

# Association of BMP-14 rs143383 polymorphism with its susceptibility to osteoarthritis

## A meta-analysis and systematic review according to PRISMA guideline

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### Abstract

**Background:** Osteoarthritis (OA) is a complex disease which can be caused by both environmental and genetic factors. A functional locus rs143383 of bone morphogenetic protein-14 (*BMP-14*) has been pointed out to be associated with OA etiology, but conflicting conclusions have been reached. To provide a more comprehensive conclusion about this issue, we performed this meta-analysis.

**Methods:** Relevant studies were searched from electronic databases including PubMed, Chinese National Knowledge Infrastructure, Embase, and Wanfang. The strength of correlations was examined with pooled odds ratios (ORs) and 95% confidence intervals (95% CIs). Subgroup analyses stratified by ethnicity and source of control were carried out. All statistical analyses were performed with STATA software (version 12.0).

**Results:** Overall, *BMP-14* rs143383 polymorphism was negatively correlated with the susceptibility to knee OA and hand OA under genetic contrasts of CC versus TT, CC+TC versus TT, CC versus TT+TC, C versus T, TC versus TT (OR=0.71, 95% CI=0.65–0.79; OR=0.81, 95% CI=0.73–0.89; OR=0.79, 95% CI=0.71–0.86; OR=0.85, 95% CI=0.81–0.90; OR=0.84, 95% CI=0.75–0.93), and TC versus TT, CC versus TT+TC, C versus T (OR=0.76, 95% CI=0.65–0.89; OR=0.79, 95% CI=0.68–0.92; OR=0.90, 95% CI=0.85–0.95), respectively; similar results were observed in subgroups after stratification analyses. Additionally, the polymorphism also reduced hip OA risk in Asian group after stratified analysis by ethnicity.

**Conclusion:** *BMP-14* rs143383 polymorphism may be a protective factor against OA occurrence.

**Abbreviations:** 95%CI = 95% confidence interval, BMP-14 = bone morphogenetic protein-14, GDF5 = growth and differentiation factor-5, NOS = Newcastle–Ottawa Scale, OA = osteoarthritis, OR = odds ratio.

**Keywords:** BMP-14, meta-analysis, osteoarthritis, polymorphism

### 1. Introduction

Osteoarthritis (OA), also called degenerative joint disease or degenerative arthritis, is the most common form of arthritis, with knee and hip OA affecting approximately 3.8% of the world population as of 2010.<sup>[1–3]</sup> The characteristics of OA include not only damage and gradual loss of articular cartilage, but also weakened periarticular muscles, osteophyte formation, ligament laxity, deformed subarticular bone as well as synovial inflammation.<sup>[4]</sup> When the synthesis and degradation of articular cartilage become imbalanced, the cartilage will be worn away and

destroyed, thus leading to OA; so, OA is a chronic degenerative noninflammatory disorder.<sup>[5]</sup> It has been reported that among people over 60 years old, about 10% of men and 18% of women suffer from this disease.<sup>[6]</sup> Aging, hormonal, environmental, and hereditary factors have all been demonstrated to be involved in the occurrence and progression of this disease; and 35% of knee OA cases are caused by genetic components.<sup>[3,7–9]</sup>

Bone morphogenetic protein-14 (*BMP-14*), also known as growth and differentiation factor-5 (*GDF5*), is one of the most frequently studied targets for OA onset.<sup>[10,11]</sup> Belonging to the transforming growth factor- $\beta$  family, it is closely associated with *BMPs*,<sup>[12]</sup> and affects the development, maintenance, and repair of cartilage, bone, and other tissues of synovial joint.<sup>[13–17]</sup> *BMP-14* is involved in chondrogenesis and joint formation, and mutations in its coding gene can lead to diseases, for example, chondrodysplasia.<sup>[18]</sup> Studies on transgenic mice also show that *BMP-14* can regulate the formation, growth, and differentiation of the skeletal elements.<sup>[19–21]</sup> Additionally, *BMP-14* expresses in adult articular cartilage and stimulates the synthesis of proteoglycan in articular cartilage explants.<sup>[22]</sup> All these evidences show that the susceptibility to OA may be affected by *BMP-14* expression. The polymorphism rs143383 in the 5'-untranslated region of *BMP-14* gene has been suggested to modulate the transcriptional activity of the gene, thus being involved in the pathogenesis of OA.<sup>[23]</sup>

The association between *BMP-14* rs143383 polymorphism and OA risk has been investigated in previous studies,<sup>[23–36]</sup> but

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their conclusions were inconsistent. For example, Miyamoto et al<sup>[23]</sup> reported that *BMP-14* rs143383 polymorphism was significantly associated with knee OA in Japanese and Han Chinese. However, a study from Tsezou et al<sup>[31]</sup> supported that rs143383 polymorphism was not related to knee OA in Greek Caucasians. In view of the conflicting results, we retrieved all eligible studies from online databases and undertook present meta-analysis to further explore the role of *BMP-14* rs143383 polymorphism in OA risk.

