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Association of GDF5 rs143383 Polymorphism with Knee Osteoarthritis Risk: an Updated Systematic Review and Meta-Analysis

A.Manoharan [1] , R.Annamalai [2] , R.Selvaraj[3] , Arvind Kumar.K[4]

1 Department of Orthopeadics, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Maduranthakam Chengalpattu - 603 308, Tamil Nadu, India.

2 Department of Orthopeadics, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Maduranthakam Chengalpattu - 603 308, Tamil Nadu, India.

3 Department of Orthopeadics, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Maduranthakam Chengalpattu - 603 308, Tamil Nadu, India.

4 Department of Orthopeadics, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Maduranthakam Chengalpattu - 603 308, Tamil Nadu, India.

Corresponding Author:

Dr.A.Manoharan.,MS*, Professor, Department of Orthopeadics, Karpaga Vinayaga Institute of Medical Sciences and Research Centre. Maduranthakam, Chengalpattu - 603 308, Tamil Nadu, India.

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KEYWORDS

Knee Osteoarthritis, GDF5, Polymorphism, Asian, Caucasian.

ABSTRACT:

Background: Knee osteoarthritis (KOA) is a major cause of chronic pain and disability, and genetic factors contribute to inter-individual susceptibility. Growth differentiation factor 5 (GDF5), a key regulator of cartilage and skeletal biology, has been widely investigated in KOA; however, findings for the commonly studied rs143383 variant remain inconsistent across studies and populations.

Objective: To update and clarify the association between GDF5 rs143383 and KOA risk using an expanded evidence base with ethnicity-stratified analyses, sensitivity testing, and assessment of small-study effects.

Methods: A PRISMA-aligned systematic review and meta-analysis was conducted using major English-language databases (PubMed, Embase, Web of Science, Cochrane Library) and Chinese databases (CNKI, Wanfang, VIP), supplemented by reference screening. Eligible studies were human case–control investigations evaluating rs143383 in KOA with extractable genotype/allele data. Data were independently extracted and cross-checked for internal consistency; study quality was assessed using the Newcastle–Ottawa Scale. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated under standard genetic models using fixed- or random-effects approaches based on heterogeneity (Q test/I^2). Subgroup analyses were performed by ethnicity (Asian vs Caucasian). Leave-one-out sensitivity analysis and publication bias evaluation (Egger's test/funnel plot) were conducted.

Results: Thirty KOA case–control studies met inclusion criteria, comprising 10,739 cases and 16,281 controls. Overall, rs143383 showed a significant association with KOA susceptibility in key models: allelic contrast OR = 1.3272 (95% CI 1.2045–1.4624; I^2 = 81.69%), recessive model OR = 1.3783 (95% CI 1.2244–1.5516; I^2 = 76.56%), and dominant model OR = 1.4788 (95% CI 1.2597–1.7359; I^2 = 71.12%). The overdominant model suggested a modest protective pattern overall (OR = 0.8953, 95% CI 0.8194–0.9783; I^2 = 58.96%). In Asians (18 studies), effects were generally stronger but heterogeneous (allelic OR = 1.4378, I^2 = 87.83%), while in Caucasians (12 studies) associations remained significant with lower heterogeneity in several contrasts (allelic OR = 1.1955, I^2 = 30.04%; dominant OR = 1.2589, I^2 = 0%). Sensitivity analysis showed stable pooled estimates (overall fixed-effect OR approximately 1.24, 95% CI 1.19–1.29). Egger's testing indicated potential small-study effects in some overall models (e.g., allelic P = 0.0182; dominant P = 0.0179), whereas most ethnicity-stratified tests were non-significant.

Conclusion: This updated meta-analysis supports GDF5 rs143383 as a significant genetic susceptibility marker for knee osteoarthritis, with consistent risk direction across major genetic models and across Asian and Caucasian populations. Interpretation should consider substantial heterogeneity in some analyses and evidence of small-study effects in select pooled contrasts.

Journal of Chemical Health Risks

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Background:

Knee osteoarthritis (KOA) is the most common form of osteoarthritis and a leading cause of chronic pain, functional impairment, and disability worldwide, particularly among middle-aged and older adults [1]. The disease is characterized by progressive degeneration of articular cartilage, subchondral bone remodeling, osteophyte formation, and synovial inflammation, resulting in pain, stiffness, and reduced joint mobility. Given population ageing and the rising prevalence of obesity, the global burden of KOA continues to increase, posing major clinical and socioeconomic challenges. Although mechanical loading, ageing, obesity, and joint injury are well-established risk factors, KOA is increasingly recognized as a complex multifactorial disorder with a substantial genetic component [2]. Family and twin studies estimate that genetic factors may account for 40–65% of susceptibility to knee osteoarthritis, highlighting the importance of identifying genetic variants that influence disease risk and progression [3]. Understanding these genetic determinants may improve risk stratification and provide insights into disease mechanisms.

