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Systematic Meta-Analysis

The BMP14 +104T/C Polymorphism Provides Protection Against Susceptibility to Total Knee Arthroplasty: A Meta-Analysis and Trial Sequential Analysis

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Abstract

Objectives: The link between the bone morphogenetic protein 14 (BMP14) +104T/C polymorphism and total knee arthroplasty (TKA) susceptibility has been previously studied with inconclusive findings. This research seeks to assess the association of the BMP14 +104T/C polymorphism with TKA predisposition.

Methods: A comprehensive search of databases such as PubMed, ResearchGate, Scopus, and CNKI was conducted up to September 01, 2023.

Results: Eight original studies involving 4,484 cases and 5,391 controls were reviewed. The findings indicate a protective effect of the BMP14 +104T/C variant against TKA susceptibility across all five genetic models: allele model (T vs. C: OR 0.856, 95% CI 0.805-0.911, p≤0.001, A), homozygote model (TT vs. CC: OR = 0.748, 95% CI 0.656-0.853, p≤0.001), dominant model (TT+TC vs. CC: OR = 0.855, 95% CI 0.705-0.975, p=0.020), and recessive model (TT vs. TC+CC: OR = 0.797, 95% CI 0.705-0.902, p≤0.001). Stratified analyses considering factors such as ethnicity, control source, country, and genotyping methods consistently revealed significant associations.

Conclusion: This finding suggests that individuals carrying the C allele of the BMP14 +104T/C polymorphism may have a lower chance of requiring TKA. These findings provide insights into the genetic factors that may influence the need for TKA and underscore the importance of further investigation in this area.

Keywords: BMP14, Osteoarthritis, Total Knee Arthroplasty, Meta-Analysis

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Knee osteoarthritis (KOA), also known as degenerative joint disease, typically results from wear and tear and progressive articular cartilage loss.[1,2] KOA is the most common type of arthritis diagnosed, with its prevalence expected to rise due to longer lifespans and increasing obesity.[3,4] Initial KOA treatments involve non-surgical methods such as regular exercise, physiotherapy, and medications like NSAIDs, acetaminophen, epidural corticosteroid injections, and Hyaluronic acid (HA).[5,6] Total knee arthroplasty (TKA) has emerged as the primary surgical solution for end-stage OA, boasting a 90% prosthesis survival rate over a decade.[7] It is the preferred choice for numerous patients whose OA pain is no longer manageable through non-invasive means.[8,9] TKA originated in the early 1970s, following the success of total hip replacement, with nearly 500,000 TKAs performed annually in the USA.[8] Globally, arthroplasty rates are on the rise, fueled by the increasing demands of aging populations.[10] While TKA remains a key player in pain relief, joint stability, range of motion (ROM), and functional improvement, challenges like implant component wear and loosening persist.[11,12] Identifying environmental and genetic factors associated with short and long-term post-TKA pain risks could pave the way for personalized medical interventions.[8,13] Additionally, research indicates that genetic and psychological factors can independently or collaboratively influence post-TKA outcomes in conjunction with environmental elements.[8]

Bone morphogenetic protein (BMP) 14, also known as growth and differentiation factor-5 gene (GDF5), belongs to the transforming growth factor-β superfamily and is crucial for joint formation, bone growth, and promoting fracture healing.[14–16] It plays a significant role in the early stages of joint interzone development, with mutations in this gene associated with various joint deformities in rats.[17,18] BMP14 also affects the growth of different tissues and cell types, such as dentition, brown adipose tissue, and nerve cells.[19,20] The +104T/C polymorphism in the 5'-UTR of the BMP14 gene impacts transcriptional activity in the gene core promoter, resulting in reduced BMP14 expression in individuals with the T alleles.[21] Studies suggest that the T allele of +104T/C is linked to lower BMP14 expression compared to the C allele, particularly affecting patients with severe osteoarthritis necessitating surgery.[22] Moreover, the +104T/C polymorphism is correlated with a higher risk of musculoskeletal disorders like knee osteoarthritis and lumbar disc degeneration.[23] The T allele of +104T/C is also upregulated in individuals with developmental dysplasia of the hip, suggesting a potential association with this condition.[24,25] Research indicates that the +104T/C polymorphism influences chondrogenesis and can impact osteoarthritis susceptibility by affecting BMP14 expression.[26,27] Additionally, studies demonstrate that the functional impact of +104T/C on BMP14 expression is modulated by DNA methylation, with epigenetic mechanisms influencing BMP14 allelic expression.[27,28] Furthermore, the presence of another SNP, rs143384, in the 5'-UTR of the BMP14 gene interacts with +104T/C, affecting BMP14 expression levels.[29]

Several studies have explored the link between the +104T/C polymorphism at the BMP14 gene and susceptibility to TKA.[30] Southam et al. conducted research to investigate how genetic variations impact BMP14 expression in vivo. They analyzed RNA extracted from the cartilage of OA patients who underwent THR or TKA and found a consistent but slight imbalance in BMP14 expression throughout their lives, potentially increasing the risk of KOA.[22] However, the findings are subject to debate due to varying sample sizes and population diversity. Meta-analysis is a potent tool for amalgamating evidence from multiple studies to enhance understanding of the link between genetic factors and disease susceptibility. By combining data from various research efforts, researchers can assess the overall impact of the BMP14 +104T/C polymorphism on predisposition to TKA. This thorough analysis aims to uncover any potential associations between this genetic variant and the risk of TKA. By overcoming individual study limitations and adjusting for sample size discrepancies and population diversity, this meta-analysis aims to provide valuable insights into the role of BMP14 in KOA pathogenesis.