## 2. Materials and methods

This meta-analysis was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

### 2.1. Search strategy

A systematic search of available studies published between 2007 and 2013 on the relationship between *BMP-14* rs143383 polymorphism and the risk of OA was performed in the databases of PubMed, Embase, Medline, Google Scholar, Wanfang, and Chinese National Knowledge Infrastructure. Primary search words included: “osteoarthritis” or “OA,” “*BMP-14*” or “*GDF5*” or “growth differentiation factor 5,” and “polymorphism” or “variant” or “single nucleotide polymorphism” or “SNP.” For instance, we adopted “osteoarthritis,” “*GDF5*,” and “polymorphism” to search relevant articles in PubMed. Both medical subject heading and nonmedical subject heading terms were applied in the searching process to obtain as many relative papers as possible. Searching language was restricted to English and Chinese. Additional studies were obtained through examining references.

### 2.2. Inclusion and exclusion criteria

The following inclusion criteria were set for eligible studies: original study evaluating the role of *BMP-14* rs143383 polymorphism in OA occurrence; with both cases and controls; providing sufficient genetic data for calculating odds ratios (ORs) and 95% confidence intervals (95% CIs); and focusing on humans. Exclusion criteria included: animal studies; without original data; insufficient genotype information; and reviews, comments, abstracts, or studies not in English and Chinese.

### 2.3. Data extraction

Two investigators undertook data extraction according to a standardized form. Essential information was extracted from all qualified studies, including first author's name, publication year, country, ethnicity, source of control, method for genotyping, the number of participants, distribution of genotypes and alleles, and *P* value for Hardy–Weinberg equilibrium in control group. Any inconsistent opinion was resolved through discussion to reach unanimity. Studies with different ethnic groups were regarded as individual studies for our analysis.

### 2.4. Quality assessment

Quality of eligible studies were independently assessed by 2 investigators based on Newcastle–Ottawa Scale (NOS) which included 3 aspects: selection, comparability and exposure, and each satisfactory answer received 1 point. Studies with a score

equal to or higher than 6 were identified as of high quality, 4 to 5 scores indicated a moderate quality.

## 2.5. Statistical analysis

The strength of correlations between *BMP-14* rs143383 polymorphism and OA risk was estimated with pooled ORs and 95% CIs.  $\chi^2$  test was applied to determine whether the observed genotype frequencies in the control group accorded with Hardy–Weinberg Equilibrium. The significance of the summary OR was assessed by *Z* test. Subgroup analyses were carried out based on ethnicity and control source. Heterogeneity among studies was detected by  $\chi^2$ -based *Q*-statistic test. When *P* value was less than .05 in *Q* test which indicated significant heterogeneity, the random-effects model was used for OR calculation; otherwise, the fixed-effects model was applied. In addition, sensitivity analysis was performed by individually omitting each single study to assess the stability of our results. Furthermore, the possible publication bias was detected with Begg funnel plot and Egger tests. STATA software (version 12.0) was applied for statistical analyses. For all tests, *P* < .05 was considered to represent statistical significance.

## 3. Results

### 3.1. Study characteristics

Figure 1 describes the selection process for eligible studies. Altogether 114 articles were initially retrieved through the database search. Among them, 47 papers were firstly deleted for irrelevant studies (26), concerning prognosis or treatment response (13), and not human studies (8). Then 37 more publications were removed from the remaining 67 papers due to not involving *BMP-14* gene (16) and OA (21). However, after full-text assessment, another 16 records were further excluded for not detecting *BMP-14* rs143383 polymorphism (9), republished data (3), and case-only studies (4). Therefore, altogether 14 eligible articles covering 53,510 participants (19,973 cases and 33,537 controls) were included in the present study.<sup>[23–36]</sup> A total of 38 independent studies published between 2007 and 2013 were incorporated finally. Thereinto, 21 studies focused on knee OA; 9 studies referred to hip OA; and 8 studies were implicated in hand OA. Table 1 displays the characteristics of all eligible studies. Two included studies<sup>[33,34]</sup> were found the relative poor quality through NOS assessment, and the rest studies had the moderate and good quality in this meta-analysis.