Among candidate genes, growth differentiation factor 5 (GDF5) a member of the TGF-β superfamily has a central role in skeletal biology, contributing to the development, maintenance, and repair of cartilage and bone [4]. Because of its biological relevance to joint tissue integrity, variation in GDF5 has been widely studied as a potential contributor to KOA susceptibility. However, genetic association findings for commonly studied variants (including rs143383) have been inconsistent across studies and populations, creating uncertainty about the direction and magnitude of risk, as well as the extent to which effects vary by joint site or ancestry [5, 6]. Despite multiple prior meta-analyses evaluating the relationship between GDF5 polymorphisms and KOA, conclusions have not fully converged. Importantly, published reviews themselves have highlighted methodological limitations in earlier syntheses most notably inaccurate data extraction and inadequate population-based subgroup analyses both of which can meaningfully distort pooled estimates and obscure true effect modification by ancestry or other factors. In parallel, the evidence base continues to expand, and newer studies add information on additional KOA phenotypes and more diverse populations, strengthening the case for a refreshed quantitative synthesis that aligns with contemporary reporting standards. Recent systematic work has also explicitly framed the field as unresolved: genetic contributions to KOA have been widely discussed, yet associations for GDF5 polymorphisms remain controversial and require confirmation using updated evidence [7]. Moreover, broader syntheses have emphasized the value of stratifying analyses by OA subtype (knee) and by demographic factors (e.g., sex and ethnicity) to produce clinically interpretable conclusions and to better inform downstream translational efforts, including risk stratification and target-oriented research. Accordingly, an updated meta-analysis is warranted to (i) incorporate newly available studies since prior search cutoffs, (ii) re-check extracted genotype/allele data to minimize avoidable errors, and (iii) apply structured subgroup and sensitivity analyses to clarify whether associations differ by joint site and population. This approach is expected to yield a more reliable and current estimate of the relationship between GDF5 rs143383 and OA susceptibility, and to better define remaining uncertainty where heterogeneity persists.

Methodology:

Protocol and reporting framework

This updated systematic review and meta-analysis was planned and reported in line with PRISMA guidance, using a prespecified approach for literature retrieval, eligibility screening, data extraction, and quantitative synthesis [8] (Figure 1).

Literature search strategy

A comprehensive search was conducted in major English-language databases (e.g., PubMed, Embase, Web of Science, Cochrane Library) and relevant Chinese databases (CNKI, Wanfang, VIP), consistent with prior KOA–GDF5 syntheses. Search terms combined gene/variant and disease descriptors using Boolean operators, for example: (“GDF5” OR “growth differentiation factor 5” OR “rs143383”) AND (“SNP” OR “polymorphism”) AND (“osteoarthritis” OR “OA”). Reference lists of relevant articles/reviews were additionally screened to identify eligible studies not captured by database indexing.

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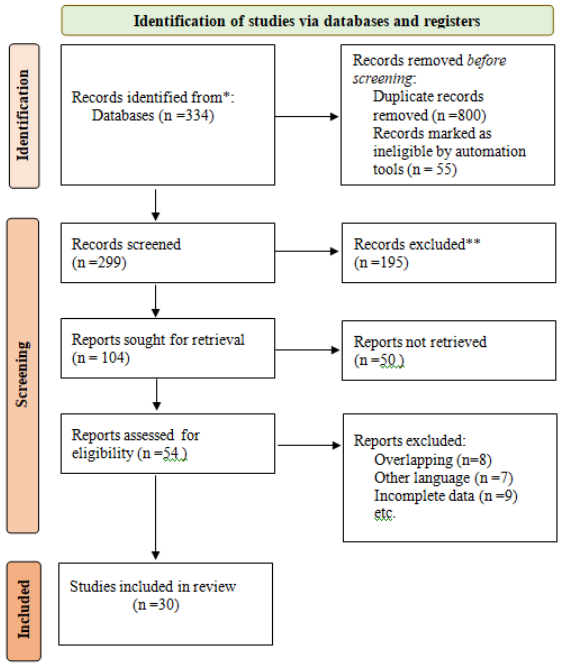

Figure 1. Prisma flow chart of included studies

Eligibility criteria

Studies were included if they: (i) were human case–control investigations; (ii) enrolled KOA cases diagnosed using recognized criteria (e.g., ACR-based diagnosis in prior work) with healthy/appropriate controls**;** (iii) evaluated GDF5 rs143383 with OA as the phenotype; and (iv) reported sufficient genotype/allele data to compute effect estimates (OR with 95% CI). Exclusions comprised non-eligible designs/publication types (e.g., pedigree correlation studies, case reports, trials, reviews/comments), studies with non-conforming KOA diagnosis or non-healthy controls, studies assessing other SNPs/phenotypes, and reports lacking retrievable full text or extractable data.

Study selection

Two reviewers independently screened titles/abstracts and then full texts against the eligibility criteria. Discrepancies were resolved by repeat review of the full text and discussion until agreement.

Data extraction

From each eligible study, two reviewers independently extracted: first author, publication year, country and ethnicity, sample size, genotyping information (when provided), and genotype/allele counts in cases and controls. Hardy–Weinberg equilibrium (HWE) information for control groups was recorded when available. To strengthen accuracy in this update, all genotype/allele tables were cross-checked for internal consistency prior to pooling (a step emphasized as important because earlier syntheses have reported extraction-related limitations).