Methods

Bibliographic Search Strategy

Ethical approval was not required for this meta-analysis, as it utilized secondary data, thus obviating the need for ethics committee approval. Various reputable online bibliographic databases, such as PubMed, Web of Science, Europe PMC, ResearchGate, Elsevier, Cochrane Library, EMBASE, SciELO, Google Scholar, Wanfang Data Company, Chaoxing, Chinese Medical Citation Index (CMCI), VIP Information Consulting Company (VIP), Chinese Medical Current Contents (CMCC), Chinese Biomedical Database (CBD), Sinomed, medrex, China/Asia On Demand (CAOD)/Asia Document Delivery, Baidu, Chinese National Knowledge Infrastructure (CNKI), and Weipu Periodical Database, were widely utilized platforms for scientific research and academic literature to identify all relevant studies on the BMP14 +104T/C polymorphism and its association with predisposition to TKA up until September 01, 2023. A comprehensive search was conducted using a combination of specific keywords and MeSH terms, in-

cluding "Knee Osteoarthritis," "Total knee arthroplasty," "KOA," "TKA," "Growth differentiation factor 5," "BMP14," "cartilage-Derived Morphogenetic Protein 1," "BMP-14," "+104T/C," "+104T>C," "Gene," "Genetic," "DNA," "Single-Nucleotide Polymorphism," "SNPs," "Polymorphism," "Genotype," "Frequency," "Mutation," "Mutant," "Allele," "Variation," and "Variant." The search is limited to English, Farsi, and Chinese languages, but not restricted by publication year. Additionally, the reference lists of eligible studies, reviews, and previous meta-analyses were manually checked to ensure the inclusion of any potentially overlooked relevant studies. The identification and evaluation of the articles were independently conducted by two authors. As this study is a systematic review and meta-analysis, ethical approval was not deemed necessary.

Inclusion Criteria

Studies meeting the specified criteria were included: a) case-control or cohort design; b) investigating the association of BMP14 +104T/C polymorphism with TKA; c) providing adequate data for calculating an odds ratio (OR) with a 95% confidence interval (CI). Exclusion criteria were: a) studies examining different BMP14 polymorphisms with TKA; b) studies lacking disclosure of genotype frequencies; c) animal experiments or cell-based assays; d) linkage or family studies; e) explanatory, case-series, editorials, abstracts, presentations, reviews, and previous metadata; and f) replications or overlapping surveys. When multiple studies were authored by the same individual(s), the study with the largest sample size or the most recent publication was included in the meta-analysis. Each distinct case-control group or cohort within a single published study was considered an independent study in the pooled analysis.

Data Extraction

Two researchers independently reviewed references, collected and cross-checked data based on inclusion and exclusion criteria. Any discrepancies will be resolved through discussion or by involving a third expert. The review process begins with screening titles and abstracts to exclude irrelevant studies, followed by a thorough assessment of full texts to make final inclusion decisions. Key information extracted from qualifying studies includes the first author's name, publication date, country of origin, ethnicity, genotyping methods, total numbers of cases and controls, genotype frequencies for BMP14 +104T/C polymorphism, Hardy-Weinberg equilibrium test, and minor allele frequencies in non-BPD infants. If a researcher conducts multiple studies with overlapping data, only the most recent or the study with the largest sample size is considered.

Statistical Analysis

The study utilized Comprehensive Meta-Analysis (Version 4.0) software from Biostat, USA for data synthesis. The correlation strength between BMP14 +104T/C polymorphism and TKA was assessed using ORS and corresponding 95% CIs. The Z-test was used for combined data analysis. The predisposition of BMP14 +104T/C variant to TKA was evaluated under five genetic models: recessive (CC vs. CT+TT), dominant (CC+CT vs. TT), homozygote (CC vs. TT), heterozygote (CT vs. TT), and allelic model (C vs. T). Chi-Square test and I2 statistics (ranging from 0 to 100%) were employed to assess heterogeneity between studies for each genetic model. Substantial heterogeneity was defined as P value <0.1 and I2 value >50%. Statistical analysis used random-effects model for substantial heterogeneity and fixed-effects model otherwise.[31] Fisher Irwin test checked HWE among healthy controls, with p-value <0.05 indicating significant disequilibrium. Sensitivity analysis assessed the impact of systematically removing one study at a time. Potential sources of heterogeneity were explored through analyses including ethnic background, source of controls, country of origin, genotyping approaches, and HWE status. Publication bias was evaluated using Begg's and Egger's tests, with an asymmetrical plot indicating bias. Egger's linear regression test on the log odds ratio scale determined plot symmetry. Statistical significance was set at a 2-sided p-value <0.05.

