A growing body of evidence suggested that *smad family member 3* gene rs12901499 polymorphism was associated with the risk of osteoarthritis. However, the results of previous studies were conflicting. In the present study, we assessed whether *smad family member 3* gene rs12901499 polymorphism was associated with the risk of osteoarthritis by the meta-analysis. We searched in the databases of PubMed, Embase, and CNKI. Pooled odds ratios and 95% confidence intervals were calculated. Seven papers involving 11 studies (5344 cases and 9080 controls) analyzed the association between *smad family member 3* gene rs12901499 polymorphism and osteoarthritis risk. This meta-analysis confirmed that *smad family member 3* gene rs12901499 polymorphism increased the risk of osteoarthritis. Stratification analysis of ethnicity found that rs12901499 polymorphism increased the risk of osteoarthritis among both Asians and Caucasians [G vs A: Asians, OR and 95%CI, 1.34(1.07, 1.69), *P*= 0.012; Caucasians, OR and 95%CI, 1.21(1.13, 1.29), *P*< 0.001]. In addition, subgroup analysis by type of osteoarthritis revealed that *smad family member 3* gene rs12901499 polymorphism was correlated with the increased risk of hip osteoarthritis, but not associated with knee osteoarthritis. Sensitivity analysis did not draw different findings. In conclusion, this meta-analysis indicates that *smad family member 3* gene rs12901499 polymorphism increased the risk of osteoarthritis.

**Introduction**

Osteoarthritis (OA), a complex and multifactorial disease, is the most common degenerative arthritis characterized by the degeneration of articular cartilage with joint space narrowing, osteophyte formation, and subcondral sclerosis resulting in pain and joint stiffness [1,2]. Accumulating evidence suggests that aging, genetic predisposition, obesity, inflammation, and excessive mechanical loading predispose to OA development [3]. Epidemiological studies suggested that OA has a strong genetic component. A number of candidate genes, such as encoding collagens (particularly for type II collagen) and other structural proteins of the extracellular cartilage matrix, have been deemed to susceptibility loci for primary OA [4,5].

Smad family member 3 (SMAD3) locates on chromosomes 15q21-22. SMAD3 is a key intracellular messenger of the transforming growth factor-β (TGF-β) signaling pathway, which is an important growth factor to the integrity of articular cartilage [6,7]. TGF-β stimulates proteoglycan and type II collagen synthesis, can down-regulate cartilage-degrading enzymes, and is able to counteract interleukin-1-induced suppression of proteoglycan synthesis [8]. Increasing evidence suggests that TGF-β takes important part in the pathogenesis and progression of OA by functioning as key regulators in bone formation, remodeling, and maintenance [6,9,10]. Therefore, it is reasonable to hypothesize that the SMAD3 may be a candidate gene for OA susceptibility.

Recently, several studies explored the relationship between SMAD3 gene rs12901499 polymorphism and OA risk [11–17]. However, the results of these studies were conflicting and inconclusive because of
the clinical heterogeneity, different ethnic populations, and small sample sizes. To precisely elucidate the genetic role for SMAD3 gene rs12901499 polymorphism in the development of OA, we performed a comprehensive meta-analysis to clarify the association between this single nucleotide polymorphism (SNP) and OA risk.

**Materials and methods**

**Identification of eligible studies and data extraction**

We performed a comprehensive literature search throughout PubMed, Embase, and CNKI databases to retrieve the genetic association studies of OA. The following terms were used in our searching strategies: “Smad family member 3”, “SMAD3”, “SNP”, “polymorphism”, “variant”, “osteoarthritis”, “OA” to identify the publications reporting on SMAD3 gene rs12901499 polymorphism and OA risk. Additional usable data were obtained by hand searching the bibliographies of genetic association studies on the subject in this analysis. We used no restrictions on the number of samples and language to minimize publications bias. All studies were carefully selected and were up to date as of March 1, 2018. The inclusion criteria for studies were as follows: (1) studies that evaluated the association between SMAD3 gene rs12901499 polymorphism and OA, (2) studied on human beings, and (3) contained genotype data for the calculation of odds ratios (ORs) and 95% confidence intervals (CIs). The following information was extracted from each study: author, year of publication, ethnicity based on the continent of origin of the study population, type of OA, source of controls (SOC), numbers of cases and controls, and the genotype methods.