Quality assessment

Methodological quality was evaluated using the Newcastle–Ottawa Scale (NOS), covering selection, comparability, and exposure/outcome domains (0–9 points) [9].
Where a modified-NOS threshold was applied, studies scoring ≥5 were considered of acceptable quality, consistent with prior KOA–GDF5 meta-analyses.

Statistical analysis

Metagenyo software was used to perform the statistical analysis of meta-analysis. Associations between rs143383 and KOA risk were summarized as pooled odds ratios (ORs) with 95% confidence intervals (CIs)**.** Analyses were performed under standard genetic contrasts including allele, over dominant, dominant, and recessive models (e.g., allele T vs C; TT vs CC; TC vs CC; TT+TC vs CC; TT vs TC+CC as used in prior work). Between-study heterogeneity was evaluated using Q testing and I^2 statistics. When heterogeneity exceeded conventional thresholds (e.g., $P<0.1$ and/or $I^2 \geq 50\%$), a random-effects model was used; otherwise, fixed-effect pooling was applied.

Subgroup, sensitivity, and bias assessment

To explore sources of heterogeneity and potential effect modification, subgroup analyses were planned by ethnicity (e.g., Asian/Caucasian and other reported groups)

Robustness was assessed using leave-one-out sensitivity analysis (removing one study at a time).

Publication bias was evaluated using funnel-plot inspection.

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JCHR (2026) 16(1), 1766-1776 | ISSN:2251-6727

Results

Study selection

The literature search identified 334 records. After removal of duplicates 135, 299 titles/abstracts were screened. Full texts 150 were assessed for eligibility, and 30 studies met inclusion criteria for KOA [10-32]. Studies were excluded at the full-text stage primarily because they: (i) did not evaluate KOA specifically (mixed OA without separable knee data), (ii) lacked extractable rs143383 genotype/allele counts, (iii) were non–case-control designs, or (iv) used overlapping datasets (the most complete dataset was retained).

Characteristics of included KOA studies

A total of 30 eligible KOA case–control studies were included, comprising 10739 KOA cases and 16281 controls. Studies were conducted in Asian / Caucasian populations. KOA diagnosis was established using radiographic grading and/or clinical criteria as reported in the original studies. Genotype frequencies (TT/TC/CC) for GDF5 rs143383 in cases and controls are summarized in Table 1. Hardy–Weinberg equilibrium (HWE) in controls was recorded and studies deviated from HWE and were retained for sensitivity evaluation.

Study quality

Using the Newcastle–Ottawa Scale, quality scores ranged from 1-10. Most studies demonstrated adequate case definition and control selection, while common limitations involved comparability and variable reporting of genotyping quality-control procedures. Overall 28 studies were categorized as higher quality (NOS ≥ 8]) and 2 studies as moderate/lower quality.

Overall association

Across 30 KOA case–control studies, GDF5 rs143383 was significantly associated with KOA susceptibility in the main genetic models (Figure 2). The allelic contrast (A vs a) showed an increased risk (OR = 1.3272, 95% CI 1.2045–1.4624; P < 0.0001) with substantial heterogeneity (I^2 = 81.69%). Consistent risk-increasing effects were also observed under the recessive model (AA vs Aa+aa) (OR = 1.3783, 95% CI 1.2244–1.5516; P < 0.0001; I^2 = 76.56%) and the dominant model (AA+Aa vs aa) (OR = 1.4788, 95% CI 1.2597–1.7359; P = 0.000002; I^2 = 71.12%). In contrast, the overdominant model (Aa vs AA+aa) suggested a modest protective pattern overall (OR = 0.8953, 95% CI 0.8194–0.9783; P = 0.014451; I^2 = 58.96%). Pairwise comparisons supported the same direction of effect, with the strongest association observed for AA vs aa (OR = 1.6972, 95% CI 1.4020–2.0545; P < 0.0001; I^2 = 76.09%).

Table 1. Characterstics of Included Studies

Study	Ethnicity	KOA Cases			Control			HW-P.value	Quality Score
		TT	TC	CC	TT	TC	CC		
Southam 2007	Caucasian	102	136	36	439	563	194	0.88	9
Southam 2007_1	Caucasian	219	238	52	324	372	126	0.6	9
Miyamoto 2007	Asian	197	97	19	473	330	58	0.96	9
Miyamoto 2007_1	Asian	444	243	31	244	193	48	0.6	8
Tsezou 2007	Caucasian	95	126	30	99	125	44	0.94	9
Yao 2008	Asian	189	93	16	232	182	38	0.94	9
Chapman 2008	Caucasian	54	72	16	289	331	104	0.88	8

Journal of Chemical Health Risks

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JCHR (2026) 16(1), 1766-1776 | ISSN:2251-6727