Trial Sequential Analysis

Trial sequential analysis (TSA) was conducted using TSA v0.9.5.10 Beta software.[32] In this research, OR reduction was set at 20%. To determine the required information size (RIS), α=0.05 for type I error and β=0.2 for type II error were utilized. If the cumulative Z value surpasses the RIS threshold, the findings are deemed statistically significant, suggesting an adequate sample size. Failure to exceed the RIS threshold by the cumulative Z value indicates an insufficient sample size.

Results

Characteristics of Selected studies

The study selection process is illustrated in Figure 1. Initially, an integrative review identified 311 relevant published papers, with 132 studies excluded in the initial screening due to overlapping eligibility criteria. Following this, 78 more studies were removed after reviewing their titles and abstracts. Additionally, 93 studies were excluded for reasons such as not conforming to the case-control study design, absence of human research, or unavailability of data. Finally, eight case-control studies from six publica-

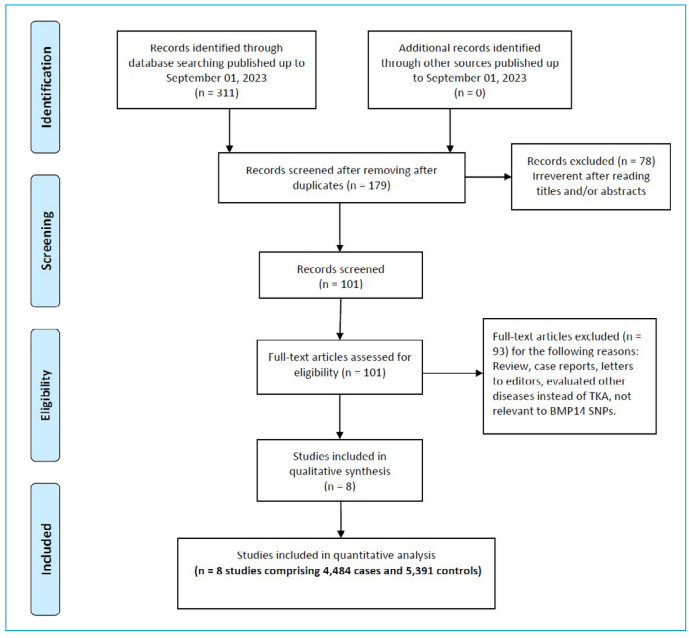

Figure 1. Flow chart illustrating the inclusion/exclusion of individual studies for meta-analysis.

tions [22,33–37] were included, with 4,484 cases and 5,391 controls. Details on the studies' characteristics can be found in Table 1. All included studies employed a case-control design and extracted DNA from the blood of the participants. The selected studies covered a range of TKA cases, from 103 to 1071. Six studies focused on Caucasian populations, while two focused on Asian individuals. The studies were conducted in various countries, including Spain, the UK, Iceland, Korea, and Thailand. Three different genotyping methods were used: TaqMan, RFLP, and AS-PCR. The distribution of genotype, allele, and MAF for the BMP14 +104T/C polymorphism in cases and controls is in Table 1. It's important to note that, except for the study by Evangelou et al. in 2009, the genotype distribution in the healthy control group adhered to HWE in all studies.

Data Synthesis

The correlation analysis results for the BMP14 +104T/C variant and its impact on TKA susceptibility are presented in Table 2. The results suggest a protective effect of the BMP14 +104T/C variant against TKA predisposition across all five genetic models. These models include the allele model (T vs. C: OR 0.856, 95% CI 0.805-0.911, p≤0.001, Fig. 2A), the homozygote model (TT vs. CC: OR = 0.748, 95% CI 0.656-0.853, p≤0.001), the dominant model (TT+TC vs. CC: OR = 0.855, 95% CI 0.705-0.975, p=0.020, Fig. 2B), and the recessive model (TT vs. TC+CC: OR = 0.797, 95% CI 0.705-0.902, p≤0.001).

In the subgroup analysis by ethnic background, individuals with the BMP14 +104T/C polymorphism showed a protec-

Table 1. Characteristics of studies included in the meta-analysis.

First Author/Year	Country (Ethnicity)	SOC	Genotyping Technique	Case/Control	Cases					Controls					MAFs		HWE
					Genotypes			Allele		Genotypes			Allele				
					TT	TC	CC	T	C	TT	TC	CC	T	C			
Southam 2007	Spain (Caucasian)	HB	TaqMan	274/1196	102	136	36	340	208	439	563	194	1441	951	0.398	0.549	
Southam 2007	UK (Caucasian)	HB	PCR-RFLP	509/822	219	238	52	676	342	324	372	126	1020	624	0.380	0.261	
Valdes 2009	UK (Caucasian)	PB	AS-PCR	259/509	126	98	35	350	168	181	244	84	606	412	0.405	0.907	
Evangelou 2009	Iceland (Caucasian)	NS	TaqMan	1071/1169	535	379	157	1449	693	552	442	175	1546	792	0.339	0.001	
Cao 2010	Korea (Asian)	PB	PCR-RFLP	276/298	150	115	11	415	137	159	113	26	431	165	0.277	0.360	
Valdes 2011	UK (Caucasian)	PB	AS-PCR	867/758	413	361	93	1187	547	294	354	110	942	574	0.379	0.836	
Valdes 2011	UK (Caucasian)	PB	AS-PCR	1141/536	467	511	163	1445	837	219	237	80	675	397	0.370	0.229	
Tawonsawatruk 2011	Thailand (Asian)	HB	PCR-RFLP	103/103	35	41	11	111	63	33	47	23	113	93	0.451	0.424	

SOC: Source of Controls; HB: Hospital-Based; PB: Population-Based; NS: Not Stated; PCR: Polymerase Chain Reaction; RFLP: Restriction Fragment Length Polymorphism; AS: Allele-Specific; MAFs: Minor Allele Frequencies; HWE: Hardy-Weinberg Equilibrium.

