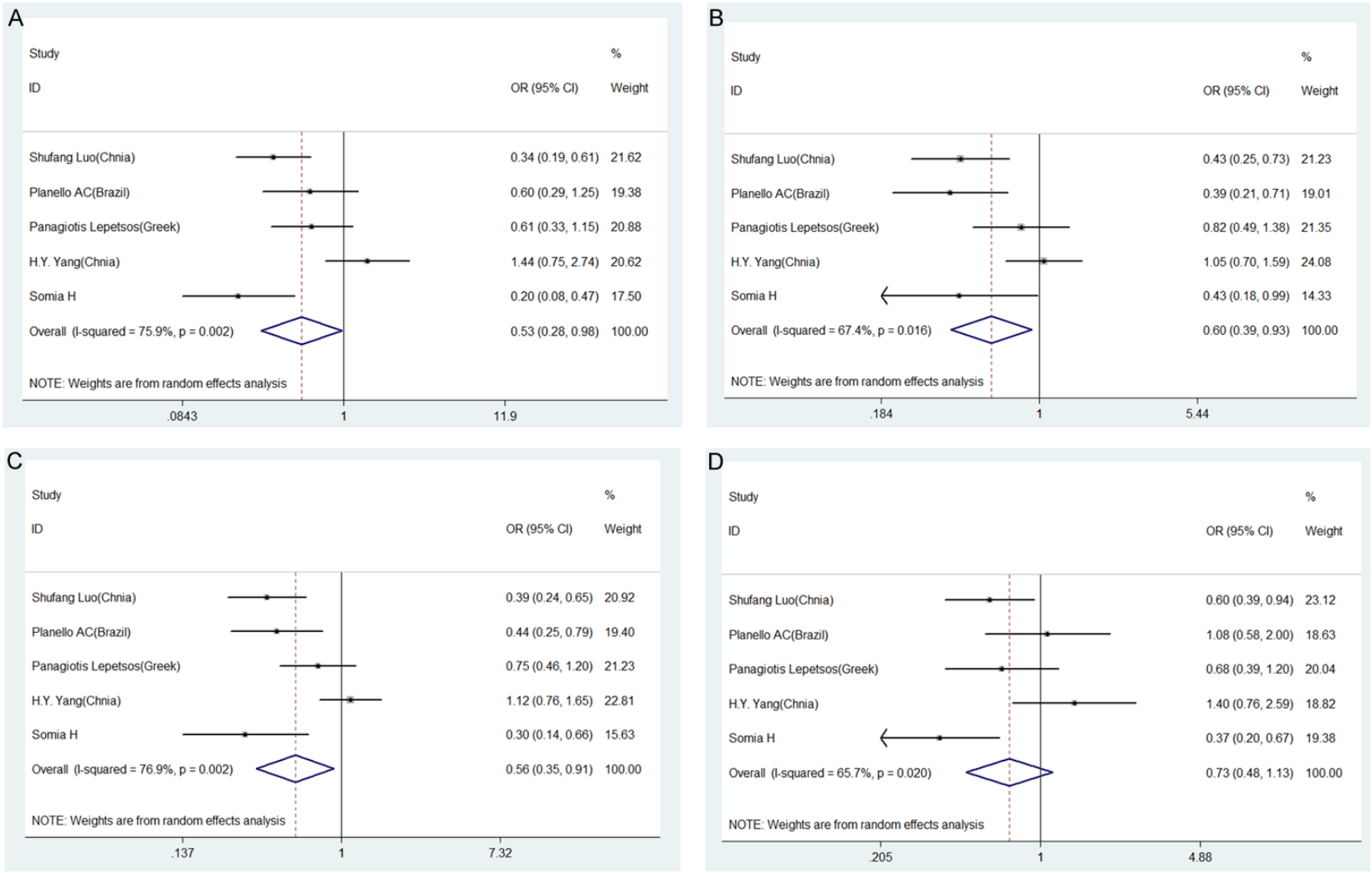


Figure 2. ORs and 95% CIs for individual studies and pooled data for the association between the different genotypes of the *MMP-1* rs1799750 polymorphism. The different genotypes of inheritance are analyzed as follows: A. Represents the forest plot of homozygote comparison for overall comparison (1G1G vs. 2G2G); B. Forest plot of heterozygote comparison for overall comparison (1G2G vs. 2G2G); C. Forest plot of dominant model (1G2G/1G1G vs. 2G2G); D. Forest plot of recessive model (1G1G vs. 2G1G/2G2G).