**Statistical analysis**

ORs and 95% CIs were used to evaluate the strength of correlation between SMAD3 gene rs12901499 polymorphism and OA risk. Stratification analyses were carried out by ethnicity, SOC, type of OA, Hardy–Weinberg equilibrium
Figure 2. Forest plot shows odds ratio for the associations between rs12901499 polymorphism and OA risk (GG vs AA)

(HWE), genotype methods, and study quality. \(P<0.05\) was considered statistically significant. Multivariate ORs and corresponding 95% CIs between extreme levels of annualized case volume (highest vs lowest) were pooled using a random-effects model, accounting for clinical heterogeneity. Heterogeneity across studies was assessed by using the \(Q\) statistic with its \(P\) value and \(I^2\) statistic [18,19]. Pooled ORs and 95% CIs were calculated in our meta-analysis which was performed using the following genetic models: (1) allele, (2) recessive, (3) homozygous, (4) heterozygous, and (5) dominant. The power of this meta-analysis was calculated with a significant value of 0.05 [20]. Two reviewers independently performed the extraction of data and assessed the study quality according to Newcastle–Ottawa scale (NOS) [21]. All disagreements were discussed and resolved with consensus. We tested HWE in controls by a Pearson’s \(\chi^2\) test (available in: http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The data analyses were conducted with Stata 11.0 software (StataCorp, College Station, TX, U.S.A.). Potential publication bias was assessed by Begg’s and Egger’s linear regression test [22]. \(P<0.05\) was considered to indicate statistically significant. We performed sensitivity analysis by omitting each study in turn to determine the effect on the test of heterogeneity and evaluated the stability of the overall results.

Results

Characteristics of the included studies

A total of 127 citations were derived after incipient search. Forty-one citations were removed due to duplication. Of the 86 remaining citations, 70 were excluded after reading titles and abstracts. Sixteen citations were selected for further full-text review. Three investigated other SNPs of SMAD3 gene; two citations did not provide detailed genotyping data and four were not case–control study. Eventually, we identified seven eligible citations (5344 cases and 9080 controls) containing eleven studies [11–17]. Selection for qualified studies was presented in Figure 1. The characteristics of included studies are summarized in Tables 1 and 2. The NOS of all included studies ranged from 5 to 7 stars, suggesting that these studies were of high methodological quality.
Table 1 Characteristics of included studies

| Author, Year | Nationality | Type     | Number of cases/controls | Genotype method |
|--------------|-------------|----------|--------------------------|-----------------|
| Sharma, 2017 [11] | India | Knee OA | 450/458 | PCR-RFLP |
| Su, 2015 [12] | China | Knee OA | 545/468 | PCR-RFLP |
| Xiao, 2015 [13] | China | TMJOA | 114/126 | PCR |
| Jiang, 2013 [14] | China | Knee OA | 102/220 | PCR-RFLP |
| Jiang, 2013 [14] | China | Hand OA | 111/220 | PCR-RFLP |
| Ana, 2010 [15] | U.K. | Knee OA | 1906/1253 | KASPar chemistry |
| Ana, 2010 [15] | U.K. | Hip OA | 1193/1253 | KASPar chemistry |
| Ana, 2010 [15] | U.K./Estonia | Knee OA | 492/1804 | KASPar chemistry |
| Ana, 2010 [15] | U.K./Estonia | Hip OA | 95/1804 | KASPar chemistry |
| Zhong, 2018 [16] | China | Hip OA | 500/1080 | TaqMan |
| Zhang, 2018 [17] | China | Knee OA | 346/394 | MALDI-TOF MS |

Abbreviations: OA, osteoarthritis; TMJOA, temporomandibular joint osteoarthritis.