Vaes 2009	Caucasian	276	298	93	752	1014	331	0.94	7
Valdes 2009	Caucasian	126	98	35	181	244	84	0.94	9
Valdes 2009_1	Caucasian	337	313	85	238	329	79	0.15	9
Cao 2010	Asian	150	115	11	159	113	26	0.72	7
Takahashi 2010	Asian	566	313	54	684	461	80	0.94	8
Valdes 2011	Caucasian	32	24	9	168	179	80	0.1	9
Valdes 2011_1	Caucasian	413	361	93	294	354	110	0.94	9
Valdes 2011_2	Caucasian	467	511	163	219	237	80	0.57	4
Tawonsawatruk 2011	Asian	35	41	11	33	47	23	0.79	3
Shin 2012	Asian	382	305	38	942	689	105	0.42	9
Mishra 2013	Asian	124	130	46	54	160	56	0.03	9
Ozcan 2017	Caucasian	37	43	14	74	153	52	0.27	9
Mishra 2017	Asian	199	226	75	131	272	97	0.15	8
Garcia-Alvarado 2018	Caucasian	87	51	7	66	65	14	0.9	7
Poornima 2018	Asian	72	45	33	39	34	77	0	7
Zhang 2019	Asian	124	105	59	206	159	32	0.94	7
Li 2020	Asian	295	212	25	474	375	78	0.94	8
Moghimi 2021	Asian	52	34	14	12	46	42	0.94	9
Amani 2020	Asian	15	26	9	10	18	22	0.28	7
Almalki 2023	Asia	18	30	12	13	21	26	0.15	9
Gundogdu 2025	Asian	19	48	33	27	47	26	0.88	8
Almaki 2023	Asian	18	30	12	13	21	26	0.15	7
Sahoo 2024	Asian	25	36	39	14	34	52	0.15	8

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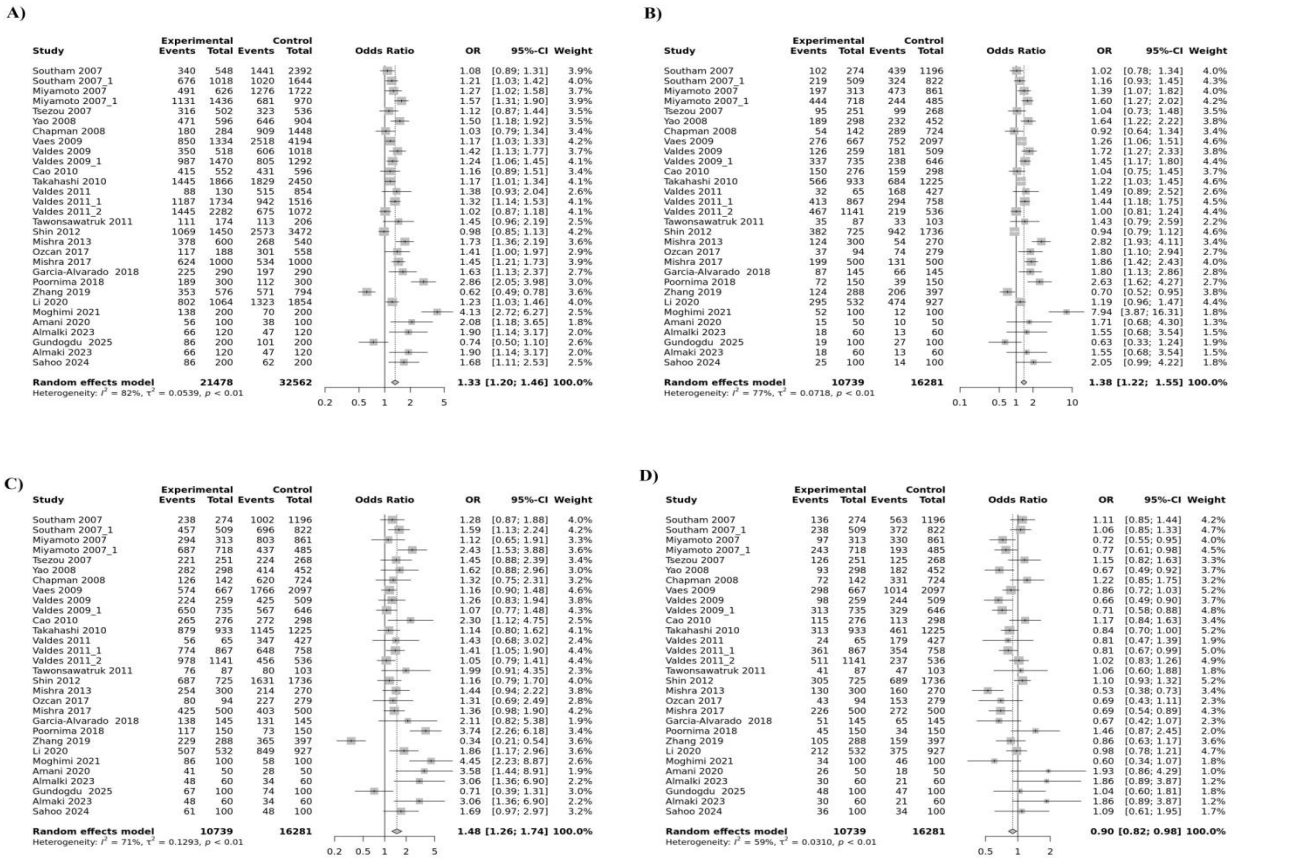