### 3.2. Quantitative synthesis

As shown in Table 2, the pooled ORs indicated that *BMP-14* rs143383 polymorphism decreased the risk of knee OA and hand OA under CC versus TT, CC+TC versus TT, CC versus TT+TC, C versus T, TC versus TT (OR=0.71, 95% CI=0.65–0.79 [Fig. 2]; OR=0.81, 95% CI=0.73–0.89; OR=0.79, 95% CI=0.71–0.86; OR=0.85, 95% CI=0.81–0.90; OR=0.84, 95% CI=0.75–0.93) and CC versus TT, CC versus TT+TC, C versus T (OR=0.76, 95% CI=0.65–0.89 [Fig. 3]; OR=0.79, 95% CI=0.68–0.92; OR=0.90, 95% CI=0.85–0.95) genetic models, respectively. Furthermore, a similar trend was observed in Asian (Fig. 2), Caucasian (Fig. 2), hospital-based, population-based, and other-source subgroups after for knee OA after stratified analyses by ethnicity and source of control, as well as in

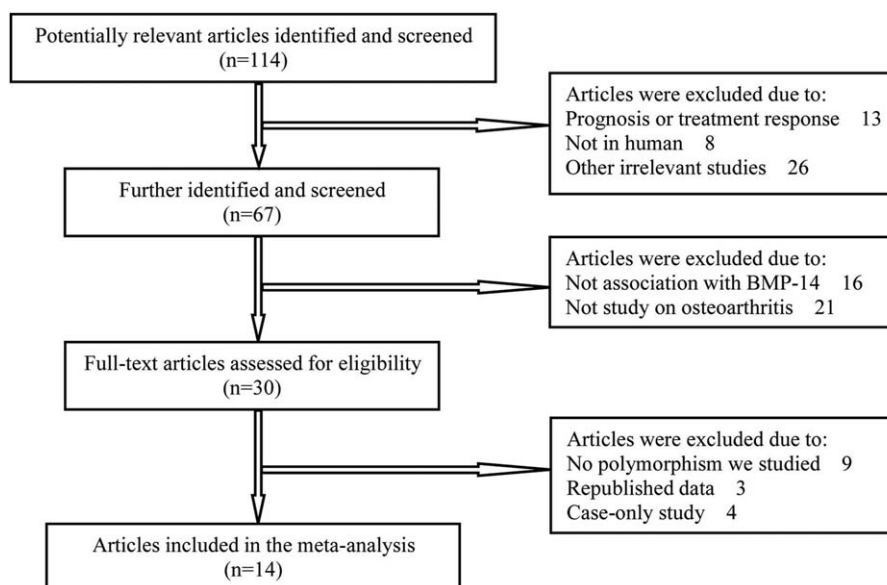


Figure 1. Flowchart of study selection.

population-based group (Fig. 3) for hand OA after stratified analysis by source of control.

As for the risk of hip OA, the polymorphism rs143383 showed no significant correlation in total analysis, but expressed a decreasing effect in Asian group under all 5 genetic comparisons after stratified analysis by ethnicity.

### 3.3. Heterogeneity test

Q test revealed significant heterogeneity for hip OA under all 5 contrasts, so the random-effects model was chosen for calculating ORs. As for knee OA and hand OA, the use of random- or fixed-effects model was determined according to the principle above mentioned. As regards the source of significant heterogeneity, we found that after stratified analysis by ethnicity and source of control, the degree of the significance was alleviated or even eliminated in some subgroups, suggesting the possible origins of heterogeneity might contain but not limit to ethnicity and source of control.

### 3.4. Sensitivity analysis

Sensitivity analysis was carried out to reflect the influence of each dataset on the summary ORs by deleting each single study included in the meta-analysis one by one. No material change was observed in corresponding pooled ORs, which suggested that our overall results were stable and robust.

### 3.5. Publication bias

The possible publication bias was assessed with Begg funnel plot and Egger test. Funnel plot seemed symmetrical (Fig. 4), which was also supported by *P* value of Egger test ( $P = .056$ ). Therefore, no significant publication bias existed in the present study.