Table 2 Characteristics of included studies

| Author, year | SOC | Ethnicity | Case | Control | NOS | HWE |
|--------------|-----|-----------|------|---------|-----|-----|
| Sharma, 2017 [11] | HB | Asians | 165 | 131 | 154 | 439 | 461 | 158 | 198 | 102 | 402 | 514 | 5 | NO |
| Su, 2015 [12] | HB | Asians | 142 | 274 | 129 | 532 | 558 | 116 | 228 | 124 | 476 | 460 | 6 | YES |
| Xiao, 2015 [13] | HB | Asians | 31 | 53 | 30 | 113 | 115 | 44 | 67 | 15 | 97 | 155 | 7 | YES |
| Jiang, 2013 [14] | PB | Asians | 22 | 68 | 12 | 92 | 112 | 114 | 83 | 23 | 129 | 311 | 6 | YES |
| Jiang, 2013 [14] | PB | Asians | 25 | 73 | 13 | 99 | 123 | 114 | 83 | 23 | 129 | 311 | 6 | YES |
| Ana, 2010 [15] | HB | Caucasians | 251 | 682 | 463 | 1608 | 1184 | 281 | 625 | 347 | 1319 | 1187 | 6 | YES |
| Ana, 2010 [15] | HB | Caucasians | 219 | 584 | 430 | 1364 | 1022 | 281 | 625 | 347 | 1319 | 1187 | 6 | YES |
| Ana, 2010 [15] | PB | Caucasians | 94 | 242 | 156 | 554 | 430 | 421 | 896 | 487 | 1870 | 1738 | 6 | YES |
| Ana, 2010 [15] | PB | Caucasians | 18 | 47 | 30 | 107 | 83 | 421 | 896 | 487 | 1870 | 1738 | 6 | YES |
| Zhang, 2018 [16] | PB | Asians | 10 | 200 | 290 | 780 | 220 | 20 | 610 | 450 | 1510 | 650 | 7 | YES |
| Zhang, 2018 [17] | HB | Asians | 82 | 173 | 91 | 355 | 337 | 81 | 202 | 111 | 424 | 364 | 7 | YES |

Table 3 Meta-analysis of association between SMAD3 rs12901499 polymorphism and OA

| Comparison | OR (95%CI) | P-value | P for heterogeneity | I² (%) | Model |
|------------|------------|---------|---------------------|--------|-------|
| G vs A | 1.26(1.12, 1.42) | <0.001 | <0.001 | 75.8 | Random |
| GG vs AA | 1.39(1.15, 1.67) | 0.001 | 0.011 | 56.2 | Random |
| GG + GA vs AA | 1.34(1.07, 1.68) | 0.010 | <0.001 | 79.9 | Random |
| GG vs GA + AA | 1.32(1.11, 1.56) | 0.001 | <0.001 | 71.6 | Random |
| GA vs AA | 1.25(0.96, 1.63) | 0.101 | <0.001 | 84.0 | Random |

Meta-analysis of SMAD3 gene rs12901499 polymorphism

In the general analysis, we found that SMAD3 gene rs12901499 polymorphism increased OA risk (G vs A: OR and 95%CI, 1.26(1.12, 1.42), P<0.001; GG vs AA: OR and 95%CI, 1.39(1.15, 1.67), P=0.001; GG + GA vs AA: OR and 95%CI, 1.34(1.07, 1.68), P=0.010; GG vs GA+AA: OR and 95%CI, 1.32(1.11, 1.56), P=0.001 Table 3 and Figure 2). And we did not obtain any different conclusion after eliminating Su et al.’s study [12] that does not meet the HWE. Stratification analyses were conducted according to ethnicity (G vs A: Asians, OR and 95%CI, 1.34(1.07, 1.69), P=0.012; Caucasians, OR and 95%CI, 1.21(1.13, 1.29), P<0.001, Figure 3), SOC, type of OA (Figure 4), HWE, genotype methods, and study quality (Table 4).