Figure 2. Association of GDF5 rs143383 gene polymorphism with risk of KOA in A) allelic B) recessive C) dominant d) Over dominant models

Subgroup analysis by ethnicity

In Asians (18 studies), the association was generally stronger, particularly in the allelic model (OR = 1.4378, 95% CI 1.2147–1.7018; P = 0.000024; I^2 = 87.83%), the recessive model (OR = 1.4878, 95% CI 1.2225–1.8106; P = 0.000073; I^2 = 83.02%), and the dominant model (OR = 1.6708, 95% CI 1.2550–2.2243; P = 0.000438; I^2 = 81.04%). The over dominant comparison was not significant in Asians (OR = 0.9070; P = 0.155439). In Caucasians (12 studies), significant associations were also observed in the allelic model (OR = 1.1955, 95% CI 1.1316–1.2630; P < 0.0001; I^2 = 30.04%), recessive model (OR = 1.2706, 95% CI 1.1298–1.4291; P = 0.000065; I^2 = 52.47%), and dominant model (OR = 1.2589, 95% CI 1.1275–1.4056; P = 0.000042; I^2 = 0%). Pairwise contrasts remained significant, including AA vs aa (OR = 1.3967; P < 0.0001) and Aa vs aa (OR = 1.1487; P = 0.019914), indicating a consistent risk direction across ancestries.

Publication bias / small-study effects

Egger's test suggested potential small-study effects in several overall comparisons, including the allelic contrast (P = 0.0182), the dominant model (P = 0.0179), AA vs aa (P = 0.0331), and Aa vs aa (P = 0.0137) (Figure 3). In ethnicity-stratified analyses, Egger's testing was largely non-significant; however, the Asian Aa vs aa comparison showed evidence of small-study effects (P = 0.0275), while Caucasian subgroup Egger's results were not significant across the evaluated models (P > 0.05). Overall, these findings indicate that although the rs143383–KOA association is statistically supported, interpretation should consider heterogeneity and potential publication bias in some pooled contrasts.

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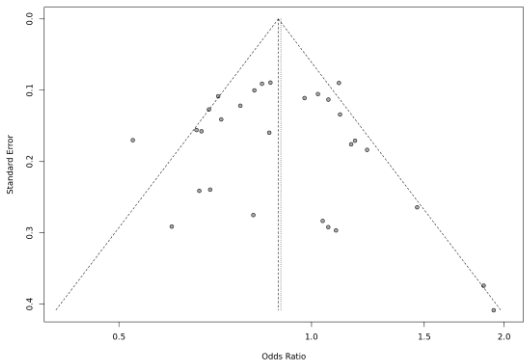

Figure 3. Funnel plot for the analysis of publication bias for the association of GDF5 rs143383 gene polymorphism with risk of KOA

Sensitivity analysis

The leave-one-out sensitivity analysis (fixed-effect) demonstrated that the association remained stable and consistently significant after omitting each study sequentially (Figure 4). The recalculated pooled odds ratios varied only slightly, ranging from OR = 1.22 to 1.26**,** with corresponding 95% CIs remaining above unity (approximately 1.18–1.27 at the lowest and up to 1.21–1.31 at the highest). The overall fixed-effect estimate from the sensitivity plot was OR = 1.24 (95% CI 1.19–1.29)**,** indicating that no single study materially influenced the pooled KOA risk estimate or altered the direction of effect.

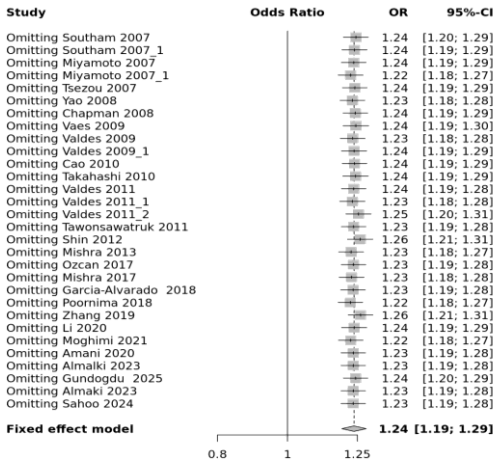

Figure 4. Sensitivity analysis for the association of GDF5 rs143383 gene polymorphism with risk of KOA

Discussion

This updated meta-analysis provides a comprehensive and methodologically rigorous synthesis of the association between the GDF5 rs143383 polymorphism and knee osteoarthritis (KOA) susceptibility, incorporating 30 case–control studies with more than 27,000 participants. By re-examining genotype data, expanding population coverage, and applying structured subgroup and sensitivity analyses, the present study addresses key limitations highlighted in earlier syntheses and offers a more reliable estimate of genetic risk.