## 4. Discussion

OA, a multifactorial disease, affects about 5% of people aged over 45 years old,<sup>[28]</sup> and causes substantial morbidity and

disability, particularly among the elderly, leading to a severe health care burden in developed countries.<sup>[33]</sup> In addition to the degradation of articular cartilage and subchondral bone deformity, OA also can result in a series of other symptoms like joint pain and stiffness; so, OA patients may fail to perform normal daily activities. As yet, OA still can not be completely cured, and the effects of existing treatments are mainly on relieving pains and on enhancing the functions of affected joints.<sup>[37,38]</sup> Therefore, it is crucial important to understand the pathology of the disease so as to facilitate the finding of prevention strategies and/or more effective treatments. Many genes have been reported to be associated with OA susceptibility, including *BMP-14*. The protein encoded by *BMP-14* can regulate chondrogenesis, and the deficiencies of this gene may cause joint development anomaly. *BMP-14* rs143383 polymorphism has been identified to be linked to *BMP-14* expression, and its relationship with the susceptibility to OA has become a hot topic of studies on this issue, but their findings were far from uniform.

In the present meta-analysis, we systematically assessed the contribution of *BMP-14* rs143383 polymorphism to the risk of OA based on 19973 cases and 33537 controls, and found that the SNP reduced the susceptibility to knee OA and hand OA not only in total analysis but also in subgroup analysis. Meanwhile, the polymorphism also exerted a similar effect on hip OA risk in Asian group, though its association with the disease had no statistical significance in total analysis. Generally, the C allele of this polymorphism played a protective role against the risk of OA.

The association of *BMP-14* rs143383 polymorphism with OA risk has been extensively explored in previous studies, but the results are controversial. For example, Tawonsawatruk et al<sup>[30]</sup> investigated the association of *BMP-14* rs143383 polymorphism with the risk of knee OA in Thai population, and found that the TT genotype enhanced the risk of knee OA compared to the CC genotype, showing that the T allele was significantly correlated with increased susceptibility to knee OA. In the study by Mishra et al,<sup>[26]</sup> the TT genotype was also found to be more frequent in case group than in control group, thus suggesting the genotype