We assessed sensitivity analysis by omitting each study once at a time in every genetic model for SMAD3 gene rs12901499. The pooled ORs for the effects of the SNP on the risk for OA indicated that our data were stable and trustworthy. Both Egger’s and Begg’s tests were used to evaluated the publication bias of this meta-analysis. Our data revealed that there was no obvious publication bias for SMAD3 gene rs12901499 (Figure 5).
Figure 3. Stratification analysis by ethnicity shows odds ratio for the association between rs12901499 polymorphism and OA risk (GG vs AA)

Discussion

To our best knowledge, the present study is the first systematical meta-analysis regarding the association between SMAD3 gene rs12901499 and OA susceptibility. TGF-β has anabolic effects on chondrocytes especially via the SMAD3 genes signaling which promote the development and progression of OA [6]. Previous study reported the relationship between the genetic variants of TGF-β itself, TGF-β signaling, and OA [7]. In the signaling pathway of TGF-β, phosphorylated SMAD3 translocates to the nucleus to regulate gene expression and promote an anabolic phenotype in cartilage by forming a complex with SMAD4 [23]. Several previous studies reported the association between SMAD3 gene rs12901499 polymorphism and risk of OA, but the results were inconsistent [11–17]. This meta-analysis summarized identified seven eligible citations (5344 cases and 9080 controls) containing 11 studies, and provided evidence that SMAD3 gene rs12901499 polymorphism increased OA risk. Stratification analyses of ethnicity, SOC, type of OA, HWE, genotype methods, and study quality revealed that SMAD3 gene rs12901499 polymorphism was also correlated with the increased risk of OA.

A single study could be underpowered because of sample size, diversity inheritance of the heterogeneous and complex OA etiology, different ethnicities, clinical heterogeneity, and so on. For instance, Sharma et al. [11] reported an increased association between SMAD3 gene rs12901499 polymorphism and knee OA in an Indian population. Xiao et al. [13] found this SNP increased the risk of temporomandibular joint OA in a Chinese population. Liying et al. [14] reported this SNP increased both knee and hand OA in a Chinese population. And the study from Valdes et al. [15] indicated that SMAD3 gene rs12901499 polymorphism is involved in increased risk of both hip and knee OA in European populations. Zhong et al. [16] found that SMAD3 SNP rs12901499 GA genotype and G variant may increase the risk of hip OA in Chinese Han patients. Zhang et al. [17] confirmed that rs12901499 polymorphism in

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Table 4 Summary of the subgroup analyses in this meta-analysis