Results

Eligible studies selected for meta-analysis of MMP-1 and OA risk

By the electronic and manual searching using above key words (SNP, rs1799750, *MMP-1*, and osteoarthritis), we have identified approximately 87 relevant papers, including 38 studies that potentially showed an association between *MMP-1* rs1799750 and OA risk. After exclusion of duplicated studies and improper studies determined by reading the title and abstracts, 5 studies were eventually subjected to meta-analysis of the association between SNP rs1799750 of *MMP-1* and OA risk. The detailed process of literature screening is outlined in **Figure 1**. In these eligible case-control studies, 783 OA cases and 748 controls were identified according to the inclusion and exclusion criteria. Among these studies, there were 2 studies of TMJ OA and 3 study of keen OA. The basic information of each included literature can be found in **Table 1**.

The diagnosis of OA in all patients was based on the radiological score > 2 in Kellgren and Lawrence scale or the history of joint replacement in all studies. Blood sample was used for genotyping in all studies. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was used for genotyping in 4 studies [13-16] and TaqMan genotyping assay was performed in the other 1 study [21]. HWE of genotype distribution in the controls was tested in all studies and they were all in consistent with HWE ($P > 0.05$).

Meta-analysis results

We observed a significantly decreased risk of OA susceptibility in homozygote comparison (1G1G vs. 2G2G: OR = 0.528, 95% CI: 0.285-0.979; $P_{heterogeneity} = 0.002$), heterozygote comparison (1G2G vs. 2G2G: OR = 0.599, 95% CI: 0.387-0.927; $P_{heterogeneity} = 0.016$) and dominant model (1G1G/2G2G vs. 2G2G: OR = 0.562, 95% CI: 0.346-0.913; $P_{heterogeneity} = 0.002$) when all eligible studies were pooled. The association strength between *MMP-1* rs1799750 polymorphism and OA risk were shown in **Table 2** and **Figure 2**. As shown in **Table 2** and **Figure 2**, no significant association was found in recessive model (1G1G vs. 1G2G/2G2G: OR = 0.734, 95% CI: 0.479-1.216; $P_{heterogeneity} = 0.020$).

We then performed sub-group analyses to investigate the effect of the types of OA and ethnicity. As for OA types, decreased the risk of TMJ OA was found in the homozygote comparison (1G1G vs. 2G2G: OR = 0.432, 95% CI: 0.251-0.746; $P_{heterogeneity} = 0.234$), heterozygote comparison (1G2G vs. 2G2G: OR = 0.411, 95% CI: 0.276-0.612; $P_{heterogeneity} = 0.790$) and dominant model (1G1G/2G2G vs. 2G2G: OR = 0.415, 95% CI: 0.285-0.603; $P_{heterogeneity} = 0.757$) (**Table 2**; **Figure 3**). In the sub-group analyses of keen OA, we did found any significant association between *MMP-1* rs1799750 polymorphism and OA risk.

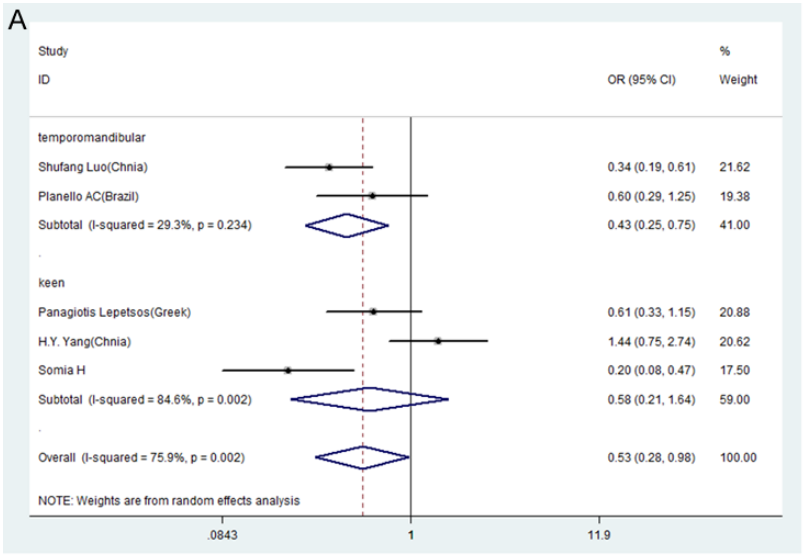
Ethnicity, however, affected OA susceptibility greatly. In European, there was a statistically decreased OA in the comparison of homozygote (1G1G vs. 2G2G: OR = 0.609, 95% CI: 0.378-0.980; $P_{heterogeneity} = 0.964$) and dominant model (1G1G/2G2G vs. 2G2G: OR = 0.591, 95% CI: 0.357-0.979; $P_{heterogeneity} = 0.174$) (**Table 2**; **Figure 4**). The results in European were similar to that of overall comparisons of pooled eligible studies. In Asian, however, no significant association was found in each comparison. Taken together, these results revealed that *MMP-1* rs1799750 polymorphism was only associated with a decreased risk of OA in European.