**Table 1**  
Major characteristics of all studies incorporated in the meta-analysis.

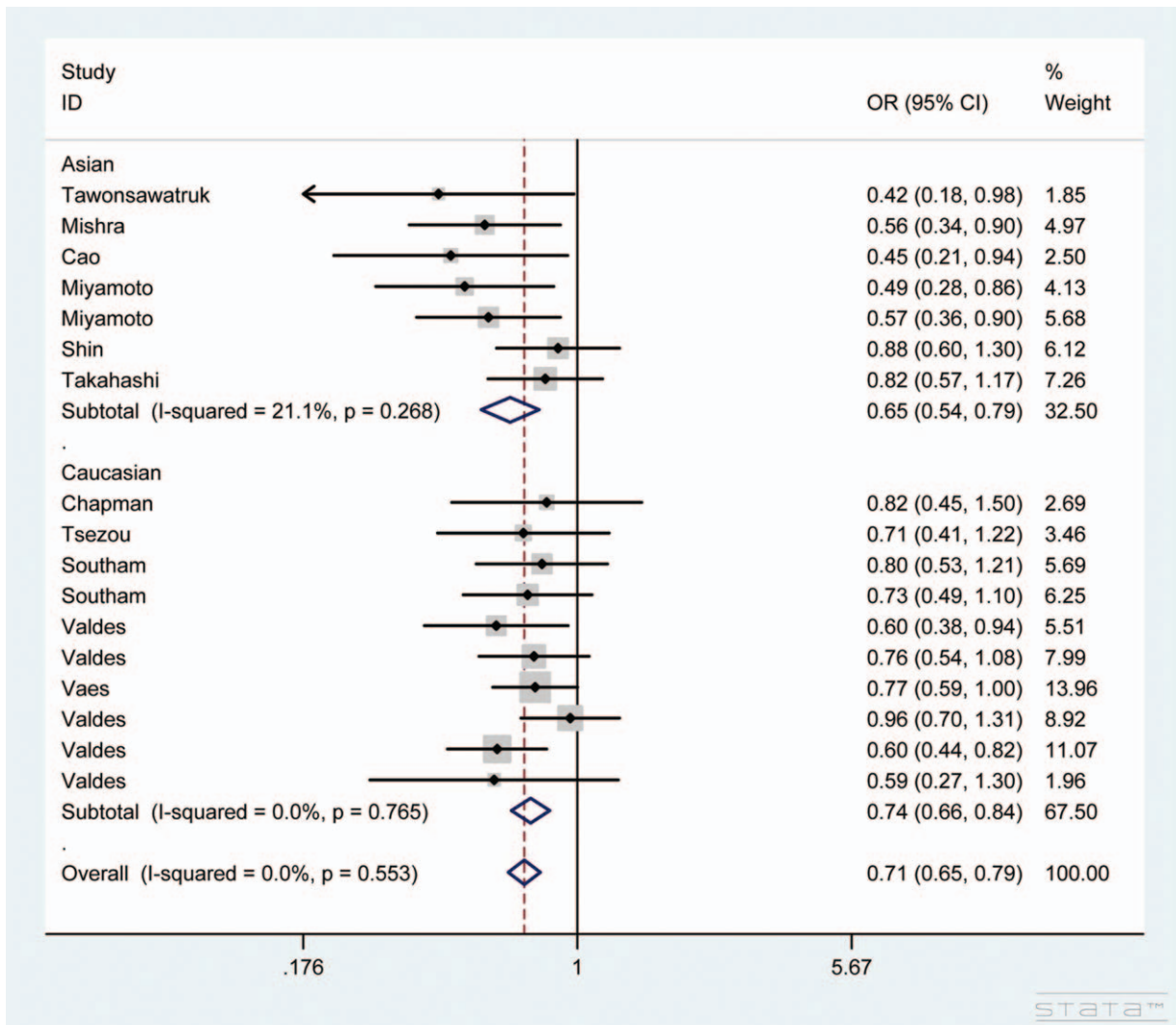
First author	Publication year	Country	Ethnicity	Control source	Genotyping method	Case/control		HWE	NOS			
						Sample size	T			C		
Knee OA												
Tawonsawatruk	2011	Thailand	Asian	HB	PCR-RFLP	90	103	113	63	93	0.424	6
Chapman	2008	UK	Caucasian	PB	Mass spectrometry	142	724	180	104	539	0.558	4
Tsezou	2007	Greece	Caucasian	HB	Direct sequence	251	268	316	186	213	0.669	5
Southern	2007	Spain	Caucasian	HB	TaqMan	274	1196	340	208	951	0.550	5
Southern	2007	UK	Caucasian	HB	PCR-RFLP	349	822	450	248	624	0.262	5
Mishra	2013	India	Asian	HB	PCR-RFLP	300	300	378	222	272	0.188	6
Valdes	2009	UK	Caucasian	PB	Allele-specific PCR	259	509	350	168	412	0.908	3
Valdes	2009	Netherlands	Caucasian	HB	Allele-specific PCR	735	646	987	483	487	0.032	3
Cao	2010	Korea	Asian	PB	PCR-RFLP	276	298	415	137	165	0.361	5
Miyamoto	2007	Japan	Asian	HB	TaqMan, Invader, DNA fragment analysis, or direct sequence	313	485	681	135	289	0.283	4
Miyamoto	2007	Japan	Asian	HB	TaqMan, Invader, DNA fragment analysis, or direct sequence	718	861	1131	305	446	0.966	4
Vaes	2009	Netherlands	Caucasian	PB	TaqMan	667	2097	850	484	1676	0.724	5
Shin	2012	Korea	Asian	PB	High resolution melting analysis	725	1737	1069	381	901	0.176	5
Takahashi	2010	Japan	Asian	HB-PB	TaqMan, Invader, DNA fragment analysis, or direct sequence	933	1225	1445	421	621	0.845	5
Valdes	2011	UK	Caucasian	PB	Allele-specific PCR	1141	536	1445	837	397	0.229	6
Valdes	2011	UK	Caucasian	PB	Allele-specific PCR	867	758	1187	942	547	0.837	6
Valdes	2011	UK	Caucasian	PB	Allele-specific PCR	65	427	88	42	339	0.010	6
Valdes	2011	UK	Caucasian	PB	TaqMan	151	1582	195	107	1234	-	6
Evangelou	2009	Iceland	Caucasian	PB	Centaurus platform	1071	1169	1471	671	755	-	3
Evangelou	2009	UK	Caucasian	Family-based	Illumina platform	177	548	230	124	417	-	3
Evangelou	2009	Finland	Caucasian	Family-based	Mass spectrometry	109	209	124	94	167	-	3
Hip OA												
Vaes	2009	Netherlands	Caucasian	PB	TaqMan	287	2757	353	221	2136	0.672	5
Chapman	2008	UK	Caucasian	PB	Mass spectrometry	106	724	136	76	539	0.558	4
Valdes	2009	UK	Caucasian	HB	Allele-specific PCR	787	646	1029	545	487	0.032	6
Valdes	2009	UK	Caucasian	PB	Allele-specific PCR	77	509	91	63	412	0.908	6
Southern	2007	Spain	Caucasian	HB	PCR-RFLP	1221	822	1565	877	624	0.262	5
Southern	2007	UK	Caucasian	HB	TaqMan	304	1196	361	247	951	0.550	5
Miyamoto	2007	Japan	Asian	HB	TaqMan, Invader, DNA fragment analysis, or direct sequence	998	983	1668	328	511	0.552	4
Evangelou	2009	UK	Caucasian	Family-based	Illumina platform	51	561	72	30	431	-	3
Evangelou	2009	Iceland	Caucasian	PB	Centaurus platform	1724	1169	2353	1095	755	-	3
Hand OA												
Vaes	2009	Netherlands	Caucasian	PB	TaqMan	870	2180	1125	615	1739	0.844	5
Chapman	2008	UK	Caucasian	PB	Mass spectrometry	515	1644	692	338	624	0.262	4
Chapman	2008	UK	Caucasian	PB	Mass spectrometry	200	724	239	909	539	0.558	4
Southern	2007	UK	Caucasian	HB	TaqMan	240	1196	301	179	951	0.550	5
Bijsterbosch	2013	-	Caucasian	PB	Mass spectrometry	248	725	303	193	540	0.480	5
Evangelou	2009	UK	Caucasian	Family-based	Illumina platform	140	645	189	91	496	-	3
Evangelou	2009	Iceland	Caucasian	PB	Centaurus platform	2510	1169	3474	1546	755	-	3
Evangelou	2009	Finland	Caucasian	Family-based	Mass spectrometry	82	209	96	68	167	-	3