| Comparison | Category | Studies | OR (95% CI) | P-value |
|------------|----------|---------|-------------|---------|
| G vs A     | Ethnicity| Asians  | 7           | 1.34(1.07, 1.69) | 0.012   |
|            |          | Caucasians | 4       | 1.21(1.13, 1.29) | <0.001  |
|            | SO        | HB      | 6           | 1.13(0.99, 1.28) | 0.053   |
|            |          | PB      | 5           | 1.49(1.22, 1.81) | <0.001  |
|            | Type      | Knee OA | 6           | 1.16(0.99, 1.35) | 0.054   |
|            |          | TMJOA   | 1           | 1.57(1.09, 2.26) | 0.015   |
|            |          | Hand OA | 1           | 1.94(1.39, 2.71) | <0.001  |
|            | Hip OA    | 3       | 1.30(1.10, 1.55) | 0.002   |
|            | HWE       | Yes     | 1           | 1.22(1.01, 1.46) | 0.037   |
|            |          | No      | 10          | 1.27(1.12, 1.44) | <0.001  |
|            | Genotype methods | PCR-RFLP | 4       | 1.40(0.99, 1.98) | 0.056   |
|            |          | PCR     | 1           | 1.57(1.09, 2.26) | 0.015   |
|            |          | KASPar chemistry | 4       | 1.21(1.13, 1.29) | <0.001  |
|            |          | Taqman  | 1           | 1.53(1.28, 1.82) | <0.001  |
|            |          | MALDI-TOF MS | 1       | 0.90(0.74, 1.11) | 0.335   |
|            | Study quality | Medium | 8           | 1.25(1.11, 1.41) | <0.001  |
|            |          | High    | 3           | 1.28(0.87, 1.88) | 0.025   |
| GG vs AA   | Ethnicity| Asians  | 7           | 1.44(0.89, 2.09) | 0.059   |
|            |          | Caucasians | 4       | 1.46(1.28, 1.67) | <0.001  |
|            | SO        | HB      | 6           | 1.28(0.99, 1.65) | 0.055   |
|            |          | PB      | 5           | 1.56(1.24, 1.96) | <0.001  |
|            | Type      | Knee OA | 6           | 1.28(0.98, 1.63) | 0.074   |
|            |          | TMJOA   | 1           | 2.84(1.31, 6.14) | 0.008   |
|            |          | Hand OA | 1           | 2.58(1.15, 5.77) | 0.021   |
|            | Hip OA    | 3       | 1.43(1.16, 1.76) | 0.001   |
|            | HWE       | Yes     | 1           | 1.45(1.04, 2.01) | 0.030   |
|            |          | No      | 10          | 1.39(1.12, 1.72) | 0.002   |
|            | Genotype methods | PCR-RFLP | 4       | 1.53(0.93, 2.54) | 0.097   |
|            |          | PCR     | 1           | 2.84(1.31, 6.14) | 0.008   |
|            |          | KASPar chemistry | 4       | 1.46(1.28, 1.67) | <0.001  |
|            |          | Taqman  | 1           | 1.29(0.59, 2.79) | 0.520   |
|            |          | MALDI-TOF MS | 1       | 0.81(0.54, 1.22) | 0.318   |
|            | Study quality | Medium | 8           | 1.42(1.19, 1.68) | <0.001  |
|            |          | High    | 3           | 1.36(0.62, 2.88) | 0.416   |
| GG + GA vs AA Ethnicity | Asians  | 7           | 1.42(0.91, 2.22) | 0.119   |
|            |          | Caucasians | 4       | 1.30(1.16, 1.46) | <0.001  |
|            | SO        | HB      | 6           | 1.10(0.92, 1.30) | 0.304   |
|            |          | PB      | 5           | 1.88(1.09, 3.25) | 0.023   |
|            | Type      | Knee OA | 6           | 1.23(0.92, 1.64) | 0.164   |
|            |          | TMJOA   | 1           | 1.44(0.83, 2.49) | 0.198   |
|            |          | Hand OA | 1           | 3.70(2.00, 6.21) | <0.001  |
|            | Hip OA    | 3       | 1.26(1.06, 1.51) | 0.011   |
|            | HWE       | Yes     | 1           | 0.91(0.69, 1.19) | 0.495   |
|            |          | No      | 10          | 1.41(1.11, 1.79) | 0.005   |
|            | Genotype methods | PCR-RFLP | 4       | 1.81(0.89, 3.66) | 0.101   |
|            |          | PCR     | 1           | 1.44(0.83, 2.49) | 0.198   |
|            |          | KASPar chemistry | 4       | 1.30(1.16, 1.46) | <0.001  |
|            |          | Taqman  | 1           | 0.92(0.43, 1.99) | 0.841   |
|            |          | MALDI-TOF MS | 1       | 0.82(0.39, 1.68) | 0.304   |
|            | Study quality | Medium | 8           | 1.46(1.12, 1.89) | 0.005   |
|            |          | High    | 3           | 0.99(0.71, 1.40) | 0.975   |
| GG vs GA + AA Ethnicity | Asians  | 7           | 1.37(0.97, 1.92) | 0.071   |
|            |          | Caucasians | 4       | 1.27(1.15, 1.41) | <0.001  |
|            | SO        | HB      | 6           | 1.27(1.01, 1.59) | 0.037   |
|            |          | PB      | 5           | 1.41(1.09, 1.83) | 0.010   |

Continued over
Table 4 Summary of the subgroup analyses in this meta-analysis (Continued)