Table 2. Summary risk estimates for the BMP14 +104T/C polymorphism and TKA.

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	C vs. T	Random	58.61	0.018	0.856	0.805-0.911	-4.913	≤0.001	0.266	0.123
	CC vs. TT	Fixed	43.78	0.087	0.748	0.656-0.853	-4.342	≤0.001	0.265	0.053
	CT vs. TT	Fixed	50.82	0.047	0.876	0.765-1.003	-1.917	0.055	0.901	0.923
	CC+CT vs. TT	Fixed	34.96	0.149	0.855	0.705-0.975	-2.332	0.020	0.107	0.048
	CC vs. CT+TT	Fixed	42.32	0.096	0.797	0.705-0.902	-3.609	≤0.001	0.063	0.014
Ethnicity										
Caucasians	C vs. T	Random	56.85	0.041	0.858	0.776-0.949	-2.988	0.003	0.707	0.386
	CC vs. TT	Fixed	45.08	0.105	0.770	0.673-0.881	-3.794	≤0.001	0.452	0.219
	CT vs. TT	Random	60.62	0.026	0.857	0.735-1.000	-1.962	0.050	1.000	0.633
	CC+CT vs. TT	Fixed	14.74	0.320	0.886	0.774-1.014	-1.757	0.079	0.452	0.410
	CC vs. CT+TT	Fixed	22.45	0.265	0.826	0.728-0.938	-2.958	0.003	0.452	0.207
Asians	C vs. T	Random	73.36	0.053	0.748	0.600-0.933	-2.580	0.010	NA	NA
	CC vs. TT	Fixed	0.00	0.992	0.450	0.256-0.788	-2.793	0.005	NA	NA
	CT vs. TT	Fixed	0.00	0.460	1.015	0.751-1.371	0.095	0.925	NA	NA
	CC+CT vs. TT	Fixed	0.00	0.628	0.471	0.270-0.822	-2.649	0.008	NA	NA
	CC vs. CT+TT	Fixed	0.00	0.937	0.426	0.250-0.723	-3.156	0.002	NA	NA
Country										
UK	C vs. T	Random	65.04	0.035	0.820	0.712-0.944	-2.758	0.006	0.734	0.539
	CC vs. TT	Fixed	47.35	0.127	0.698	0.586-0.831	-4.038	≤0.001	1.000	0.536
	CT vs. TT	Random	71.55	0.014	0.809	0.644-1.017	-1.816	0.069	0.734	0.454
	CC+CT vs. TT	Fixed	12.42	0.331	0.842	0.708-1.002	-1.937	0.053	1.000	0.857
	CC vs. CT+TT	Fixed	18.59	0.298	0.769	0.653-0.906	-3.142	0.002	0.734	0.728
Source of Controls										
PB	C vs. T	Random	65.35	0.034	0.825	0.703-0.967	-2.376	0.017	0.734	0.777
	CC vs. TT	Fixed	54.23	0.087	0.702	0.580-0.851	-3.602	≤0.001	0.308	0.399
	CT vs. TT	Random	74.15	0.009	0.823	0.633-1.070	-1.452	0.146	1.000	0.945
	CC+CT vs. TT	Fixed	35.38	0.200	0.867	0.716-1.050	-1.462	0.144	0.734	0.324
	CC vs. CT+TT	Fixed	36.18	0.195	0.785	0.656-0.940	-2.634	0.008	0.308	0.275
HB	C vs. T	Random	65.60	0.055	0.832	0.739-0.937	-3.025	0.002	1.000	0.365
	CC vs. TT	Fixed	0.00	0.420	0.660	0.508-0.858	-3.108	0.002	1.000	0.622
	CT vs. TT	Fixed	0.00	0.768	0.970	0.814-1.156	-0.340	0.733	1.000	0.623
	CC+CT vs. TT	Fixed	0.00	0.707	0.682	0.528-0.881	-2.934	0.003	1.000	0.641
	CC vs. CT+TT	Fixed	8.06	0.337	0.659	0.517-0.840	-3.362	0.001	1.000	0.473
Genotyping Methods										
PCR-RFLP	C vs. T	Random	53.14	0.118	0.798	0.700-0.910	-3.363	0.001	0.296	0.447
	CC vs. TT	Fixed	0.00	0.669	0.557	0.410-0.757	-3.740	≤0.001	1.000	0.113
	CT vs. TT	Fixed	0.00	0.715	0.972	0.807-1.171	-0.300	0.764	1.000	0.818
	CC+CT vs. TT	Fixed	0.00	0.578	0.588	0.434-0.796	-3.435	0.001	1.000	0.376
	CC vs. CT+TT	Fixed	0.00	0.480	0.560	0.420-0.747	-3.937	≤0.001	0.296	0.007
AS-PCR	C vs. T	Random	76.69	0.014	0.814	0.665-0.997	-1.991	0.046	1.000	0.695
	CC vs. TT	Fixed	60.30	0.081	0.726	0.595-0.885	-3.158	0.002	1.000	0.720
	CT vs. TT	Random	77.55	0.012	0.763	0.565-1.033	-1.752	0.080	1.000	0.592
	CC+CT vs. TT	Fixed	0.00	0.701	0.912	0.748-1.112	-0.908	0.364	1.000	0.506
	CC vs. CT+TT	Fixed	0.00	0.373	0.816	0.678-0.983	-2.141	0.032	1.000	0.896
HWE*	C vs. T	Random	58.54	0.025	0.818	0.728-0.919	-3.381	0.001	0.367	0.248
	CC vs. TT	Fixed	28.80	0.208	0.687	0.589-0.803	-4.743	≤0.001	0.229	0.174
	CT vs. TT	Random	57.81	0.027	0.874	0.739-1.033	-1.579	0.114	0.763	0.947
	CC+CT vs. TT	Fixed	20.05	0.277	0.795	0.682-0.927	-2.929	0.003	0.229	0.142
	CC vs. CT+TT	Fixed	26.45	0.227	0.738	0.638-0.853	-4.118	≤0.001	0.133	0.057