HB = hospital-based, HWE = Hardy-Weinberg equilibrium, NOS = Newcastle-Ottawa scale, OA = osteoarthritis, PB = population-based.

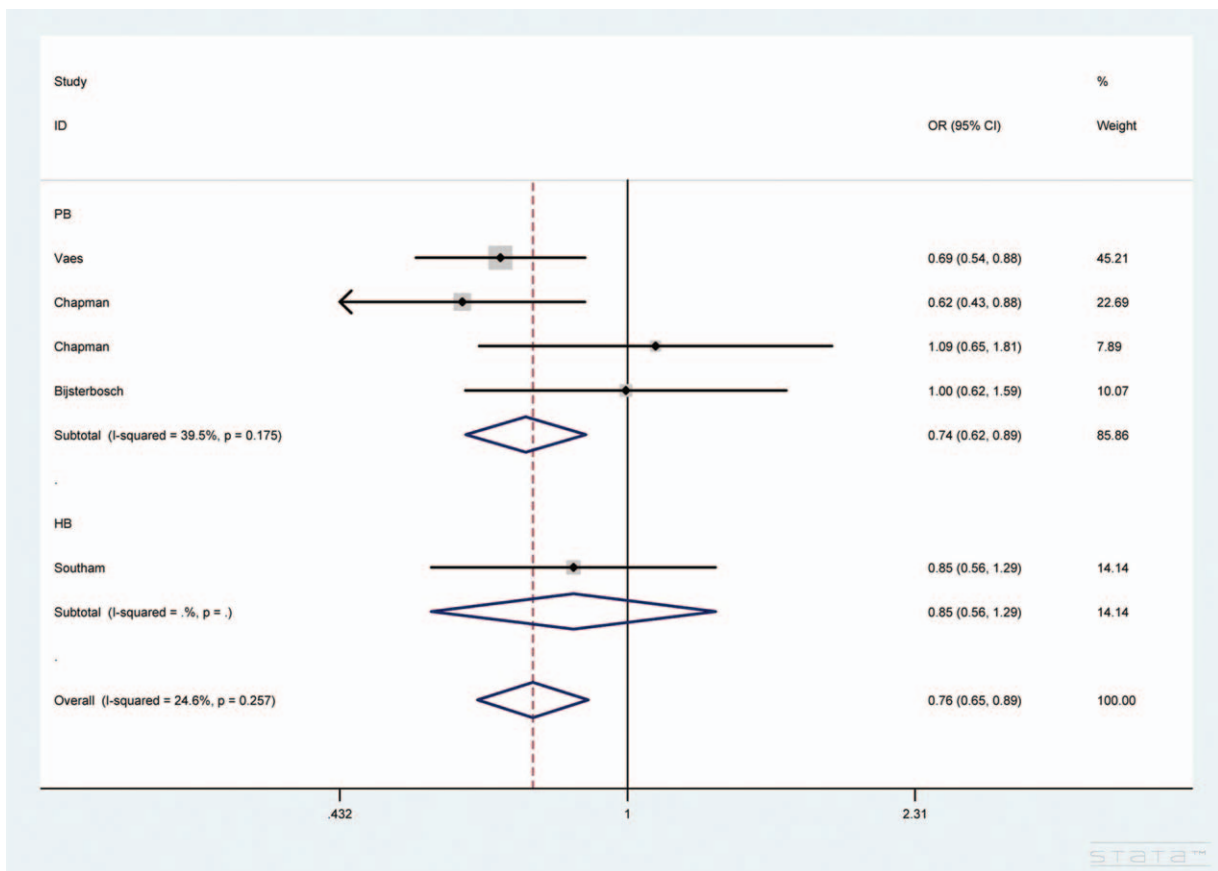
**Table 2**  
**BMP-14 rs143383 polymorphism and OA risk.**