| Comparison | Category | Category | Studies | OR (95% CI)          | P-value |
|------------|----------|----------|---------|----------------------|---------|
| Type       | Knee OA  | 6        | 1.19(0.97, 1.47) | 0.102 |
|            | TMJOA    | 1        | 2.64(1.34, 5.22) | 0.005 |
|            | Hand OA  | 1        | 1.14(0.55, 2.34) | 0.729 |
|            | Hip OA   | 3        | 1.48(1.07, 2.03) | 0.016 |
|            |          |          |         |                      |         |
| HWE        | Yes      | 1        | 1.82(1.35, 2.44) | <0.001 |
|            | No       | 10       | 1.27(1.07, 1.51) | 0.007 |
| Genotype methods | PCR-RFLP | 4        | 1.21(0.76, 1.90) | 0.420 |
|            | PCR      | 1        | 2.64(1.34, 5.22) | 0.005 |
|            | KASPar chemistry | 4 | 1.27(1.15, 1.41) | <0.001 |
|            | Taqman   | 1        | 1.93(1.56, 2.40) | <0.001 |
|            | MALDI-TOF MS | 1 | 0.91(0.66, 1.28) | 0.568 |
| Study quality | Medium    | 8        | 1.25(1.09, 1.44) | 0.001 |
|            | High     | 3        | 1.60(0.88, 2.92) | 0.122 |
| GA vs AA   |          |          |         |                      |         |
| Ethnicity  | Asians   | 7        | 1.30(0.76, 2.21) | 0.335 |
|            | Caucasians | 4    | 1.21(1.07, 1.37) | 0.002 |
| SOC        | HB       | 6        | 0.99(0.80, 1.22) | 0.898 |
|            | PB       | 5        | 1.78(0.94, 3.39) | 0.078 |
| Type       | Knee OA  | 6        | 1.16(0.82, 1.65) | 0.391 |
|            | TMJOA    | 1        | 1.12(0.63, 2.01) | 0.698 |
|            | Hand OA  | 1        | 4.01(2.35, 6.85) | <0.001 |
|            | Hip OA   | 3        | 1.14(0.91, 1.44) | 0.249 |
| HWE        | Yes      | 1        | 0.63(0.46, 0.86) | 0.004 |
|            | No       | 10       | 1.34(1.04, 1.74) | 0.025 |
| Genotype methods | PCR-RFLP | 4 | 1.75(0.73, 4.19) | 0.206 |
|            | PCR      | 1        | 1.12(0.63, 2.01) | 0.698 |
|            | KASPar chemistry | 4 | 1.21(1.07, 1.37) | 0.002 |
|            | Taqman   | 1        | 0.66(0.30, 1.42) | 0.286 |
|            | MALDI-TOF MS | 1 | 0.85(0.59, 1.22) | 0.373 |
| Study quality | Medium    | 8        | 1.40(1.02, 1.92) | 0.038 |
|            | High     | 3        | 0.88(0.66, 1.17) | 0.366 |

Abbreviations: HB, hospital-based controls; PB, population-based controls; SOC, source of controls; TMJOA, temporomandibular joint osteoarthritis. Medium quality: NOS = 5–6; High quality: NOS = 7.

the SMAD3 gene plays a protective role in the pathology of knee OA in a Chinese population. However, Su et al. [12] failed to obtain any relationship between SMAD3 gene rs12901499 polymorphism and knee OA from a Chinese population. It is worthy of note that Valdes et al. [15] conducted eight separate studies (while we divided them into four groups depend on the SOC and type of OA), but three knee OA studies and two hip OA studies did not achieve statistical significance. The nature of OA-genetic susceptibility is likely to vary between different joint sites because the phenotype of osteoarthritis is site-specific. The proportion of genetic contribution of certain polymorphic locus to OA susceptibility may be influenced by other local environmental factors such as anatomical and biomechanical effects and by some joint-specific genetic factors most of which were postulated to be involved in cell signaling and signal transduction. In order to overcome the problem of conflicting results, we performed this comprehensive meta-analysis to evaluate the association of SMAD3 gene rs12901499 polymorphism with OA risk.