Overall association and biological plausibility

Our pooled analyses demonstrate a significant association between the rs143383 risk allele and increased KOA susceptibility across multiple genetic models, with the strongest effects observed in homozygous comparisons (AA vs aa) and dominant/recessive contrasts. These findings reinforce the hypothesis that rs143383 contributes meaningfully to KOA risk rather than representing a spurious association.

From a biological standpoint, this association is highly plausible. GDF5 is a critical regulator of joint morphogenesis, cartilage maintenance, and repair, and functional studies have shown that the rs143383 T allele reduces transcriptional activity of GDF5 in chondrocytes [33]. Reduced GDF5 expression may impair cartilage homeostasis, extracellular matrix synthesis, and the ability of joint tissues to respond to mechanical stress, thereby predisposing individuals to cartilage degeneration and KOA development. The consistent direction of effect across allele-based and genotype-based models supports a dose-dependent genetic influence, with homozygous carriers exhibiting the highest risk.

Ethnicity-specific effects and heterogeneity

Subgroup analyses revealed that the association between rs143383 and KOA was stronger in Asian populations than in Caucasians, although statistically significant effects were observed in both groups. This difference may reflect variation in allele frequency, linkage disequilibrium patterns, environmental exposures, or gene–environment interactions across ancestries. For example, lifestyle factors such as

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JCHR (2026) 16(1), 1766-1776 | ISSN:2251-6727

occupational knee loading, squatting habits, and body mass index distributions differ substantially between populations and may modify genetic susceptibility.

Importantly, heterogeneity was substantial in the overall and Asian analyses but markedly lower in Caucasian subgroups, particularly under the dominant model. This suggests that ethnicity is a major contributor to between-study heterogeneity, underscoring the importance of population-stratified analyses in genetic association studies. The persistence of heterogeneity even after stratification indicates that additional factors such as KOA definition, radiographic grading thresholds, age structure, sex distribution, and genotyping platforms may further influence effect estimates.

Interpretation of the over dominant model

Interestingly, the over dominant comparison suggested a modest protective effect overall, although this pattern was not consistently observed across ethnic subgroups. Such findings may reflect non-linear genotype effects, population-specific genetic architectures, or residual confounding. Alternatively, the apparent heterozygote advantage could arise from sampling variation or study design differences and should be interpreted cautiously, particularly given the moderate heterogeneity and evidence of small-study effects in some contrasts.

Robustness of findings

The stability of the pooled estimates was confirmed through leave-one-out sensitivity analysis, which showed that no single study materially influenced the overall association. This robustness strengthens confidence in the observed relationship between rs143383 and KOA risk and suggests that the findings are not driven by outlier studies or disproportionately large datasets.

Publication bias and limitations

Evidence of small-study effects was detected in several overall comparisons, indicating that effect sizes may be modestly inflated in the pooled estimates. However, the absence of significant publication bias in most ethnicity-specific analyses, particularly among Caucasian studies, suggests that the core association is unlikely to be solely an artifact of selective reporting.

Several limitations should be acknowledged. First, substantial heterogeneity remained in some analyses despite stratification, limiting precise quantification of effect size. Second, most included studies relied on unadjusted genotype frequencies; therefore, the pooled estimates do not account for potential confounders such as age, sex, body mass index, or mechanical loading. Third, gene–gene and gene–environment interactions could not be evaluated due to insufficient data. Finally, although rs143383 is functionally relevant, KOA is a polygenic and multifactorial disease, and this variant alone cannot explain the full genetic architecture of KOA susceptibility.

Implications and future directions

Despite these limitations, the present meta-analysis provides strong and updated evidence that GDF5 rs143383 is a genuine genetic risk factor for KOA, with consistent effects across populations and genetic models. These findings support the inclusion of GDF5 in polygenic risk profiling and highlight its relevance as a potential target for mechanistic and translational research. Future studies should prioritize large, well-phenotyped cohorts, standardized KOA definitions, and integrated analyses incorporating environmental exposures and other OA-related loci. Functional studies exploring how rs143383 interacts with biomechanical stress and inflammatory pathways may further clarify its role in KOA pathogenesis and inform preventive or therapeutic strategies.

Conclusion

This updated meta-analysis of 30 KOA case–control studies provides robust evidence that GDF5 rs143383 is significantly associated with increased susceptibility to knee osteoarthritis, with consistent risk direction across major genetic models and genotype contrasts. The association was observed in both Asian and Caucasian populations, with generally stronger effects and higher heterogeneity in Asians, highlighting the importance of ancestry-stratified interpretation. Sensitivity analyses confirmed that the pooled estimates were stable and not driven by any single study, supporting the reliability of the findings. However, the presence of substantial heterogeneity in several models and indications of small-study effects in some overall comparisons suggest that effect sizes should be interpreted cautiously. Overall, these results support rs143383 as a credible

Journal of Chemical Health Risks

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JCHR (2026) 16(1), 1766-1776 | ISSN:2251-6727

KOA susceptibility locus and reinforce the need for large, well-phenotyped, multi-ethnic studies with standardized KOA definitions and reporting to clarify residual heterogeneity and strengthen translational relevance

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Conflict of interest:

The authors declare that there is no conflict of interest.