HB: Hospital-Based; PB: Population-Based; NA: Not Applicable; PCR: Polymerase Chain Reaction; RFLP: Restriction Fragment Length Polymorphism; AS: Allele-Specific; HWE: Hardy-Weinberg Equilibrium. *By excluding HWE-violating studies.

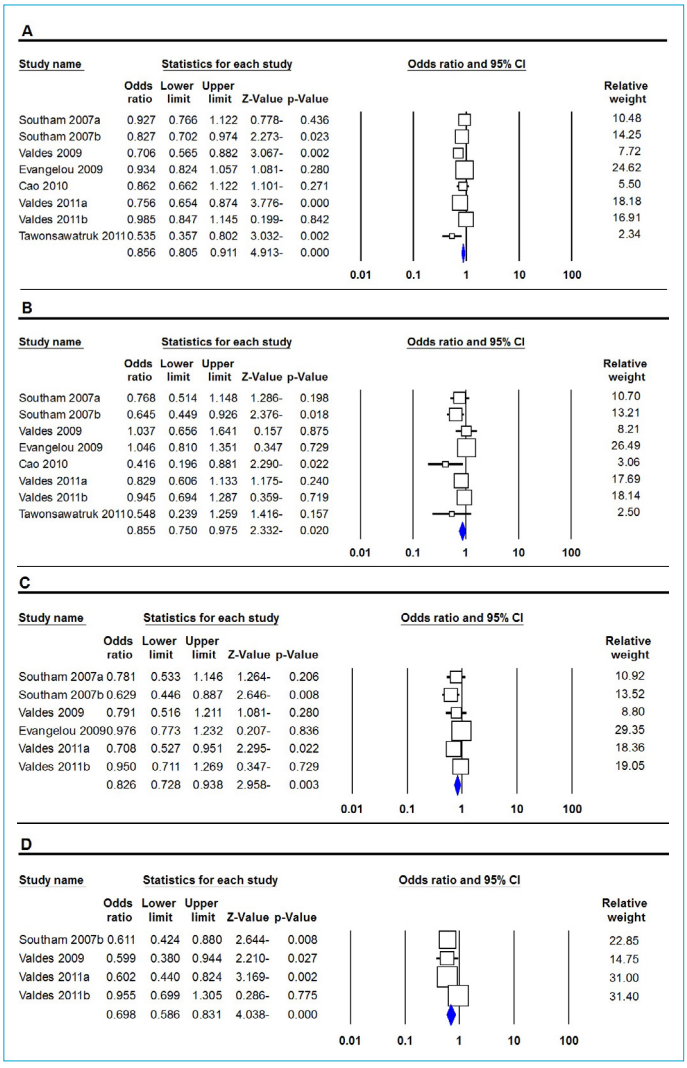

Figure 2. Forest plot showing the correlation between BMP14 +104T/C polymorphism and susceptibility to TKA. **(a)** overall population (allele model: C vs. T), **(b)** overall population (dominant model: CC+CT vs. TT); **(c)** Caucasians (recessive model: CC vs. CT+TT); **(d)** UK (homozygote model: CC vs. TT).

tive effect against TKA in Caucasian descent (T vs. C: OR = 0.858, 95% CI 0.776-0.949, p=0.003; TT vs. CC: OR = 0.770, 95% CI 0.673-0.881, p≤0.001; CT vs. TT: OR = 0.857, 95% CI 0.735-1.000, p=0.050; and TT vs. TC+CC: OR = 0.826, 95% CI 0.728-0.938, p=0.003, as shown in Fig. 2C) and Asian descent (T vs. C: OR = 0.748, 95% CI 0.600-0.933, p=0.010; TT vs. CC: OR = 0.450, 95% CI 0.256-0.788, p=0.005; TT+TC vs. CC: OR = 0.471, 95% CI 0.270-0.822, p=0.008; and TT vs. TC+CC: OR = 0.426, 95% CI 0.250-0.723, p=0.002). Furthermore, in the subgroup analysis based on country, control source, and genotyping methods, a significant protective association with TKA related to the BMP14 +104T/C polymorphism was notably observed in UK-Caucasians (Figure 2D), as well as in the population-based, hospital-based, RFLP-PCR, and AS-PCR survey groups (Table 2).