Large sample and unbiased epidemiological studies of predisposition gene polymorphisms could provide insight into the association between candidate genes and diseases. When we dropped the study [11] which is not in agreement with HWE, the increased risk of OA was still found, suggesting the robustness of our findings. In addition, the power analysis indicated that this meta-analysis had a power of 99.9% to detect the effect of rs12901499 polymorphism on OA susceptibility with an OR of 1.26, also indicating that our data were robust. Some limitations encountered in this meta-analysis should be considered when these results are interpreted. First, the heterogeneity of this meta-analysis is high, so the data should be interpreted with caution. Second, due to limited data, we could not conduct further stratification analyses of other potential factors, such as age, gender, and body mass index (BMI). Third, our results were based on unadjusted estimates for confounding factors, which might have affected the final results. Fourth, we could not assess potential gene–gene and gene–environment interactions because of the lack of relevant data. Fifth,
the conclusions of some stratification analyses about rs12901499 polymorphism should be interpreted with caution due to limited sample size. Sixth, we only can infer but cannot conclude that SMAD3 gene rs12901499 polymorphisms are susceptibility loci of other types of OA, highlighting the necessity for the further investigation of more types of OA.
In conclusion, this meta-analysis confirms that SMAD3 gene rs12901499 polymorphism increased OA risk. Stratification analysis of ethnicity found that rs12901499 polymorphism increased the risk of osteoarthritis among both Asians and Caucasians, subgroup analysis by type of osteoarthritis revealed that smad family member 3 gene rs12901499 polymorphism was correlated with the increased risk of hip osteoarthritis, but not associated with knee osteoarthritis. Further, studies with large sample size and multiple OA type are necessary to validate whether SMAD3 gene rs12901499 polymorphism contribute to OA susceptibility.

Author Contribution
H.-W.H., J.T., and Z.H conceived and designed the meta-analysis; Y.H.-Y. and H.-W.H performed the literature search; Y.H.-Y. and J.T. Analyzed the data; Y.H.-Y. and Z.H contributed reagents/materials/analysis tools; Y.H.-Y. and H.-W.H wrote the paper.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

Abbreviations
CI, confidence interval; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle–Ottawa Scale; OA, osteoarthritis; OR, odds ratio; SMAD3, SMAD family member 3; SNP, single nucleotide polymorphism; SOC, source of controls; TGF-β, transforming growth factor-β.