OA location	Group/subgroup	Odds ratio (95% confidence interval)/P value for heterogeneity									
		CC vs TT		CC+TC vs TT		CC vs TT+TC		C vs T		TC vs TT	
Knee OA	Asian	0.65 (0.54–0.79)	.268	0.77 (0.65–0.93)	.002	0.72 (0.61–0.86)	.437	0.80 (0.71–0.91)	.011	0.81 (0.67–0.98)	.003
	Caucasian	0.74 (0.66–0.84)	.765	0.82 (0.73–0.93)	.017	0.81 (0.73–0.91)	.907	0.87 (0.82–0.93)	.187	0.85 (0.74–0.98)	.008
	HB	0.66 (0.56–0.78)	.681	0.76 (0.65–0.88)	.032	0.74 (0.64–0.86)	.703	0.80 (0.73–0.87)	.196	0.80 (0.67–0.94)	.013
	PB	0.74 (0.65–0.85)	.321	0.85 (0.72–0.99)	.003	0.81 (0.71–0.92)	.616	0.88 (0.81–0.95)	.040	0.88 (0.75–1.04)	.003
	Other-source	0.82 (0.57–1.17)	–	0.82 (0.69–0.97)	–	0.88 (0.62–1.26)	–	0.90 (0.79–1.03)	.302	0.82 (0.68–0.98)	–
	Total	0.71 (0.65–0.79)	.553	0.81 (0.73–0.89)	.001	0.79 (0.71–0.86)	.803	0.85 (0.81–0.90)	.020	0.84 (0.75–0.93)	.000
Model for heterogeneity		Fixed		Random		Fixed		Random		Random	
Hip OA	Caucasian	0.91 (0.78–1.06)	.799	0.92 (0.81–1.05)	.214	0.96 (0.82–1.12)	.317	0.95 (0.89–1.01)	.624	0.92 (0.77–1.10)	.043
	Asian	0.34 (0.22–0.53)	–	0.52 (0.43–0.63)	–	0.42 (0.27–0.64)	–	0.56 (0.48–0.65)	–	0.55 (0.46–0.67)	–
	PB	1.01 (0.76–1.34)	.734	0.93 (0.77–1.13)	.727	1.09 (0.82–1.44)	.331	0.98 (0.90–1.07)	.988	0.90 (0.72–1.12)	.347
	HB	0.71 (0.48–1.07)	.001	0.80 (0.57–1.12)	.000	0.77 (0.55–1.08)	.006	0.83 (0.64–1.06)	.000	0.82 (0.59–1.15)	.000
	Other-source	–	–	–	–	–	–	0.67 (0.43–1.04)	–	–	–
	Total	0.81 (0.61–1.07)	.004	0.84 (0.67–1.05)	.000	0.88 (0.68–1.13)	.005	0.88 (0.76–1.01)	.000	0.84 (0.66–1.06)	.000
Model for heterogeneity		Random		Random		Random		Random		Random	
Hand OA	PB	0.74 (0.62–0.89)	.175	0.99 (0.75–1.32)	.001	0.77 (0.65–0.90)	.811	0.92 (0.82–1.04)*	.021	1.06 (0.79–1.42)	.001
	HB	0.85 (0.56–1.29)	–	0.84 (0.63–1.12)	–	0.94 (0.64–1.38)	–	0.90 (0.74–1.10)	–	0.84 (0.62–1.13)	–
	Other-source	–	–	–	–	–	–	0.86 (0.69–1.07)	.167	–	–
	Total	0.76 (0.65–0.89)	.257	0.96 (0.76–1.20)	.003	0.79 (0.68–0.92)	.758	0.90 (0.85–0.95)	.060	1.00 (0.79–1.27)	.002
Model for heterogeneity		Fixed		Random		Fixed		Fixed		Random	