Between-Study Heterogeneity

We conducted sorted analyses to pinpoint the source of heterogeneity under the allele genetic model (C vs. T: I2=58.61; PH=0.018). Factors like participant ethnicity, genotyping techniques' country of origin, control source, and HWE status were examined. Nevertheless, these covariates were not the primary reason for the heterogeneity as per the results (Table 2). Moreover, excluding HWE violating studies did not significantly alter the combined outcomes, showing an increase in between-study heterogeneity under the heterozygote genetic model (CT vs. TT: I2 = 57.81, PH = 0.027; OR = 0.874, 95% CI 0.739-1.033, p=0.114, Table 2).

Sensitivity Analysis

A sensitivity analysis was conducted by successively excluding each study in the five genetic models to assess the impact of each study on the overall findings. Minor adjustments were made to the calculations when individual studies were excluded. Furthermore, a sensitivity analysis was carried out by excluding studies that deviated from the HWE. The exclusion of these studies did not significantly alter the overall OR, and consistent results were obtained. These findings indicate that the results are robust and dependable, with slight variations observed when individual studies were omitted. The overall conclusions from this meta-analysis are supported by the consistency of results across various sensitivity analyses, further enhancing the study's validity.

Publication Bias

Begg's funnel plot and Egger's test were analyzed to evaluate potential publication bias in the combined study. The funnel plots of the nine studies displayed asymmetry under both dominant and recessive genetic models. Egger's test revealed indications of publication bias in two genetic models: dominant (CC+CT vs. TT: P_{Beggs} = 0.107; P_{Eggers} = 0.048, Fig. 3A) and recessive (CC vs. CT+TT: P_{Beggs} = 0.063; P_{Eggers} = 0.014, Fig. 3B). To address this bias, we utilized the Duval and Tweedie non-parametric "trim and fill" approach. Despite this adjustment, the meta-analysis outcomes remained consistent, underscoring the stability and reliability of our results (Fig. 3A and B).

TSA

We performed TSA analysis using the homozygote model of BMP14 +104T/C polymorphism. The results, depicted in Figure 4, reveal a significant pooled effect size ranging from 0.65 to 0.85 with a confidence interval. The p-value, below 0.0001, provides strong evidence for the observed effect. While some heterogeneity is present (Q=12.45, p=0.0866), metrics such as inconsistency (I^2=0.44) and di-

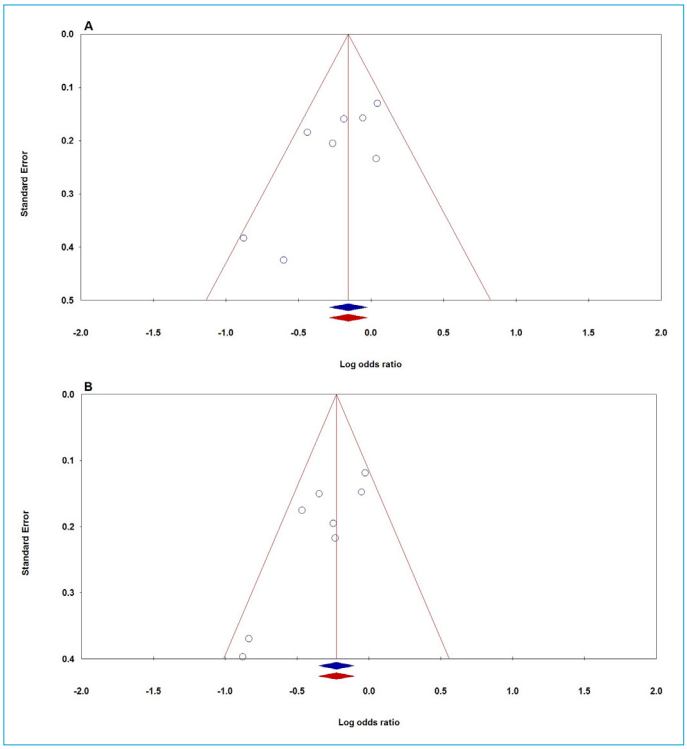

Figure 3. Begg's funnel plot of the relationship between BMP14 +104T/C polymorphism and predisposition to TKA. **(a)** dominant model (CC+CT vs. TT); **(b)** recessive model (CC vs. CT+TT). Each dot represents an individual study for the specified correlation.

versity (D^2=0.51) suggest moderate variation among studies. The Z-curves intersect the conventional boundary to reach the RIS. These statistical outcomes indicate a moderate pooled effect size with a precise confidence interval, highlighting the intervention's significant impact. The low P-value reinforces the treatment's effectiveness. Despite some heterogeneity, the inconsistency and diversity metrics point to a reasonable level of variation in study outcomes. In summary, these results endorse the notion of a meaningful and consistent effect of the intervention across the studies analyzed. This implies that the cumulative evidence of association in this meta-analysis is substantial, although further studies are necessary.