References
1 Felson, D.T., Lawrence, R.C., Dieppe, P.A., Hirsch, R., Helmick, C.G., Jordan, J.M. et al. (2000) Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann. Intern. Med. 133, 635–646, https://doi.org/10.1037/00203-4819-133-8-200010170-00016
2 Reginster, J.Y. (2002) The prevalence and burden of arthritis. Rheumatology (Oxford) 41, 3–6, https://doi.org/10.1093/rheumatology/41.S1.3
3 Neogi, T. and Zhang, Y. (2013) Epidemiology of osteoarthritis. Rheum. Dis. Clin. North Am. 39, 1–19, https://doi.org/10.1016/j.rdc.2012.10.004
4 Loughlin, J. (2005) The genetic epidemiology of human primary osteoarthritis: current status. Expert Rev. Mol. Med. 7, 1–12, https://doi.org/10.1017/S1462399405009257
5 Valdes, A.M., Loughlin, J., Genn, M.V., Chapman, K., Surdulac, G.L., Doherty, M. et al. (2007) Sex and ethnic differences in the association of ASPN, CALM1, COL2A1, COMP, and FRZB with genetic susceptibility to osteoarthritis of the knee. Arthritis Rheum. 56, 137–146, https://doi.org/10.1002/art.22301
6 van der Kraan, P.M., Blainey Davidson, E.N., Blom, A. and van den Berg, W.B. (2009) TGF-beta signaling in cartilage homeostasis and osteoarthritis: modulation and integration of signaling pathways through receptor-Smads. Osteoarthritis Cartilage 17, 1539–1545, https://doi.org/10.1016/j.joca.2009.06.008
7 Finnson, K.W., Chi, Y., Bou-Gharios, G., Leask, A. and Philip, A. (2012) TGF-β signaling in cartilage homeostasis and osteoarthritis. Front. Biosci. 4, 251–268, https://doi.org/10.2741/s266
8 Furumatsu, T., Tsuda, M., Taniguchi, N., Tajima, Y. and Asahara, H. (2005) Smad3 induces chondrogenesis through the activation of SOX9 via CREB-binding protein/p300 recruitment. J. Biol. Chem. 280, 8343–8350, https://doi.org/10.1074/jbc.M413913200
9 Neame, R.L., Muir, K., Doherty, S. and Doherty, M. (2004) Genetic risk of knee osteoarthritis: a sibling study. Ann. Rheum. Dis. 63, 1022–1027, https://doi.org/10.1136/ard.2003.014498
10 Yang, X., Chen, L., Xu, X., Li, C., Huang, C. and Deng, C.X. (2001) TGF-beta/Smad3 signals repress chondrocyte hypertrophic differentiation and are required for maintaining articular cartilage. J. Cell Biol. 153, 35–46, https://doi.org/10.1083/jcb.153.1.35
11 Sharma, A.C., Srivastava, R.N., Srivastava, S.R., Parmar, D., Singh, A. and Raj, S. (2017) Association between single nucleotide polymorphisms of SMAD3 and BMP5 with the risk of knee osteoarthritis. J. Clin. Diagn. Res. 11, GC01–GC04
12 Su, S.L., Yang, H.Y., Lee, H.S., Huang, G.S., Lee, C.H., Liu, W.S. et al. (2015) Gene-gene interactions between TGF-beta/Smad3 signalling pathway polymorphisms affect susceptibility to knee osteoarthritis. BMJ Open 5, e007931, https://doi.org/10.1136/bmjopen-2015-007931
13 Xiao, J.L., Meng, J.H., Yan, Y., Zhou, C.Y., and Xiao, J.X. (2015) Association of GDF5, SMAD3 and RUNX2 polymorphisms with temporomandibular joint osteoarthritis in female Han Chinese. J. Oral. Rehabil. 42, 529–536, https://doi.org/10.1111/joor.12286
14 Liying, J., Yuchun, T., Youchung, W., Yingchen, W., Chunya, J., Yanling, Y. et al. (2013) A SMAD3 gene polymorphism is related to knee osteoarthritis in a Northeast Chinese population. Rheumatol. Int. 33, 1763–1768, https://doi.org/10.1007/s00296-012-2593-z
15 Valdes, A.M., Spector, T.D., Parmar, D., Kisand, K., Doherty, S.A., Dennison, E.M. et al. (2010) Genetic variation in the SMAD3 gene is associated with hip and knee osteoarthritis. Arthritis Rheum. 62, 2347–2352, https://doi.org/10.1002/art.27530
16 Zhong, F., Lu, J., Wang, Y. and Song, H. (2018) Genetic variation of SMAD3 is associated with hip osteoarthritis in a Chinese Han population. J. Int. Med. Res. 46, 1178–1186, https://doi.org/10.1177/030006717745186
17 Zhang, L., Zhang, L., Zhang, H., Wang, W. and Zhao, Y. (2018) Association between SMAD3 gene rs12901499 polymorphism and knee osteoarthritis in a Chinese population. J. Clin. Lab. Anal., https://doi.org/10.1002/jcla.22383
18 Higgins, J.P., Thompson, S.G., Deeks, J.J. and Altman, D.G. (2003) Measuring inconsistency in meta-analyses. BMJ 327, 557–560, https://doi.org/10.1002/art.27530
19 Higgins, J.P. and Thompson, S.G. (2002) Quantifying heterogeneity in a meta-analysis. Stat. Med. 21, 1539–1558, https://doi.org/10.1002/sim.1186
20 Hedges, L.V. and Pigott, T.D. (2004) The power of statistical tests for moderators in meta-analysis. Psychol. Methods 9, 426–445, https://doi.org/10.1037/1082-989X.9.4.426

21 Stang, A. (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur. J. Epidemiol. 25, 603–605, https://doi.org/10.1007/s10654-010-9491-z

22 Peters, J.L., Sutton, A.J., Jones, D.R., Abrams, K.R. and Rushton, L. (2006) Comparison of two methods to detect publication bias in meta-analysis. JAMA 295, 676–680, https://doi.org/10.1001/jama.295.6.676

23 Finnson, K.W., Parker, W.L., Chi, Y., Hoemann, C.D., Goldring, M.B., Antoniou, J. et al. (2010) Endoglin differentially regulates TGF-beta-induced Smad2/3 and Smad1/5 signalling and its expression correlates with extracellular matrix production and cellular differentiation state in human chondrocytes. Osteoarthritis Cartilage 18, 1518–1527, https://doi.org/10.1016/j.joca.2010.09.002