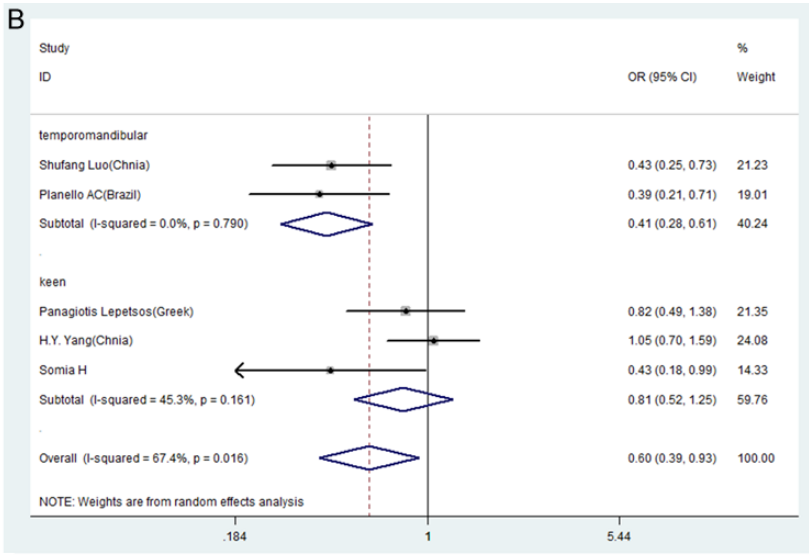
Test of heterogeneity and sensitivity

Between-study heterogeneity was observed in meta-analysis of the *MMP-1* rs1799750 polymorphism and OA risk in the overall group (**Table 2**). However, the heterogeneity was resolved when the analysis was stratified by ethnicity and OA types (**Table 2**). 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. Publication bias was assessed by Begg's funnel plot and Egger's test. The results showed no evidence of publication bias in the meta-analyses of association between the *MMP-1* rs1799750 polymorphism and susceptibility to OA (Egger's regression test *p*-values > 0.1, **Figure 5**).

Discussion

OA, involving environmental and genetic factors, is characterized by morphological, biochemical, molecular, and biomechanical chang-