References:

1. Geng R, Li J, Yu C, Zhang C, Chen F, Chen J, Ni H, Wang J, Kang K, Wei Z, Xu Y. Knee osteoarthritis: Current status and research progress in treatment. Experimental and therapeutic medicine. 2023 Oct 1;26(4):1-1.

2. Lin C, Yang J, Su H, Zhang X, Wang B. The Bidirectional Role of Obesity and Aging in the Pathogenesis of Osteoarthritis: Molecular Mechanisms, Epigenetic Insights, and Therapeutic Implications. Journal of Inflammation Research. 2025 Dec 31:12637-76.

3. Aubourg G, Rice SJ, Bruce-Wootton P, Loughlin J. Genetics of osteoarthritis. Osteoarthritis and Cartilage. 2022 May;30(5):636.

4. Sun K, Guo J, Yao X, Guo Z, Guo F. Growth differentiation factor 5 in cartilage and osteoarthritis: a possible therapeutic candidate. Cell Proliferation. 2021 Mar;54(3):e12998.

5. Chapman K, Valdes AM. Genetic factors in OA pathogenesis. Bone. 2012 Aug 1;51(2):258-64.

6. Zengini E, Hatzikotoulas K, Tachmazidou I, Steinberg J, Hartwig FP, Southam L, Hackinger S, Boer CG, Styrkarsdottir U, Gilly A, Suveges D. Genome-wide analyses using UK Biobank data provide insights into the genetic architecture of osteoarthritis. Nature genetics. 2018 Apr;50(4):549-58.

7. Wang YP, Di WJ, Yang S, Qin SL, Xu YF, Han PF, Hou KD. The association of growth differentiation factor 5 rs143383 gene polymorphism with osteoarthritis: a systematic review and meta-analysis. Journal of orthopaedic surgery and research. 2023 Oct 10;18(1):763.

8.Veroniki AA, Tricco AC, Rangira D, McKenzie JE, Li T, Straus SE, Smith M, Catalá-López F, Wolfe D, Nincic V, Konstantinidis M. Updating the PRISMA reporting guideline for network meta-analysis: a scoping review. medRxiv. 2025 Feb 10:2025-02.

9. De Cassai A, Dost B, Tulgar S, Boscolo A. Methodological standards for conducting high-quality systematic reviews. Biology. 2025 Aug 1;14(8):973.

10. Southam L, Rodriguez-Lopez J, Wilkins JM, Pombo-Suarez M, Snelling S, Gomez-Reino JJ, Chapman K, Gonzalez A, Loughlin J. An SNP in the 5′-UTR of GDF5 is associated with osteoarthritis susceptibility in Europeans and with in vivo differences in allelic expression in articular cartilage. Human molecular genetics. 2007 Sep 15;16(18):2226-32.

11. Miyamoto Y, Mabuchi A, Shi D, Kubo T, Takatori Y, Saito S, Fujioka M, Sudo A, Uchida A, Yamamoto S, Ozaki K. A functional polymorphism in the 5′ UTR of GDF5 is associated with susceptibility to osteoarthritis. Nature genetics. 2007 Apr;39(4):529-33.

12. Tsezou A, Satra M, Oikonomou P, Bargiotas K, Malizos KN. The growth differentiation factor 5 (GDF5) core promoter polymorphism is not associated with knee osteoarthritis in the Greek population. Journal of Orthopaedic Research. 2008 Jan;26(1):136-40.

13. Yao, C.; Jin, D.; Q., J. A Single Nucleotide Polymorphism (SNP) in the 5′-UTR of GDF5 Is Associated with Knee Osteoarthritis. *Jiangsu Med. J.* **2008**, *34*, 1198–1199.

14. Chapman K, Takahashi A, Meulenbelt I, Watson C, Rodriguez-Lopez J, Egli R, Tsezou A, Malizos KN, Kloppenburg M, Shi D, Southam L. A meta-analysis of European and Asian cohorts reveals a global role of a functional SNP in the 5′ UTR of GDF5 with osteoarthritis susceptibility. Human

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(1), 1766-1776 | ISSN:2251-6727

molecular genetics. 2008 May 15;17(10):1497-504.

15. Vaes RB, Rivadeneira F, Kerkhof JM, Hofman A, Pols HA, Uitterlinden AG, Van Meurs JB. Genetic variation in the GDF5 region is associated with osteoarthritis, height, hip axis length and fracture risk: the Rotterdam study. Annals of the rheumatic diseases. 2009 Nov 1;68(11):1754-60.

16. Valdes AM, Spector TD, Doherty S, Wheeler M, Hart DJ, Doherty M. Association of the DVWA and GDF5 polymorphisms with osteoarthritis in UK populations. Annals of the rheumatic diseases. 2009 Dec 1;68(12):1916-20.