Discussion

Research on gene variants related to TKA is increasingly important in orthopedic disorder studies. For example, Sychev et al. discovered a connection between the ABCB1 rs1045642 polymorphism, elevated dabigatran levels, and an increased risk of bleeding after TKA.[38] Blanco et al.'s work identified genetic variations like rs2073508, rs10845493, rs2206593, rs10519263, rs874692, rs7342880, rs780094, and rs12009 linked to the progression of KOA to severe stages.[39] Conversely, Jurewicz et al.'s research did not find significant genetic links between COMT and OPRM1 vari-

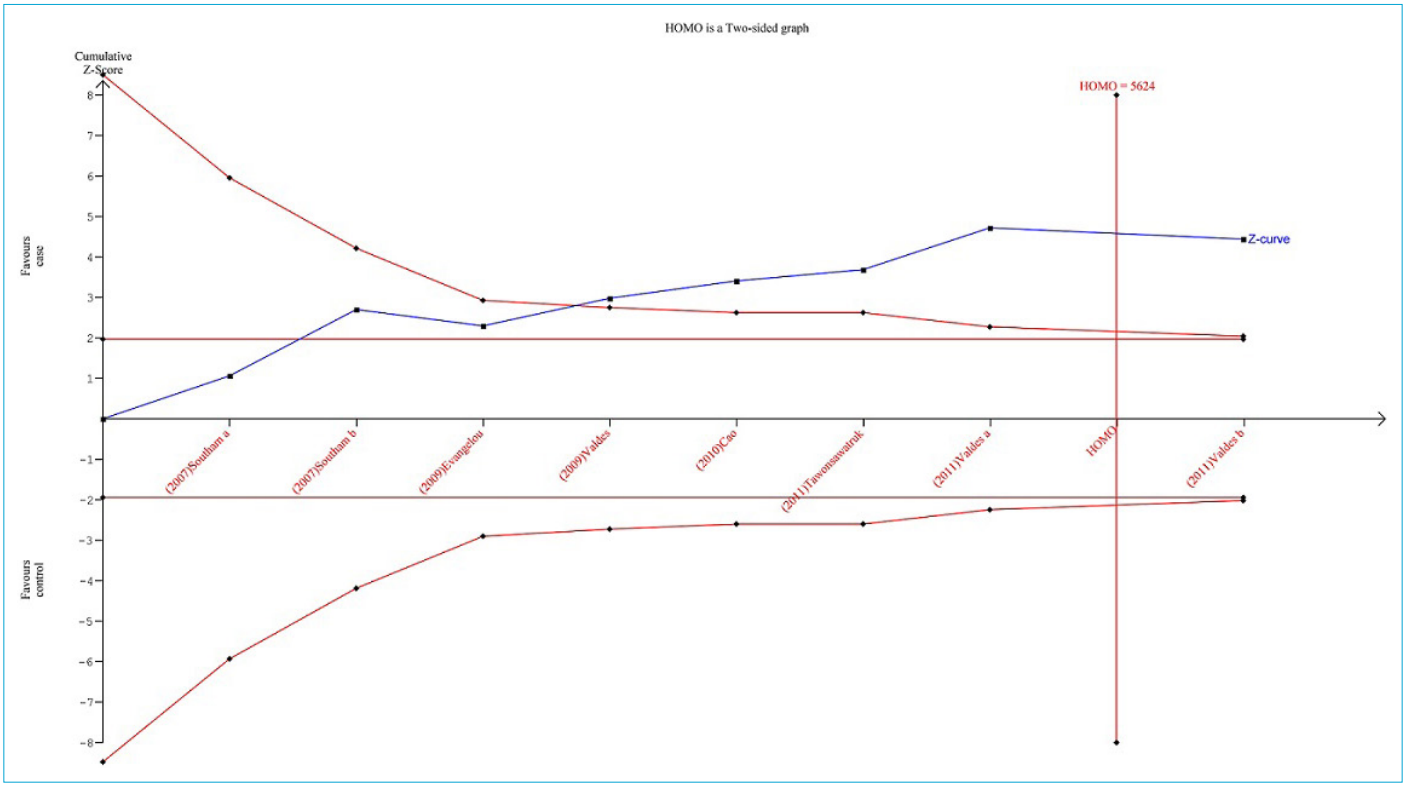

Figure 4. Trial Sequential Analysis (TSA) for the meta-analysis on the link between BMP14 +104T/C polymorphism and predisposition to TKA in the homozygote model.

ants and pain perception in TKA patients.[40] Furthermore, it was revealed that the FRZB Arg200Trp variant was associated with osteophyte and heterotopic ossification formation, as well as a decreased risk of osteolysis post-TKA.[41] Xu et al. identified gene variants such as CASP5, RASGEF1A, and CYP4B1 that were notably associated with severe chronic pain in elderly patients after lower extremity arthroplasty.[42] Similarly, recent studies have explored the genetic basis of postoperative complications and outcomes in orthopedic surgeries. These discoveries emphasize the complex interaction between genetic factors and orthopedic outcomes, paving the way for personalized approaches to surgical management and rehabilitation in musculoskeletal health.