TT, wild homozygous genotype; TC, heterozygous genotype; CC, mutant homozygous genotype. HB=hospital-based, OA=osteoarthritis, PB=population-based.



**Figure 2.** Forest plot for the association between *BMP-14* rs143383 polymorphism and knee OA risk under CC versus TT genetic model. OA=osteoarthritis, BMP-14=bone morphogenetic protein-14.

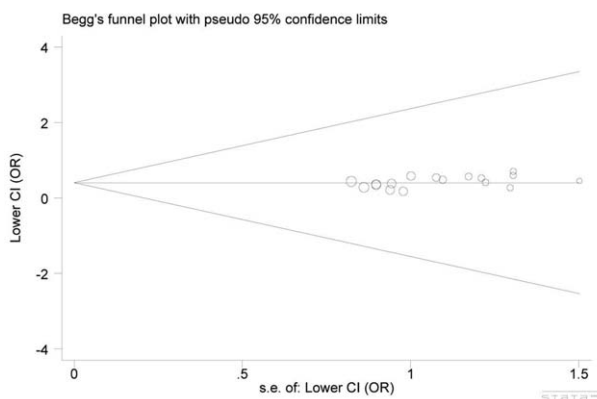


**Figure 3.** Forest plot for the association between *BMP-14* rs143383 polymorphism and hand OA risk under CC versus TT genetic model. OA=osteoarthritis, BMP-14=bone morphogenetic protein-14.

was as a risk factor for knee OA. However, no apparent relationship between rs143383 polymorphism and knee OA risk was detected by Tsezou et al in Greek population.<sup>[31]</sup> Focusing on hand OA risk, Evangelou et al<sup>[33]</sup> revealed that the SNP was also significantly related to the susceptibility to hand OA. Moreover, the C allele of *BMP-14* rs143383 polymorphism was manifested to reduce the risk of hip OA in female carriers.<sup>[35]</sup> Nevertheless, Chapman et al<sup>[28]</sup> revealed no obvious effects of the SNP on the susceptibility to either hand OA or hip OA.

The inconsistent results may be explained by the following aspects: the studied population varied in terms of ethnicity, age, gender, and lifestyle; restricted number of cases and controls might affect the study results; different criteria were used for selecting study participants; and interfering factors were not adjusted in all studies.

Since the present study included altogether 19973 cases and 33537 controls, our results were statistically more powerful than results in any single study. Nevertheless, some limitations of the present study should be addressed. First of all, the majority of included studies provided original data toward Caucasian population, which might reduce the representativeness of our findings in other ethnicity or in general population. Next, language limitation in search strategy might miss some potent reports in other languages, thus leading to possible publication bias not detected by Begg funnel plot or Egger test. Then, significant interstudy heterogeneity existed in the meta-analysis which inevitably affected the precision of our results although we adopted the random-effects model to calculate OR. Besides, about a half of included studies are modulated quality by NOS assessment and the high quality studies are relative small. Last but not least, due to the lack of available information, synergies between genetic and environmental factors were not discussed. Overall, the present study indicates that *BMP-14* rs143383 polymorphism may be correlated with decreased risk of OA. However, better-designed studies covering more ethnicity groups as well as gene-gene and gene-environment interactions should be carried out to verify our results.



**Figure 4.** Begg funnel plot of publication bias.

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