17. Cao Z, Lee HS, Song JH, Yoon J, Park YK, Nam SW, Lee JY, Park WS. Growth differentiation factor 5 [GDF5] Core promoter polymorphism is not associated with susceptibility to osteoarthritis of the knee in the Korean population. The Korean Journal of Pathology 2010; 44: 404-9

18. Takahashi H, Nakajima M, Ozaki K, Tanaka T, Kamatani N, Ikegawa S. Prediction model for knee osteoarthritis based on genetic and clinical information. Arthritis research & therapy. 2010 Oct 12;12(5):R187.

19. Valdes AM, Evangelou E, Kerkhof HJ, Tamm A, Doherty SA, Kisand K, Tamm A, Kerna I, Uitterlinden A, Hofman A, Rivadeneira F. The GDF5 rs143383 polymorphism is associated with osteoarthritis of the knee with genome-wide statistical significance. Annals of the rheumatic diseases. 2011 May 1;70(5):873-5.

20. Tawonsawatruk T, Changthong T, Pingsuthiwong S, Trachoo O, Sura T, Wajanavisit W. A genetic association study between growth differentiation factor 5 (GDF 5) polymorphism and knee osteoarthritis in Thai population. Journal of orthopaedic surgery and research. 2011 Sep 21;6(1):47.

21. Shin MH, Lee SJ, Kee SJ, Song SK, Kweon SS, Park DJ, Park YW, Lee SS, Kim TJ. Genetic association analysis of GDF5 and ADAM12 for knee osteoarthritis. Joint Bone Spine. 2012 Oct 1;79(5):488-91.

22. Mishra A, Sanghi D, Srivastava RN, Raj S. AB0001 Genetic polymorphism in GDF-5 gene as risk factor for development and progression of osteoarthritis. Annals of the Rheumatic Diseases. 2012 Jun 1;71:637.

23. Ozcan S, Korkmaz M, Balbaloglu O, Percin F, Yilmaz N, Erdogan Y, Gunaydin I. Polymorphisms in the growth differentiation factor 5 (GDF 5) gene in knee osteoarthritis. Jcpsp-J Coll Physici. 2017 Oct 1;27:602-5.

24. Mishra A, Srivastava RN, Awasthi S, Parmar D, Mishra P. Expression of genes and their polymorphism influences the risk of knee osteoarthritis. Journal of Nucleic Acids. 2017;2017(1):3138254.

25. Garcia-Alvarado F, Rosales-González M, Arellano-Perez-Vertti D, Espino-Silva P, Meza-Velazquez M, Ruiz-Flores P. Association Between the SNP rs143383+ 104T/C in the GDF5 Gene and the Risk of Knee Osteoarthritis in a Population from Northern Mexico–A Case–Control Study. Genetic testing and molecular biomarkers. 2018 Aug 1;22(8):503-6.

26. Zhang S, Wang J, Ji H, Jia H, Guan D. Interaction between GDF5 gene polymorphisms and environment factors increased the risk of knee osteoarthritis: a case–control study. Bioscience Reports. 2019 Feb;39(2):BSR20182423.

27. Li Y, Liu F, Xu X, Zhang H, Lu M, Gao W, Yin L, Yin Z. A novel variant near LSP1P3 is associated with knee osteoarthritis in the Chinese population. Clinical Rheumatology. 2020 Aug;39(8):2393-8.

28. Moghimi N, Nasseri S, Ghafouri F, Jalili A. Frequency of Growth Differentiation Factor 5 rs143383 and asporin D-repeat polymorphisms in patients with hand and knee osteoarthritis in Kurdistan province, Iran. International Journal of Rheumatic Diseases. 2021 May;24(5):694-700.

29. Amani AA, Ismail KA, Shami A, Algethami MK, Elsawy HW, et al. (2020) Association of Growth Differentiation Factor 5 (GDF5) Gene Polymorphisms with Susceptibility to Knee Osteoarthritis in Saudi Population. Int J Immunol

Immunother 7:048. doi.org/10.23937/2378-3672/1410048.

30. Almalki A, Gharib AF, Almehmadi M, Alharthi A, Alsalmi O, Alsulimani AH, Alanazi RH, AlWthenani AA, Alotaibi M, AlZaidi FT, Gharib A. The association of vitamin D, growth/differentiation factor 5 (GDF-5) gene polymorphism, and serum GDF-5 protein in obese patients with knee osteoarthritis. Cureus. 2023 Nov 6;15(11).

31. Gundogdu K, Dodurga Y, Gungor HR, Gundogdu G, Akkaya S. A cross-sectional study on the assessment of COLL11A1, VEGF, and GDF5 gene polymorphisms in Turkish patients with primary knee osteoarthritis. BMC Musculoskeletal Disorders. 2025 Feb 14;26(1):153.

32. Sahoo SS, Thakur RK, Verma S, Mishra J, Kabi BC. Growth Differentiation Factor 5 (GDF5) Polymorphism and Risk of Knee Osteoarthritis: A Case-Control Study. JK Science: Journal of Medical Education & Research. 2024 Jan 10;26(1):26-30.

33. Sun K, Guo J, Yao X, Guo Z, Guo F. Growth differentiation factor 5 in cartilage and osteoarthritis: a possible therapeutic candidate. Cell Proliferation. 2021 Mar;54(3):e12998.