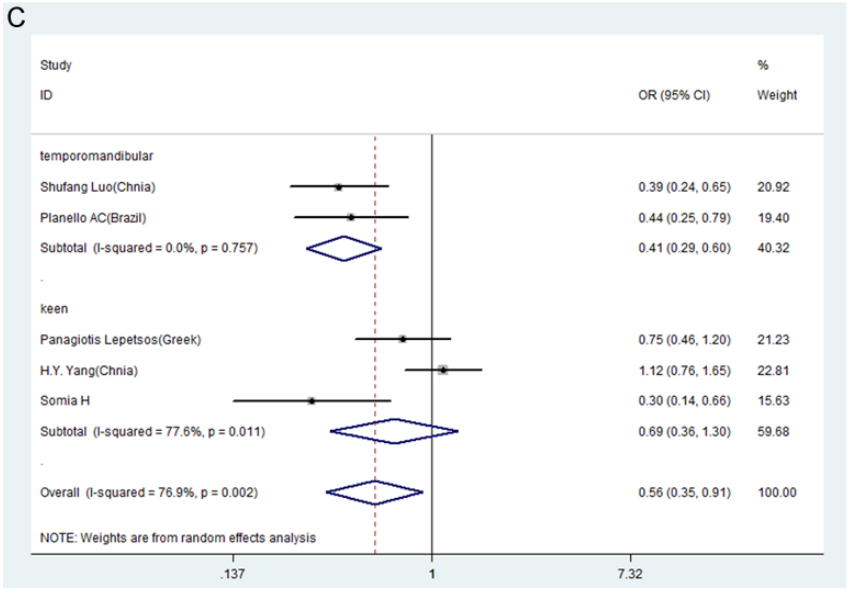


Figure 3. ORs and 95% CIs for individual studies and pooled data for the association between the different genotypes of the *MMP-1* rs1799750 polymorphism and TMJ OA. The different genotypes of inheritance are analyzed as follows: A. Represents the forest plot of homozygote comparison for overall comparison (1G1G vs. 2G2G); B. Heterozygote model (1G2G vs. 2G2G); C. Dominant model (1G2G/1G1G vs. 2G2G).

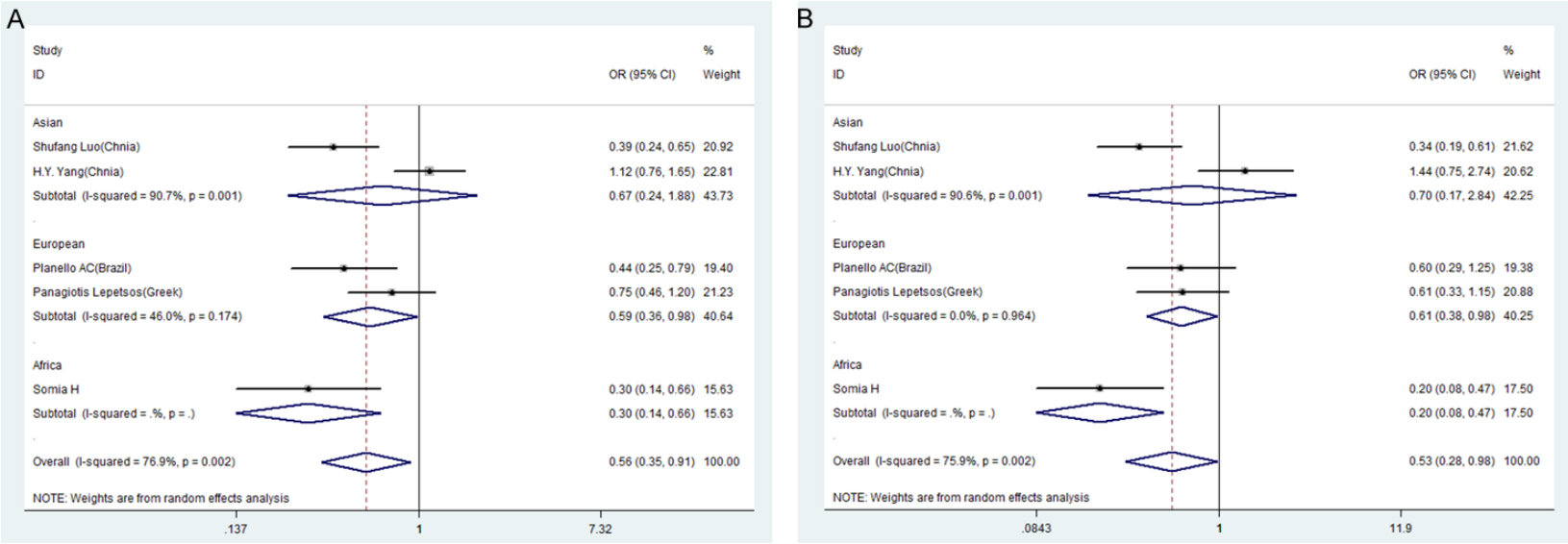


Figure 4. ORs and 95% CIs for individual studies and pooled data for the association between the different genotypes of the *MMP-1* rs1799750 polymorphism and OA risk in sub-group analyses by ethnicity. The different genotypes of inheritance are analyzed as follows: A. Forest plot of dominant model comparison for overall comparison (1G2G/1G1G vs. 2G2G); B. Represents the forest plot of homozygote comparison for overall comparison (1G1G vs. 2G2G).