The BMP14 +104T/C polymorphism emerges as a key player in the intricate landscape of KOA pathogenesis. Extensive research spanning diverse populations has underscored a robust link between this genetic variant and KOA susceptibility, transcending ethnic boundaries. Pan et al. conducted a meta-analysis with a large sample size, revealing a significant connection between the BMP14 +104T/C polymorphism and KOA.[23] Valdes et al. also reported a genome-wide statistically significant association between this polymorphism and KOA.[43] Lei et al. highlighted that this genetic variation increases the risk of KOA in Caucasian populations.[44] Furthermore, the BMP14 +104T/C polymorphism is associated with the severity of primary KOA, as indicated by higher WOMAC and HAQ scores in patients with the TT genotype. However, direct correlation with primary KOA development was not established in this study. Additionally, this polymorphism has been linked to radiographic severity in KOA. Valdes et al. demonstrated an association with tibiofemoral K/L grade, suggesting a modest but significant impact on radiographic severity in individuals with KOA.[36] These findings imply that the BMP14 +104T/C polymorphism could serve as a valuable risk indicator for radiographically defined KOA and help identify patients at higher risk of disease progression. Exploring its implications in TKA, the landscape becomes more nuanced, with conflicting results clouding the picture. Previous studies have explored the association between the BMP14 +104T/C polymorphism and susceptibility to TKA, with conflicting results likely due to sample size limitations and outcome variations. Our analysis of eight case-control studies involving 4,484 TKA patients and 5,391 healthy controls suggests a protective role of this polymorphism against TKA susceptibility globally. Moreover, this protective effect was consistent across Caucasian and Asian populations, indicating that ethnic differences may not be a confounding factor. Subgroup analysis based on data sources further supports a consistent role of the BMP14 +104T/C polymorphism in relation to TKA. Future research efforts should focus on elucidating the underlying biological mechanisms through which this genetic variant exerts its protective effects, ultimately paving the way for personalized medicine approaches in the management of TKA susceptibility.

Meta-analysis has been widely used to combine findings from different studies.[45–47] However, heterogeneity, which refers to the variation in study results among studies, can affect the conclusions drawn from a meta-analysis. It is often used to determine how studies should be merged and to assess the consistency or inconsistency of results.[48,49] Significant evidence of heterogeneity was not found in the combined studies, except for the allele genetic model. We conducted a thorough analysis considering various factors to explore the potential sources of heterogeneity.[50,51] Our results showed that factors such as ethnic background, control source, country of origin, genotyping methods, and HWE did not definitively contribute to heterogeneity. The detailed analysis revealed that the allele genetic model was the main driver of heterogeneity in the combined studies. Further investigation into this specific model could provide insights into the underlying factors causing the observed variation in study results. More research focusing on genetic models and their interaction with other factors could enhance our understanding of the sources of heterogeneity in meta-analyses.

Our meta-analysis had notable strengths. Firstly, it was the first to explore the connection between BMP14 +104T/C polymorphism and susceptibility to TKA. Secondly, the systematic review of this polymorphism's association with TKA risk was more statistically robust than individual studies. Thirdly, the selected studies in this combined analysis met satisfactory quality standards and aligned with our inclusion criteria. Lastly, the minimal heterogeneity among the selected studies could enhance the credibility of the findings. Despite these advantages, there are some limitations to consider. Firstly, our meta-analysis only included nine studies from six publications, which is relatively small and may not offer sufficient power to assess the correlation effectively. Secondly, most selected articles focused on Caucasian populations, providing limited data on Asian populations. Therefore, analyzing ethnic backgrounds in other groups like African and mixed populations was challenging due to limited studies. Caution is advised when interpreting the analysis results. Furthermore, data from comprehensive, multicentric studies involving diverse ethnicities are vital to validate the correlation. Thirdly, the meta-analysis included only published articles, potentially overlooking unpublished studies that align with our analysis objectives. This may introduce publication bias, although no evidence supports this within our meta-analysis. Additionally, the search was limited to English, Farsi,

and Chinese languages, raising the possibility of language bias. However, assessments like Begg's funnel plot and Eggers test did not reveal significant publication bias. Due to the lack of individual preliminary data, evaluating risks related to other variables such as age, gender, KOA severity, post-surgical pain, smoking, obesity, prior knee injuries, knee-straining activities, etc., was not feasible. Finally, due to insufficient data, the potential effects of gene-gene and gene-environment interactions on TKA were not explored. Therefore, caution is advised when drawing conclusions from our meta-analysis.

In conclusion, our meta-analysis shows that the BMP14 +104T/C polymorphism provides protection against TKA. This suggests that individuals with the C allele of this polymorphism may have a reduced likelihood of needing TKA. Further research with larger sample sizes and diverse populations is required to confirm these findings and investigate potential gene-gene and gene-environment interactions that could affect the observed protective effects of the BMP14 +104T/C polymorphism against TKA. Moreover, functional studies are essential to understand the mechanisms by which this polymorphism influences TKA susceptibility. In general, our findings add to the increasing body of evidence on genetic factors influencing TKA risk and could guide personalized medicine strategies in KOA management.

Disclosures

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