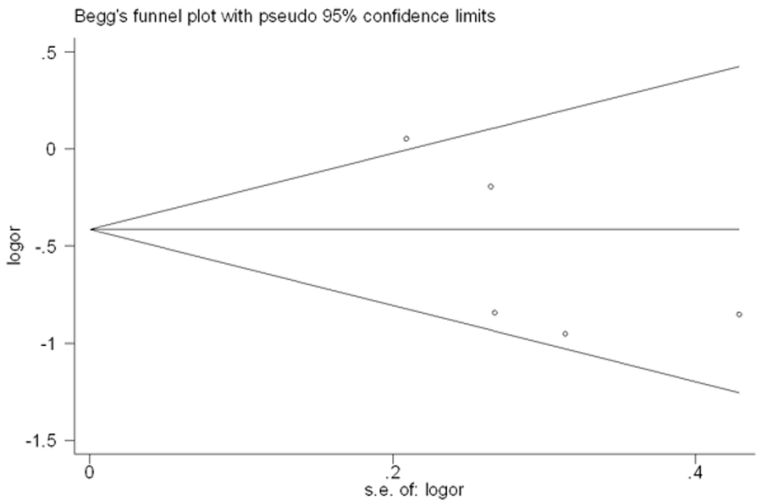


Figure 5. Funnel plot of all 5 eligible studies, Egger's test $P = 0.154$.

es of both cells and extracellular matrix (ECM) which lead to a softening, fibrillation, ulceration, loss of articular cartilage, sclerosis of subchondral bone, osteophytes, and subchondral cysts. Matrix metalloproteinases (MMPs) are the family of degradation enzymes, which play a role in breaking down the components of the ECM [22, 23]. Interestingly, *MMP-1* is a collagenase that splitting the triple helical part of the fibrillar collagen of types I, II and III, and initiates the degradation process [12, 24, 25]. An insertion/deletion of guanine at position -1607 has been identified in the promoter of the human *MMP-1* gene. Nevertheless, the SNP rs1799750 has been reported that it is associated with the rapid progression of several types of inflammatory diseases [26].

In the present study, 5 eligible studies, including 783 cases and 748 controls, were identified and analyzed. We demonstrated the association between *MMP-1* rs1799750 and OA risk by a meta-analysis to obtain a powerful conclusion. To the best of our knowledge, this is the first meta-analysis providing comprehensive insights into the effects of the *MMP-1* rs1799750 and risk of OA in European and African, with very highly significant association for the TMJ OA strata as measured by homozygote, heterozygote, dominant model comparison.

In the sub-group analysis of OA types, no significant association was found in keen OA. But for the 3 studies of keen OA, one of them was found increased risk with 1G variant allele carriers; one had no significant difference; and the other play a protective role against the development OA. This discrepancy may be explained by the reason that ethnicity of the studies was completely different. Additionally, the sample size was relatively small and there was a high possibility of chance due to insufficient statistical power.

Our ethnic-specific meta-analysis shows that there was a decreased OA risk with 1G2G and 1G2G/1G1G genotype in European population. In addition, a trend of reduced OA risk was found in African population, which was in consistent with our pooled analysis. But, there was no significant difference between OA risk and rs1799750 in Asian. The differences may be explained by genetic diversities, different risk factors in life styles, and the exposure to different environmental factors.

For heterogeneity, ethnicity and sample size were found as the source of heterogeneity. Studies of small size may contribute to a small-study effect, but sample size was not considered for heterogeneity in previous meta-analyses. However, this kind heterogeneity is difficult to exclude, because recruitment of enough cases with specific kind of OA is difficult. It is expected that more studies are published in several ethnicity and larger size.

However, some limitations in our meta-analysis should be mentioned. First, our results were based on unadjusted estimates; more accurate outcomes would result from adjustments for other confounders such as gender, age, body mass index, lifestyle, and so on. Second, the studies included in this analysis were insufficient, especially in terms of a subgroup analysis. Thus, potential publication bias is very likely to exist, in spite of no evidence obtained from our statistical tests. Third, language of studies was limited to English, which may results in potential language bias.

In conclusion, our meta-analysis confirms that the *MMP-1* rs1799750 polymorphism was associated with susceptibility to OA in Europeans.

Our data supports the notion that common genetic variants were shared OA risk. Given the important roles of *MMP-1* in immunologic processes and the ethnic differences in *MMP-1* allele frequencies, larger-scale studies in different ethnic populations will help to elucidate the roles of specific *MMP-1* gene polymorphisms in the pathogeneses of OA.

Disclosure of conflict of interest

None.

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